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To all of my patients, students and others who bring inspiration and grace into my life (including Drs. Kottil Rammohan, John Stang, Ralph Jozeftowicz, John Kissel, Miriam Freimer, Sheryl Pfeil, and Jerry Mendell) and, most of all, to my daughters Kate and Patty who are not always patient, but who never fail to bring the blessing of love to each of my days.

D. J. L.

To my wife, Cheryl, and my children, Alex and Ashley, for their love, support, and patience. In addition, I’d like to thank all of my neuro-oncology patients for the inspiration they have given me.

H.B.N

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The 5-Minute Neurology Consult
Preface

We are pleased to bring a Neurology volume to the 5-Minute Consult series. This book is intended to present current clinical information to several groups:

• Busy clinical practitioners in neurology, general practice, emergency rooms, and nonneurologic specialties who need rapid access to basic data about diagnosis and treatment for various neurologic conditions
• Residents and students seeking a reference where they can quickly refresh their knowledge about the basics of a neurologic condition
• Patients and their families who want quick information about their diagnoses and referrals to patient information and support organizations

Neurology is an area of medicine that incites anxiety and discomfort for many students, nurses, and physicians who have not trained in the specialty. In this decade following the Decade of the Brain, therapeutic interventions for neurologic disease are flourishing; every practitioner must understand the diagnosis and treatment of basic neurologic conditions. We hope that this rapid information source will help all to approach patients suffering from neurologic disorders with more confidence.

Information is provided in a structured format that allows easy access and rapid assimilation. We have attempted to offer relevant and current references. The information is readily adaptable to handheld devices and will be available from the publisher in that format shortly following publication of the book.

It has been a great honor and pleasure to work with the many chapter authors who have shared their expertise in and enthusiasm for clinical neurology. Some are young stars while others are accomplished masters in neurology, but all have attempted to provide the best distillation of relevant information for each condition. The staff at Lippincott Williams & Wilkins, including Keith Donnellan and Charley Mitchell, kept us on track in this effort with advice, encouragement, and humor.

Practice is science touched with emotion.  
-Stephen Paget, Confessio Medici, 1909

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SECTION I

Neurologic Symptoms and Signs
Aphasia is an acquired impairment of language characterized by word-finding difficulty and paraphasias with a variable disturbance of comprehension. In right-handed people and most left-handers, aphasia results from a lesion in the left cerebral hemisphere. Occasionally a right-hander is seen with aphasia due to a right hemisphere lesion, a phenomenon known as crossed aphasia. The term aphasia refers to spoken language, but aphasics almost always have impaired reading (alexia) and writing (agraphia).

**DEFINITIONS**

Paraphasias are errors in word production. They may be phonemic, with substitution of a wrong sound ("bup" for "cup"); semantic, with substitution of a wrong word that is often related in meaning ("dinner" for "cup"); or neologisms, with production of a meaningless nonword ("bitko" for "cup"). Fluency refers to the flow of speech and may be thought of as number of words per unit time or length of longest utterance. Nonfluent speech is halting, with long pauses and phrases shorter than four words. Fluent speech retains long phrases and normal melody of speech. Nonfluent aphasics can often make themselves understood in a few words produced with great effort, while fluent aphasics often make very little sense despite lengthy output.

**CLINICAL CHARACTERISTICS**

Aphasia is usually readily apparent during history-taking. The patient exhibits word-finding difficulty resulting in paraphasias, circumlocutory descriptions ("that thing you write with" for "pen"), obvious searching for words with pauses and Her phrases ("oh, um, you know"). Aphasia, a disorder of language, must be distinguished from disorders of speech. Dysarthria is a disturbance of articulation usually due to lesions lower in the nervous system. Although aphasia and dysarthria may coexist, a patient with only dysarthria should be able to read and write normally. Dysphonia, a disturbance of voice, may be due to problems with the larynx or its innervation. Aphasia must also be distinguished from more diffuse disturbances of cerebral function such as delirium or dementia where disturbances of attention or other cognitive functions are also found.

**PATHOPHYSIOLOGY**

Language centers surround the left sylvian fissure within territory supplied by the middle cerebral artery (MCA). The diagram of Lictheim's house (Fig. 1) presents a schematic of language processing based on the work of Lictheim. While obviously a gross oversimplification of a complex process, it nonetheless serves as a useful mnemonic for bedside assessment of aphasia. Auditory input (I) is presented to Wernicke's area (W) in the posterior third of the superior temporal gyrus where sounds heard are linked to representations of words that Lictheim called "auditory word engrams." Broca's area (B) in the inferior frontal gyrus programs lower centers to articulate a word, producing speech output (O) and may be thought of as containing Lictheim's "motor word engrams." Broca's area is also important in producing correct word order so that sentences make grammatical sense. Wernicke's and Broca's areas are strongly connected by white matter tracts such as the arcuate fasciculus (the line W-B). Lictheim visualized an extra-sylvian area of concepts (C) where engrams were linked to actual meanings of words and, while there is no one brain area corresponding to this, C may be thought of as the rest of the cerebrum, beyond left MCA territory. Lesions disrupting the line C-B-O impair fluency. Lesions along I-W-C impair comprehension. Repetition is impaired by lesions along I-W-B-O.

**DIAGNOSIS**

**Aphasia** is an acquired impairment of language. It is most often due to ischemic or hemorrhagic stroke within or adjacent to the territory of the left MCA but may result from trauma, tumor, infection, or other lesions in this location. Aphasia is uncommon in a white matter disease like multiple sclerosis and is also distinctly uncommon with compressive lesions such as subdural hematomas. A hemiparetic patient with aphasia is thus likely to have an intraparenchymal rather than an extraparenchymal lesion. Language disturbance is often present in cortical dementias such as Alzheimer's disease and is often prominent in frontotemporal dementia.

**DIFFERENTIAL DIAGNOSIS**

Aphasia is often due to ischemic or hemorrhagic stroke within or adjacent to the territory of the left MCA but may result from trauma, tumor, infection, or other lesions in this location. Aphasia is uncommon in a white matter disease like multiple sclerosis and is also distinctly uncommon with compressive lesions such as subdural hematomas. A hemiparetic patient with aphasia is thus likely to have an intraparenchymal rather than an extraparenchymal lesion. Language disturbance is often present in cortical dementias such as Alzheimer's disease and is often prominent in frontotemporal dementia.

**SIGNS AND SYMPTOMS**

Patients' spontaneous speech reveals paraphasias and word-finding difficulty and is also used to judge whether they are fluent or nonfluent. Naming is tested by showing patients objects to name. Patients with mild aphasia may name common objects well but have more difficulty producing less common words such as parts of objects. Thus, aphasics tend to have more difficulty naming a watch strap than a watch. Comprehension is tested by asking the patient to carry out commands of varying levels of difficulty. One can begin with simple one-step commands and progress to complex three-stage commands. Repetition is tested beginning with single words and progressing to complex phrases such as "no ifs, ands, or buts." Peri-sylvian aphasia (Broca's, Wernicke's, conduction, and global) are typically due to infarcts in left MCA territory and since all disrupt I-W-B-O, they have in common a disturbance of repetition.

**Broca's Aphasia**

A lesion in Broca's area (B) causes nonfluent speech with poor repetition but relatively preserved comprehension, particularly for nouns and verbs. Since Broca's area is adjacent to the precentral gyrus, this is usually accompanied by right hemiparesis.

**Wernicke's Aphasia**

A lesion in Wernicke's area (W) results in fluent speech with impaired comprehension and repetition. Although it may be accompanied by a right superior homonymous quadrantanopia due to involvement of temporal fibers of the optic radiations, Wernicke's aphasia is generally not accompanied by hemiparesis. Due to the paucity of other findings on examination it is not unusual to see a patient referred with "confusion" who actually has Wernicke's aphasia.
A lesion between Wernicke's and Broca's areas in the arcuate fasciculus/insular area (W-B) results in fluent speech with good comprehension and poor repetition. Global Aphasia

A large middle cerebral territory infarct causes nonfluent speech with poor comprehension and repetition and is typically accompanied by severe hemiparesis. Global aphasia unaccompanied by hemiparesis suggests multiple lesions sparing motor cortex, often of cardioembolic or metastatic origin.

Transcortical Aphasias

These result from lesions in the watersheds between middle, anterior and posterior cerebral arteries (ACA and PCA) or within ACA or PCA territory, disconnecting perisylvian language centers from the rest of the cerebrum. Watershed infarcts may result from hypotension, a shower of small emboli, or carotid occlusion. During cardiac surgery, either of the first two of these may occur and this is a typical clinical setting for transcortical aphasia. Because perisylvian language centers are spared, repetition is intact.

Transcortical Motor Aphasia

A frontal lesion outside of Broca's area (C-B) results in a language deficit similar to Broca's aphasia except that repetition is preserved.

Transcortical Sensory Aphasia

Temporo-occipital Lesions (W-C) may result in a deficit similar to Wernicke's aphasia except that repetition is preserved.

Mixed Transcortical Aphasia

An aphasia similar to global aphasia but with preserved repetition may result from a large MCA/PCA/ACA watershed infarcts (C-B and W-C).

Anomic Aphasia

Impairment of naming with good comprehension, repetition, and fluency is a common but poorly localizing aphasia type. Lesions in many left cerebral areas may cause this mild aphasia.

Subcortical Aphasia

Lesions in thalamus or subcortical white matter can cause aphasia syndromes rather similar to the cortical aphasia types described above. Associated deficits may be atypical (e.g., Wernicke's like aphasia with dense hemiparesis). These patients are often quite dysarthric and repetition is often relatively preserved. Particularly with thalamic lesions, patients may fluctuate dramatically between near-normal output and mumbled jargon.

Management

GENERAL MEASURES

The underlying lesion type determines overall management.

SURGICAL MEASURES

Determined by underlying lesion. Symptomatic

TREATMENT

Determined by underlying lesion. Patients with poor comprehension often benefit from being told information repeatedly and in different words.

ADJUNCTIVE TREATMENT

Large trials suggest that speech therapy by speech pathologists improves recovery.

ADMISSION/DISCHARGE CRITERIA

Determined by underlying lesion type.

IMAGING STUDIES

CT or MRI scanning confirms the localization and nature of the causative lesion.

SPECIAL TESTS

Bedside examination is generally sufficient to determine aphasia type and severity, but numerous standardized aphasia test batteries provide more detailed assessment. These range from 3- to 10-minute screening tests, such as the Frenchay Aphasia Screening Test, to the Boston Diagnostic Aphasia Examination, which may take several hours. In 45 minutes the Western Aphasia Battery determines the type and severity of aphasia.

Medications

DRUG(S) OF CHOICE

Although some reports suggest that bromocriptine or stimulant drugs may improve speech output, pharmacotherapy of aphasia has been disappointing and is not generally used.

ALTERNATIVE DRUGS

N/A

LABORATORY PROCEDURES

N/A

Follow-Up

PATIENT MONITORING

Usually determined by the underlying cause.

EXPECTED COURSE AND PROGNOSIS

Aphasia following stroke generally improves the most in the first 3 months but may continue at a slower rate for 1 to 2 years. Global aphasia may evolve into Broca's, while Wernicke's may become conduction or anomic aphasia during recovery.

PATIENT EDUCATION

Family members benefit from an explanation of language impairment. They often do not understand that patient's answers may not reflect true understanding of questions asked. National Aphasia Association, 156 5th Avenue, Suite 707, New York, NY 10010, (800)922-4622, www.aphasia.org.

SYNONYMS

Dysphasias.

ICD-9-CM: 784.3 Aphasia

SEE ALSO: CEREBROVASCULAR DISEASE

REFERENCES


Author(s) Andrew Kirk, MD, FRCP(C)
Ataxia

DESCRIPTION
Ataxia is defined as incoordination of movements, especially voluntary movements. Gait, limb movements, balance, speech, eye movements, and tone can be involved. Movements appear clumsy or irregular. Velocity and force may not be normally regulated, leading to overshoot of movements.

DEFINITIONS
N/A

CLINICAL CHARACTERISTICS
Ataxia may be of sudden or insidious onset. Disorderly and irregular movements are observed. These are especially prominent with directed movements of the limbs and become more pronounced closer to the target (hypermetria, intention tremor). Gait may appear similar to the gait observed with alcohol intoxication—wide based and unsteady. Speech may be hesitant or explosive. Nystagmus and irregular eye movements may be seen. Association with acute headache, nausea, vomiting, and diplopia may be a sign of acute cerebellar infarct or hemorrhage and should be treated as potentially life threatening.

Hereditary ataxias progress slowly and are divided by pattern of inheritance and genotype. In autosomal-dominant ataxias risk to offspring is 50%. In autosomal-recessive forms risk to siblings is a 25% chance of being affected, 50% of being an unaffected carrier, and 25% chance of being unaffected and not a carrier. Offspring of an affected individual are obligate carriers. In X-linked recessive inheritance, all daughters of an affected mate are carriers; sons are not affected.

For siblings, if the mother of the affected individual is a carrier, brothers are at 50% risk of being affected; sisters have a 50% chance to be unaffected and carriers.

PATHOPHYSIOLOGY
Varies depending on the specific cause of ataxia. Ataxia is most commonly related to disruption of cerebellar pathways. However, coordinated movements require synchronization of multiple sensory and motor pathways and injury to the spinal cord, brainstem, cortex or peripheral nervous system can also cause ataxia.

DIFFERENTIAL DIAGNOSIS
• Vascular: infarcts (cerebellum, brainstem, anterior thalamus, frontal cortex, or parietal lobe), hemorrhage, basilar migraine
• Structural: tumors, ab sciss, arteriovenous malformations, Chiari malformations, Dandy-Walker malformation, and hydrocephalus
• Multiple sclerosis
• Infectious: postinfectious cerebellitis, aseptic meningitis, Creutzfeldt-Jakob disease
• Toxins: alcohol, antidepressants, heavy metals (thallium, lead, mercury, lithium), toluene, cytarabine (Ara-C), cyclosporine
• Endocrine: hypothyroidism
• Nutritional: vitamin E deficiency, vitamin B6 deficiency, Wernicke-Korsakoff disease
• Immune: gluten sensitivity and glutamic acid decarboxylase antibodies, Miller-Fisher variant of Guillain-Barre syndrome
• Paraneoplastic: cerebellar degeneration, opsoclonus-myoctonus
• Sporadic neurodegenerative diseases: olivoponto cerebellar atrophy, cerebellar cortical atrophy, multiple system atrophy
• Hereditary:
  — Autosomal dominant: SCA1-21, DRPLA, episodic ataxia type 1 (EA1), episodic ataxia type 2 (EA2)
  — Autosomal recessive: Friedreich ataxia, ataxia telangiectasia, ataxia with vitamin E deficiency (AVED), infantile-onset spinocerebellar ataxia (ISCRA), ataxia with oculomotor apraxia, Marinesco-Sjogren, spastic ataxia (ARSACS), myoclonus-ataxia syndromes, ataxia with hypothenar dystrophy.
  — X-linked: X-linked ataxia with spasticity, X-linked ataxia with sideroblastic anemia, X-linked ataxia with deafness and blindness and other reported families
  — Mitochondrial: NARP (neuropathy, ataxia, and retinitis pigmentosa) and MERRF (myoclonic epilepsy with ragged red fibers)
  — Metabolic: atabitolipoproteinemia, hexosaminidase deficiency, Refsum disease, cerebrotendinous xanthomatosis, metachromatic leukodystrophy, adrenoleukodystrophy, urea cycle disorders, intermittent branched-chain ketocaridia, Hartnup disease, pyruvate dehydrogenase deficiency

SIGNS AND SYMPTOMS
Ataxic disorders cause static or progressive generalization incoordination affecting gait, limb coordination, speech, and extraocular movements. The brainstem, basal ganglia, spinal cord, retina, or peripheral nervous system are often involved. Other signs of neurologic dysfunction may be seen in vascular disease or multiple sclerosis. Parkinsonian features and autonomic failure may be seen in multisystem atrophy and SCA3.

There is great overlap in the phenotype of the hereditary spinocerebellar ataxias. Most are caused by trinucleotide repeat expansions. There are a few distinguishing features for some types. Molecular diagnosis is needed for definitive classification.

• Distinguishing features of some of the autosomal-dominant hereditary ataxias:
  — SCA2: Slow saccadic eye movements, hyporeflexia or areflexia
  — SCA4: Sensory axonal neuropathy
  — SCA6: Mitochondrial syndrome
  — SCA10: Myoclonus-ataxia type 1

• Distinguishing features of the autosomal-recessive disorders:
  — Friedreich ataxia (FA): hyporeflexia or areflexia, extensor plantar, ataxia with areflexia and ophthalmoplegia, ataxia with areflexia and ophthalmoplegia
  — FA: Ataxia with vitamin E deficiency: similar to FA, plus head titubation and dystonia
  — Ataxia telangiectasia: telangiectasia, immunodeficiency, cancer and endocrine abnormalities
  — Ataxia with oculomotor apraxia: oculomotor apraxia, choreoathetosis, and mental retardation
  — Spastic ataxia (ARSACS): pyramidal signs, peripheral neuropathy, and retinal striations

LABORATORY PROCEDURES
Serum levels of vitamin B12, thyroid-stimulating hormone (TSH), and vitamin E should be checked. Heavy metal screening in cases of suspected exposure. Plasma amino acids and urine organic acids are helpful when an inherited metabolic cause is suspected. If the Miller-Fisher variant of Guillain-Barre syndrome is suspected (ataxia with areflexia and ophthalmoplegia), lumbar puncture for cell count and protein level and nerve conduction studies should be considered.

IMAGING STUDIES
Cranial MRI may identify strabismus abnormalities including infarcts, hemorrhage, tumors, and demyelination. Atrophy of involved structures in the brain or spinal cord can be found in some
Ataxia

SPECIAL TESTS
Antigladin antibodies and glutamic acid decarboxylase antibodies (GAD-Abs) should be searched in all patients with cerebellar ataxia of unknown etiology. Paraneoplastic cerebellar syndrome is associated with anti-Yo, -Hu -Ri, -Ta, -Ma, or -CV2. Paraneoplastic symptoms may be the first sign of an occult cancer. In cases where a hereditary disorder is suspected, DNA testing is commercially available for SCA1, SCA2, SCA3, SCA6, SCAT, SCAB, SCA10, DRLPA, Friedreich ataxia, and ataxia-telangiectasia. These tests are expensive. Genetic counseling prior to testing is advised. In ataxia-telangiectasia serum electrophoresis shows decreased concentrations of immunoglobulin A (IgA) and IgG, while serum a-fetoprotein Levels are elevated. Cultured cells show cytogenetic abnormalities and increased sensitivity to ionizing radiation. Muscle biopsy may confirm a mitochondrial disorder.

Management

GENERAL MEASURES
Protect from fall risks. Acute-onset ataxia needs to be treated as a possible neurosurgical emergency. Cerebellar hemorrhages and large infarcts are associated with a high risk of swelling and may compromise brainstem respiratory centers leading to death. CT scan or MRI should be obtained immediately.

SURGICAL MEASURES
Decompression of hematomas or infarcts associated with edema compressing the cerebellum, brainstem, and forth ventricle. Surgical removal of tumors.

SYMPTOMATIC TREATMENT
Antiemetics for nausea and vomiting; eye patching for diplopia. Antispasitic medications for those with spasticity.

ADJUNCTIVE TREATMENTS
Physical, occupational, and speech therapy. Patients with antigladin antibodies may respond to a gluten-free diet. Patients with GAD-Abs and the Miller-Fisher variant of Guillain-Barre syndrome may respond to IV immunoglobulin.

ADMISSION/DISCHARGE CRITERIA
Acte ataxia associated with inability to walk generally requires admission and evaluation. Ataxia of insidious onset can be evaluated as an outpatient after radiologic studies rule out mass lesions. Individuals with ataxia secondary to intoxication with alcohol or phenytoin may need admission until levels decrease. Discharge criteria include assurance of safety from falls.

Follow-Up

PATIENT MONITORING
In ataxia secondary to cerebellar atrophy or hemorrhage, patients are followed closely (often in the ICU) for cerebral edema and brainstem compromise. Offer genetic counseling to those with hereditary ataxias.

EXPECTED COURSE AND PROGNOSIS
Prognosis depends on the underlying etiology. Recovery after cerebellar insult is possible. Ataxia secondary to tumors, multiple sclerosis, or other areas of infarction may improve. Recovery from alcohol or toxin exposure depends on degree of exposure. Idiopathic and hereditary cerebellar ataxias have a progressive course, and life span may be decreased.

PATIENT EDUCATION
- National Ataxia Foundation, 2800 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. Phone: 763-553-0020, Web: www.ataxia.org
- WE MOVE (Worldwide Education and Awareness for Movement Disorders), 204 East 84th St., New York, NY 10024. Phone: 212-875-8312, Web: www.wemove.org
- International Network of Ataxia Friends (INTERNAF), Web: www.internaf.org

Medications

DRUG(S) OF CHOICE
In most cases, no effective medications are available.
- Adults with vitam in E deficiency: replace with 60 to 75 IU PO or IM. Adjust dosage to normal plasma levels.
- Thiamine deficiency in chronic alcoholics and malnourished patients: thiamine 50 mg PO daily. In Wernicke encephalopathy, thiamine 50 to 100 mg IV and IM immediately, 50 mg/day IM for 3 days, and then 50 mg PO daily.
- Vitamin B12 deficiency: cyanocobalamin 1,000 µg IM daily for 5 to 7 days, then weekly for a month and then monthly for life.
- For episodic ataxia: acetazolamide.
- Stroke prevention, multiple sclerosis, or cancer treatment as indicated.

Contraindications
Limit medications with cerebellar toxicity (anticonvulsants).

Precautions
Alcohol and benzo diazepines may worsen symptoms.

ALTERNATIVE DRUGS
N/A

Miscellaneous

SYNONYMS
Cerebellar ataxia
Spinocerebellar ataxia

ICD-9-CM: 334.2 Primary cerebellar degeneration (familial); 334.3 Cerebellar ataxia; 334.8 Ataxia telangiectasia; 334.9 Spinocerebellar degeneration; 331.9 Cerebral ataxia; 781.3 Ataxia NOS; 781.2 Ataxic gait; 303.9 Alcohol associated

SEE ALSO: FRIEDREICH'S ATAXIA, SPINOCEREBELLAR ATAXIAS

REFERENCES

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**Back Pain**

### Basics

**DESCRIPTION**
Back pain is a constellation of signs of symptoms that can be of mechanical, neurologic (nonmechanical), or visceral origin. The clinical presentation can be categorized into central and peripheral components. The neurologic complaints may not always match the clinical and neurologic findings. Fifty-six percent of adults have back pain and 3% have pain lasting greater than 3 months.

**DEFINITIONS**
- **Axial pain**: pain centralized to the midline structures of the back to include pain from the facet joints, intervertebral disc, vertebral body, sacrolilac joint, and spinal ligaments and muscles.
- **Dermatomal pain**: pain in a specified area of skin in the distribution of a single nerve root with or without neurologicologic changes.
- **Discogenic pain**: pain emanating from the intervertebral disc with or without neurologicologic symptoms or findings (such as annular tears, protrusions, and degenerative disc disease).
- **Myofascial pain**: pain in the musculoligamentous structures with discrete and defined tender or trigger points with reproducible referred pain patterns.
- **Myotomal pain**: pain in a muscle group innervated by a single nerve root with or without neurologicologic changes.
- **Peripheral pain**: spinal pain referred to an extremity with or without neurologicologic findings.
- **Radiculopathy**: pain associated with neurologicologic deficits in the distribution of a single nerve root.
- **Referred pain**: pain referred from a remote structure or organ with or without neurologicologic defect. The pain patterns depend on the dermatomal, myotomal, and sclerotomal of the inciting struture or organ.
- **Sclerotomal (somatic) pain**: pain in bone and fascia in distribution of a single nerve root.

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<th>CLINICAL CHARACTERISTICS</th>
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<td>Back pain can be associated with acte trauma, single mechanical injury, cumulative trauma, degenerative changes, and no identifiable events. It can be associated with remote internal organ disease processes with local or metastatic pathology. Back pain with peripheral symptoms may not have classic neurologicologic deficits and clinical findings even though identifiable pathology is present, such as discogenic pain that may have radicular pain but not true radiculopathy. Back pain may be axial, unilateral, or bilateral with or without radiculopathy to the gluteal region, iliac crest, or extremities. It may be associated with decreased range of motion, muscle spasm, trigger point tenderness and referral pain patterns, antalgic trunk deviation and gait abnormalities, body posture and altered function.</td>
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**PATHOPHYSIOLOGY**
Degenerative and cumulative trauma may lead to alteration of the weight distribution between the anterior elements, disc and vertebral body, and the posterior elements, facet joints and capsule, ligaments and muscles. This trauma leads to annular tears, loss of disc height, osteophyte formation, facet synovial reaction and meniscus tear, cartilage destruction, and facet capsular laxity and subluxation. This trauma also leads to spinal canal and neural foraminal stenosis with resulting neural element encroachment and compromise. Before mechanical compromise occurs, chemical substances producing inflammation from various structures in the back can produce symptoms and physical findings with minimal neural compromise. Some of the known mediators are phospholipase A₂, leukotrienes, prostaandins, platelet-activating factors, bradykinins, cytokines, interleukins, nitric oxide, tumor necrosis factor, macrophages, and other inflammatory cells. The dorsal root ganglion is sensitive to mechanical compression and chemical or inflammatory mediators and it will increase nerve fiber firing and alter neural pathways and increases pain perception. Neural sensitivity increases as the biomechanical deterioration occurs.

### Diagnosis

**DIFFERENTIAL DIAGNOSIS**
- **Axial pain**: lumbosacral sprain and strain, internal disc disruption and annular tears, facet joint pathology, (arthropathy, capsulitis, and synovitis), sacroiliac joint dysfunction, myofascial dysfunction, spondylothesis, and radiculopathy.
- **Radiculopathy**: discogenic pain with chemical radiculopathy, disc herniation, and foraminal stenosis, spondylothesis with nerve root compromise, degenerative disc disease, tumors (primary and metastatic), aneurysms, diabetic neuropathies, perinomal syndrome, hypertrophic facet joint changes with foraminal stenosis, and vertebral trauma with cord or nerve root compromise.
- **Visceral pain**: gynecologic, urologic, renal, stomach and duodenal ulcers, pancreatic pathology, retroperitoneal pathology.
- **Miscellaneous**: rheumatic diseases, spinal infections, vascular pathology, abdominal aortic aneurysm.
- **Nonorganic/psychogenic**: depression, anxiety, somatization, and malingering.

**SIGNS AND SYMPTOMS**
**Axial**
- Lumbosacral sprain and strain: caused by uncustomed eccentric contraction, trauma, muscle strain, back pain with 24- to 28-hour delay, tenderness in tabarparaspinal muscles.
- Internal disc disruption/annular tear/discogenic pain: caused by high-speed accidents, extreme axial loads, trauma, twisting, and degenerative changes. Deep axial ache* and can progress to radicular symptoms. Pain decreased with unloading axial spine; flexion increases pain; usually neurologic findings are absent unless significant disc degeneration occurs.
- Facet arthropathy/capsulitis: can be caused by trauma, degeneration, arthritis, lifting, extension and torsional injury; 15% to 30% of back pain. Pain increases with extension and rotation and may radiate to buttock and leg. Neurologic exam is normal.
- Sacroiliac (SI) dysfunction: can be caused by a fall, step off a curb, or heavy lifting. Pain and tenderness at SI joint. Patrick’s test (also called the FABERE test: flexion, abduction, external rotation, and extension) and pelvic rock are positive on involved side, asymmetric pelvis, no neurologic findings.
Back Pain

- **Discogenic pain:** can be caused by sprain, whiplash, and industrial and cumulative trauma. Pain is localized with discrete trigger points and has nongendermatal radion pattern. Palpation of muscle reproduces the pain and a localized muscle twitch may be present. No neurologic findings are present.
- **Spondylolysis:** can be caused by congenital or acute or chronic trauma. Low back pain is present, possibly radiates to leg, and increases with activity. Decreased range of motion may be present.
- **Vertebral compression fracture:** may be secondary to osteoporosis, major trauma; pain is localized to back and is worse with movement, especially flexion. Neurologic symptoms are usually absent unless bone fragment is in spinal or neural foramina canal. If greater than 50% loss of vertebral body height, consider the fracture unstable.
- **Vertebral somatic/segmental dysfunction:** can be caused by major or minor trauma, overuse, and lifting. Altered segmental motion is present, decreased tissue compliance; radicular symptoms may be present without neurologic findings.

**Radicular**
- **Patterns of radicular findings:**
  - L2: Motor—hip flexion; sensory—groin extension; sensory—medial ankle
  - L3-L4: Motor—extensor hallucis longus (EHL) and ankle dorsiflexion; sensory—dorsal foot
  - L5-S1: Motor—plantar flexion and ankle eversion; sensory—lateral foot
- **Discogenic pain with radicular symptoms:** can be caused by flexion, extension, or rotational injury with or without axial load. Prominent in 30- to 40-year-olds. Low back and radicular pain with or radicular findings. Straight leg test positive, deep tendon reflexes may be absent, dermatomal sensory loss may be present, and muscular weakness specific to a nerve root injury may be present.
- **Spinal stenosis/foraminal stenosis:** commonly degenerative, but may be traumatic with leg pain with activity/walking; may be relieved by forward flexed posture, and nighttime pain relieved by walking. Paresthesia and weakness may be present. In foraminal stenosis, extension may produce radicular symptoms from nerve root compromise. Multidifferentiate neurogenic from vascular claudication.
- **Degenerative disc disease:** degenerative process with progressive symptoms. Symptoms and findings are similar to those of discogenic pain and spinal stenosis.
- **Spinal tumors:** pain and symptoms may progress as tumor grows. Pain may be constant and worse at night, associated with red flags (unexplained fever, chills, weight loss, anorexia) change in bowel and bladder function, and neurologic symptoms and findings may be present. Tumor may be in spinal canal or extension from bone and associated with pathologic fracture. Evaluate for primary tumor with bone metastasis (lung, breast, prostate, and renal are most common).
- **Arachnoiditis:** cause is from adhesions and scar formation from previous back surgery, disc space infection, myetography, intrathecal drugs, and radiation therapy. Radicular pain is present but neurologic findings may or may not be present. Flexion, of spine may increase radicular symptoms.
- **Diabetic neuropathy:** sensory and motor symptoms are present, pain is constant, worse at night, and may be associated with weight loss. May be confused with hemiated disc.
- **Pinformis syndrome:** cause may be from a bony or chronic trauma, hip fracture or surgery, and extended driving. Pain is in buttocks but may have radicular symptoms. Internal rotation of hip will increase pain. Tenderness along piriformis muscle. (Muscle courses from sacrum to greater trochanter.)
- **Nephtropic facet joint pain with foramina( stenosis:** see Spinal stenosis/foraminal stenosis, above.
- **Vertebral trauma:** cause may be fall, motor vehicle accident, or other trauma. Symptoms vary according to degree of nerve root or cord compromise from disc hemiation or vertebral fracture.
- **Viscera/miscellaneous/nonorganic/ psychogenic:** a detailed history, physical examination, and diagnostic work help to differentiate these causes and proper referral.

**LABORATORY PROCEDURES**
If symptoms warrant or clinical red flags are present, consider the following diagnostic laboratory procedures: ESR, ANA, rheumatoid factor, CBC with differential, CPK, thyroid panel, comprehensive metabolic panel, SPEP, or urine analysis.

**IMAGING PROCEDURES**
- **MRI** is helpful to identify soft tissue pathology, such as tumors and disc. CAT scan is best to evaluate bone pathology. CT-myelogram helps to evaluate both b one and nerve or cord compression. Bone scan is useful for metabolic and metastatic pathology and stress fractures. Provocative discography is helpful for internal disc disruption and anular tears. Plain films are good for fractures, degenerative changes, postural analysis, to evaluate pars defects, and spondylolisthesis. Flexion and extension views are important to evaluate segmental instability. Oblique views are best to evaluate pars defects.
- **Significance of imaging studies,** in particular disc changes on MRI, need to be viewed and interpreted based on clinical examination and findings. Diagnostic ultrasound has not proven to be effective for evaluation of low back pain.

**SPECIAL TESTS**
EMG/NCV studies are of benefit to evaluate degree of nerve root damage or compromise and to differentiate peripheral neuropathy from radiculopathy and myopathic diseases. Medial branch blocks and intraarticular facet injections can evaluate facet joints as a pain generator. Three-phase bone scan of the legs is helpful if reflex sympathetic dystrophy (RSD) is suspected. Selective nerve root blocks are helpful to determine the level of nerve root compromise.
Back Pain

MANAGEMENT

GENERAL MEASURES
Limited rest may be of benefit with initial injury. Cold packs for acute pain and inflammation. Heat after acute episode. Home exercise for strengthening, flexibility, and stretching. Analgesics are of benefit. Start with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for intense pain.

SURGICAL MEASURES
After conservative treatment has been exhausted, referral to a neurosurgeon or orthopedic spine surgeon is appropriate. Cauda equina syndrome is a surgical emergency. Spinal tumors require a surgical evaluation. Surgical considerations may include open and percutaneous and spinal endoscopy for delivery of steroids and analgesics.

SYMPTOMATIC TREATMENT
• NSAIDs and opiates for acute pain. If breakthrough pain. The goal is to control the pain and discomfort and to improve function with scheduled medications and reducing the frequency of dosage. Use a long-acting scheduled preparation with a short-acting one for breakthrough pain.

ADJUNCTIVE TREATMENTS
• NSAIDs and opiates for acute pain. If radicular symptoms are present, oral or IM administration is advisable. Muscle relaxants for spasm. Antiepileptic medications for neurogenic and nociceptive pain. Antidepressants for chronic pain and improved sleep. Lumbar supports and bracing may help with pain and posturing. Transcutaneous electrical nerve stimulation (TENS) unit for pain.

ADJUNCTIVE TREATMENTS
• Physical therapy to include modalities, aquatic therapy, active therapy, aerobic conditioning, proprioceptive and dynamic lumbar stabilization exercises. Chiropractic and osteopathic spinal manipulation and massage.

ACUTE/CHRONIC MEDICATIONS
• NSAIDs and opiates for acute pain. If radicular symptoms are present, oral or IM administration is advisable. Muscle relaxants for spasm. Antiepileptic medications for neurogenic and nociceptive pain. Antidepressants for chronic pain and improved sleep. Lumbar supports and bracing may help with pain and posturing. Transcutaneous electrical nerve stimulation (TENS) unit for pain.

ADMISSION/DISCHARGE CRITERIA
Cauda equina syndrome for surgical intervention. Acute and progressive neurologic compromise and urgent surgical evaluation.

DRUG(S) OF CHOICE

Acute/Subacute Medications
The primary goal at this stage is symptom control with analgesics, muscle relaxants, and antiinflammatory drugs, both steroidal and nonsteroidal.

Persistent/Chronic Medications
The goal is to control the pain and discomfort and to improve function with scheduled medications and reducing the frequency of dosage. Use a long-acting scheduled preparation with a short-acting one for breakthrough pain.

Analgesics
• Acute/breakthrough pain
  — Mild pain
    - Tramadol 50-100 mg q6-8h PRN (Ultram)
    - Tramadol 37.5 mg/APAP 1-2 q6-8h PRN (Ultracet)
    - Propoxyphene 100 mg/APAP q4-6h PRN (Darvocet)
    - Ibuprofen/naproxen/APAP q4-6h (Ultracet)
  — Moderate pain
    - Hydrocodone 5-10 mg/APAP q4-6h PRN (Vicodin, Lortab)
    - Hydrocodone 7.5 mg/ibuprofen q4-6h PRN (Vicoprofen)
    - Oxycodone 5-7.5-10 mg/APAP q4-6h (Percocet, Endocet)
    - Oxycodone 5 mg q4-6h PRN (OxyIR)
  — Severe pain
    - Hydrocodone 10 mg/APAP q4-6h PRN (Percocet)
    - Oxycodone 15-30 mg q4-6h PRN (Roxicodone)
    - Hydromorphone 2-4 mg q4-6h (Dilaudid)
  — Persistent/chronic pain
    - Oxycodone 10-160 mg q2h (scheduled and not PRN) (Oxycodone)
    - Hydromorphone 2-4 mg q4-6h (Dilaudid)
    - Morphine sustained release
      - MS Contin 15-200 mg q12h
      - Kadian 30-100 mg q12-24h
      - Avinza 30-120 mg q24h

NSAIDs
There is an abundance of these medications. We are listing a limited few and you must determine those that are effective for your use.
• Ibuprofen 400-800 mg q6-8h
• Naproxen 250-500 mg q24h
• Rofecoxib 25-50 mg q24h (Vioxx)
• Celecoxib 200-400 mg q24h (Celebrex)
• Valdecoxib 10-20 mg q24h (Bextra)

Steroid Antiinflammatory Medications
These medications are used to reduce the inflammation of disc herniation on the nerve root (chemical and compressive radiculitis) and for the inflammatory diseases of the spine (ankylosing spondylitis). Dosages and protocols vary. Below are options.
• Prednisolone 2 mg, prepackaged dosing (Medrol)
• Prednisone 20 mg: 3 PO qd for 3 days; 2 PO qd for 3 days; 1 PO qd for 3 days

Muscle Relaxants
• Cyclobenzaprine 5-10 mg q8h PRN (Flexeril)
• Tizanidine 1-4 mg hs to qd (Zanaflex)
• Baclofen 5-20 mg hs to qd (Lioresal)
• Carisoprodol 350 mg q6-8h
• Diazepam 5-10 mg qhs to qid (Valium)

Anticonvulsants
These are used for acute radicular symptoms and chronic pain (neurogenic and nociceptive pain). The list below is abbreviated. Many are available.
• Gabapentin 100-3,600 mg per day in divided doses (Neurontin)
• Topiramate 25-400 mg q24h (Topamax)
• Tiagabine 4-32 mg qd to qid in divided doses (Gabitril)

Antidepressants
These are initially used for acute and chronic pain. In the chronic state, depression may accompany the chronic back pain. Many antidepressants are available and used for pain management. A partial list of commonly used medications is listed below.
• Amitriptyline 10-100 mg qhs (Elavil)
• Nortriptyline 10-100 mg qhs (Pamelor)
• Fluoxetine 10-80 mg daily (Prozac)
• Paroxetine 10-40 mg daily (Paxil)
• Venlafaxine 37.5-200 mg qd to bid (Effexor)
**Contraindications**

NSAIDs can cause peptic ulcer disease (PUD), and some are contraindicated with anticoagulants. Renal and hepatic side effects are possible. Opioid medications need to be titrated for pain relief and side effects.

Tolerance and dependence can develop, especially in long-term use, and must be differentiated from addiction. In general most of the medications used can cause anticholinergic side effects, fatigue and drowsiness, and impaired mental functions.

**Precautions**

Polypharmacy is possible and drug interactions and physical and mental functional status should be monitored. Alcohol and recreational drugs may be used by the patient, especially in chronic pain. Caution must be used, and consideration may be given to compliance drug screening.

**Alternatives**

Lidoderm patch, capsaicin cream, acetaminophen, and herbal and nutritional supplements.

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**Follow-Up**

**Patient Monitoring**

Patients should be monitored for their pain, neurologic symptoms and findings, and their functional status and medications.

**Expected Course and Prognosis**

Prognosis is usually good, with 3% becoming chronic back pain sufferers. Concomitant diseases, and psychosocial, employment, and financial issues may complicate and impede recovery.

**Patient Education**

Patient education has proven to be effective in the treatment of back pain. There are many preprinted materials, supportive organizations, and Web sites available.

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**Miscellaneous**

**Synonyms**

- Sciatica
- Radiculopathy
- Pinched nerve
- Muscle strain
- Ruptured disc
- Slipped disc
- Back arthritis
- Back and disc degeneration

ICD-9-CM: 846.0 Lumbosacral sprain and strain; 847.2 Lumbar sprain and strain; 846.1 Sacroiliac sprain and strain; 724.2 Lumbar back pain syndrome; 74.5 Meningeal back pain; 70.1 Myofascial pain and fibromyalgia.

Facet arthropathy/spondylosis without myelopathy; 724.02 Lumbar spinal stenosis; 736.4 Spondylolisthesis, acquired and degenerative; 733.13 Pathologic fracture of vertebra; 805.4 Closed fracture of lumbar spine; 72.2 Lumbar radiculopathy; 72.1 Neuralgia/neuritis; 724.2 Sciatica; 720.2 Sacroilitis, 722.83 Postlaminectomy syndrome; 722.52 Lumbar disc degeneration; 722.10 Lumbar disc displacement without myelopathy; 722.73 Lumbar disc displacement with myelopathy; 355.0 Sciatic nerve lesion; 728.85 Muscle spasm; Piriformis syndrome is coded as a combination code (355.0 and 728.85).

**References**


Author(s): Gordon J. Kathy, DO, DC, Brian E. Higgins, DO
Brain Herniation Syndromes

**DESCRIPTION**

The intracranial space is filled with brain, CSF, and blood. Since this is a nonexpandable space, any increase in one of the constituents of the compartment must be balanced by a reduction of another constituent, or mutua lly an increase in the intracranial pressure. Mass lesions of various types, and brain swelling of various etiologies, can cause increase in the intracranial pressure. Above a threshold of pressure, the contents of the intracranial compartment begin to move through spaces of lower pressure, causing brain herniation. There are well-defined major types of brain herniation that occur under these circumstances.

**DEFINITIONS**

Herniation: a shift of brain tissue from its proper location to another location due to an imbalance of pressure between the two locations.

**CLINICAL CHARACTERISTICS**

Brain swelling occurs under a variety of conditions: infarction, hemorrhage, infection (including abscess), neoplasia, toxic injury, and ischemia. When there is enough difference in pressure between contiguous spaces intracranially, the brain may herniate to the space of lower pressure. The location of herniation determines the general characteristic of the herniation syndrome.

**Lateral Herniation**

Laterally placed mass lesions of the brain, usually extracerebral or in the temporal lobe, cause a side-to-side shift of the brain contents. Such mass lesions displace the brain medially, both pushing the medial temporal lobe inward, and distorting the midbrain. Clinical characteristics include alterations of consciousness (confusion, stupor, coma). Pupillary dilation, which traditionally is ipsilateral to the mass lesions, may occur on either side. A contralateral hemiparesis may occur, but on occasion pressure of the midbrain against the rigid dural edge contralaterally may cause an ipsilateral hemiparesis, a "false" localizing sign (Kernohan's phenomenon).

**Central Herniation**

Downward pressure from supratentorial mass lesions may cause central herniation syndromes. These are due to downward pressure on the diencephalon and midbrain. Clinically this causes an altered consciousness early in the syndrome, followed by progressively worsened consciousness, posturing, and respiratory dysfunction. Such "rostrocaudal" deterioration does not necessarily occur in a stepwise pattern, but may occur suddenly.

**Subfalcine Herniation**

Laterally placed supratentorial lesions may cause herniation of the cingulate gyrus under the falx cerebri. Such herniation may compromise blood flow in the anterior cerebral arteries, ultimately leading to leg weakness due to infarction in the territory of the anterior cerebral arteries.

**Infratentorial Herniation**

Less commonly recognized, this syndrome develops when lesions in the infratentorial compartment cause upward herniation of the brainstem and cerebellum through the tentorium. This may result in midbrain dysfunction (pupillary dysfunction, loss of up and down gaze), de cerebrate posturing, abnormal respirations, and coma.

**Cerebellar Herniation**

Herniation of the cerebellar tonsils into the foramen magnum may occur. This may cause compression of the medulla, with altered respiration, meningismus, altered autonomic function, vertigo, skew deviation, vomiting, coma, and death.

**PATHOPHYSIOLOGY**

Herniation of brain material causes injury to the brain in various manners:

- Direct pressure on brain tissue may cause ischemic change with a loss of neural function.
- Compression of arteries may cause infarction in the territory of that artery. Most commonly the artery affected is the posterior cerebral artery compressed over the edge of the tentorium in a lateral herniation syndrome, causing hemorrhagic infarction of the occipital lobe. The anterior cerebral artery may be compressed by a subfalcine herniation syndrome, causing infarction in one or both anterior cerebral artery territories.
- Torting of neural structures. Elegant work by Ropper et al. has shown that torting (twisting) of the midbrain may underlie the symptoms of the lateral herniation syndrome, rather than direct tissue compression. Thus, while it is clinically taught that the ipsilateral third nerve becomes compressed in the lateral herniation syndrome, in fact either third nerve may become dysfunctional, and both pupillary constriction and dilatation may occur.
- Occasionally lateral lesions will cause secondary hydrocephalus due to compression of cerebospinal outflow, increasing intracranial fluid and further compromising the situation. Lesions in the posterior fossa commonly block CSF flow at the level of the aqueduct of Sylvius, again causing obstructive hydrocephalus.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

Any pathology that causes increased intracranial pressure can cause cerebral herniation syndromes. Diffuse processes are less likely to cause herniation due to the general distribution of the pressure. Focal lesions, particularly laterally placed lesions and infratentorial lesions, are most likely to cause herniation, particularly if they are rapidly progressive. Various pathologic processes may cause the common pathway of brain herniation to occur.

**SIGNS AND SYMPTOMS**

Key to the diagnosis of cerebral herniation syndrome is the recognition of the possibility that they might occur. Patients with any intracranial mass lesion should be observed for signs of herniation. New or progressive neurologic symptoms, altered consciousness, or progressive headache are all signs of impending herniation. Uncontrolled vomiting may presage more severe herniation. Signs of cerebral herniation depend on the type of herniation as detailed above, but key in the diagnosis is recognizing changing signs indicating ongoing alteration of neurologic activity.

**LABORATORY PROCEDURES**

**SPECIAL TESTS**

**IMAGING STUDIES**

Neuroimaging is key to the diagnosis and management of cerebral herniation syndromes. Frequently patients are known to have an underlying lesion, and the role of neuroimaging is to rapidly diagnose the type and extent of herniation, presence of secondary pathologies, and presence of specific treatable components of the herniation syndrome. Either CT or MRI may be used. CT scanning may be preferred since scanning times tend to be shorter, depending on the scan sequences used for MRI. Newer scan methodologies may allow for more rapid MRI evaluation. Key features to note on scanning are the location of the primary lesions (tumor, abscess, etc.), location of the herniation syndrome, secondary infarctions, and the presence of obstructive hydrocephalus. Such imaging is key to planning of surgical approaches to treating cerebral herniation.
Brain Herniation Syndromes

Management

GENERAL MEASURES
Patient should be kept well oxygenated to avoid secondary injury due to hypoxia. The head of the bed should be kept upright to avoid increasing intracranial pressure due to positioning. Similarly keeping the neck in a neutral position may reduce pressure on the jugular veins with secondary increases in back flow pressure. Patients should be kept NPO until the situation is stabilized in case they require emergency surgery.

SURGICAL MEASURES
Neurosurgical consultation is key in the management of cerebral herniation syndromes. Definitive treatment may depend on removal or debulking of the primary mass lesion; ventricular drainage for secondary hydrocephalus; removal of infarcted brain tissue causing herniation; and occasionally hemicraniectomy for massive unilateral brain swelling with cerebral infarction. The placement of a ventricular pressure measurement device may aid in the treatment of increased intracranial pressure, reducing the likelihood of secondary herniation syndromes.

SYMPTOMATIC TREATMENT
While cerebral herniation syndrome is a medical emergency, some attention to pain management in patients with headache is appropriate. It is best to avoid oral dosing of medications. Treatment of intracranial pressure (ICP) elevation is a crucial component of care, and ICP monitoring devices may aid in the rational provision of care. Cerebral blood flow needs to be maintained with a cerebral perfusion pressure of 70 mm Hg or more being optimal.

DRUG(S) OF CHOICE
• Mannitol is the most commonly used medication for increased ICP (see Increased Intracranial Pressure). Recently hypertonic saline has been used with some benefit in patients with raised ICP. Once herniation syndromes are apparent, attention to surgical approaches may be more important than medical management.
• In patients with known intracerebral brain tumors, dexamethasone given either orally or IV may reduce mass effect. For patients with impending herniation syndrome, higher doses may be used (e.g., 10 mg IV q6h), though no precise data exist on dosing regimens in this situation. Again, medical therapy tends to be a temporizing strategy, not the definitive therapy.

Contraindications
Mannitol may be contraindicated in patients with congestive heart failure or specific allergy to mannitol.

Precautions
Hyperventilation may cause a reflex vasoconstriction of the pCO₂ is dropped below 25 mm Hg. Hypersomotic agents such as mannitol may cause a rebound in intracranial pressure when stopped. Careful attention to fluid and electrolyte management is imperative during the management of brain herniation syndromes. Excessive hypernatremia or dehydration may be counterproductive.

ALTERNATIVE DRUGS
N/A

ADJUNCTIVE TREATMENT
• IV fluids should be kept isotonic and at a low rate, to avoid the risk of overhydration. Mechanical hyperventilation may be used to rapidly reduce ICP, by achieving pCO₂ of 20 to 25 mm Hg. This maneuver is only effective for a few minutes. Achievement of lower pCO₂ values risks secondary arterial constriction, which is counterproductive.
• In patients with brain neoplasms, radiation therapy may be used to reduce the mass size, depending on the tumor and the clinical situation.

ADMISSION/DISCHARGE CRITERIA
Patients with increased ICP or with signs of cerebral herniation syndromes should be admitted to the hospital, and remain there until the situation is definitively stabilized.

Follow-Up

PATIENT MONITORING
The ICU is necessary for patients with impending herniation syndromes. Cardiac monitoring, ICP pressure, respiratory monitoring, and fluid status monitoring are all important.

EXPECTED COURSE AND PROGNOSIS
Course and prognosis depends on the extent of the herniation, its potential for treatment, secondary injury, and the primary pathology underlying the herniation syndrome.

PATIENT EDUCATION
N/A

Miscellaneous

SYNONYMS
Cerebral herniation
ICD-9-CM: 348.4 Herniation, cerebral or brainstem
SEE ALSO: INCREASED INTRACRANIAL PRESSURE, HYDROCEPHALUS

REFERENCES

Author(s): Alexander D. Rae-Grant, MD, FRCP(C)
Choreoathetosis

Description
Choreoathetosis is a combination of the term chorea and the term athetosis. These are two abnormal types of movement that are often combined in the same disorder. Chorea refers to rapid, involuntary, brief, irregular, and unpredictable jerks of muscles and can occur in the limbs, face, or trunk muscles. Athetosis is characterized by slow, writhing, uncoordinated involuntary movements usually involving the limbs, though similar movements may affect the face and trunk muscles as well.

Definitions
Chorea: rapid, involuntary, brief, irregular movements
Athetosis: writhing, involuntary, slow, uncoordinated movements
Parakinesia: a choreic movement camouflaged by a spastic used purposeful act

Clinical Characteristics
Choreoathetosis may occur acutely or on a chronic basis, be transient, or be a persistent, lifelong phenomenon. It may interfere with the ability to speak, use the limbs, walk, or stand still. The movements may be unilateral (hemichorea), and at times are flinging (merging into hemiballismus separate but related disorder). Tone is usually reduced, but strength is unaffected. Patients may be unable to sustain a tight hand grip (milkmans hand). The tongue may dart in and out irregularly while attempting to protrude it.

Pathophysiology
Choreoathetosis is caused by a degeneration or fixed injuries to the striatum (putamen, globus pallidus, caudate), or to a biochemical imbalance affecting these parts of the brain. The basal ganglia are critical in modulating motor activity from the corticospinal tract, and help maintain the posture, tone, and amplitude of motor activity both at rest and in action.

Diagnosis

Differential Diagnosis
- Huntington disease (HD): autosomal dominant, onset in 20s and 30s, with a combination of progressive chorea, a personality disorder and dementia. HD gene (IT15) on short arm of chromosome 4 (4p16.3).
- Sydenham chorea: rheumatic chorea in childhood and adolescence, often hemichorea, occurring after rheumatic fever, now rare. Self-limited disease.
- Chorea gravidarum: chorea occurring with pregnancy. May also be seen with use of oral contraceptives.
- Choreoathetosis with medications: may occur with dopaminergic medications (L-dopa, bromocriptine, newer dopaminergic medications). Occasionally with famiclovir (in dialysis patients), digoxin, oral contraceptives, and gabapentin. Case reports with cocaine use.
- Choreoathetosis with systemic diseases: may occur with lupus erythematosus, thyrotoxicosis, polycythemia vera, and hyperosmolar, nonketotic hyperglycemia, antiphospholipid antibody syndrome, Creutzfeld-Jakob disease. Rarely postpump choreoathetosis after cardiac surgery.
- Neuroacanthocytosis: familial multisystem progressive disorder with chorea, cognitive impairment, neuropathy, reduced reflexes, abnormal red cells (acanthocytes).
- Developmental disorders: a variety of prenatal and perinatal insults including kernicterus may cause choreoathetosis, which is nonprogressive and present from infancy or early childhood.
- Hereditary nonprogressive chorea: rare autosomal-dominant disorder, with chorea, no dementia or progression, no other neurologic signs.
- Paroxysmal kinesigenic choreoathetosis: choreoathetotic movements brought on by volitional movements. May be familial.
- Dentatorubral-pallidoluysian atrophy: rare autosomal-dominant disorder sometimes confounded with Huntington disease. Patients show chorea, myoclonus, ataxia, seizures, and dementia.

Signs and Symptoms
In a patient presenting with choreoathetosis, symptoms suggesting cognitive dysfunction (memory loss, altered judgment, impulsivity, altered sexuality) may suggest Huntington disease. The clinical setting suggests Sydenham chorea, chorea gravidarum, and chorea related to systemic disease or medications. Choreoathetosis related to prenatal and perinatal insults is usually self-evident. Signs to seek include presence of associated neurologic findings (hyporeflexia, sensory loss suggesting neuropathy; cognitive dysfunction; presence of focal signs suggesting stroke).

Laboratory Procedures
Directed by clinical circumstances. In suspected cases of systemic causes of choreoathetosis, with blood smear (polycythemia vera, neuroacanthocytosis), glucose (hyperosmolar nonketotic hyperglycemia), thyroid indices (thyrotoxicosis), liver function studies (Wilson disease, kernicterus), antiphospholipid antibodies (antiphospholipid antibody syndrome). Genetic testing is available in Huntington disease but should be linked with counseling.

Imaging Studies
CT scanning and MRI may both show focal basal ganglia lesions causing choreoathetosis. In situations such as acute chorea, imaging to assess for infarction, hemorrhage, tumor, or vascular malformation may be useful. Carbon monoxide poisoning may show hypodensities in the globus pallidus bilaterally. In Huntington disease, MRI later in disease may show atrophy of both caudate nuclei.

Special Tests
For specific diseases special tests may be applicable. Tuberculous meningitis requires lumbar puncture, moyamoya may require angiography, multiple sclerosis may require evoked potentials and lumbar puncture. Positron emission tomography (PET) scanning may show caudate nucleohypometabolism early in Huntington disease.
Management

GENERAL MEASURES
There are no specific measures to treat choreoathetosis. Treatment is directed at symptomatic management of the movements of chorea and athetosis, if necessary. If choreoathetosis is the result of a specific disease, that disease management should be used.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
Using neuroleptic medications can control choreic movements. These include dopamine receptor blocking agents (such as haloperidol and perphenazine). Other medications that deplete presynaptic dopamine, such as reserpine or tetrabenazine, can be used. Newer atypical antipsychotic agents (e.g., quetiapine or olanzapine) may be tried.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
Patients with acute onset of chorea may require hospitalization for diagnosis and stabilization. Patients with Huntington disease may require admission if at risk of harming themselves or others based on their psychiatric state.

Medications

DRUG(S) OF CHOICE
See individual diseases for drug information.

Follow-Up

PATIENT MONITORING
See individual disease chapters.

EXPECTED COURSE AND PROGNOSIS
See individual disease chapters.

PATIENT EDUCATION
See Huntington disease section for patient education.

SYNONYMS

• St. Vitus dance, chorea minor, acte chorea, rheumatic chorea (Sydenham chorea)
• Chorea-acanthocytosis (neuroacanthocytosis)
• Benign hereditary chorea (hereditary nonprogressive chorea)

ICD-9-CM: 333.4 Chorea, Huntington’s; 333.5 Choreathetosis (paroxysmal); 333.5 Chorea, senile; 392.9 Chorea, Synderhams; 780.3 Chorea, gravidarum

SEE ALSO: CEREBROVASCULAR DISEASE, ANTIPHOSPHOLIPID ANTIBODY SYNDROME, HUNTINGTON’S DISEASE, SYDENHAM’S CHOREA, PARKINSON’S DISEASE, SYSTEMIC LUPUS ERYTHEMATOSUS

REFERENCES


Author(s): Alexander D. Rae-Grant, MD, FRCP (C)
**Coma**

**Description**
Coma is the most severe form of unresponsiveness. The subject is unarousable.

Either there is severe diffuse cerebral dysfunction or significant brainstem impairment. Strutural, metabolic, and infectious causes are typical. Clinical presentation, neurologic assessment, neuroimaging, and laboratory evaluations determine the specific cause and guide treatment options.

**Definition**
Coma is a state of unconsciousness with complete absence of awareness of the environment even when externally stimulated. A persistent vegetative state usually emerges in about 2 weeks and refers to unresponsiveness despite wakefulness with return of sleep-wake cycles. Related terms include stupor, where subjects can be aroused with noxious stimuli, and lethargy, referring to someone arousable with verbal stimuli. Acute confusional states represent levels of attentional deficits between full responsiveness and lethargy. A locked-in state mute and quadriplegic but conscious.

**Clinical Characteristics**
The subject lies with eyes closed and cannot be aroused verbally or with noxious painful stimuli. There is no spontaneous eye opening, facial movements, urgings, or body movements. Painful stimuli may produce nondoncet reflexive movements related to spinal cord or lower brainstem pathways, but will not result in any conscious responsiveness.

**Pathophysiology**
Coma results only from conditions that disrupt both cerebral hemispheres or the brainstem ascending reticular activating system. Conscious behavior requires both arousal and cognitive processing. The brainstem reticular activating system extending from the midpons to the hypothalamus is responsible for arousal. The cerebral hemispheres are responsible for cognitive abilities. The locked-in syndrome results from conditions affecting the nervous system below the midpons, which preserves that portion of the reticular activating system responsible for arousal and consciousness.

**Diagnosis**

**Differential Diagnosis**

**Diffuse Encephalopathies**
- Cerebral anoxia/ischemia
- Encephalitis/meningitis
- Subarachnoid hemorrhage
- Vasculitis
- Metabolic encephalopathy (e.g., uremia)
- Hypoxemia
- Diabetes (ketoacidosis, hypoglycemia, nonketotic hyperosmolar coma)
- Nutritional deficiency (thiamine)
- Alcohol/narcotic abuse
- Drug overdose/intoxication
- Hepatic encephalopathy
- Hypothyroidism
- Multorgan failure
- Seizures
- Status epilepticus
- Hypertension
- Hypotension
- Sepsis
- Infections
- Fungal infection
- Meningitis or subarachnoid hemorrhage
- Hypertensive encephalopathy

**Structural Lesions**
- Brain herniation syndromes
- Brain tumor
- Brain abscess
- Epidural/subdural hematoma
- Subdural empyema
- Intracerebral infarction or hemorrhage
- Brainstem infarction or hemorrhage
- Cerebellar infarction or hemorrhage
- Basilar artery thrombosis
- Head trauma (cerebral contusion)

**Signs and Symptoms**

**History**
- Ask about onset and time course. Sudden onset with rapid progression suggests stroke or hemorrhage, whereas subacute course may indicate tumor or abscess. Coma preceded by acute confusional states without focal neurologic complaints suggests diffuse encephalopathies.
- Ask about recent history or recent hospitalization.
- Ask about recent interventions or medications.
- Ask about recent comorbidities.
- Ask about recent travel.
- Ask about recent exposures.

**Motor Exam**
- Look for spontaneous movements of limbs to external stimuli.
- Check postural responses (e.g., plantar response).
- Check for muscle tone and reflexes.
- Check for movement of extremities.

**Laboratory**
- Blood cultures.
- CBC.
- Serum electrolytes.
- Glucose.
- Blood urea nitrogen.
- Creatinine.
- Liver function tests.
- Renal function tests.
- Coagulation studies.
- ECG.
- CT brain.
- MRI brain.
- EEG.

**Differential Diagnosis**
- Seizure disorders
- Metabolic disorders
- Infections
- Malignancies
- Drug poisoning
- Trauma
- Anoxia
- Hypertension
- Hypotension
- Hypothyroidism
- Hypoglycemia
- Hypothermia
- Hyperthermia

**SIGNS AND SYMPTOMS**

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- Hypertension
- Hypotension
- Hypothyroidism
- Hypoglycemia
- Hypothermia
- Hyperthermia

**SIGNS AND SYMPTOMS**

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- Renal function tests.
- Coagulation studies.
- ECG.
- CT brain.
- MRI brain.
- EEG.
Coma

Management

GENERAL MEASURES
- Airway, breathing, and circulation.
- Check for and stabilize cervical spine fractures before examination.
- Every comatose patient should be given thiamine 100 mg IV for possible Wernicke’s encephalopathy, 50% dextrose 50 mL IV for possible hypoglycemic coma, and naloxone 0.4-1.2 mg IV for possible opiate overdose.
- Treat seizures.
- Perform laboratory and imaging studies to determine cause of the coma.
- Wean off any sedative medications.

SURGICAL MEASURES
- Neurosurgical evaluation is helpful in the management and treatment of patients with subarachnoid hemorrhage, intracerebral hemorrhage, hematoma, tumor, abscess, and brain herniation.

SYMPTOMATIC TREATMENT
- Stabilize vital signs.
- Correct metabolic and other treatable causes.
- Meningitis, encephalitis, and brain abscess are treated with antibiotics.
- Decreasing protein intake and reducing ammonia levels with lactulose and neomycin can treat hepatic encephalopathy.

Treatment of Herniation Syndromes and Cerebral Edema
- Ischemic stroke causing cerebral edema and transtentorial herniation is not helped by osmotic diuretics or corticosteroids.
- Elevate head.
- Intubate and hyperventilate to reduce PaCO₂ to 25 mm Hg.
- Administer mannitol 20% 1.5-2.0 g/kg IV over 30 to 60 minutes.
- Give normal saline two-thirds maintenance.
- For those with tumor, abscess, and possibly intracerebral hemorrhage, give dexamethasone 10 mg IV then 4 mg PO or IV every 6 hours with an H₂ block and monitor blood sugar.

ADJUNCTIVE TREATMENT
Supportive care is critical.

ADMISSION/DISCHARGE CRITERIA
- Admit to the intensive care unit for initial evaluation and treatment.

IMAGING STUDIES
- CT and MRI scans will show strabular lesions. MRI is better for visualizing the brainstem.

SPECIAL TESTS
N/A

LABORATORY PROCEDURES
- Lab tests should include arterial blood gas, electrolytes, BUN, creatinine, glucose, calcium, magnesium, liver function tests, ammonia, CBC, PT, PTT, sedimentation rate, thyroid function tests, and toxicology screen.
- Cervical spine films if trauma suspected.
- Lumbar puncture: cerebrospinal fluid may identify meningitis or encephalitis. Should be avoided with mass lesions as herniation can occur.
- Electrocardiogram to evaluate the heart.
- Electroencephalogram if seizures suspected.

Discharges to convalescent or rehabilitation units occur if recovery is not complete.

Medications

DRUG(S) OF CHOICE
- See general measures and symptomatic treatment sections above.

Contraindications
N/A
Precautions
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Neurologic checks required frequently for detecting changes in neurologic function.

EXPECTED COURSE AND PROGNOSIS
- If the underlying cause of the coma can be treated, prognosis depends on how much irreversible brain damage has occurred.
- Given the severe nature of many of the underlying causes of coma, mortality is high.

PATIENT EDUCATION
Provide strategies to reduce recurrence of preventable metabolic or other forms of coma.

Miscellaneous

SYNONYMS
N/A

ICD-9-CM: 780.01 Coma

SEE ALSO: N/A

REFERENCES

Author(s): Douglas W. Scharre, MD
Delirium/Encephalopathy

DESCRIPTION
Delirium describes a state where the patient is confused, with an agitated, inattentive behavior. Delirious patients frequently hallucinate or have delusional thoughts. This syndrome develops over a brief period of time, usually hours or days. Patients often have an autonomic disorder with sweating, tachycardia, and excessive movement. Encephalopathy is a more nonspecific term that describes a state of altered consciousness that is usually acute, sometimes used by metabolic or systemic disorders, and often is reversible (see specific chapters on encephalopathies).

DEFINITIONS
- Delirium: acute confusional state in patients with agitation and hallucinations.
- Dementia: chronic, progressive cognitive impairment in alert patients.
- Encephalopathy: nonspecific term for altered mental state, usually of acute onset.

CLINICAL CHARACTERISTICS
Delirium and acute encephalopathy are common in the inpatient setting. The prevalence of delirium has been estimated at 10% to 30% of inpatient medical populations. Up to 50% of patients with hip fractures experience delirium at some time, and delirium is common in patients with severe burns. Clinical characteristics of delirium include an acute onset of mental status changes, usually over hours or a few days. The mental state is marked by inattention, in which the patient cannot focus on specific stimuli for any period of time. Patients are either drowsy or hyperalert, and show an altered response to their environment. Patients have difficulty interacting for mental status examination, and tend to either not interact appropriately with the examiner or make errors in orientation, repetition, and memory testing related to their inattention and clouded sensorium. Characteristic of delirium is agitation, frequently with hallucinations, which may be visual, and at times form (e.g., insects crawling). Patients may make perceptual errors, misidentifying objects in the room. Patients may also have signs of autonomic hyperactivity, including tachycardia, diaphoresis, flushed facies, and hyperventilation.

PATHOPHYSIOLOGY
Delirium is caused by a variety of toxic, metabolic, infectious, and medication-related disorders. The specific pathophysiology of neurologic dysfunction depends on the etiology. Different delirious states have in common dysfunction of CNS neurons, due to reduced/altered substrates, acid-base disorders, hypoxemia, toxins or medications that affect neuronal function, secondary immunologic effects, or inflammatory activity in the CNS. Each of these causes an alter ion of function of CNS neurons, leading to the clinical state.

Diagnosis

DIFFERENTIAL DIAGNOSIS
A variety of disorders may cause delirium or encephalopathy during their course. Patients with elderly brain disorders are more likely to show delirious encephalopathy as a result of disease. Thrus patients with severe dementia who have new infections commonly become delirious. Patients who are either very old or very young are at more risk of responding to disease with delirium or encephalopathy. Other risk factors include a history of alcohol abuse, multiple medical problems, visual or hearing impairment, and sleep deprivation.
- Medical/surgical diseases: sepsis, focal infections, postoperative states, endocrine disorders (e.g., thyrotoxicosis, Cushing's disease), metabolic disorders (e.g., hyperammonia, hyperglycemia, hypoglycemia, etc.), hepatic or renal failure, hypoxia or hypercarbia.
- Neurologic diseases: meningitis, encephalitis, subarachnoid hemorrhage, traumatic brain injury, vascular, neoplastic, inflammatory, or other disorders. May occur after seizures.
- Drug or medication use or withdrawal states: street drugs, alcohol withdrawal or intoxication, sedative/hypnotic agents, opiates, anticholinergics, atropine, amphetamines, drug overdoses, steroids. • Toxins: organophosphates, heavy metals, organic solvents, etc.

SIGNS AND SYMPTOMS
Patients with delirium show inattention, with difficulty doing tasks such as counting backward by 7 from 100, listing the months backward, etc. They drift off in conversation, and are unable to give a history. More complex tasks of mental status are clouded by inattention. Patients are often restless, but usually show no focal neurologic signs. Reflexes and cranial nerves are unaffected. The toes are usually downgoing unless there is neurologic disease causing delirium. Patients may show signs of hallucinating. They may be drowsy or frankly stuporous. Patients may have asterixis, particularly with hepatic encephalopathy.

LABORATORY PROCEDURES
Depending on the history, laboratory studies may assist in diagnosis. CBC (for increased WBC); electrolytes (for hypo- or hypernatremia, low bicarbonate associated with metabolic acidosis); glucose (for hypo- or hyperglycemia); liver function tests; BUN and creatinine; drug screen; levels of therapeutic medications for intoxication. Arterial blood gases. Consider vitamin B12, autoimmune studies, sedimentation rate in selected cases.

IMAGING STUDIES
Imaging of the brain may be important to exclude focal disorders causing encephalopathy. Depending on the clinical circumstance, CT scanning or MRI may be used.

SPECIAL TESTS
Lumbar puncture should be used once an intracranial mass lesion is excluded in those patients considered to have an intracranial infection (encephalitis or meningitis). If CT scanning is negative and subarachnoid hemorrhage is suspected, lumbar puncture may be diagnostic. EEG may be useful in showing triphasic waves, characteristic of metabolic encephalopathy, as well as excluding nonconvulsive status epilepticus.
Delirium/Encephalopathy

Management

**GENERAL MEASURES**
Careful attention must be given to the maintenance or establishment of an airway, breathing, and circulation. Any evidence of cardiovascular instability must be treated immediately. IV access is important to allow medication to be provided, as well as electrolyte solutions. Consider providing IV thiamine (patients suspected of having Wernicke syndrome), glucose (suspected hypoglycemia), and naloxone (opioid intoxication). Measures should be taken to protect patients from harming themselves; a bed check may help prevent falls, or if necessary, restraints or provision of 1:1 nursing may be helpful. Consider a secure environment if the patient is a potential threat to others.

**SURGICAL MEASURES**
N/A

**SYMPTOMATIC TREATMENT**
Once an etiology or delirium or encephalopathy is determined, treating the cause of this state is required. Treatment guidelines pertinent to the etiology should be followed.

**ADJUNCTIVE TREATMENT**
Ensure that all drugs or toxins that may be causing the delirium are withdrawn. Make sure that fluid requirements, particularly in patients with autonomic overactivity, are met.

**ADMISSION/DISCHARGE CRITERIA**
Patients with delirium or encephalopathy require admission for their diagnosis and safety. Such patients are at risk of falls and injuries in the home setting. Patients should be fully alert and oriented if possible before discharge. They should usually be discharged into the care of a responsible party if possible.

**Follow-Up**

**PATIENT MONITORING**
Patients with delirium or encephalopathy should be closely monitored until stabilization occurs.

**EXPECTED COURSE AND PROGNOSIS**
Delirium and encephalopathy are self-limited conditions that should resolve with improvement of the medical condition. Prognosis is related to the underlying medical conditions.

**PATIENT EDUCATION**
Since this is a self-limited disorder, patient education is limited to reassurance, reorientation, and explanation of the clinical condition after the patient has returned to a more normal mental status.

**Medications**

**DRUG(S) OF CHOICE**
The primary treatments for delirium or encephalopathy are to treat the underlying disorder. At times patients may require treatment to reduce their symptoms of agitation or restlessness. Care should be taken to avoid respiratory suppression by medications in such patients. If necessary, medication such as haloperidol in low doses may be useful without significant risk of respiratory compromise. Haloperidol 0.5–2 mg IM or IV repeated q4–6h as needed, depending on age, weight, degree of agitation. Switch to oral when possible. For alcohol withdrawal use benzodiazepines.

**Contraindications**
Avoid with significant hypotension or sensitivity to similar medications.

**Precautions**
Watch for dystonic reactions and hypotension.

**ALTERNATIVE DRUGS**
Risperidone may be used.

**Miscellaneous**

**SYNONYMS**
Acute confusional state
ICD-9-CM: 291.0 Acute alcohol delirium; 293.0 Acute psychotic delirium; 293.1 Subacute delirium; 292.81 Drug-induced delirium; 349.82 Toxic encephalopathy; 348.3 Encephalopathy NOS

**SEE ALSO:** DEMENTIA; ENCEPHALOPATHY, HEPATIC; ENCEPHALOPATHY, SEPTIC; ENCEPHALOPATHY, RENAL

**REFERENCES**

Author(s): Alexander D. Rae-Grant, MD, FRCP (C)
Dizziness

Basics

DESCRIPTION
Dizziness is a common, nonspecific symptom that affects approximately 15% to 30% of the population at some point during one's lifetime. It describes an altered sense of position of patients in relation to their surroundings. The etiology can be central or peripheral with a broad differential ranging from benign to life-threatening conditions.

DEFINITIONS
Dizziness can be defined as central or peripheral in origin. Peripheral etiologies refer to lesions of the temporal bone, middle ear, labyrinth, and cranial nerve VIII before it enters the brainstem. Central etiologies include lesions of the vestibular nuclei, brainstem, cerebellum, or cerebrum.

CLINICAL CHARACTERISTICS
Dizziness can affect patients of all ages; however, it is more common in elderly patients. There is a slight female preponderance. All races are affected equally. Risk factors to develop dizziness include older age, infections, inner ear problems, vision problems, trauma, hypertension, dehydration, orthostatic hypotension, atherosclerotic vascular disease, anemia, menopause, and familial factors.

PATHOPHYSIOLOGY
The two most common causes of dizziness are vestibular disorders (35%–55%) and psychiatric illnesses (10%–25%). The most common CNS cause is cerebrovascular ischemia or infarction (2%–10%). Neoplasms are an infrequent cause of dizziness, noted in less than 1% of patients. Dizziness can be secondary to inflammation, infections, metabolic abnormalities, autoimmune disorders, medications (e.g., ototoxic), developmental anomalies, autonomic nervous system dysfunction, neurodegenerative diseases, trauma, and other systemic disorders. The cause of dizziness is often multifactorial, especially in elderly patients. In 15% to 25% of patients the etiology remains unknown. Familial causes of vertiginous dizziness have been reported.

Diagnosis

DIFFERENTIAL DIAGNOSIS

• Benign paroxysmal positional vertigo
• Vestibular neuritis
• Ramsay Hunt syndrome
• Meniere’s disease
• Meniere’s syndrome
• Multiple sclerosis
• Vertebrobasilar migraine
• Autonomic dysfunction
• Orthostatic hypotension
• Hypoglycemia
• Infectious (otitis media, syphilitic, delayed-onset Meniere’s disease, meningitis, AIDS, viral encephalitis)
• CNS vasculitis
• Cerebellar lesion (infarct, vascular malformation, hemorrhage, neoplasm)
• Lateral medullary syndrome
• Pontine syndrome
• Posterior fossa neoplasm (e.g., vestibular schwannoma, brainstem glioma)
• Neurofibrromatosis type 2
• Paraneoplastic syndrome
• Posterior fossa structural lesion (e.g., Chiari malformation)
• Postconcussion syndrome
• Alcoholic cerebellar degeneration
• Vitamin E deficiency
• Vitamin B12 or folate deficiency

SIGNS AND SYMPTOMS

Dizziness can be divided into four major categories: vertigo, presyncope, dysequilibrium, and light-headedness. The symptoms can range from mild light-headedness, the sensation of losing one’s balance when standing or walking (dysequilibrium), spiking movements relative to the surroundings (vertigo), to an impending loss of consciousness (presyncope). The onset of dizziness can be spontaneous or provoked by certain movements or head position, and be episodic or persistent. Dizziness is commonly associated with varying degrees of nausea, vomiting, pallor, and perspiration. It also can be associated with tinnitus, hearing loss, aural fullness, ataxia, headache, vision disturbances, memory difficulties, seizures, and focal neurologic deficits. Focal neurologic findings such as cranial neuropathies, hemiparesis, dysarthria, dysphagia, diplopia, ataxia, and dysmetria suggest a central etiology.

LABORATORY PROCEDURES

Blood tests have a low yield in identifying a specific cause of dizziness. Lumbar puncture is important in evaluating CNS infection and idiopathic intracranial hypo- or hypertension. Spinal fluid can also be tested for cytology, VDRL, ACE level, oligoclonal bands, and IgG synthesis index.

IMAGING STUDIES

MRI with and without contrast is important to exclude structural lesions or malformations, infarction, demyelinating disorders, or upper cervical spine dysfunction. Imaging studies are strongly indicated for patients with focal neurologic findings and persistent vertigo or imbalance for longer than 6 months. MR and cerebral angiography are used to identify vertebrobasilar insufficiency or atherosclerosis.

SPECIAL TESTS

The Dix-Hallpike test can be helpful to distinguish peripheral from central causes of dizziness. Tests of vestibular function may be of benefit, including audiometry, electroneurography, and rotational testing. Cardiac evaluation may be indicated in some patients. Neurologic studies may include autonomic function testing, EEG, brainstem auditory evoked responses, and EMG.

Management

GENERAL MEASURES

Specific therapies are directed to the underlying etiology of the dizziness. Antibiotics, antiviral, or antifungal agents may be used for infection. Antiepileptic drugs are effective in treating paroxysmal vestibular disorders. Beta-Mockers are effective for basilar or vestibular migraine attacks. Corticosteroids can be used in inflammatory processes such as vestibular neuritis or Cogan's disease. Antiplaquelet and anticoagulation therapies are indicated for infarction and dizziness associated with vascular etiologies. Vestibular exercises and rehabilitation programs are designed to readjust perceptual, vestibulo-ocular, and vestibulospinal reflexes by fostering central compensation of vestibular tone imbalance.

SURGICAL MEASURES

Surgery is the treatment of choice for posterior fossa tumors and cysts. It is also appropriate for rotational vertebral artery syndrome or upper cervical spine dysfunction. In patients with refractory Meniere’s disease, surgical intervention such as endolymphatic shuntplacement and selective vestibular nerve section can be performed. Surgical patching may be necessary for refractory cases of perilymphatic fistula.
**SYMPTOMATIC TREATMENT**

Most causes of dizziness are benign and self-limiting, and antivertigo drugs and antiemetics can provide symptomatic relief in the acute phase. Symptomatic therapy for hypertension, hypoglycemia, anemia, arrhythmia, seizures, headache, muscle spasm, and thyroid and other systemic disorders may be indicated for specific etiologies. For psychogenic dizziness, reassurance, short-term benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), or psychiatric consultation may be needed.

**ADJUNCTIVE TREATMENTS**

In the acute phase, bed rest, mental relaxation, and visual fixation are helpful. Vestibular habituation and balance retraining exercises are beneficial for chronic persistent dizziness. Physical and occupational therapies involving eye, head, and body movements are also beneficial for dizziness due to upper cervical dysfunction and CVA, and should be begun as soon as the acute stage of nausea and vomiting has ended.

**ADMISSION/DISCHARGE CRITERIA**

Patient with profound disequilibrium or intractable vomiting may require hospitalization and IV rehydration. Patients with acute onset and severe dizziness of central origin (e.g., cerebellar or brainstem stroke) are admitted for evaluation and close monitoring through the acute phase.

**DRUG(S) OF CHOICE**

**Vestibular Suppressants**

- **Antihistamines:** meclizine (Antivert 25-50 mg q6h PRN) is most commonly used; dimenhydrinate (Dramamine 50 mg q4-6h PO or IM), diphenhydramine, and cyclizine are also used as vestibular sedative medications. Central anticholinergic activity may be the elderly ing mechanism.
- Benzodiazepines: diazepam (Valium 2.5-5 mg PO, IN, or IV tid or PRN) or clonazepam (Klonopin 0.5 mg PO tid) can be helpful in alleviating severe vertigo and anxiety.
- Anticholinergics: scopolamine (0.6 mg q4-6h or transdermal patch 1 q3d, no longer than 10 days) is effective for motion sickness and posttraumatic vertigo.

**Antiemetics**

Promethazine (Phenergan, 25 mg q6h PO, IN, sup, IV, PRN) and prochlorperazine (Compazine 5-10 mg PO im q6h or 25 mg sup q8h) are useful in relieving the severe nausea associated with vertigo. Ondansetron (4 mg q8h PRN) and prochlorperazine are used for severe nausea from central vertigo.

**Follow-Up**

For Meniere’s disease, low-sodium diet and diuretics (acetazolamide 250-500 mg bid) for 3 months to 1 year have been recommended. Also, a trial course of prednisone at 1 mg/kg for 10 days given orally or intramuscular injection of methylprednisolone 60-80 mg followed by oral prednisone taper are recommended for Meniere’s disease, vestibular neuritis, or inner ear autoimmune process.

**Contraindications**

Prior history of hypersensitivity or allergic reaction. Transtympanic aminoglycoside treatment of Meniere’s disease is associated with risk of profound hearing loss; bilateral involvement of Meniere’s disease is a relative contraindication for ototoxic treatment.

**Precautions**

Drowsiness is commonly associated with antihistamines and antiemetics. Steroid therapy for vestibular neuritis or autoimmune inner ear disease can be associated with hypertension, hyperglycemia, gastric ulcers, osteoporosis, and cataract.

**ALTERNATIVE DRUGS**

Symphathomimetic agents such as amphetamine and ephedrine may be useful in specific situations. Baclofen (20mg tid P O) has been used for downbeat or upbeat nystagmus. SSRIs such as paroxetine (Paxil 10-20mg qd) are used for chronic anxiety. Glycopyrrolate (Robinul, 2 mg bid or tid PO) can be tried in cases of antihistamine failure in patients without glaucoma, congestive heart failure, hyperthyroidism, or gastrointestinal reflex.

**REFERENCES**


**AUTHORS:** Yi Qun Flu, MD, PhD


**DESCRIPTION**

Dysarthria is defined as a defect in the production of speech affecting the volume, rate, tone, or quality of spoken language. Abnormalities in a number of neurologic structures can lead to dysarthria by altering the function of the muscles of phonation and articulation. Dysarthria must be distinguished from aphasia, in which there is a disorder of the production of language with or without articulation disorder.

**DEINITIONS**

**Phonation:** the production of vocal sounds.

**Articulation:** contractions of the pharynx, palate, tongue, and lips that alter the vocal sound to form components of speech.

**Anarthria:** inability to produce speech with sparing of comprehension of speech and ability to read and write.

**CLINICAL CHARACTERISTICS**

The origin of dysarthria is neurologic, associated with damage to either the central or peripheral nervous system. It is a disorder of movement and abnormal speech execution, disrupting the range, timing, speed, or accuracy of the movement producing speech. It does not therefore disrupt the structure of speech, or its linguistic or cognitive components. Disorders affecting the physical structures of the speech apparatus, such as a cleft lip or palate, are not referred to as dysarthrias.

Dysarthria can be characterized by the major neurologic abnormality causing it. Each level of the neuraxis causes a different quality of dysarthric speech.

- Lower motor neuron dysarthria (bulbar palsy): speech slurred, nasal, drooling, raspy quality, monotonous, indistinct. Tongue atrophy, flaccid palate, reduced gag.
- Spastic dysarthria (pseudobulbar palsy): speech explosive, forced, effortful. No tongue atrophy, brisk jaw jerk, brisk gag. Slow tongue movements.
- Extrapyramidal dysarthria: rapid, slurred speech, low pitched, trailing off at the end of sentences. May be whispering.
- Ataxic dysarthria: arrhythmic, slurred, syllables of words broken up (scanning speech). Variable force, rate, rhythm of speech.
- Choreiform dysarthria: prolonged sentences interspersed with silences, improper stresses in words. Speech may come in outbursts.

**PATHOPHYSIOLOGY**

Speaking depends on the coordinated movement of the respiratory muscles, the pharynx and larynx, the lips, palate, tongue, and jaw. These structures are innervated by cranial nerve nuclei (facial, trigeminal, vagal, hypoglossal, and phrenic). They are controlled by corticobulbar connections and ultimately by the motor cortex. There are influences from cerebellar and extrapyramidal inputs, which modify the rate, range, volume, and force of speech. By varying the amount of expelled air, the physical qualities of the sound passage, and the tension of the vocal cords, various sounds and words can be developed. Thus disorders at multiple levels of the nervous system may lead to dysarthria.

**DIFFERENTIAL DIAGNOSIS**

- **Muscular disorders:** muscular dystrophies may occasionally cause slurred speech of the bulbar type.
- **Neuromuscular disorders:** myasthenia gravis may cause bulbar muscles; involvement with characteristics of a fluctuating, bulbar dysarthria.
- **Cranial nerve diseases:** combinations of disorders of vagal, hypoglossal, and facial nerves may cause dysarthria, whose characteristics are those of the specific cranial nerve involvement. Chronic meningitis, leptomeningeal disorders, skull base tumors, inflammatory disorders.
- **Brainstem diseases:** bulbar or pseudobulbar speech, depending on the level in the brainstem. Stroke, demyelination, tumor, vascular malformations, etc.
- **Cerebellar and cerebellar connection disorders:** ataxic dysarthria associated with gait ataxia, nystagmus and incoordination. Various causes.
- **Extrapyramidal disorders:** Parkinson's and related disorders, Huntington's and other choreoathetotic disorders.
- **Corticobulbar disorders:** strokes, cerebral palsy, anoxic encephalopathy, etc. Motor neuron disease may give a mixture of upper and lower motor neuron signs, i.e., wasted tongue, brisk gag, pseudobulbar affect, etc.

**SIGNS AND SYMPTOMS**

Ask about difficulty swallowing liquids and solids, cranial nerve symptoms (diplopia, facial numbness, vertigo), Parkinsonian symptoms, muscular weakness, toxins or chemical ingestion, medical problems. Evaluate oropharynx for mass lesions. Listen to the quality of speech and reading. Have patient repeat language (sounds I and T), labials (b, p), and gutterals (nk, ng). Have the patient hold a vowel to assess the stability of phonation.

**LABORATORY PROCEDURES**

Depends on underlying disorders.

**IMAGING STUDIES**

Depends on level of neuraxis affected.

**SPECIAL TESTS**

Patients with unexplained dysarthria should be considered for a Tensilon test for myasthenia gravis and other neuromuscular disorders. EMG-NCS may be helpful in muscular disorders and neuromuscular disorders.
Management

GENERAL MEASURES
Speech therapy to retrain speech precision, or if necessary training in alternative communication strategies may be useful. For severe dysarthria, alternative or augmentative communication strategies may be useful. These include communicators or computer systems that may incorporate computer-synthesized voice. Speech therapy should be aimed at the particular aspect of speech that is most affected to improve comprehensibility and speech output.

SURGICAL MEASURES
For patients with certain kinds of dysarthria, there may be surgical options. A pharyngeal flap may be considered for patients with hypernasal speech. Procedures aimed at improving vocal cord apposition may help speech in disorders of vocal cord paralysis.

SYMPTOMATIC TREATMENT
Depends on specific diagnosis.

ADJUNCTIVE TREATMENT
Depends on specific diagnosis.

ADMISSION/DISCHARGE CRITERIA
Dysarthria does not usually require hospital admission. But associated neurologic problems such as aspiration due to dysphagia, respiratory disorders, and weakness may require admission.

Medications

DRUG(S) OF CHOICE
This depends on the clinical basis of dysarthria. For example, for myasthenia gravis, use of pyridostigmine (Mestinon), steroids, or other immunomodulating therapy may improve speech. Treatment of Parkinson's disease with L-dopa or dopaminergic agents may modulate speech disorders.

CONTRAINdications
N/A

PRECAUTIONS
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

on specific diagnosis.

EXPECTED COURSE AND PROGNOSIS
Depends on specific diagnosis.

PATIENT EDUCATION
Depends on specific diagnosis.

Dysarthria

SYNONYMS
None

ICD-9-CM: 784.5 Dysarthria

SEE ALSO: MYASTHENIA GRAVIS, AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON, PARKINSON'S DISEASE

REFERENCES

Author(s) Alexander D. Rae-Grant, MD
**Falls**

### Basics

**DESCRIPTION**

Falls are a common and serious problem encountered by older persons associated with significant morbidity and mortality, reduced functioning, and an increased chance of nursing home admission. A complex interaction among host factors, activities (situational) and environmental factors is usually required to predispose an individual to falling. Evaluating fall risk and instituting preventive measures has been shown to be effective in reducing falls in the older population.

**DEFINITION**

A fall is an unintentional coming to rest on the ground, floor, or other lower level. A drop attack is a sudden loss of postural tone leading to a fall without warning.

**CLINICAL CHARACTERISTICS**

- Most falls are multifactorial. Causes of falls include (in descending order of frequency):
  - environmental hazards, gait and balance disorders, weakness, dizziness and vertigo, drop attacks, confusion, postural hypotension, visual disorders, syncope, and miscellaneous (arthritis, acute illness, drugs, alcohol, pain, epilepsy, falling from bed).
  - Environmental hazards interact with individual susceptibilities (due to age and disease) to encompass the largest cause of fall risk. Age-related changes (stiffer gait, decreased muscle strength and step height), specific diseases (parkinsonism, stroke, arthritis), and deconditioning contribute to gait disorders and weakness. Dizziness can be due to a variety of disorders (vertigo, near-syncope, gait dysfunction). Drop attacks occur without associated dizziness, loss of consciousness, or postural symptoms. They are often provoked by a sudden change in head position. Confusion as a cause of fall risk may be due to an acute medical illness causing delirium or a chronic condition that impairs judgment or perception. Orthostatic hypotension is common in normal older persons (5-25%) and in those with autonomic dysfunction, hypovolemia, and parkinsonism; and in those taking certain medications (sedative-hypnotics, vasodilators, tricyclic antidepressants). Defined as a drop of at least 20 mm Hg in systolic blood pressure. It can cause falls, although many individuals can compensate without falling. Syncope is underrepresented as a cause of fall risk because many studies have excluded this cause, and some patients have difficulty remembering the exact circumstances of their fall. Up to 50% of older persons with carotid sinus syndrome present with falls. Medications most strongly linked to falls are neuroleptics, benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, class I antiarrhythmics, and anticonvulsants. Less common causes include anemia, osteoporosis with spontaneous fracture, and foot problems.
- Risk factors for falls include a history of falls, gait impairments, balance disorders, use of an assistive device, lower extremity weakness, visual deficits, cognitive impairment, age over 80, arthritis, and use of 1 or more medications. Of these, lower extremity weakness is the most significant. The risk of falling increases as the number of risk factors increases. Using three risk factors (balance deficit, four or more prescription medications, and hip weakness), the risk of falling within 1 year is 1.2% with zero risk factors to 100% with all three.
- Thirty-five percent to 40% of community-dwelling persons older than 65 and roughly half of those 80 years and older fall annually. Annual incidence rates are 0.2 to 1.6 falls per person year. 5% to 7% of nursing home patients fall each year. Annual incidence of falls in long-term care facilities is 0.2 to 1.6 per bed. Hospital-based annual incidence rates range from 0.5 to 2.7 falls per bed. Accidents are the fifth leading cause of death in older adults; 5% to 10% of fall injuries in older persons in the community result in serious injury: 10% to 25% of institutional falls result in fracture, laceration, or hospitalization.

### Diagnosis

**DIFFERENTIAL DIAGNOSIS**

Symptoms of falls and syncope overlap. Persons with preexisting gait instability may develop imbalance secondary to a hypertensive episode. Patients may be unaware of loss of consciousness; syncope should be considered in patients who are “found down.” Older persons with carotid sinus hypersensitivity can present with falls. Atonic seizures characterized by sudden loss of muscle tone (more frequent in children) can cause falls.

**SIGNS AND SYMPTOMS**

- All persons older than 70 years or their caregivers should be assessed annually about balance or gait difficulties and falls. High-risk groups (nursing home residents, injurious falls, recurrent fallers, a new presentation after a fall) require a more comprehensive assessment. History should include circumstances of the falls (including activity during the fall), warning/associated symptoms, how the patient felt immediately after the fall, loss of consciousness. Falls that occur immediately after arising from a lying or sitting position could be due to orthostatic hypotension. If the person tipped, environmental hazards should be assessed, as well as the possibilities of weak ankle dorsiflexors, spasticity, or parkinsonism. Collapse at the knees could indicate a syncopal episode, seizure, or knee instability. Falling backward could indicate an extrapyramidal disorder. A fall after a meal could be secondary to postprandial hypotension. Vertigo, vision changes, urinary incontinence (normal pressure hydrocephalus), clumsiness, and impaired judgment should be sought. Medication history should explore use of benzodiazepines, neuroleptics, sedative-hypnotics, alcohol, and vasodilators. Medical comorbidities, functional status and environmental risks should be assessed.
- Physical examination should include orthostatic blood pressure measurements, strength, sensation (especially proprioception), feet, and gait. A good screening gait test is the “Get Up and Go” test, which asks a patient to arise from a chair without using arms, walk 10 feet, turn around, and return to sit in the chair. Stride length, steppeage, start hesitation, freezing, postural stability, and sway can all be evaluated.

**LABORATORY PROCEDURES**

Testing based on history and physical examination.

**IMAGING STUDIES**

MR/CT scan may be indicated based on symptoms and signs.
SPECIAL TESTS
The following studies may be necessary depending on the history and physical exam:
- Echocardiogram
- EEG
- Nerve conduction studies/EMG
- Hotter/event monitor
- Electromyogram
- CSF—large volume (30-50 mL) spinal tap for NPH

Management
GENERAL MEASURES
- If fall related to syncope, exclude cardiac or neurologic cause.
- If nonsyncope fall, best results are achieved with multicomponent interventions. — Medication modification—reduce or discontinue psychotropics and other offending meds if possible.
- Postural hypotension treatment.
  — Environmental hazard modification (occupational therapy consult to evaluate home safety and need for raised toilet seat, grab bars, handrails, adequate lighting, removal of loose cords or slip rugs).
  — Exercise programs with balance (e.g., tai chi and gait training).
  — Treatment of cardiovascular disorders (e.g., arrhythmias).
  — Vision and hearing aids if needed.
- Osteoporosis evaluation (bone densitometry) for age over 65 years (and 60-65 years if risk factors present—thin body habitus, smoker, family history of maternal hip fracture).

SURGICAL MEASURES
May be necessary if injury from the fall.

SYMPTOMATIC TREATMENT
Determined by underlying etiology.

ADJUNCTIVE TREATMENT
- Physical therapy/occupational therapy.
- Treat osteoporosis if present.
  - Hip protectors do not affect falling risk, and use for prevention of hip fractures is controversial—recent study showed no benefit.
  - No evidence to support restraint or removal of restraints for fall prevention.
  - No specific footwear to reduce falls. Gait and balance improved more with walking shoes than barefoot. Balance is better in low-heeled rather than high-heeled shoes. Stability in men is improved with high midsole hardness and low midsole thickness.

ADMISSION/DISCHARGE CRITERIA
Determined by severity of associated injuries and by underlying cause(s) of fall.


drugs

Medications

**DRUG(S) OF CHOICE**
- No medications indicated for fall prevention or treatment other than in some cases of orthostatic hypotension.
- Minimize medications that affect postural stability.

**Contraindications**
None

**Precautions**
None

**ALTERNATIVE DRUGS**
- Fluorcholone or midodrine may be necessary for orthostatic hypotension.
- Calcium 1,500 mg/day, vitamin D 800 units/day, and bisphosphonates (alendronate 70 mg orally once a week or risedronate 35 mg orally once a week) or oral oxoxolone 60 mg orally once a day if osteoporosis.

Follow-Up

PATIENT MONITORING
- Determined by underlying cause.
- Ask about falls at each visit in patient with history of falls or gait/balance disorder.

EXPECTED COURSE AND PROGNOSIS
- Fifty percent of falls have multiple falls.
- Determined by underlying cause and interventions to reduce/prevent falls.

PATIENT EDUCATION
- Does not reduce falls when used as an isolated intervention.
- Benefit is demonstrated when education is included as part of a multifactorial intervention.
- Home safety modifications.
  - Strategies for what to do if person falls and cannot get up (accessible telephone; emergency-response system).
  - Calcium and vitamin D for bone protection.
  - Review risk factors for falling.

Miscellaneous

**SYNONYMS**
N/A

ICD-9-CM: E885.9 Fall from other slipping, tripping, or stumbling
SEE ALSO: N/A

REFERENCES

Author(s) James F. Lamb, MD
Gait Disorders

Basics

DESCRIPTION
Walking is a complex, fundamental human skill that is often taken for granted. Many neurologic systems are required for effective walking and balance. Disorders of many types involving these systems may cause disorders of gait. Disorders of gait may be characterized by the level in the nervous system, the particular nervous system structure, or the underlying disease that causes them. Gait disorders are common in the elderly. In a cohort of the elderly from Sweden, one in four patients age 79 and over has a gait disorder. The patients may have difficulty with walking. Their families may notice an altered gait. They may complain of weakness, numbness, back pain, or other symptoms.

DEFINITIONS
Gait disorder: a problem with the initiation or maintenance of walking.

CLINICAL CHARACTERISTICS
Patients with gait disorders present with a variety of symptoms. Often they present with falling repeatedly, not noticing that they have an altered gait. They may complain of wooness or imbalance, a vague sense of instability when walking. Their family may notice an altered pattern of walking or posture, or may be worried that they may fall. The patients may limit their activities in an attempt to avoid dangerous areas for walking (outside, slippery surfaces, on an incline, etc.). They may have associated leg weakness, numbness, back pain, or other symptoms depending on the specific cause of gait dysfunction. Often gait disorders are progressive depending again on the underlying cause or causes.

PATHOPHYSIOLOGY
Walking depends on the effective interaction of a number of neurologic systems to integrate the gait into a smooth, balanced activity. Disorders of neurologic systems that underlie gait, or musculoskeletal systems that participate in gait are key to gait disorders. Often patients have more than one neurologic or musculoskeletal system involved (multifactorial gait disorder). The normal gait is complex, though it seldom attracts attention. It consists of a stance phase, in which the foot is in contact with the ground, and a swing phase, which begins when the foot leaves the ground. Normal gait requires antigravity support of the body, stepping, the maintenance of equilibrium, and proprioception. Antigravity support requires input from vestibular, proprioceptive, and visual responses integrated at multiple levels. Stepping is a basic motor pattern present at birth and depends on spinal cord, midbrain, and diencephalic interactions. Locomotor pattern generators permit rhythmic motion. Equilibrium depends on highly tuned interactions between reflex arcs and input from visual, vestibular, and proprioceptive systems. Propulsion depends on muscles generating appropriate timed force, as well as the appropriate inhibition of antagonistic muscle groups. All of the above can be overridden by conscious cortical centers so one can go where one wants to. Neurologic systems that are involved in walking include the frontal lobes, basal ganglia, diencephalon and midbrain, spinal cord, peripheral nervous system, vestibular system, and cerebellum.

Diagnosis

DIFFERENTIAL DIAGNOSES
The analysis of the gait and categorization of the type of gait disorder helps in directing the diagnostic process. Certain kinds of gait are relatively distinctive, while others are harder to characterize.

• Apraxic gait: wide based, short steps, uncertainty, shuffling. Patient appears unsure how to proceed. Able to do complex movements while lying down (bicycling movements with legs). No ataxia or weakness of individual limb movements. Seen in frontal lobe disorders, multiple in farction syndromes, normal pressure hydrocephalus.

• Cerebellar gait: wide based, unsteady, consisting of steps that vary in rate, rhythm, and force. May be described as reeling or drunk. Marked difficulty in walking heel to toe. May be associated with nystagmus or overshoot dysmetria, reverb, intention tremor, hypotonia. Seen in patients with cerebellar disease, and frequently in multiple sclerosis.

• Choreiform gait: jerky, irregular, erratic gait, sometimes appears dancing, incorporating choreiform movements. Seen in Huntington’s disease and other choreiform disorders.

• Equine gait: excessive raising of legs, feet fall limply due to weakness of anterior shin muscles, slapping when foot falls. Seen in neuropathies, spinal muscular atrophies, distal muscular dystrophies.

• Festinating gait: shuffling, hastening, with forward flexed posture, associated with difficulty initiating gait and turning. Associated with parkinsonism.

• Senile gait: cautious, short steps, unsteady, with limited ability to step. Seen in patients with multisystem atrophy, cerebellar disorders, and patients with prior falls.

• Sensory gait: Feet placed wide apart, stamping gait, legs flung outward, very positive Romberg sign. Seen in disorders of dorsal column system (classically tabes dorsalis, seen in sensory ganglionopathies).

• Spastic gait: stiff legged, with tendency for the toes to turn in and scrape, leg circumduction, leg scissoring. Seen with upper motor neuron disorders.

• Toppling gait: Patient suddenly, precipitously falls, often without warning. May fall backward. Gait is hesitant, uncertain, but not specifically ataxic. Seen in progressive supranuclear palsy, midbrain strokes.

• Waddling gait: Alternating waddle due to weakness of hip girdle muscles, pelvis falls due to weakness of supporting muscles. Seen in proximal myopathies.

SIGNS AND SYMPTOMS
The gait should be assessed by watching the person arise from a chair, walk, stand, turn, and balance. Note whether the patient is unsteady, whether the steps are short or shuffling, and whether there is evidence of a hemiparesis, spasticity, or a foot drop. Signs of a neuropathy (decreased reflexes, distal sensory loss, distal muscle weakness), spinal cord disease (spasticity, brisk reflexes, sensory level, Babinski sign), brainstem disease (diplopia, dysarthria, nystagmus, cranial nerve palsies, long tract signs), and dementia (abnormal cognition, memory, affect, or judgment) should be sought. The Romberg sign (swaying or falling with eyes closed, not with eyes open) is an indication of a proprioceptive deficit. The presence of ataxia and other cerebellar signs should be evaluated (rebound, intention tremor, truncal instability). Hearing and vision should be measured.

LABORATORY PROCEDURES
There are no specific laboratory procedures for this problem. Laboratory studies are directed at specific diseases once the type of gait disorder is ascertained, i.e., cerebellar ataxia, anti-Purkinje cell antibodies.

IMAGING STUDIES
MRI or CT scanning may be useful in excluding intracranial disorders causing gait difficulty (i.e., mass lesions, normal pressure hydrocephalus, stroke), MRI scanning of the spine may be useful in assessing for myelopathic gait disorders.

SPECIAL TESTS
EMG-NCS may document the presence of peripheral neuropathies or polyradiculopathies underlying gait disorders. Computerized gait analysis may be most useful in developing rehabilitative programs for gait disorders.
Gait Disorders

**Management**

**GENERAL MEASURES**
The initial measure is to assess for reversible factors contributing to gait dysfunction. Medications contributing to gait disorders include sedative-hypnotics, anxiolytics, anticholinergics, narcotics; drugs and alcohol should be avoided. Visual disorders should be corrected if possible. An assessment of home factors contributing to gait disorders (uneven flooring, lack of a shower mat, lack of banisters for stairs, etc.) may be useful. Stabilizing walking aids such as canes, walkers, rolling rollators, and other supports may be necessary. Specific training is necessary for any walking aid. Physical therapy aimed at strengthening leg muscles may be helpful. If available, a program of computerized evaluation for gait and gait rehabilitation may be used.

**SURGICAL MEASURES**
Not applicable, unless related to the underlying etiology of gait disorder.

**SYMPTOMATIC TREATMENT**
Therapies such as antiparkinsonian medication may be useful and are directed at the underlying etiology of gait disorder.

**ADJUNCTIVE TREATMENT**
Grab bars particularly in the bathroom and shower are worthwhile safety measures. Consider stair glide if stairs are a problem.

**ADMISSION/DISCHARGE CRITERIA**
Most gait disorders are treated on an outpatient basis. If patients are at risk of falling and cannot ambulate to care for themselves, and do not have support in the home environment, admission may be necessary, with early transfer to a rehabilitative or skilled nursing facility setting. Discharge to rehabilitation or home is based on safe ambulation or a secure environment.

**Follow-Up**

**PATIENT MONITORING**
Patients should be followed for changes in gait as a result of therapy.

**EXPECTED COURSE AND PROGNOSIS**
If a specific disease is identified, the course and prognosis is that of the underlying disease. Patients with multifactorial gait disorders may respond to therapy and changes in walking aids.

**PATIENT EDUCATION**
Patients should be educated about the multifactorial nature of gait disorders, and the effect of medication, drugs, and alcohol on gait. They should be taught about home safety and appropriate walking aids. What to do in case of falls should be reviewed with the patient and family.

**Medications**

**DRUG(S) OF CHOICE**
See specific diseases.

**ALTERNATIVE DRUGS**
See specific diseases.

**Gait Disorders**

**SYNONYMS**
Ambulation disorders
Balance disorders
ICD-9-CM: 719.79 Multiple gait disorder; 781.2 Ataxia
SEE ALSO: ATAXIA, PARKINSON'S DISEASE

**REFERENCES**
• Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology 1993;43:268-279.

Author(s): Alexander D. Rae-Grant, MD
Headache

DESCRIPTION

• Headache is one of the most common medical complaints of modern society, affecting virtually every person during his or her lifetime. Each year, >5% of the US population will seek medical attention for headache. More than 1% of primary care and emergency room visits are because of headache. Most recurrent headaches are symptomatic of a chronic primary headache disorder.

DEFINITIONS

• Primary headaches occur without an underlying cause and include migraine, tension type, cluster, and miscellaneous headaches (such as benign exertional headache). Secondary headaches always have a direct underlying cause (e.g., subarachnoid hemorrhage [SAH], brain tumor, meningitis, carotid dissection, sinusitis), some of which can be life threatening.

CLINICAL CHARACTERISTICS

• Headache history is essential to establish the proper diagnosis. Several key issues should be discussed.
  — Age of onset: Migraines usually begin before age 40 years. Temporal arteritis typically begins after age 50.
  — Time to maximum intensity: Thunderclap headaches are severe, with maximum intensity within 1 minute, and can be caused by SAH, carotid artery dissection, and migraine. Severe headaches also can have a gradual onset, such as migraine or viral meningitis.
  — Frequency: Primary headaches are variable in frequency, ranging from a few migraines in a lifetime to cluster headaches occurring up to eight times daily.
  — Time of day: Cluster headaches often occur during certain times of the day and may awaken the sleeper from sleep about the same time. Headaches that awaken the patient from sleep usually are benign (e.g., migraine, cluster); however, they also can occur with brain tumors, meningitis, and SAH. Tension-type headaches often occur in the afternoon.
  — Duration: Migraine typically lasts 4-72 hours without treatment. Cluster headaches typically last 15-180 minutes. Tension-type headaches typically last 30 minutes to days. Trigeminal neuralgia is characterized by volleys of pain lasting a few seconds to <2 minutes.

PATHOPHYSIOLOGY

• The pain of headache can be caused by several different mechanisms, including elevated intracranial pressure, inflammation or irritation of pain-sensitive intracranial structures (e.g., vessels, meninges) and inflammation or damage to structures in the head and neck region (e.g., muscles). Migraine pain is incompletely understood but involves dysfunction of brainstem control over the trigeminovascular system, with dilation and inflammation of innervated vessels and release of vasoactive neuropeptides. Cluster headaches may involve abnormal interactions between the trigeminovascular system and the posterior hypothalamic circadian cycling mechanism. Tension headache involves inflammation and tenderness of the pericranial and upper cervical musculature. Central mechanisms also may be involved, including oversensitization to peripheral activation of muscle nociceptive afferent input.

SIGNS AND SYMPTOMS

• About 60% of migraineurs have a prodrome before the headache. Complaints may involve the mental state (irritability, depression, euphoria) and neurologic function (decreased concentration; light, noise, and smell hypersensitivity), as well as more general function (diarrhea or constipation, thirst, sluggish feeling, food cravings, neck stiffness). About 2% of migraineurs have an aura that generally develop over 5-20 minutes and last <60 minutes. The headache can begin before, during, or after the aura. The most common auras in descending frequency are visual, sensory, motor, and speech and language abnormalities. Prodromal low-grade fever and upper respiratory symptoms or diaphoresis are present in 10% of cases.

• An important feature of the headache is the location of the pain. Cluster headaches are always unilateral, whereas about 40%-60% of migraines are unilateral. Trigeminal neuralgia typically is unilateral, occurring more often in the second or third trigeminal distributions than in the first. Headaches from brain tumors or subdural hematomas can be bilateral or unilateral.

• Quality of pain is another important aspect. In about 85% of cases, migraine pain is throbbing, pounding, or pulsatile. Tension-type headaches present as a pressure, aching, tight, or squeezing sensation. Cluster headaches are described as boring or burning. Trigeminal neuralgia is usually an electrical or stabbing pain. Headaches due to brain tumors can produce a variety of pains, ranging from a dull steady ache to throbbing.

• Severity of pain can help differentiate headache syndromes. Migraine pain can vary from mild to severe in general, and from attack to attack. Severity of pain does not equate with the presence of life-threatening causes. The vast majority of severe headaches are due to migraine or cluster types. However, a patient complaining of acute onset of the worst headache of his or her life should be evaluated for SAH.

• After the headache resolves, many migraineurs report feeling tired and drained, with decreased mental acuity. Depression or euphoria sometimes is reported. In some systemic disorders, high fever and headache may be followed by other symptoms or signs.
Headache

LABORATORY PROCEDURES
• Erythrocyte sedimentation rate (ESR) is necessary when temporal arteritis is under consideration. A vasculitis screen (e.g., ESR, antinuclear antibody, rheumatoid factor, extractable nuclear antigen) is helpful in patients with headache and arthralgias. Endocrine and metabolic testing may be necessary to rule out other systemic disorders that can cause secondary headache.

IMAGING STUDIES
• CT scan of the head will detect most pathology able to cause headaches and is the preferred study for acute head trauma and SAH. MRI scan of the brain (with and without gadolinium) is more sensitive than CT and is superior for the evaluation of all other causes. MR angiography may detect intracranial aneurysms and carotid dissection. The yield of a CT or MRI scan in a patient with headache and a normal neurologic examination is about 27%.

SPECIAL TESTS
• Lumbar puncture, usually after CT/MRI, may be helpful to exclude SAH, infection (e.g., meningitis, encephalitis, HIV), or low or high CSF pressure.

Management

GENERAL MEASURES
• Will vary with the specific form of primary or secondary headache disorder

SURGICAL MEASURES
• Surgery is not indicated for primary headache disorders but may be appropriate for specific secondary headache disorders (e.g., brain tumor, SAH, abscess).

SYMPTOMATIC TREATMENT
• Will vary significantly depending on the type of headache disorder; see specific form of headache

ADJUNCTIVE TREATMENT
• Nonpharmacologic methods of treatment may be helpful. Migraine headaches may resolve with sleep or improve with lying down in a dark quiet room. Application of ice to the forehead may help. Tension-type headaches may improve with relaxation techniques in some patients and an exercise regimen in others.

ADMISSION/DISCHARGE CRITERIA
• Admission is not indicated for most patients with primary headache disorders, except for treatment of status migrainosus. Admission often is appropriate for work-up and treatment of patients with secondary headache syndromes (e.g., SAH, brain tumor, meningitis).

Medications

DRUGS OF CHOICE
• For abortive treatment of migraine, the triptan medications are preferred. For prophylactic treatment, choices include Q-blockers, valproate, and amitriptyline. Cluster headaches respond best to oxygen and subcutaneous sumatriptan; corticosteroids also may be of benefit.

Contraindications
• Hypersensitivity to medication

Precautions

N/A

ALTERNATIVE DRUGS
• Other drugs to consider for migraine or cluster headaches include ergot derivatives, serotonin antagonists, calcium channel blockers, gabapentin, nonsteroidal antiinflammatory drugs, topiramate, and selective serotonin reuptake inhibitors.

Follow-Up

PATIENT MONITORING
• Patients with primary and secondary headaches will need intermittent follow-up to assess response to treatment and, in some cases, to follow neurologic status.

EXPECTED COURSE AND PROGNOSIS
• The course and prognosis for most patients with primary headache disorders are good, with adequate control of headache pain after appropriate diagnosis and treatment. For secondary headache disorders, the course and prognosis are quite variable and depend on the specific cause.

PATIENT EDUCATION
• Patients with primary headache disorders should be thoroughly educated about the specifics of their form of headache and instructed about behavioral and lifestyle changes that might improve control (e.g., avoidance of triggers).
Muscle Cramps and Pain

Basics

DESCRIPTION
• Myalgia or muscle pain may be of varying intensity and character and may involve any muscle. Muscle cramps are associated with severe pain of acute onset and short duration.

DEFINITIONS
• Muscle pain is a sensation. A cramp or spasm is an involuntary contraction of muscle.

CLINICAL CHARACTERISTICS
• Patients use subjective terms, such as "charley horse," "spasm," "seizing up," and "lame ness," to describe muscle pain. Cramps are associated with a hard muscular contraction and are relieved by stretching the muscle.

PATHOPHYSIOLOGY
• Muscle pain during exercise may result from ischemia, claudication, tearing of muscle fibers, rupture of muscle tendons, muscle cramping, or exhaustion of fuel supply with resultant contracture in patients with metabolic defects.

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Muscle disorders
  — Inflammatory myopathy: dermatomyositis, polymyositis with collagen vascular disease, viral, bacterial, and parasitic myositis
  — Substrate utilization defects: glycolgenolysis, glycogen, fatty acid oxidation, purine nucleotide cycle
  — Toxic myopathy: alcohol, narcotics, clofibrate, zidovudine
  — Endocrinopathies: hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism
  — Metabolic disorders: lowered sodium, pota ssium, calcium, magnesium, phosphate; elevated sodium, ca lcium
  — Metabolic myopathies, such as McArdle's disease
  — Myotonia (occasionally may cause cramps) — Local muscle injury, such as neoplasm, hematoma, ruptured tendon
  — Nonmuscle disease
  — Joint disease, such as limber ness
  — Peripheral neuropathies of many different causes can cause both muscle pains and cramps
  — Circulatory insufﬁciency
  — Anterior horn cell disease, such as amyotrophic lateral sclerosis (ALS)

  — Fascitis
  — Restless leg syndrome
  — Fibromyalgia: generalized pain at rest without weakness, tender spots, normal CK level with no objective laboratory or clinical abnormalities
  — Polymyalgia rheumatica: pain at rest without weakness; in patients >50 years, pain is proximal with stiffness, often accompanied by weight loss and low-grade fever; no muscle tenderness; ESR nearly always elevated
  — Stiff person syndrome: cramps and spasms
  — Bone diseases: pain and myopathic weakness but normal CK. Bones hurt during movement and are tender to pressure or percussion.
  — Cramps may occur in normal individuals (during swimming and at night). The cramps are of explosive onset, visible contraction, painful may leave soreness, tend to be conﬁned to one muscle or parts of a muscle, start and end with twitching, and occur after forceful contraction, especially when muscle shortens. Usually can be terminated by passive stretching of the muscle.

SIGNS AND SYMPTOMS
• In taking a medical history, it is useful to inquire whether the pain occurs at rest or only during exercise. Severe pain and cramps are associated with other symptoms that vary depending on the etiology:
  — Muscle pain and severe cramps that occur after exertion and are associated with echymosis and local swelling are due to tearing of muscle ﬁbers or rupturing of the tendon.
  — In metabolic myopathies, associated features include a "second-wind" phenomenon (i.e., improvement of the cramps after resting for a short time).
  — Cramps are induced with exercise, never spontaneously at rest. They are electrically silent on EMG.
  — Joint pain and swelling
  — Skin rash in dermatomyositis
  — Contractures: active muscle contraction that is not dependent on excitation of the outer muscle membrane; EMG electrically silent.
  — Stiffness induced by exercise (by cold in certain myotonias)
  — Dark urine if myoglobinuria occurs
  — Muscle atrophy in cases of anterior horn cell diseases
  — Hypertrophic calves muscles in some dystrophies
  — Pathologic reexes and spasticity in patients with ALS
  — Tender points, fatigue, disturbed sleep pattern, and morning stiffness in patients with fibromyalgia

LABORATORY PROCEDURES

Blood Tests
• Creatine kinase may be elevated, indicating muscle damage. If CK levels are >10,000, then myoglobinuria is expected. Nodal CK excludes necrotizing myopathy.
• Electrolytes, thyroid function tests, creatine (will be below normal in patients with severe muscle wasting from any cause)
• ESR, ANA if autoimmune disease is suspected
• Specific enzymes such as myophosphorylase in metabolic myopathies
• Forearm ischemic exercise test is indicated in patients with suspected metabolic myopathies due to defect in glycogenolysis. It should be performed under careful monitoring to prevent ischemia. Lactate and ammonia levels are evaluated. In the normal condition, both levels are increased after the test; in metabolic defects, lactate level does not increase after exercise.

IMAGING STUDIES
• Plain x-ray views of the joint or bones if injury is suspected.
• Plain roentgenography of muscle is helpful in evaluation of mass lesions for calcium, fat, or tumor.
• CT scan and MRI of the muscle show distinctive and diagnostically helpful abnormalities in many muscle diseases. They are particularly helpful in differentiating fat from muscle, thus helping to distinguish true hypertrophy from pseudohypertrophy of muscle. They also may aid in differentiating inﬂammatory myopathy from muscular dystrophy.
• Radionuclide scanning with gallium can detect muscle abscesses in patients with pyomyositis.
• NMR spectroscopy to evaluate muscle metabolism. Phosphocreatine, inorganic phosphate, intracellular pH, APT, and lactate level are monitored continuously during exercise.

SPECIAL TESTS
• Electromyography/nerve conduction velocity (EMG/NCV) studies
  — EMG/NCV studies are useful to conﬁrm a clinical diagnosis of myopathic or neurogenic muscle weakness. These electrophysiological studies also are helpful in the diagnosis of myotonia, motor neuron disease, or neuromuscular junction disease as a cause for the pa in and cramps.
  — Cramps are characterized on EMG by repetitive firing of normal motor unit potentials. The EMG shows a full recruitment pattern on the oscilloscope screen.
  — Cramps may be electrically silent on EMG in some conditions, as mentioned earlier.
• Muscle biopsy
  — Useful in evaluating for storage diseases, focal myopathy, inflamma tory myopathy, and necrosis

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## Muscle Cramps and Pain

### Management

**GENERAL MEASURES**
- Patient assurance is very important.
- Prevent the pain and cramps by limiting the triggering activity.
- It is advisable to limit activity at the onset of symptoms in patients with second-wind phenomenon.
- Genetic evaluation of the patient and family members if indicated (in cases of motor neuron diseases, muscular dystrophies).

**SURGICAL MEASURES**
- Surgical treatment is considered for:
  - Tendon rupture with severe pain that did not respond to conservative management.
  - Localized abscess that did not respond to a full course of antibiotics.
  - Inserting devices for pain control in certain conditions.

**SYMPTOMATIC TREATMENT**
- Local massage to relieve the contractions; passive stretching of the contracted muscle may be helpful.
- Fluid replacement is indicated in certain conditions.
- Analgesics can be given in severe cases.

**ADJUNCTIVE TREATMENT**
- Physical and occupational therapy.
- Hypnotics provide short-term benefit for sleep disturbances, but long-term value is not established.
- Aerobic exercise program, physical conditioning.

### Admissions/Discharge Criteria
- Patients are admitted for the severity of symptoms and deficits in cases of acte or isis with myoglobinuria. They need close monitoring for pain control and for aggressive hydration to prevent renal insufficiency. Cardiac monitoring is also indicated in these conditions, as cardiomyopathy may be another manifestation of the disease.
- In patients with inflammatory myopathy, intravenous steroids, plasma exchange, or immunoglobulin therapy in sometimes indicated. Respiratory function, as well as renal and cardiac function, should be monitored to prevent complications.
- Patients may need subacute inpatient rehabilitation care, depending on the condition.

### Medications

**DRUGS OF CHOICE**
- Nonsteroidal antiinflammatory drugs (NSAIDs) are helpful in reducing pain and inflammation. In patients who previously experienced less than optimal relief with NSAIDs, it is important for psychological reasons to start a new and as yet untied drug.
- Antidepressants
  - Tricyclic antidepressants, such as amitriptyline and nortriptyline, increase serotonin, thus lowering the perception of pain. They also cause drowsiness, which may help with sleep in cases of chronic pain and fibromyalgia.
- Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and venlafaxine, may lower perception of pain by their effects on serotoninergic pain systems.
- Anticonvulsants, such as gabapentin, carbamazepine, phenytoin, and clonazepam, are very helpful for muscle cramps and control of neuropathic pain.
- Muscle relaxants, such as the benzodiazepines, baclofen, and dantrolene.
- Quinine sulfate 38 mg given at night will provide some relief from the cramps. It is especially helpful for cramps induced by anterior horn cell disease.

**Contraindications**
- Quinine sulfate is contraindicated in pregnancy because of its potential teratogenicity (particularly the development of deafness).
- Dantrolene is used less often than baclofen. Its serious side effects include fulminant liver failure.

**Precautions**
- Sde effects of NSAIDs include, but are not limited to, GI discomfort, anaphylactic reaction, interstitial nephritis, and renal toxicity. Serious hepatic reactions may occur.
- Major side effects of SSRIs include serotonin syndrome, GI upset, and sleep disturbances.
- Sde effects of anticonvulsants include fatal aplastic anemia and serious liver toxicity in the case of carbamazepine. Skin rash and cardia arrhythmias can occur with dilantin.
- Dependency with tolerance can develop with benzodiazepines.
- Sde effects of antidepressants include sedation and anticholinergic effects (tachycardia, orthostatic hypotension, urinary retention).

### Alternative Drugs
- Dantrolene

### Follow-Up

**PATIENT MONITORING**
- Frequent clinical evaluation with adjustment of medications according to the response and tolerance.
- Periodic blood tests (CBC, hepatic and kidney function) may be indicated in patients who are taking anticonvulsants.

**EXPECTED COURSE AND PROGNOSIS**
- Most conditions that cause muscle pain and cramps are benign and self-limited. Prognosis in general is good, except in certain conditions such as anterior horn cell disease where the symptoms of weakness continue to progress with association of dysphagia and respiratory insufficiency.

**PATIENT EDUCATION**
- Patient assurance is recommended. It is very important to educate patients about other condition and how to avoid activities and vigorous exercise that trigger their muscle pain.

### Miscellaneous

**SYNONYMS**
- Myalgias
- Cramps

**ICD-9-CM**: 728.85 Spasm of muscle; 729.1 Myalgia and myositis, unspecified, fibromyositis

**REFERENCES**

**AUTHOR(S)**: Roula al-Dahhak, MD
Syncope

**Basics**

**DESCRIPTION**
Transient loss of consciousness and postural tone with spontaneous recovery.

**DEFINITIONS**
N/A

**CLINICAL CHARACTERISTICS**
The onset of syncope may either be abrupt or subacute with or without prodromal symptoms. The patient may only recall "passing out," while someone who observed the event may provide more detailed information. Thus a thorough history involves both the patient and any observers the patient wishes to include in the interview.

**PATHOPHYSIOLOGY**
Syncope occurs as a result of global reduction in cerebral blood flow. In cardiac disorders such as hypertrophic cardiomyopathy or severe aortic stenosis, syncope results from obstruction to cardiac output. Any mechanical obstruction to cerebral blood flow may produce syncope in a similar mechanism; less frequent causes include ascending aortic dissection flap or occlusion of the left ventricular outflow tract by a dislodged left atrial myxoma. In neurocardiogenic syncope, physiological changes in heart rate or blood pressure fail to appropriately maintain cardiac output; this may include an abnormal fall in heart rate or blood pressure or simply a failure to adequately augment these parameters. Faulty signals from baroreceptor feedback to CNS centers may impair the execution of appropriate compensatory changes that would otherwise stabilize the patient. Cardiac arrhythmias may produce syncope; bradyarrhythmias in particular should be considered in elderly patients with resting bradycardia or atrioventricular conduction disease.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
Establishing that syncope occurred is usually straightforward; the patient will say, "I passed out." Distinguishing near-syncope from vertigo or nonspecific neurologic syndromes may be more challenging. The history from the patient or an observer will allow the clinician to distinguish vestibular phenomena from true syncope. In eliciting a history of tonic-clonic movements or incontinence, keep in mind that seizure-like activity may ensue from syncope of any etiology, but focal neurologic signs should prompt consideration of a primary neurologic disorder. Identifying other autonomic disturbances raises the possibility of diseases such as Shy-Drager syndrome, Parkinson's disease, and diabetic neuropathy. Volume depletion due to any cause may predispose a susceptible patient to syncopeal episodes.

**SIGNS AND SYMPTOMS**
In the majority of cases the clue to the etiology of syncope results from a careful history. The history begins with characterizing the onset of syncope; for example, focal dysesthesias may suggest that the syncope is related to a seizure disorder. If syncope is preceded by lightheadedness upon standing, consider postural hypotension or vasodepressor syncope. Proximal nausea and warmth often signal vasodepressor syncope. Certain maneuvers such as micturition, defecation, cough, and sneezing may trigger neurally mediated syncope. Identifying a history of coronary artery disease or cardiovascular risk factors as well as an abnormal cardiac examination should flag patients in whom structural heart disease is suspected. A family history of sudden death or drowning may help identify arrhythmic causes of syncope. History related by a witness often yields pertinent information; for example, a spouse may observe tonic-clonic movements in a patient with seizure-induced syncpe or pallor and diaphoresis in vasodepressor syncope.

**LABORATORY PROCEDURES**
Most patients with syncope warrant 12-lead electrocardiography (ECG). Review of the baseline ECG permits identification of intrinsic conduction system disease such as bradycardic rhythms, high-grade A-V block, or significant His-Purkinje system abnormalities. Measurement of the baseline QT interval may identify patients at risk for torsade de pointe. ECG performed at the time of the event, if feasible, may capture tachycardia or bradycardia.

**IMAGING STUDIES**
Assessment for structural heart disease is mandated in elderly patients with syncope or any patient with risk factors or physical findings of cardiovascular disease. In general, this is performed with surface echocardiography. If the history suggests exertional syncope or angina, stress testing should be considered. Caution should be exerted in the patient suspected of having aortic stenosis or any mechanical obstruction to cardiac output prior to treadmill exercise testing; a significant fall in peripheral vascular resistance without the ability to augment cardiac output adequately may produce syncope or cardiac arrest.

**SPECIAL TESTS**
- A history of syncope only after prolonged standing coupled with orthostatic vital sign measurement at the bedside concludes the diagnostic workup in an otherwise healthy patient. Tilt testing can be useful given the same history when bedside measures are nondiagnostic.
- Appropriate use of initially expensive diagnostic tests may prevent the greater cost to patient and society of an erroneous diagnosis. One such test is the electrophysiologic study (EPS), which is indicated if an arrhythmic event has occurred or is suspected based on other findings. In the CAD population, EPS has been shown to identify high-risk patients. Syncope that occurs in the setting of known CAD or remote myocardial infarction merits EPS, particularly in those patients with reduced LV function. EPS should also be performed for patients with symptomatic hypertrophic cardiomyopathy.
- Capturing an arrhythmic cause of syncope may be difficult, especially with infrequent episodes; 24- or 48-hour ambulatory ECG monitoring may be useful but longer periods of monitoring may be required. This can be done with external 30-day event monitors or implantable electrophysiologic event monitors; the latter can capture an arrhythmic diagnosis several months after implantation.
Management

GENERAL MEASURES
The key to selecting an appropriate management strategy for the patient with syncope is risk stratification. The clinician must determine the likelihood of a recurrent syncopal event, and estimate the risk to the patient in the event of recurrent syncpe.

SURGICAL MEASURES
• Bradycardia that results in syncope may be treated with pacemaker implantation. Permanent pacing may also be indicated in vasodepressor syncope when profound chronotropic incompetence is part of the pathophysiology producing syncope.
• Surgical measures are reserved for treating mechanical causes of syncope such as aortic stenosis (AS) and hypertrophic obstructive cardiomyopathy. The vast majority of sudden deaths in AS occur only in patients who had previously been symptomatic; further underscoring the need for surgical evaluation in the patient with syncope due to AS.
• Altering the sequence of myocardial activation with permanent pacemaker implantation in hypertrophic obstructive cardiomyopathy has shown mixed results in preventing syncope, but may be an option for the patient who does not respond to medical therapy and is not a candidate for surgery. Surgical myectomy or percutaneous alcohol septal ablation effectively removes the myocardial obstruction of the left ventricular outflow tract; these therapies may be considered depending on the availability of experienced operators.

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
• Since vasodepressor syncope is the most common cause of syncpe, such patients should be instructed on the use of self-therapy measures that can be highly effective. These include avoidance of abrupt standing, liberalization of water and sodium intake, and avoidance of prolonged standing. Use of compression stockings meets with occasional patient acceptance and symptomatic improvement.
• In patients with ventricular tachycardia or ventricular fibrillation as the cause of syncpe, implantation of a cardiac defibrillator (ICD) may prove lifesaving. All current-generation defibrillators also provide antitachycardia pacing routines. These can terminate sustained tachycardia often without administration of a shock. Note that the substrate for syncpe is not altered; thus, at old frequent firings of the ICD, the elderly syncpe substrate should be altered if possible. An example of this is the patient with sustained VT and CAD; identifying reversible ischemia should prompt revascularization if possible or concomitant use of antiarrhythm ic drug therapy.

ADMISSION/DISCHARGE CRITERIA
Any episode of syncope resulting in significant harm to the patient mandates inpatient evaluation. Furthermore, patients with structural heart disease and syncope probably should be admitted to a telemetry ward given the risk of sudden death. Or the other hand, a young person with a clearly identified reversible precipitant such as dehydration or presumed vasodepressor (neuropathicogenic) syncope could be managed as an outpatient in the absence of high-risk features.

Medications

DRUG(S) OF CHOICE
In general, drug therapy for syncpe is reserved for the patient with vasodepressor syncope whom adjunctive measures have failed. Useful drugs include midodrine, which stimulates adrenergic receptors, and fludrocoritone, which augments renal latent ion of water and sodium.
• In the absence of contraindications, patients with orthostatic hypotension requiring drug therapy may be treated with midodrine 2.5-5 mg tid as tolerated. Fludrocoritone 0.1 mg can be given once daily. Careful patient selection and follow-up minimizes the risk of supine hypertension with these drugs.
• Theophylline (300 mg once daily or in divided doses) may help some patients with its propensity to produce tachycardia, though patients should be queried as to possible sleep disturbances, tremor, or palpitations that may ensue.
• Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline may also be useful.

Contraindications
Midodrine should not be used in patients with hypertension, significant cardiovascular disease, acute renal disease, pheochromocytoma, or thyrotoxicosis.

Precautions
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Patient monitoring is indicated particularly if an arrhythmic cause is suspected but a diagnosis has not been made.

EXPECTED COURSE AND PROGNOSIS
Prognosis in syncope is intimately related to etiology and management. Patients with cardiovascular disease likely have a worse prognosis because of the underlying disorders (e.g., CAD, hypertension, AS) compared with patients with vasodepressor syncope. Primary arrhythmic disorders such as the congenital long QT syndromes have varying long-term survival rates; further studies of risks associated with various genetic polymorphisms may help define prognosis for these patients.

PATIENT EDUCATION

Miscellaneous

SYNONYMS
Fainting, spells, loss of consciousness.
ICD-9-CM: 780.2 Syncope and collapse
SEE ALSO: AUTONOMIC REFLEX TESTING, ORTHOSTATIC HYPOTENSION, EPILEPSY

REFERENCES

Author(s): Subba V. Raman, MD; Stephen F. Smaal, MD
Tremor

DESCRIPTION
Tremor is involuntary repetitive contraction of agonist and antagonist muscles producing rhythmic oscillation about a joint at a regular frequency.

DEFINITION
Rest Tremor
Exhibited with complete relaxation.
• Parkinsonian tremor
  — Idiopathic Parkinson’s disease (PD)
  — Parkinsonian syndromes: Parkinson’s plus
  — Drug-induced parkinsonism
  — Heredodegenerative disease
• Nonparkinsonian rest tremor
  — Drug-induced tremor
  — Metabolic abnormalities — Heredodegenerative disease
Action Tremor
Exhibited with muscle activity
• Postural tremor—during held posture
  — Enhanced physiologic tremor
  — Essential tremor (ET)
  — Drug-induced, dystonic, and neuropathic tremor
• Kinetic tremor—during volitional movement
  — Midbrain tremor
  — Cerebellar tremor
  — Task-specific tremor

If mixed pattern present, observe for associated findings; or consider psychogenic origin.

CLINICAL CHARACTERISTICS
The clinical spectrum of tremor disorders is of diverse phenomenology and etiology. Most tremors are worsened by anxiety and improved during sleep.

PATHOPHYSIOLOG
Y General
• Central—nests of oscillatory CNS neurons generate tremor
• Peripheral—tissue properties, rhythmicity of respiration and cardiac movements create resonating frequency
Rest Tremor
• Idiopathic PD and Parkinson’s plus syndromes—degeneration of dopaminergic neurons; likely multifactorial causation, including genetic and environmental
• Drug-induced parkinsonism—dopamine blockers, other agents
• Cerebrovascular disease, toxins, trauma, endocrine abnormalities, infectious/postinfectious, normal pressure hydrocephalus, and heredodegenerative diseases
• Nonparkinsonian rest tremor—caused by tremorgenic drugs, heredodegenerative diseases

Diagnosis
Differential Diagnosis
Rest Tremor
PD, Parkinson’s syndromes, drug-induced tremor, normal pressure hydrocephalus, conditions of calcium or iron abnormalities, cerebrovascular disease, psychogenic.
• Tremor-like movements—tics, myoclonus, chorea
Action Tremor
• Postural—ET, physiologic tremor, drug-induced tremor, dystonia, neuropathy, cerebellar lesion (titubation), psychogenic
• Kinetic—midbrain (stroke, multiple sclerosis, neoplasm) cerebellar lesion, psychogenic

SIGNS AND SYMPTOMS
• Rhythmic oscillation about a joint.
• Note enunciating positions, and activity during distraction.
• Note associated neurologic findings—rigidity, bradykinesia, gait disturbance, dystonia, neuropathy.
• Note pattern and location of onset, work, social, medication and health history, psychiatric history.
• Rest tremor—observed with relaxation of involved part, attenuates during voluntary movement.
  — Parkinsonian tremor
    - 4- to 7-Hz frequency
    - Commonly involving upper extremity, jaw, or lower extremity
  — Unilateral onset in typical PD (bilateral onset indicating atypical parkinsonian syndrome, secondary parkinsonism)
  — Accompanied by bradykinesia and/or rigidity
  — Faster rest tremor and no other parkinsonian signs: toxin exposure, heredodegenerative disease, or tremorgenic drugs
  — Myorhythmia: 1- to 3-Hz frequency; usually seen in the face or proximal upper extremities
  — Palatal tremor: 2-Hz frequency; rhythmic elevation of soft palate often producing subjectively “clicking” sound in ear
• Postural tremor—during held posture (arms outstretched or winged position)
  — Resting the part decreases tremor
  — ET
    - Onset insidious
    - Fine motor tasks impaired
    - No bradykinesia or rigidity
    - 4- to 12-Hz frequency
  — Distal extremities with flexion/extension movements
  — May be whole head or voice tremor
    - Handwriting, drawing Archimedes spiral, or water pouring enhances tremor
    - Alcohol intake reduces ET in 50°7°
    - Worsens with stress, fatigue, excitement, or stimulants (common to many tremors)
  — Enhanced physiologic tremor
    - Similar to ET, finer amplitude, faster frequency (8-12 Hz)
    - Usually symmetrical
  — Orthostatic tremor
    - Standing in one position, relieved by movement
    - Subjective discomfort or pain in legs immediately relieved with movement
    - Best observed by electrophysiologic studies due to 10- to 18-Hz frequency and extremely fine amplitude
Follow-Up

PATIENT MONITORING

• Monitor effectiveness of therapy and u tteward effects.
• Some medications require lab moni to ring (e.g., weekly WBC counts with Clozaril).

EXPECTED COURSE AND PROGNOSIS

• PD
— Progressive neurodegenerative disease —
— As rigidity and bradykinesia worsen, tremor lessens
— ET—Benign
— Subtle for years, increasing with age

DRUGS OF CHOICE

• Parkinson's disease
— Carbipoda/levodopa, bensera zide/levodopa
— Ropinirole, pramipexole, pergolide
— Amantadine
— Trihexyphenidyl, benztrpine, biperidene
• Essential tremor: Propranolol, nadolol, primidone, gabapentin, topiramate, alprazolam, clonazepam
— Dystonic tremor: Trihexyphenidyl, benztrpine
— Task-specific tremor: Clonazepam, botulinum toxin injections
• Kinetic tremor: Clonazepam, trihexyphenidyl, benztrpine, carbipoda/levodopa, propranolol, carbamazepine
— Isometric/orthostatic tremor: Clonazepam, gabapentin

Contraindications

Beta-Mockers in reactive airway disease, congestive heart failure.

Precautions

• Primidone: Flu-like symptoms, drowsiness.
• Anticholinergic effects in trihexyphenidyl and benztrpine.
• Benzodiazepines have addiction potential.

ALTERNATIVE DRUGS

• ET—acetazolamide, clozapin e
• PD and ET—Mirtazapin e

DRUG(S) OF CHOICE

• Parkinson's disease
• Dystonic tremor; dystoni a often prog resses over 3 to 5 years, then plateaus
• Task-specific tremor
— Worsens with repetition of specific task
— Avoidance of or changing performance may alleviate symptoms

PATIENT EDUCATION

• Community support gr ops for ET, PD, and dystonia
• National organizations:
— International Tremor Foundation (ITF), 7046 West 100th Street, Overland Park, KS 66212-1803; Tel: 913-341-3880, www. essentialtremor.org.

SYNONYMS

• Parkinson's disease: paralysis agitans, shaking palsy
• Essential tremor: benign essential tremor, familial tremor
• Cervical dystonia: spasmodic torticollis
• Midbrain kinetic tremor. rubral tremor
• Cerebellar tremor: intention tremor, titubation

ICD-9-CM: 332.0 PD; 333.1 ET; 781.0 Tremor (NOS); 333.83 Cervical dystonia

REFERENCES


Author(s) Karen M. Thomas, DO
**Weakness**

**Basics**

**DESCRIPTION**

Weakness can be defined as a deficit in the motor system, with decreased strength in one or more muscles or limbs, or generalized weakness. Patients may use the term weakness to refer to other problems, such as fatigue, muscle and joint pain, and incoordination. Therefore, it is important to explore with the patient exactly what is meant when the term weakness is used.

**DEFINITIONS**

- **Upper motor neuron deficit** refers to an injury to the central nervous system (brain or spinal cord) causing weakness. A lower motor neuron syndrome refers to weakness caused by injury to any of several levels of the peripheral nervous system (including anterior horn cell, nerve root, plexus, neuromuscular junction, and, for general purposes, muscle).

**CLINICAL CHARACTERISTICS**

- The most important factors to ascertain the correct etiology of weakness include rapidity of onset and speed of development of weakness, distribution of weakness, fluctuating versus fixed weakness, and associated findings such as abnormal reflexes, sensory loss, impaired bowel and bladder function, exposure to toxins, and family history of weakness.
  - In developed countries, the most common causes of acute weakness are Guillain-Barre syndrome (GBS), myasthenia gravis, drug effects, botulism, and hypokalemic weakness.
  - Family history of episodes of acute weakness may suggest porphyria, periodic paralysis, or rhabdomyolysis.
  - In-hospital onset suggests hyperkalemia, hypokalemia, myasthenia gravis, GBS, botulism, critical illness polyneuropathy, or myopathy.
  - Travel history suggests fish poisoning, polio, diphtheria, botulism, tick paralysis, rabies, or snake or other envenomation.
  - Gastrointestinal symptoms suggest porphyria, botulism, or organophosphate, thallium, or arsenic poisoning.

**PATHOPHYSIOLOGY**

- Weakness of upper motor neuron etiology is caused by injury to the major descending motor pathway, the corticospinal tract. The corticospinal tract may be injured at multiple levels, including its cortical origin, through the cerebral white matter, internal capsule, caudal brainstem, or within the spinal cord. Lower motor neuron weakness is caused by more diverse sites of injury, including the anterior horn cells of the spinal cord, roots, plexus, nerves, neuromuscular junction, and muscle.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

- The differential diagnosis of weakness is extremely broad and only a few major causes are listed here.
  - Cerebrum/brainstem
  - Cerebrovascular accident
  - Multiple sclerosis
  - Mass lesions (tumors, abscess)
  - Trauma
  - Spinal cord
  - Trauma
  - Compressive myelopathy (neoplastic, herniated disc, spondylotic)
  - Transverse myelitis
  - Anterior spinal artery syndrome
  - Motor neuron
  - Amyotrophic lateral sclerosis
  - Acute anterior poliomyelitis
  - Peripheral nerve
  - GBS
  - Porphyria - Toxic neuropathies (heavy metals [e.g., arsenic, lead, thallium, gold], hexacarbons, nitrofurantoin, lithium, disulfiram)
  - Diphtheria - HIV-associated neuropathies
  - Neuromuscular junction
  - Myasthenia gravis and myasthenic syndromes
  - Organophosphate poisoning
  - Drug-induced neuromuscular blockade
  - Botulism
  - Animal venom/poisons
  - Electrolyte derangements (hyperkalemia, hypokalemia, hypophosphatemia)

**SIGNS AND SYMPTOMS**

- Upper motor neuron weakness typically is associated with hypertonia or spasticity, hyperreflexia, and extensor plantar responses. Myelopathy that develops slowly is generally associated with hyperactive reflexes and Babinski signs. Acute spinal cord injury may present with "spinal shock" and flaccid areflexic paralysis, which can be confused with a lower motor neuron pathology. Differentiation from root, plexus, or peripheral nerve disease usually can be made based on determination of sensory level, urinary symptoms (urinary retention, urgency, frequency, and incontinence), frequent asymmetry of weakness, and eventual development of upper motor neuron signs.

- Lower motor neuron weakness typically is associated with hypotonia or flaccidity if the weakness is severe, with hyporeflexia or areflexia and flexor or absent plantar responses. Fasciculations may be present if the anterior horn cell or motor nerve has been injured with resultant denervation of muscle.

- Patterns of weakness help to localize the site of pathology.
  - Hemiparesis includes the face suggests cerebral or high brainstem lesions.
  - Hemiparesis without facial and other cranial nerve involvement suggests lower brainstem or spinal cord.
  - Myotomal level suggests spinal cord pathology.
  - Proximal weakness in all limbs suggests myopathy.
  - Distal weakness suggests peripheral neuropathy.

- Weakness of eye movements suggests a differential diagnosis of botulism, myasthenia gravis, myasthenesemia, diphtheria, antibiotic-induced weakness, tick paralysis, and thallium intoxication.

- Decreased or absent pupillary responses suggest a differential diagnosis of diphtheria, botulism, anticholinergic toxicity, antibiotic-induced weakness, snake venoms, and Lambert-Eaton syndrome.

- Various types of pain may suggest different causes of weak knees.
  - Neck and back pain may herald weakness for GBS, porphyria, p. olio.
  - Tender muscles: rhabdomyolysis
  - Proximal myalgias: periodic paralysis, GBS
  - Distal dyesthesias: toxic neuropathies

- Respiratory failure disproportionate to limb weakness: myasthenia gravis, botulism, antibiotic-induced weakness, hyperkalemia, hypophosphatemia, rhabies, amyotrophic lateral sclerosis, high cervical cord lesions, critical care polyneuropathy, rhabies, snake envenomations.
LABORATORY PROCEDURES
- Electrolytes
- Creatine kinase for question of muscle injury
- Antiacetylcholine receptor antibodies for suspicion of myasthenia gravis
- Cerebrospinal fluid analysis for evaluation of GB3 (elevated ion of protein with normal or near-normal cell count), carcinomatous meningitis (cytology, tumor markers), multiple sclerosis (IgG synthesis rate and index and oligoclonal bands), transverse myelitis
- Serum levels of organophosphates (TEPP, parathion)
- Urine studies for toxins such as arsenic
- Serum, feces, and gastric contents for botulinum toxin assay
- Hair and fingernail analysis for metals such as arsenic and thallium

IMAGING STUDIES
- CT brain to investigate for mass lesion or stroke
- MRI brain to investigate for stroke, mass lesion, or multiple sclerosis
- MRI spine to evaluate for compressive myelopathy (e.g., stenosis, disc herniation, tumor, abscess) or demyelination/inflammation
- MRI cauda equina to evaluate for compressive lesions or thickening of roots that might represent neoplastic infiltration
- MRI plexus occasionally helpful to investigate neoplastic involvement of plexus

SPECIAL TESTS
- Nerve conduction velocity studies/electromyography to investigate pattern and type of radiculopathy, plexopathy, neuropathy, or myopathy
- Repetitive stimulation nerve study to explore neuromuscular junction function in suspected myasthenia gravis, myasthenic syndromes, or botulinum poisoning
- Edrophonium (Tensilon) test for suspected myasthenia gravis

SURGICAL MEASURES
- Potential surgical measures include
  - Decompression/excision of cord lesions
  - Stabilization of vertebral fractures or spinal instability
  - Biopsy of cerebral/cord lesions
  - Release of nerve entrapments as in carpal tunnel syndrome

SYMPTOMATIC TREATMENT
- Physical therapy, including range of motion and frequent turning for those with severe weakness
- Splinting to prevent contractures
- Occupational therapy
- Measures to prevent deep vein thrombosis if patient is nonambulatory
- Speech therapy if weakness affects the ability to speak

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
- Admission criteria for this diverse group of causes of weakness vary but include
  - Rapidly progressive course of generalized weakness
  - Impending respiratory failure or inability to protect the airway
  - Need for expedited workup
  - Inability to perform activities of daily living and transfers

MATERNAL MEDICATIONS
- Inability to perform activities of daily living and transfers

GENERAL MEASURES
- The initial approach to treatment of weakness depends upon the etiology. Separate chapters on causes of weakness will go into greater detail. Patients with progressive generalized weakness with possibility of threatened respiratory insufficiency must be monitored closely for vital capacities and inspiratory pressures to determine the need for intubation and ventilation.

COMPLICATIONS
- Botulinum antitoxin for botulism
- IV calcium gluconate for hypermagnesemia

PRECAUTIONS
- See specific disease chapters for details

CONTRAINDICATIONS
- Known hypersensitivity to medications

ALTERNATIVE DRUGS
N/A

DRUG(S) OF CHOICE
- The choice of medications for the vast spectrum of disorders that can cause weakness depends on the cause. Treatments for some of the commonly considered causes of weakness include:
  - Patients with weakness from acte cerebral infarction who present within 3 hours and meet inclusion/exclusion criteria should be considered for treatment with thrombolytic therapy.
  - Treatment with high-dose corticosteroids should be considered for patients with weakness from acte exacerbations of multiple sclerosis, transverse myelitis, spinal cord compression, myasthenia gravis, inflammatory myopathies, and CIDP.
  - CBS/CIDP, myasthenia gravis, and inflammatory myopathies may respond to intravenous immunoglobulin therapy.
  - Porphyric neuropathy may respond to infusions of intravenous glucose 10-20 g/hour and hemato in 4 mg/kg every 12 hours.
  - Atropine and pralidoxime (a cholinesterase reactivator) for organophosphate poisoning

ADDITIONAL DRUGS
- Botulinum antitoxin for botulism
- IV calcium gluconate for hypermagnesemia

PRECAUTIONS
- See specific disease chapters for details

CONTRAINDICATIONS
- Known hypersensitivity to medications

ALTERNATIVE DRUGS
N/A

RELATED DISEASES
- Guillain-Barré syndrome
- Transverse myelitis
- Polymyositis
- Dermatomyositis

SYNONYMS
- Paralysis
- Paresis

ICD-9-CM: 780.7 Weakness (generalized); 728.8 Weakness, muscle; 344.1 Paraplegia; 344.9 Paralysis (with many subheadings)

SEE ALSO: NEUROPATHY, PERIPHERAL; GUILLEMIN-BARRÉ SYNDROME; MYASTHENIA GRAVIS; LAMBERT-EATON SYNDROME; TRANSVERSE MYELITIS; POLYMYOSITIS; DERMATOMYOSITIS

REFERENCES

Author(s) D. Joanne Lynn, MD
SECTION II

Neurologic Diagnostic Tests
Neurologic Examination

Mental Status

- A rough assessment of mental status can be made by observing the patient during history taking and examination. Patients should be observed for signs of self-neglect, depression, anxiety, inappropriate behavior, emotional lability, thought disorder, and disorders of memory, language, and other cognitive functions.

- Screening tests include:
  - Simple questions to test orientation to time, place, and person
  - Digit span to assess attention: Ask patient to repeat presented numbers forward or backward, starting with three or four digits and increasing up to seven digits
  - Assess registration: Ask patient to repeat back three objects
  - Short-term memory: Ask patient to recall these objects at 5 minutes
  - Assess calculations with tasks such as serial subtract ions of 7's or 3's or simple addition problems
  - Abstract thoughts, such as proverbs, similarities, estimations
  - Spatial: Ask patient to draw in a clock face, place major cities on a map outline, draw interlocking pentagons
  - Visual and body perception: Ask patient to recognize famous faces, identify his or her own index finger, touch right ear with left index finger, test stereognosis and graphesthesia
  - Test for apraxias

Cranial Nerves

CRANIAL NERVE I (OLFACTORY)
- Cranial nerve I is tested by asking the patient to smell bedside objects, such as food or formally prepared sb sta nces. Anosmia may be caused by rhinitis, trauma, degenerative illnesses such as Parkinson's and Alzheimer's disease, medications, and frontal meningiomas. Hyposmia is common with aging.

CRANIAL NERVE II (OPTIC)
- Cranial nerve II is tested by checking pupillary responses, visual acuity, visual fields, and fud.

CRANIAL NERVE VII (FACIAL)
- Motor: Examine facial symmetry, nasolabial folds, forehead wrinkles, smiling, eye closure. Ask patient to show teeth, close eyes tightly, look up at the ceiling, whistle.
- Upper motor neuron lesions spare forehead compared with lower face. Lower motor neuron or nuclear lesions involve upper and lower face equally. Taste may be altered because the facial nerve carries taste fibers for the anterior two thirds of the tongue.

CRANIAL NERVE VIII (AUDITORY)
- Assess hearing acuity with whispered speech or a ticking watch, or rub fingers in each ear. If there is a decrease in acuity in one ear, perform the Rinne and Weber tests.
- Rinne: Hold a 516-Hz tuning fork on the mastoid process and then in front of the ear and ask the patient which is louder.
- Weber: Position the end of the tuning fork on the vertex of the head and ask if the sound is louder in the good ear or the deaf ear.

- In conductive hearing loss, bone conduction via the mastoid is better than air conduction, and the sound is heard loudest in the affected ear on Weber testing. In sensorineural hearing loss, air is better than bone conduction, and the sound is heard loudest in the good ear.
- Vertibular nerve dysfunc tion is associated with unilateral horizontal nystagmus that is associated with vertigo. Gait may be unsteady, veering toward the side of the lesion. In the Hallpike test, the patient is brought quickly from a sitting to a supine position, with head tilted below the horizontal and turned 45 degrees to the right or left. Fatigable rotary nystagmus with delay indicates a peripheral vertigo syndrome.

CRANIAL NERVES III, IV, AND VI (EYE MOVEMENTS)
- Look at position of eyes in primary gaze: Are they conjugate or dy sconjugate?
- Test movements to cardinal positions, noting any positions in which the patient develops diplopia. Note any path ologic nystagmus.

CRANIAL NERVE V (TRIGEMINAL)
- Sensory: Test light touch and pinprick for each division of the trigeminal nerve (V1—forehead, V2—cheek, V3—lower lip). If a sensory deficit is found, map otthhe edges.
- Motor: muscles of mastication
  - Look for wasting of the temporalis muscle.
  - Ask the patient to clen ch the jaw and palpate the masseter and temporalis muscles. Try to open the jaw.
  - Ask the patient to forcefully open the mouth against the resistance of your hand beneath the jaw. Look for deviation of the jaw to one side.
  - Jaw jerk: Ask the patient to let the mouth hang open loosely. Place your finger on his or her chin and percuss it with hammer. Observe jaw movement.

CRANIAL NERVES IX (GLOSSOPHARYNGEAL) AND X (VAGUS)
- Watch resting position and then movement of the uvula when the patient says "ahh." Touch the pharyngeal wall behind the pillars to elicit a "gag reflex" and observe the uvula: Does it Lift, and is the movement symmetric or deviated to one side? Also ask abd obtuse nsation in the pharynx. Movement of the uvula to one side suggests upper or lower motor neuron lesion of the vagus on the other side. If the uvula does not move at all, bilateral palatal muscle paresis may be suggested.
Neurologic Examination

CRANIAL NERVE XI (ACCESSORY)
• This nerve arises from the medulla with contributions from C2-4. The ipsilateral cerebral hemisphere innervates the ipsilateral sternocleidomastoid and the contralateral trapezius. Examine for wasting or fasciculation of the sternocleidomastoid muscle. Have the patient turn the head to either side against your resistance and to shrug shoulders, noting any asymmetry of the trapezi muscles.

CRANIAL NERVE XII (HYPOGLOSSAL)
• Examine the tongue for size and fasciculations (when the tongue is at rest in the mouth), and ask the patient to protrude the tongue, noting any deviation. Test power by asking the patient to push the tongue into each cheek. Deviation to one side suggests weakness on the side to which the tongue moves. This can be upper motor neuron weakness associated with hemiparesis. Lower motor neuron weakness is associated with atrophy and fasciculations.

Motor/Reflexes
• Motor examination assesses not only the strength of various muscle groups but also bulk, tone, and abnormal spontaneous movements of the muscles. Judgment should be made as to whether muscle tone is decreased, normal, or increased. Hypertonicity may be due to spasticity, rigidity, or paratonia. Patients with weakness should be assessed for atrophy and fasciculations.
• Power should be graded and reported on a scale such as the Medical Research Council scale:
  - 5 = Full strength
  - 4 = Movement against some resistance
  - 3 = Movement against gravity - 2 = Movement with gravity eliminated
  - 1 = Trace movement
  - 0 = No movement
• Muscle stretch reflexes are tested at the
  — Biceps C5
  — Brachioradialis C6
  — Triceps C7
  — Finger flexors C8
  — Knees L2-4
  — Ankles S1
• Reflexes are recorded on a scale of 0 = absent, 1 = normal or mildly pathologically reduced depending on the context, 2 = normal, 3 = hyporeflexic, and 4 = hyperreflexic with clonus. The examiner should note asymmetries and spread to adjacent segments of the body.

Sensory
• The primary sensory modalities, that is, light touch, vibration, proprioception, pinprick (pain), and temperature sense, should be assessed in each limb starting distally and moving proximally as a quick screen. More extensive testing, such as touching upon each dermatome and major nerve distribution, is required if there are sensory complaints. A 128-Hz tuning fork is needed for testing of vibration.
• Higher integrative sensory modalities may be checked if the primary modalities are found to be intact. These include two-point discrimination and sensory inattention. A blunted pair of compasses or two pins can be used to test two-point pain discrimination; normal values include index finger <5mm, little finger <7 mm, great toe <10 mm. In parietal lobe injury, primary modalities may be intact, but the patient may localize these inputs poorly with decreased two-point discrimination, astereognosis, and sensory inattention.

Cerebellar
• Several different tests assess cerebellar function.
  — Finger-to-nose testing and heel-to-shin testing to look for ipsilateral limb ataxia, which may be manifest as intention tremor, dysmetria, and dysdiadochokinesia (incoordination or disorganization in tests of repeated movements or rapid alternating movements).
  — Rebound: Ask the patient to hold arms out and close eyes. Then push the arms up or down suddenly and see if the patient has an exaggerated correction.
  — Observation of gait may show evidence of midline cerebellar dysfunction with truncal ataxia with broad base and/or titubation. If there is very severe truncal ataxia, the patient may not be able to sit without falling to one side.
  — Dysarthria, cerebellar type

Stance and Gait
• Patients who can stand should be asked to do so normally, with feet touching and eyes closed for Romberg testing. Heel-to-toe walking stresses normal balance mechanisms. Patients should be assessed for narrow versus broad base, shuffling, ataxia, circumduction, footdrop, and apractic gait.

Author(s) D. Joanne Lynn, MD
**Autonomic Reflex Testing (ART)**

**Description of Procedure**

Noninvasive ART techniques are designed to detect and quantify autonomic failure by evaluation of sudomotor, cardio vagal, and adrenergic autonomic functions.

**QUANTITATIVE SUDOMOTOR AXON REFLEX TEST (QSART)**

Evaluates postganglionic sudomotor function. Acetylcholine (10^-7/ sterile saline solution) is iontophoresed into the skin, where it activates the axon terminal of the nearest sweat gland. This impulse propagates antidromically to the branching point and then travels orthodromically to the nearby sweat gland where sweat is released.

**RECORDING SITES**

Dorsal of the foot (sural nerve), distal leg (saphenous), proximal leg (peroneal) and medial forearm (ulnar).

**Normal Response**

Similar volume on all sites; men > women; declines with age.

**Abnormal Response**

Reduced, excessive, persistent sweating.

**SILASTIC IMPRINTS**

Measures direct sweat gland response to iontophoresis of 1% pilocarpine or acetylcholine. Silastic material is spread onto skin and sweat droplets are imprinted into it.

**SYMPATHETIC SKIN RESPONSES (SSR)**

The sympathetic skin response measures change in skin resistance using EMG electrodes using electrical or other stimulation (deep breathing, noise).

**RECORDING SITES**

Palm/dorsum of hand, sole/dorsum of foot.

**Normal Response**

Readily elicitable, amplitude in hands > foot.

**Abnormal Response**

Absent or <50%.

**THERMOREGULATORY SWEAT TEST (TST)**

TST evaluates the entire efferent sympathetic cholinergic pathway. Body is covered by a mixture of alizarin red/cornstarch/sodium carbonate (50:100:50 g) which turns red with sweating. Sweating is induced by rising oral temperature by at least 1.0°C in a heated cabinet. Anhidrosis (white areas) is measured as percent of total sweat area (red areas).

**Normal Response**

Homogeneous sweating.

**Abnormal Response**

Distal, segmental, regional, focal, mixed, and global sweat loss patterns.

**SPECIAL INSTRUCTIONS**

- **DEEP BREATHING TEST (DB)**
  - Cardiovascular and adrenergic functions are evaluated using deep breathing, Valsalva maneuver, and head-up tilt with beat-to-beat heart rate and blood pressure monitoring. Heart rate variation to DB is measured at maximum inspiration and expiration at breathing frequency 6/cycles/min.
  - **Normal Response**
    - Age 26-89 (14-41 bpm), 40-59 (10-33 bpm), >60 (7-22 bpm).
  - **Abnormal Response**
    - Reduced heart rate variation is an early sign of autonomic neuropathy and is associated with increased cardiovascular risks.

**VALSALVA MANEUVER (VM)**

The subject performs a forced expiration for 15 seconds, against a fixed resistance, maintaining an expiratory pressure of 40 mm Hg. Valsalva ratio evaluates parasympathetic; beat-to-beat blood pressure profile evaluates peripheral adrenergic function.

- **Phase I:** Respiration.
  - **Phase II-early (IIe):** Progressive fall of blood pressure, venous return and cardiac output compensated with baroreflex-mediated tachycardia.
  - **Phase II-late (IIl):** Restoration blood pressure to the resting level occurs due to increasing peripheral resistance.
  - **Phase III:** Inspiration.
  - **Phase IV:** Blood pressure overshoots baseline, as venous return and cardiac output have returned to normal but peripheral vasoconstriction persists. Baroreflex-mediated bradycardia is present. Valsalva ratio: an index of baroreflex integrity is calculated ratio between tachycardia during phase II and bradycardia during phase IV.

**Abnormal Response**

Adrenergic overactivity—reduced pulse pressure, increased phase IV.

**Adrenergic failure—increased fall of blood pressure, reduced or absent late phase IT, reduced phase IV**

Cholinergic failure—flat heart rate response.

**HEAD-UP TILT (HUT)**

Blood pressure and heart rate are continuously recorded for 5 to 45 minutes during a head-up tilt to 60 to 80 degrees. Prolonged HUT is recommended for evaluation of syncope.

**Normal Response**

Heart rate increment >10 and <30 bpm, stable blood pressure and cerebral blood flow.

**Abnormal Response**

- **Orthostatic intolerance: heart rate increment >30 bpm and <120 bpm, pulse pressure reduced <50% of baseline.**
- **Postural tachycardia syndrome (POTS): heart rate >120 bpm, pulse pressure falls >50% of baseline, >10% reduction of cerebral blood flow.**

**Syncope: rapid fall of blood pressure with brady- or tachycardia and cerebral hyperfusion.**

**Orthostatic hypotension: sustained fall of blood pressure >30/10 mm Hg for 3 minutes with or without ostatic symptoms.**

**Time-Frequency Analysis**

Power spectrum of R-R intervals, beat-to-beat variation, etc., are sensitive methods for evaluation of heart rate variability.

**Indications**

Unexplained loss of consciousness (seizures vs. syncope), dizziness, light-headedness, orthostatic and postprandial hypotension, Parkinson’s disease, multiple system atrophy, peripheral neuropathies (diabetes), small fiber neuropathy, hypo- or hyperhidrosis, chronic pain.

**Strengths**

Noninvasive and reproducible.

**Limitations**

Interpretation may be limited in older people with medications (anticholinergic, sympatholytics, and sympathomimetics).

Withdrawal of these medications for 24 hours may be indicated. Heart rate variation is reduced by aging, tachycardia, hypocapnia, anticholinergic medications.

**Risks**

HUT may induce orthostatic hypotension, syncope with tachy-, brady- and cerebral arrest. Risks of stopping cardioactive medications, e.g., beta-Mockers.

**Contraindications**

Caution needed for tilt testing of older people with cardiac disease and pacemakers.

**Preparation/Special Instructions for Patients**

No caffeine or cigarettes for 8 hours and 1 hour after meal.

**Miscellaneous**

None

Author(s): Vera Naka, MD
Description of Procedure

Cerebral angiography provides images depicting contrast material as it flows through the vasculature of the CNS, head, and neck. A catheter is entered into the peripheral vasculature (typically via the common femoral artery), and access is gained into the head and neck vasculature. An iodine-based contrast is injected through the catheter and into the vessels as sequential x-ray images are taken over 5 to 20 seconds in order to record the contrast flowing through the head and neck arteries, capillaries, and veins.

Indications

Because of its invasive nature and potential risks, angiography should be considered in situations where diagnostic information regarding the CNS vasculature is not adequately evaluated by other imaging modalities such as MRI, MRA, CTA, or SPELT. Cerebral angiography, therefore, can be considered under the following circumstances:

- Suspicion for asymptomatic cerebrovascular disease based on physical findings such as a bruit, ophthalmoscopic findings, or neurologic findings suggesting potential disease involving the carotid or vertebrobasilar systems.
- Screening for cerebrovascular source of disease following a transient ischemic attack or stroke involving the carotid or vertebrobasilar territories.
- Fixed or worsening focal neurologic deficit, occurring for less than 6 hours, suspected to be due to acute cerebrovascular occlusion.
- Suspicion for nonatherosclerotic occlusive cerebrovascular disease such as vasculitis, vasculopathy, vasospasm, or venous occlusive disease.
- Unexplained or suspected subarachnoid hemorrhage.
- Unexplained intraparenchymal hemorrhage.
- Penetrating injury to the head and neck.
- Unexplained neurologic findings following blunt trauma.
- Head and neck trauma with suspicion for dissection, traumatic aneurysms, traumatic arteriovenous fistulas, traumatic venous thrombosis.
- Vascular malformations or arteriovenous fistulas.
- Functional testing for speech and memory prior to epilepsy surgery (Wada test).
- Presurgical investigation and embolization of hypervascular tumors.
- Vertebrospinal angiography.

Strengths

Relative to other angiographic modalities, conventional angiography provides greater spatial resolution. As a result, it is the most precise and accurate imaging method in assessing intracranial and extracranial carotid and vertebral territory cerebrovascular disease allowing for the detection of smaller vascular lesions and disease in smaller vessels. Furthermore, due to its temporal fashion of acquisition, angiography is able to depict collateral blood flow and delayed cerebrovascular blood flow. Transcatheter interventions can be performed during angiography if needed.

Limitations

Although it is possible to deduce the approximate anatomic location based on the identification of the intracranial cerebrovascular structures, cross-sectional imaging can identify structural CNS abnormalities in a more precise and accurate fashion than conventional angiography.

Risks

The incidence of cerebrovascular ischemic events within 24 hours of cerebral angiography (<1%) varies according to the angiographer's experience, the length of the procedure, and the degree of carotid artery disease. Anaphylactoid reactions to contrast medium can result in hives or pruritus; however, in 40,000 patients undergoing diagnostic examinations using nonionic iodinated contrast medium suffer anaphylactoid shock and death. Significant hematoma formation at the puncture site is common (6.9-10.7%). Other complications may include death, myocardial infarction, angina pectoris, retroperitoneal hematoma, pseudoaneurysm at the puncture site, abscess at the puncture site, nausea, vomiting, benign bradycardia, transient leg paresthesia due to local anesthesia, aneurysm rupture during angiography, transient global amnesia, and cortical blindness.

Contraindications

Relative contraindications to angiography include:
- Renal failure
- Prior contrast reaction
- Pregnancy
- Bleeding diathesis

Preparation/Special Instructions for Patients

Patients are asked not to eat or drink anything with the exception of oral medications beginning 4 hours prior to the exam. Premedication with steroid and Benadryl reduces the risk for contrast reaction in patients with prior history of contrast reaction. Patients with poor renal function who are not being dialyzed are hydrated before and after the procedure. Glucophage (metformin) should be withheld temporarily (48 hours) prior to myelography due to potential risk for renal failure and reinstated only after renal function has been reevaluated and found to be normal. Correction of any bleeding diathesis prior to the procedure may reduce the risk of hemorrhagic complications. Consideration should be given to the administration of anxiolytics or conscious sedation during the examination.

Miscellaneous

At the end of the procedure the catheter is removed and pressure is applied over the arteriotomy to achieve hemostasis. In the setting of bleeding diathesis, an arteriography closure device may be deployed for hemostasis. Following the procedure the patient is placed on strict bed rest while keeping the puncture sight immobilized, and oral fluids are encouraged. The patient is asked not to drive or operate heavy machinery for 24 hours and avoid activities during the next 2 to 3 days that may stress the incision site, such as lifting heavy objects or repeated movements that flex the joint around the incision site.

Author(s): Gregory Christoforides, MD
Biopsy, Brain

Description of Procedure

Brain biopsy can be obtained by open craniotomy or via computer-assisted stereotactic procedures (i.e., needle biopsies using a stereotactic frame, under local anesthesia). Several considerations are important in deciding between the two techniques and whether or not to pursue surgery. The most important issues relate to the lesion or process in the brain: Is it too deep or too small to be accessible? Is it located in an eloquent region of brain? Are the lesions solitary or multiple? Is the process too diffuse to define an adequate target? Other considerations focus on the patients, such as, Are they too old or too ill to undergo biopsy? Do they have a specific preference? Lesions that are generally considered most appropriate for stereotactic biopsy include those that are small and deep, located in eloquent cortex, diffuse within deep portions of the brain, and multifocal. Biopsy by open craniotomy requires general anesthesia and is most appropriate for lesions of non-eloquent cortical and adjacent subcortical tissues, and the meninges. A wedge of tissue that includes the cortex, meninges, and underlying white matter is usually optimal.

Indications

Diseases that require biopsy may be infectious, neoplastic, degenerative, vascular, metabolic, or developmental. The differential diagnosis of diseases where biopsy may be helpful is broad and includes enhancing lesions (infarct, abscess, glioma, metastasis, necrosis), tumors (primary versus metastasis), degenerative or dementing illnesses (prion diseases, Pick’s disease, Lewy body disease), skull and soft tissue disorders (histiocytosis X), inflammatory conditions (vasculitis, tumefactive multiple sclerosis, neurosarcoidosis), infectious processes (abscess, progressive multifocal leukoencephalopathy), and AIDS patients (lymphoma, toxoplasmosis).

Strengths

Diagnostic accuracy based on neuroimaging criteria alone is limited. Clinically significant alterations of the preoperative diagnosis occur in 12% to 25% of cases after tissue is obtained and analyzed. In many patients, this allows for the administration of more specific and appropriate therapy.

Limitations

The major limitation of brain biopsy involves the decision of which region of the mass lesion or abnormal area of brain to access. If there is not a well-defined target, it is possible to miss the target and obtain normal or nondiagnostic tissue. This can also occur with a mass lesion, if the needle removes tissue only from the edge or transition zone. Biopsy of the center of a mass may also be nondiagnostic, by obtaining only necrotic tissue. There is an 8% to 9% failure rate associated with brain biopsy, in which the obtained tissue does not result in a definitive histologic or microbiologic diagnosis. The problem of sampling error is improved by taking multiple samples of the lesion, as well as samples of the region of interface between the lesion and normal brain. Intraoperative pathologic assessment by frozen section is also useful to ensure diagnostic adequacy of samples.

Risks

• The risks involved in brain biopsy include those to the patient, in the form of surgical complications during or after the brain biopsy, as well as potential risks to the surgical team and pathologist. In most series of brain biopsy, surgical mortality is less than 1%, while surgical morbidity ranges between 1% and 6%. The most significant risks during the procedure are intracranial hemorrhage, brain swelling and edema, and new focal neurologic deficits. Other potential risks include cerebral infarction, infection, and scarring with formation of an epileptic focus.

• The surgical team and pathology staff must handle specimens with care, since they may be at risk for infection from agents such as HIV, hepatitis, and Creutzfeldt-Jakob disease.

Contraindications

Include patients at high risk of hemorrhage due to excessive anticoagulation, liver abnormalities, thrombocytopenia, and related conditions. Patients who are medically unstable or too ill may not be suitable for anesthesia and brain biopsy.

Preparation/Special Instructions for Patients

The pathologist should be aware of the differential diagnosis before surgery to ensure proper tissue handling and to improve diagnostic yield at the time of frozen section review. For a frozen section, biopsy tissue is snap frozen in liquid nitrogen and then prepped onto slides for microscopic interpretation. Based on this preliminary diagnosis (which takes 15 to 20 minutes), the pathologist advises the neurosurgeon about the need for further samples. The definitive diagnosis will be made after review of the permanent (i.e., paraffin embedded) tissue slides.

Miscellaneous

• Special stains may be helpful to improve diagnostic accuracy. Immunohistochemical analyses of specific protein antigens on the cell stace or in the nucleus are particularly useful for differentiating between categories of disease (e.g., lymphoma versus an inflammatory condition). Genetic studies may also be of benefit for diagnosis (e.g., immunoglobulin gene rearrangement studies of lymphoma) or prognosis (e.g., chromosome 1p and 19q deletion status of oligodendrogial neoplasms).

• A postoperative CT scan is necessary to screen for hemorrhage and to evaluate the accuracy of the biopsy in relation to the target lesion.

Author(s): Dan Brown, MD; Herbert B. Newton, MD
### Description of Procedure

- Muscle may be biopsied using either a needle or open surgical technique. Open muscle biopsy is generally preferred to needle biopsy in most cases because of the larger samples obtained. The muscles often biopsied are the biceps, quadriceps (usually vastus lateralis), and deltoid. It is usually best to biopsy a muscle with moderate weakness in a chronic situation, as a severely weak muscle may yield pathology of end-stage scarring and fibrosis that obscures the underlying disorder. It is best to avoid muscles that were the site of EMG investigation, injections, etc., because of traumatic pathologic changes. Sometimes the peroneus brevis muscle is biopsied at the same time as the superficial peroneal nerve when vasculitis is suspected to increase diagnostic yield.

- A skin incision is made after local anesthesia. The muscle fascia is then anesthetized and opened. Sections of muscle are excised, and samples are sent for frozen section (for histocchemistry and light microscopy), fixation in glutaraldehyde, embedding in plastic (for ultrastructural analysis), and embedding in paraffin (for examination for inflammation).

- Needle biopsy may be used for sampling of multiple sites and provides samples sufficient for biochemical and DNA studies. However, the samples obtained by needle biopsy are smaller and less satisfactory for electron microscopy.

### Strengths

Many muscle disorders such as dystrophies and inflammatory myopathies have distinct cytoarchitectural characteristics that readily allow diagnosis. Patterns and distribution of inflammatory cells may help distinguish polymyositis, dermatomyositis, vasculitis, fasciitis, and other inflammatory disorders. Special histochemical analysis may identify disorders such as lipid-storage myopathy, inclusion body myositis, or mitochondrial myopathies (ragged-red fibers). Immunohistology for dystrophin may confirm Duchenne dystrophy when DNA studies are uninformative. Histologic features of individual muscle fibers may suggest a neuropathic cause (fiber type grouping, atrophic and angular fibers, and target fibers) but muscle biopsy is rarely diagnostic for neurogenic etiologies.

### Limitations

Unfortunately, many types of muscle disease may share common pathologic features on biopsy, such as increased connective tissue, changes in fiber size and shape, and fiber necrosis. In recent years, expanding knowledge of the genetic defects that cause many myopathies has supplemented routine muscle histology to increase definitive diagnosis. Muscle biopsy cannot differentiate between various neuropathic causes for weakness. In addition, there is the risk of sampling error in multifocal disease such as polymyositis. Needle biopsies are even more prone to miss patchy (as in inflammatory myopathies) or endomyssial pathology.

### Risks

Risks include hemorrhage, hematoma, infection, and pain.

### Indications

A muscle biopsy is indicated for investigation of etiology when a patient presents with clinical and laboratory evidence of myopathy such as weakness, myopathic EMG findings, elevated serum creatine kinase, and/or chronic or intermittent muscle pain. A muscle biopsy may also be useful for diagnosis of systemic conditions that may have relatively silent muscle manifestations such as vasculitis or sarcoidosis.

### Contraindications

Contraindications include uncorrected coagulopathy and thrombocytopenia.

### Preparation/Special Instructions for Patients

Patients should limit heavy use of the biopsied limb for several days after biopsy, and monitor for signs of infection such as excessive drainage, swelling, or erythema. No submersion in water for bathing or showering until the sutures have been removed. Sutures are generally removed in 7 to 10 days.

### References


Author(s) D. Joanne Lynn, MD
Biopsy, Nerve

Description of Procedure

Nerve biopsy for diagnosis of the cause of peripheral neuropathy is most commonly performed on the sural nerve, but also on the superficial radial nerve. For sural nerve biopsy, an incision is made, after local anesthesia, approximately 25 cm above the plantar surface of the heel, 1 cm lateral to the midline, and the nerve is dissected out. One segment is frozen for identification of immune deposits; immunocytochemistry studies are useful to stain for immunoglobulin and complement deposition. A second segment is placed in buffered formalin to be processed for paraffin sections, most useful for demonstration of vasculitis, inflammation, and granulomas. Another section is fixed in glutaraldehyde for preparation for light microscopy. Nerve fascicles are separated for single nerve fiber teasing, which allows detailed determination of nerve pathology, e.g., axonal vs. demyelinating.

Indications

Peripheral nerve biopsy is indicated to evaluate for a specific cause of neuropathy, which may be diagnosed with certainty only by pathologic examination. Conditions for which peripheral nerve biopsy is most helpful include:

- Vasculitis
- Sarcoidosis
- Amyloidosis
- Tumor infiltration
- Leprosy
- Fabry disease
- Storage diseases (Niemann-Pick disease, metachromatic leukodystrophy, sialidosis, Farber disease)
- Hereditary neuropathy with liability to pressure palsies
- Neuropathy associated with antibody to MAG (myelin-associated glycoprotein)

Strengths

The nerve biopsy is especially useful to identify changes in blood vessels and connecting tissue elements of the nerve. This makes it most useful to identify inflammatory changes in vasculitis, granulomatous disease such as sarcoidosis, neoplastic infiltration, and infection such as leprosy. If there is clinical evidence of peripheral nerve involvement in suspected multisystem vasculitis, peripheral nerve may be the least invasive site for biopsy. The yield of biopsy is usually greater if a nerve is biopsied that is abnormal on electrophysiologic studies.

Limitations

Peripheral nerves respond to the myriad diseases that affect them with a narrow spectrum of pathologic responses. This limits the diagnostic utility of nerve biopsy in most patients presenting with common types of neuropathy. It should be emphasized that the diagnosis of peripheral neuropathy is generally based on neurologic examination and electrophysiologic study findings. In addition, sampling error may be an issue with nerve biopsy; sampling of a single segment of a single nerve may miss multifocal pathology such as vasculitic lesions that may occur in the nerve proximal or distal to the site of biopsy. In addition, nerve biopsy may fail to demonstrate significant pathology in small-fiber neuropathies. In that situation, skin biopsy to examine intraepidermal small nerve fibers may be a more powerful technique.

Risks

Nerve biopsy is a surgical procedure and is associated with the typical risks of hemorrhage, hematoma, wound infection, and wound dehiscence. It can also be painful both during the procedure and in the postoperative period.

Contraindications

Uncorrected coagulopathy or thrombocytopenia. The risk/benefit ratio should be evaluated appropriately in patients with diabetes mellitus, peripheral vascular disease, and significant edema, as complications such as infection are more common in these groups.

Preparation/Special Instructions for Patients

There is no special preoperative preparation required except for temporary discontinuation of anticoagulation if present (after judicious consideration of risk/benefit ratio for doing so). However, patients should be apprised of what to expect after the biopsy. Patients often experience spontaneous paresthesias starting 24 to 48 hours after the biopsy, which may be precipitated by stretching of the proximal nerve stump by certain movements or positions of the involved limb. Pain usually wanes by 2 to 3 weeks, but lesser discomfort may persist for much longer. Electric dysesthesias or hypersensitivity to touch may persist for more than a year in a minority of patients. For sural nerve biopsies, there is a sensory deficit along the lateral aspect of the foot, which generally recedes or even resolves by 18 months.

Miscellaneous

N/A

REFERENCES


Author(s) D. Joanne Lynn, MD
Computed Tomography of the Brain and Spine

Description

Computed tomography (CT), or computed axial tomography, is an imaging technique that uses x-rays to obtain cross-sectional images. The appearance of x-ray imaged structures depends on their density. Water is arbitrarily assigned the value of zero, with denser structures like bone having positive values and less dense tissues such as fat and air having negative values. Most CT scanners today are third generation (spiral) or forth generation (multislice, volumetric acquisition). Multislice detectors allow faster imaging, acquisition of thinner slices, faster reconstruction, and improved image quality.

TECHNIQUES AND APPLICATIONS

- Conventional CT
  - Axial images only, except for the head—direct coronal images can be obtained if the patient is able to lay prone with head extended.
- Reconstructions—computer generated: sagittal, coronal, 3D
- Cisternography and myelography—after the intrathecal administration of contrast
- CT angiography (CTA)—requires contrast with 3D reconstructions
  - Circle of Willis
  - Carotid arteries
- Functional CT
  - CT perfusion—requires contrast, cerebral blood flow imaging
  - Xenon CT—cerebral blood flow imaging
- Interventional
  - CT fluoroscopy—real-time imaging
- Intraoperative CT, portable CT

Indications

INDICATIONS FOR HEAD CT

Examination of choice for evaluation of acute intracranial hemorrhage, calcifications, and cortical bone:
- Acute intracranial hemorrhage—subdural, epidural, subarachnoid, intraparenchymal, intraventricular
- Mental status—cognitive change—rule out R/O hemorrhage
- Headache—for "worst headache of my life"; R/O subarachnoid hemorrhage. For chronic headaches MR is preferable, although imaging is generally not indicated.
- Stroke—R/O hemorrhage; early CT findings of acute ischemic stroke:
  - Hyperdense artery sign: thrombus seen in 35% to 50% with clinical signs of acute middle cerebral artery (MCA) stroke; poor prognostic sign
  - Obliteration of lentiform nucleus
- Insular ribbon sign

- Sulcal effacement
- Parenchymal hypodensity
- Trauma—R/O hemorrhage, edema, herniation, pneumocephalus, fracture.
  - Any patient with loss of consciousness, neurologic deficit, anisocoria, fixed or dilated pupils, bleeding diathesis, or anticoagulation, and all penetrating head injuries.
- Hydrocephalus
- New-onset seizure
- Postoperative craniotomy—R/O hemorrhage, herniation
- In patients where MR is contraindicated (e.g., pacemaker): for:
  - Tumor
  - Infection—abscess, empyema, AIDS—Seizures
  - Multiple sclerosis
  - Neurodegenerative disorders
  - Granulomatous disease

Phantoms

INDICATIONS FOR SPINE CT

- Trauma—R/O fracture
- Postoperative fusion—metal will cause some artifacts limiting the exam
- Spondylosis
- Arthritis
- Spinal stenosis (MR is exam of choice)
- Disc disease (MR is exam of choice)
- Cord compression—only postmyelography with injection of intrathecal contrast
- Characterization of an isolated indeterminate bone lesion noted on MR or nuclear medicine scan (e.g., hemangioma).
- In patients where MR is contraindicated (e.g., pacemaker): for:
  - Tumor—ideally after intrathecal contrast
  - Infection—epidural abscess, discitis, osteomyelitis, although CT even with contrast is relatively insensitive.

INDICATIONS FOR CONTRAST WITH HEAD CT

- Tumor—(MR is exam of choice)
- Infection—abscess, empyema, AIDS, (MR is exam of choice)
- Seizure—R/O tumor (MR is exam of choice)
- Arteriovenous malformations
- CT angiography/venography
- CT perfusion

INDICATIONS FOR INTRAVENOUS CONTRAST WITH SPINE CT

- Tumor—if MR contraindicated
- Infection—if MR contraindicated
- Disc disease—to enhance the epidural space/veins and better define the margins of the discs, although MR still best

INDICATIONS FOR INTRatheCAL CONTRAST WITH SPINE CT (POSTMYELOGRAM CT)

- Cord compression—when MR is contraindicated
- Disc disease, spinal stenosis, radiculopathy if MR is contraindicated or if MR findings do not correlate with clinical findings

Strengths

- Readily available 24h even at small hospitals
- Noninvasive
- Fast—ideal for uncooperative and critically ill patients
- Extremely sensitive for acute intracranial hemorrhage
- Ideal for evaluation of calcifications and cortical bone

Limitations

- Beam-hardening artifacts limit posterior fossa evaluation
- Insensitive to acute ischemia
- Limited spinal cord evaluation
- Axial plane only
- Limited soft tissue contrast
- Metal streak artifacts

Contraindications

- If giving contrast: contrast allergy, renal insufficiency, multiple myeloma are relative contraindications.
- Pregnancy—relative contraindication especially first trimester; contrast contraindicated.

Preparation/Special Instructions for Patients

Patients who are scheduled for a CT with contrast are instructed to be NPO 2 hours prior to the exam. At the time of the exam they are asked to remove earrings, hair clips, hearing aids, glasses, and removable dental work.

Miscellaneous

Approximately 1% of patients are claustrophobic and require some sedation. Diazepam 5 to 10 mg PO is adequate for most.

REFERENCES

- Tanenbaum LN, ed. CT in neuroimaging revisited. Neuroimag Clin North Am 8(3), 1998; Author(s): Eric C. Bourekas, MD; H. Wayne Stone, MD

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Magnetic Resonance Imaging of the Brain and Spine

Description Of Procedure

- Magnetic resonance imaging (MRI) uses a powerful magnetic field and radiofrequency waves to produce images. No ionizing radiation is involved. Most MRI units in clinical use are 1.5 tesla.
- Depending on imaging parameters, different pulse sequences can be obtained producing images yielding different information. Traditional imaging involves T1-weighted (T1W) and T2-weighted (T2W) spin echo imaging. Gradient echo imaging allows for faster imaging. T1W images are obtained after intravenous contrast, which does not affect T2W images very much. Fat suppression images help identify lesions obscured by fat. Proton density and FLAIR images are useful in evaluation of white matter disease. Functional imaging such as diffusion and perfusion imaging is invaluable in evaluation of stroke, MR angiography (MRA) and venography (MRV) images yielding different information. Pulsed sequences can be obtained producing waves to produce images. No ionizing radiation is involved. Most MRI units in clinical use are 1.5 tesla.
- Any cord lesion
- No beam hardening artifacts related to bone
- No ionizing radiation
- Direct multiplanar imaging

INDICATIONS FOR BRAIN MRI

- Stroke—diffusion imaging very sensitive to acute ischemia
- Tumor
- Infection—encephalitis, abscess, empyema
- Demyelinating disorders—MS
- Seizures
- Neurodegenerative disorders—Alzheimer’s, parkinsonism
- Granulomatous disease—sarcoid
- Negative CT with continuing neurologic deficits

INDICATIONS FOR BRAIN MRI WITH CONTRAST

- Tumor
- Infection
- Demyelinating disorders—helpful to monitor disease activity
- Seizures—new onset to R/O tumor

INDICATIONS FOR SPINE MRI

- Tumor—primary spinal cord, metastatic to bone, R/O cord compression, leptomeningeal carcinomatosis, R/O drop metastases
- Infection—osteomyelitis, discitis, epidural abscess
- Trauma—cord or ligamentous injury
- Degenerative disc disease/R/O disc herniation, spinal or foraminal stenosis
- Cord abnormalities—tumor, demyelination, extremity weakness, incontinence, paralysis

INDICATIONS FOR CONTRAST FOR SPINE MRI

- Tumor
- NOT necessary for vertebral metastases

---Primary spinal cord or nerve root tumors, leptomeningeal carcinomatosis
- Infection—osteomyelitis, discitis, epidural abscess
- Demyelination
- Granulomatous disease
- Any cord lesion
- Prior laminar spine surgery—R/O epidural scar

Strengths

- Superior soft tissue contrast/resolution
- Direct multiplanar imaging
- No ionizing contrast
- No beam hardening artifacts related to bone

Limitations

- Length of exam—at least 20 minutes
- Sensitivity to motion
- Cost
- Difficulty in monitoring critically ill patients—ECGs don’t work during scanning; only pulse oximeter monitoring available; MR compatible ventilator required.
- Difficulty in obtaining STAT off hours—technologist availability limited
- Metal artifacts
- Cortical bone, although MR is excellent for evaluation of bone marrow

Contraindications

Many contraindications are relative; it is best to consult MR facility for local policy. Electrically, magnetically, or mechanically activated implants are generally contraindicated.

ABSOLUTE CONTRAINDICATIONS

- Pacemakers
- Defibrillators
- Neurostimulators
- Bone growth stimulators
- Cochlear implants
- Ocular metallic foreign bodies
- Swan-Ganz catheters
- Allergy to IV gadolinium (MR) contrast for contrast study

RELATIVE CONTRAINDICATIONS

- Aneurysm clips—most used today are MR compatible; however, safety concerns exist and many facilities consider them absolute contraindications
- Heart valves—certain valves are not contraindicated; old Starr Edwards (pre-6000 series) contraindicated
- IVC filters—current filters mostly MR compatible, although recommendations are to wait 2 to 6 weeks after insertion prior to imaging
- Inner ear implants—cochlear implants contraindicated, some stapes implants
- Drug infusion pumps—generally not contraindicated, although MR may stop infusion and necessitate pump reprogramming
- Bullets, pellets, shrapnel—must use judgment; duration, proximity to vessel? Most bullets are not contraindicated.

NOT CONTRAINDICATED

Hemostatic clips, wire stores, plates, p ins, screws, nails, dental devices (e.g., braces, bridges despite artifacts) orthopedic implants (joint replacements, spinal rods), ocular implants, ventricular shunts.

Preparations/Special Instructions for Patients

Patients must remove all jewelry and metal items from their body and clothing, including glasses, dentures and all other removable dental work, wigs, and hairpins. An extensive history and screening form designed to ensure that there are no contraindications and safety of the exam is filled out.

Miscellaneous

Claustrophobia is a problem in 5% to 10% of patients. Often this is transient and eliminated by reassurance from the technologist. Most are able to get through the exam with mild sedation usually 5 mg PO of Valium. Approximately 1% will require heavy sedation in order to complete the exam in a closed MR. Open MRIs accommodate such patients at the cost of reduced image quality.

MR has not been proven safe in pregnancy but is not believed hazardous. It is indicated in pregnancy if it will provide information critical to the patient’s well-being or because the patient would otherwise require exposure to ionizing radiation.

REFERENCES


Author(s): Eric C. Bourekas, MD; H. Wayne Slone, MD
Description of Procedure

Myelography is an invasive imaging test that allows for the radiographic depiction of the spinal cord and associated nerve roots within the thecal sac via the intrathecal injection of water-soluble nonionic iodinated contrast agents. Changes in the contour of the thecal sac and its contents allows for the indirect diagnosis of extradural compression of spinal nerve roots and spinal cord as well as the inference of intradural neoplasms, arachnoiditis, and arachnoid cysts. Plain myelography does not accurately depict nerve root structures after exit ing the thecal sac; however, the adjunct use of CT immediately following myelography (CT myelography) allows for a more accurate delineation of the anatomic relationship between discogenic and osseous structures in relation to the nerve roots and its contents. As a result, CT is almost always performed immediately following myelography.

Indications

MRI has replaced myelography as a screening tool for spinal disease. There are, however, circumstanc es where myelography can provide useful information. In general myelography provides higher spatial resolution than MRI and depicts osseous structures more consistently than MRI. This information is often useful for surgical planning especially in the cervical spine. If MRI is contraindicated or not possible, myelography can provide diagnostic information screening for spinal cord or nerve root compression. Keeping this in mind, myelography and CT myelography can be considered under the following circumstanc es:

- Suspected nerve root or spinal cord compression based on clinical symptoms such as radiculopathy or tower extremity weakness or incontinence
- Suspected spinal AVM
- Suspected tumor affecting the spinal canal
- Suspected arachnoiditis
- Suspected meningial cyst (arachnoid cyst, meningocele, perineural cyst)

Strengths

Myelography with CT myelography provide high-resolution images depicting the relationship of osseous struc tures to the thecal sac and its contents in a more precise manner than MRI. Even though the sensitivity of MRI is at least as good, CT myelography is felt to more accurately depict symptomatic pathology in the setting of degenerative spine disease. Certain pathologies are more readily depicted on myelography rather than plain CT or MRI. These include arachnoid cysts, meningoceles, and arachnoiditis. Plain film myelography is less encumbered by surgically placed metallic hardware than other MRI. Fathere more, myelography allows for the collection of spinal fluid for analysis.

Limitations

Myelography can depict spinal cord morphology but cannot identify intrinsic lesions of the spinal cord such as demyelination or transverse myelitis. Infectious processes such as discitis or epidural abscess and spinal canal neoplasms are more readily identified on MRI than on myelography or CT myelography.

Risks

Complications associated with myelography include headache, nausea, vomiting, cerebrospinal fluid leak, seizure, infection, vaso vagal reaction, spinal cord injury, and nerve root damage. Improper injection of contrast medium into the epidural or subdural space may confound the examination and transiently exacerbate symptoms.

Contraindications

Relative contraindication to myelography include:
- Raised intracranial pressure (papilledema)
- Bleeding abnormalities (elevated PT, PTT, decreased platelet count or patients on anticoagulation)
- Allergy to iodinated contrast agents
- Medications that lower seizure threshold such as phenothiazines, tricyclic antidepressants, CNS stimulants, MAO inhibitors
- Glucophage (metformin) should be withheld temporarily (48 hours) prior to myelography due to potential risk for renal failure
- Pregnancy
- Bacteremia or sepsis

Preparation/Special Instructions for Patients

Patients are asked not to eat or drink anything with the exception of oral medications beginning 4 hours prior to the exam. In patients with a prior history of contrast reaction, premedication with steroid and Benadryl reduces their risk for contrast reaction. Patients with poor renal function who are not being dialyzed are hydrated prior to the procedure. Glucophage (metformin) should be withheld temporarily (48 hours) prior to myelography due to potential risk for renal failure and reinstated only after renal function has been reevaluated and found to be normal. Additionally, phenothiazines, tricyclic antidepressants, or Tigan is held prior to the examination. Sedation is not typically required; however, consideration should be given to the administration of amoxylcins or conscious sedation during the examination under appropriate circumstanc es.

Miscellaneous

With regard to nerve root compression due to degenerative disease of the spine, clinical decisions should not be based exclusively on the basis of imaging findings alone. Objective clinical findings should be supported by radiologic findings.

To reduce the risk for cerebrospinal fluid leakage and headache following the procedure, patients are placed on strict bed rest for 4 hours, with the head of bed elevated 30 degrees, and are limited to light activity for 24 to 48 hours following the procedure. Oral fluids are encouraged following the procedure. Additionally, phenothiazines, tricyclic antidepressants, or Tigan is held for 48 hours after the study.

Author(s): Gregory Christoforidis, MD
Nerve Conduction Studies/Electromyography

Description of Procedure

- Series of diagnostic tools that evaluate the integrity and function of nerve and muscle
- Nerve conduction velocity (NCV) studies rely on the ability of nerve to conduct electrical potentials.
- Usually use sftice stimulation, less often near-needle or, rarely, magnetic stimulation.
- Usually recorded with sftice electrodes, less often with near-needle electrodes.
- Small electric shocks are applied over a nerve and the response is recorded.
- Electromyography (EMG) studies rely on the electrical activity of the muscle membrane.
- Usually performed using a small needle placed into the muscle(s) of interest.
- Electrodagnostic studies are an extension of the neurologic exam to localize disorders of:
  - Peripheral nerve
  - Sensory and/or motor nerves
  - Small or large diameter fibers
  - Plexus
  - Brachial
  - Lumbosacral
  - Nerve root
  - Motor neuron
  - Sensory ganglion
  - Muscle
  - Neuromuscular junction

Indications

- Useful in answering questions raised by the clinical exam.
- What is the pattern of injury?
  - Is it distal or proximal?
  - Is it diffuse?
  - Is it symmetric or asymmetric?
  - Is it multifocal?
  - Is it focal in a named nerve distribution?
  - Is it focal in a nerve root (or radicular) pattern?
- What is the underlying pathophysiology?
  - Is it primarily demyelinating?
  - Is it primarily axonal?
  - Is this a nerve and/or a muscle process?
  - If just muscle, what are the characteristics of the EMG?
  - Is it a primary neuromuscular junction disorder?
- To confirm a clinical diagnosis
- To aid in differential diagnosis and direct further evaluation if necessary
- To identify subclinical disease
- To characterize the disease
- To quantitate the disease
- Symptoms that might have an etiology elucidated by NCV/EMG:
  - Numbness
  - Pain

Strengths

- Noninvasive
- Can narrow the differential diagnosis in order to more efficiently direct other forms of testing

Limitations

- Nerve conduction studies are useful in evaluating large fiber neuropathies. Other modalities may be necessary to define small fiber neuropathies:
  - Quantitative sensory testing (QST)
  - Autonomic reflex testing
  - Skin biopsy
  - Evaluation of proximal nerves is technically difficult and less reliable.
  - Timing of evaluation is important.
    - In Guillain-Barre syndrome (GBS), findings may be minimal for 7 to 10 days.
    - In axonal injuries, nerve conduction studies may be normal for 10 to 14 days.
    - In long-standing and/or severe neuropathies, nerve responses may be unevakable.
  - Electrophy cannot be determined by electrodagnostic testing.

Risks

- Equipment must be properly grounded to avoid electrical injury to the patient.
- Patients must be properly grounded.
- Extra care should be taken with patients with indwelling cardiac catheters.
- Care should be taken when performing needle EMG on patients with bleeding diatheses or coagulopathies. Deep muscles where local pressure cannot be applied should be avoided.

Contraindications

- EMG in patients with platelets counts below 20,000 should be avoided or limited as much as possible.
- Needle EMG may interfere with histologic findings in a muscle biopsy. Avoid placing a needle in a muscle that will be biopsied.
- Needle EMG may artificially elevate the serum CK. Obtain blood samples prior to EMG.

Preparation/Special Instructions for Patients

- Inform the physician of any medications that thin blood or increase bleeding times.
- Wear loose fitting clothing.
- Do not apply lotions or creams to skin on day of test.
- If the is referred for evaluation of a neuromuscular junction disorder (e.g., myasthenia gravis), hold pyridostigmine (Mestinon) for 12 hours before the test.

Miscellaneous

If patient has excessive anxiety regarding this test, administration of a benzodiazepine (diazepam 10 mg) before the test is acceptable.

REFERENCES


Author(s): Miriam L. Freimer, MD
Ultrasonography, Extracranial Vascular

Description of Procedure

• Doppler ultrasonography is a noninvasive method of examining the extracranial arteries supplying the brain that relies on the Doppler effect to generate audio signals and frequency spectrum. Three measurements used to diagnose internal carotid artery stenosis are peak systolic velocity, end diastolic velocity, and the ratio of peak systolic velocity in the internal carotid artery to that in the ipsilateral middle to distal common carotid artery. The peak systolic velocity is the most accurate and reproducible Doppler parameter measured and is therefore the most commonly reported. Stenosis results are reported as 0-15%, 16-49%, 50-79%, 80-99%, or occlusion. The frequency spectrum and waveform appearance of the internal, external, and common carotid arteries are different and distinguishable.

• Continuous-wave Doppler systems are instruments with two transducers that continuously emit and receive ultrasound signals. Pulse wave Dopplers are used in duplex systems in combination with B-mode ultrasonography. A single transducer alternatively emits and then receives ultrasound signals. The method allows distance measurements to be made from the transducer probe to the ultrasound-reflecting source.

• Conventional duplex scanning and color Doppler flow imaging are ultrasonographic techniques that use high-resolution B-mode scanning to generate a gray scale picture of soft tissue structures and vessels. Measurements of percent stenosis or cross-sectional area can be made in sagittal or transverse images, respectively. Color Doppler flow imaging adds color-coded blood flow patterns. Using a defined color scale, the direction and average mean velocity of blood cells moving in a sample volume at a given point in time is assigned a color.

• Gel is used to improve ultrasound conductance, and the transducer probe is moved on the neck from above the clavicle to the angle of the jaw. Several longitudinal planes and the transverse plane are routinely scanned allowing evaluation of the proximal, middle, and distal common carotid arteries, carotid bulb, and proximal internal and external carotid arteries.

Indications

Doppler ultrasonography and B-mode imaging is a noninvasive method to evaluate the extracranial carotid and vertebral arteries in patients with carotid or subclavian bruits, transient ischemic attacks, or stroke as a preangiography screening test to detect carotid stenosis in patients who are carotid endarterectomy candidates.

Strengths

As a noninvasive screen for carotid artery stenosis, ultrasonography is less costly than CT or magnetic resonance angiography. The procedure is well tolerated and can be completed in 20–40 minutes. Sonography does not involve the use of contrast agents and has no risks or contraindications. Carotid ultrasound results correlate well with angiographic findings. The sensitivity and specificity of Doppler threshold measurements for detecting stenosis of greater than 50% by angiography is in the 85% to 95% range.

Limitations

The quality of ultrasonographic results is dependent on the experience of the examiner and interpreter as well as the equipment used. Some patients image poorly, and those with large, thick necks may be difficult to study.

Depending on the level of the carotid bifurcation relative to the mandible, 3 to 4 cm of the proximal internal or external carotid artery can be studied. With high bifurcations these arteries may not be visualized at all. Examination of the vertebral artery is limited by anatomic accessibility to the origin, proximal pretransverse segment, and intertransverse segments between the third and sixth cervical vertebrae and the atlas loop. Frequent arterial caliber variations and asymmetries of the vertebral arteries make correct assessment of stenosis or occlusion difficult.

Risks

Although there are two potential physical effects of ultrasonography related to safety, cavitation, which involves ultrasound-induced production and motion of bubbles in a fluid, and thermal effects from heating of the insinuated medium due to conversion of ultrasound energy, no clinical adverse effects from diagnostic ultrasonography have been reported.

Contraindications

None.

Preparation/Special Instructions for Patients

None.

Miscellaneous

Although some practitioners rely solely on carotid duplex results to make decisions about carotid endarterectomy, concern about the extension of the stenosis into the inaccessible distal internal carotid artery, the possible presence of significant stenosis in the cavernous carotid artery, the coincidental existence of unsuspected intracranial aneurysms, and the presence of intraluminal thrombus beyond the stenosis are deterrents to making decisions to proceed with surgery based on ultrasound results alone.

Several large multinational studies suggest that Doppler and duplex ultrasonography do not have the high specificities and sensitivities reported by selected individual laboratories. Furthermore the risk of stroke and benefit from carotid endarterectomy correlate with the degree of stenosis determined angiographically. Such a correlation has not been demonstrated with percent stenosis measured by ultrasonography. For these reasons most practitioners use ultrasonography as a screening tool to exclude patients with no carotid artery stenosis from further testing and rely on results from conventional angiography before recommending carotid endarterectomy.

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SECTION III

Neurologic Diseases and Disorders
Acquired Immunodeficiency Syndrome: Neurologic Complications

**DESCRIPTION**

Neurologic complications are common in patients with HIV infection and AIDS, affecting all levels of the central and peripheral nervous system. The etiology of these disorders is variable and may result from direct effects of HIV infection, damage from inflammatory processes and cytokine production, opportunistic infections, metabolic abnormalities, vascular damage, and toxic effects of HIV therapy.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Exact incidence/prevalence figures are not available. Before highly active antiretroviral therapy (HAART), it was estimated that 10% of AIDS patients presented with a neurologic complaint, while 30% to 50% developed neurologic complications during their disease. The incidence of HIV dementia was estimated to be 7.5% to 20% in retrospective studies. More recently, the incidence of neurologic complications appears to be decreasing, likely due to widespread use of HAART.

**Race**

All races affected; most common in Caucasians and blacks.

**Age**

Any age can be affected; most common 20 to 40 years of age.

**Sex**

Both sexes can be affected; most often diagnosed in males.

**ETIOLOGY**

- The etiology is variable and depends on the specific process involving the nervous system. In severely immuno compromised patients, opportunistic infections and neoplasms can involve the central or peripheral nervous system, including toxoplasmosis, cryptococcal and tuberculous meningitis, neurosyphilis, progressive multifocal leukoencephalopathy (PML, papovavirus), cytomegalovirus(CMV), herpes simplex virus, and primary CNS lymphoma (PCNSL).
- HIV is neurotropic and can be cultured early from the nervous system. However, productive infection within neural tissues does not appear to be the major cause of HIV dementia, vacuolar myelopathy, myopathy, or peripheral neuropathy. Although HIV does shed toxic substances such as gp 120 viral initiation of inflammation and secretion of toxic cytokines (e.g., tumor necrosis factor-a, interleukins 10 and 6) may be more critical in mediating neural tissue injury.
- Neurologic complications can also develop as a result of treatment with antiretroviral therapy (e.g., zidovudine myopathy).
- Genetics
  - Genetic factors have not been identified.

**RISK FACTORS**

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 100/4), and lack of antiretroviral therapy.

**PREGNANCY**

Pregnancy has not been shown to affect the neurologic complications of HIV.

**ASSOCIATED CONDITIONS**

N/A

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis is extensive and includes any non-HIV-related disease with a similar presentation affecting the nervous system. See Dementia, Focal Brain Lesions, and neuromuscular topics for a more detailed differential diagnosis.

**SIGNS AND SYMPTOMS**

- HIV dementia (i.e., AIDS dementia complex) usually manifests with progressive impairment of short-term memory, cognition, concentration, and motivation. Associated motor abnormalities include unsteady gait, leg weakness, tremor, and incoordination. Late-stage patients have global dementia with severe psychomotor slowing, confusion, reduced verbal output, wakening, and spasticity.
- Space-occupying lesions include cerebral toxoplasmosis, PCNSL, PML, tuberculous or fungal abscess, focal viral encephalitis, and metastatic tumors (e.g., lymphoma or Kaposi’s sarcoma). Symptoms consist of progressive headache, confusion, lethargy, personality changes, memory loss, seizures, nausea/vomiting, and focal deficits (e.g., hemiparesis, dysphasia).
- Encephalitis typically develops from toxoplasmosis, CMV, and herpes simplex virus, while meningitis is most frequently caused by cryptococcus and other fungi, tuberculosis, and leptomeningeal lymphoma. HIV can cause an aseptic meningitis syndrome. Encephalitic patients present with acute confusion, lethargy, seizures, fever, headache, and meningismus. Patients with menigitis develop subacute headache, fever, meningismus, lethargy, and na usea.
- Vacular myelopathy usually develops as part of HIV dementia, but can occur in isolation. It presents as a progressive myelopathy with spastic paraparesis, hyperactive reflexes, Babinski’s signs, gait ataxia, tremor, and urinary incontinence. In some patients, a sensory level may be appreciated.
- Neuromuscular complications present as polyradiculopathy, neuropathy, or myopathy. Polyradiculopathy (usually caused by CMV) is characterized by a painful, subacute, progressive loss of strength and reflexes that ascends from lower to upper extremities. Most of the neuropathies cause a progressive mixture of motor and sensory loss in the extremities, accompanied by reduced or absent distal reflexes. The acute inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre syndrome. Autonomic neuropathy causes orthostatic dizziness, fainting, impotence, diarrhea, and urinary dysfunction. Myopathies all cause slowly progressive, painless, proximal extremity weakness.

**LABORATORY PROCEDURES**

In general, the most important tests consist of blood counts (including CD4 counts, to determine stage of HIV infection), infectious cultures of appropriate tissues, and serum antibody titers of various infectious agents. Other specific tests may be helpful in certain cases, such as VDRL or vitamin B12 levels.

**IMAGING STUDIES**

Magnetic resonance imaging (MRI), with and without gadolinium, is the most sensitive technique to evaluate HIV patients with cranial or spinal neurologic complaints. HIV dementia may demonstrate atrophy or scattered, nonenhancing, white matter lesions. Similarly, PML presents with patchy, nonenhancing, periventricular white matter lesions that slowly enlarge and coalesce. Cerebral toxoplasmosis usually demonstrates multiple ring-enhancing lesions with surrounding edema. PCNSL presents as a solitary or multifocal lesion within the deep periventricular white matter that typically enhances with contrast. Mild edema and/or mass effect may be noted. Tuberculous or fungal abscesses cause ring-enhancing lesions with surrounding edema. Focal viral encephalitis (e.g., CMV, varicella-zoster virus, herpes simplex virus) may produce mass lesions with minimal enhancement. Other potential enhancing masses include primary CNS lymphoma, metastatic systemic lymphoma and Kaposi’s sarcoma.
Acquired Immunodeficiency Syndrome: Neurologic Complications

SPECIAL TESTS
Lumbar puncture is often helpful to differentiate the etiology of brain or spinal processes, and should at least include routine CSF studies, bacterial/fungal antigens, cytoplogy, CSF/bacterial/viral/ fungal cultures, smear and culture for acid-fast bacilli, and VDRL. Other tests that may be helpful in selected patients include electroencephalography (i.e., seizure activity), electromyography and nerve conduction studies (i.e., neuropathy and myopathy), and neuropsychological testing (i.e., HIV dementia).

GENERAL MEASURES
Antiretroviral therapy should be maximized, if possible (i.e., HAART). HAART consists of a combination of two nucleoside reverse transcriptase inhibitors (e.g., zidovudine, didanosine, abacavir) and at least one protease inhibitor (e.g., saquinavir, indinavir), and/or one nonnucleoside reverse transcriptase inhibitor (e.g., nevirapine, delavirdine). Nutritional and metabolic deficiencies should be corrected, especially those that might impact on neurologic function. All systemic infections should be diagnosed and treated. Medications should be reviewed for potential central or peripheral neurotoxicity.

SURGICAL MEASURES
Biopsy may be required to differentiate focal intracranial lesions. Less often, biopsy may be helpful to diagnose the cause of neuropathy or myopathy.

SYMPTOMATIC TREATMENT
Patients with HIV dementia may stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART). Cerebral toxoplasmosis usually responds to combination therapy with pyrimethamine (50-75 mg/d), sulfadiazine (100 mg/d), and leucovorin (10 mg/d). Patients with PCNSL should receive whole brain irradiation (4,000-5,000 cGy), although chemotherapy can be beneficial in selected patients with good performance status. Infectious neurologic complications require therapy specific to the agent involved. The acte and chronic forms of demyelinating polyneuropathy may respond to plasmapheresis or IVIG. Inflammatory myopathy secondary to HIV may respond to corticosteroids. Painful neuropathic symptoms often improve with tricyclic antidepressants or anticonvulsants. There are no proven beneficial therapies for PML.

ADJUNCTIVE TREATMENTS
N/A

ADMISSION/DISCHARGE CRITERIA
Patients are generally admitted for acute neurologic changes such as altered level of consciousness, confusion, focal or generalized weakness, seizure activity, headache, and focal neurologic deficits. Patients with persistent neurologic deficits should be considered for rehabilitation.

DRUGS OR CHOICE
All patients should be evaluated for HAART, since this may prevent or abrogate the direct effects of HIV on the nervous system. In addition, HAART may prevent or reduce the risk of opportunistic infectious and neoplastic complications. Other drug decisions have to be individualized to the specific neurologic complication of each patient.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Follow-up of neurologic status is required. This is particularly true for some of the infectious complications that need long-term therapy (e.g., toxoplasmosis, CMV).

EXPECTED COURSE AND PROGNOSIS
The course and prognosis for many of the neurologic complications mentioned above is quite poor, since most occur in patients with low CD4 counts and advanced disease. The 6-month cumulative mirta lity rate for stage 2 to 4 HIV dementia is 67%. Similar 6-month cumulative mortality rates are noted for PML (85%), PCNSL (70%), and cerebral toxoplasmosis (51%). Some infectious complications caused by specific agents may respond to appropriate therapy, such as CMV encephalitis and neurosyphilis.

PATIENT EDUCATION

References

Author(s): Herbert B. Newton, MD

Miscellaneous

SYNONYMS
N/A

ICD-9-CM:
- 331.9 Cerebral degeneration, unspecified (HIV dementia); 322.9 Meningitis, cause unspecified; 320.0 Coccal meningitis; 323.9 Encephalitis, cause unspecified; 336.9 Myelopathy, unspecified; 046.3 Progressive multifocal leukoencephalopathy; 191.9 Malignant neoplasm of brain, unspecified (PCNSL); 357.9 Polyneuropathy, unspecified; 359.9 Myopathy, unspecified

SEE ALSO: ACQUIRED IMMUNODEFICIENCY SYNDROME: DEMENTIA, HIV; ACQUIRED IMMUNODEFICIENCY SYNDROME: NEUROMUSCULAR COMPLICATIONS; ACQUIRED IMMUNODEFICIENCY SYNDROME: FO CAL BRAIN LESIONS

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Acquired Immunodeficiency Syndrome: Dementia, HIV

**Basics**

**DESCRIPTION**

HIV dementia (i.e., AIDS dementia complex, HIV encephalopathy, HIV-1-associated cognitive/motor complex) is a syndrome of progressive deterioration of memory, cognition, behavior, and motor function in HIV-infected individuals during the late stages of the disease, when immunodeficiency is severe.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Exact incidence and prevalence figures are not available. HIV dementia is the most common neurologic complication of HIV infection and is estimated to have an overall incidence of 7.5% to 20% in retrospective studies. The incidence varies with CD4 counts: 7.3 cases/100 person-years with CD4 counts less than 100, 3.0 cases/100 person-years with CD4 counts between 101 to 200, and 1.5 cases/100 person-years with CD4 counts between 201 and 500, and 0.5 cases/100 person-years with CD4 counts above 500. More recently, the incidence appears to be decreasing, most likely due to widespread use of highly active antiretroviral therapy (HAART).

**Race**

All races affected; most common in Caucasians and blacks.

**Age**

Any age can be affected; most common 20 to 40 years of age.

**Sex**

Both sexes can be affected; most often diagnosed in males.

**ETIOLOGY**

Neuropathologic evaluation of patients with HIV dementia often reveals cortical atrophy and ventricular dilatation, as well as abnormalities of deep structures including the hemisphere white matter, basal ganglia, and thalamus, consistent with a subcortical deoxygenating process. Histologically, there is diffuse white-matter pallor and vacuolation, astrocytic gliosis, and cortical neuronal loss. Regions of HIV encephalitis contain multiple foci of multinucleated giant cells, foamy macrophages, lymphocytes, and microglia. The characteristic histologic findings of vacuolar myelopathy consist of spongiform (vacuolar) changes of the dorsal and lateral columns, in association with lipid-filled macrophages. HIV is neurotropic and can be cultured early from the nervous system. However, productive infection within neurons or astrocytes does not appear to be the major cause of HIV dementia or vacuolar myelopathy. Brain macrophages (i.e., microglia) can develop productive HIV in fection and are the major vehicle for introducing the virus into the nervous system. Recent hypotheses suggest that neural injury and dysfunction may be due to an innocent bystander effect. HIV does shed toxic substances, such as whole or fragmented gp 120 envelope glycoprotein, which can cause neuronal death in vitro. In addition, other neurotoxic substances, such as tumor necrosis factor-a, interleukin-1Q, interleukin-6, and quinolinic acid. The proposed "final common pathway" of neurotoxicity is excessive stimulation of N-methyl-D-aspartate (NMDA) receptors. Overstimulation of NMDA receptors by gp 120, quinolinic acid, and other small nes could cause toxic buildup of intracellular calcium, thereby killing neuronal cells.

**Risk Factors**

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 200/μl) and an advanced stage of disease, and lack of antiretroviral therapy.

**Pregnancy**

Pregnancy has not been shown to affect the course of HIV dementia.

**ASSOCIATED CONDITIONS**

Vacuolar myelopathy.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis includes HIV-related and non-HIV-related diseases that can lead to deterioration of memory and cognition. HIV-related diseases to consider include progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, primary CNS lymphoma (PCNSL), bacterial or fungal abscesses, and various toxic/metabolic encephalopathies. See chapter on Dementia and AIDS: Focal Brain Lesions.

**SIGNS AND SYMPTOMS**

Patients with HIV dementia demonstrate progressive dysfunction of memory, cognition, behavior, and motor function. During early stages of disease (stages 0.5, 1, and 2), patients note difficulty with concentration, mild memory impairment, loss of mental agility, behavioral changes, and slowness of thinking. Mild motor dysfunction may occur, affecting strength, gait, balance, and coordination. The neurologic examination often reveals subtle psychomotor slowing, mild memory deficits, reduced concentration, saccadic ocular pursuit movements, and soft motor signs (e.g., mild leg weakness, hyperreflexia, slowed rapid alternating movements, unsteady gait, tremor, frontal lobe release reflexes).

In advanced stages of HIV dementia (stages 3 and 4), patients develop progressively more severe neurologic dysfunction with pronounced psychomotor slowing, reduced verbal output, apathy, confusion, disorientation, disorientation, and reduced awareness of illness. Smooth-pursuit ocular movements become very saccadic, and frontal lobe release reflexes are common. Motor dysfunction becomes profound and may include ataxia, severe leg weakness and spasticity, hyperreflexia, Babinski's signs, gait ataxia, tremor, and urinary incontinence. In some patients, a sensory level may be appreciated.

**LABORATORY PROCEDURES**

In general, HIV dementia is a diagnosis of exclusion after other infections, space-occupying lesions, and processes are ruled out. The most important tests consist of blood counts (including CD4 counts, to determine stage of HIV infection), infectious cultures of appropriate tissues, and serum antibody titers of various infectious agents. Other specific tests may be helpful in certain cases, such as VDRL or vitamin B12 levels.

**IMAGING STUDIES**

MRI, with and without administration of gadolinium, is the most sensitive technique to evaluate HIV patients with loss of memory and intellectual function. HIV dementia may demonstrate atrophy or scattered, nonenhancing, white matter lesions, as well as ventricular enlargement. Similarly, PML presents with patchy, nonenhancing, periventricular white matter lesions that slowly enlarge and coalesce. Cerebral toxoplasmosis usually demonstrates multiple ring-enhancing lesions with surrounding edema. PCNSL presents as a solitary or multifocal lesion within the deep periventricular white matter that typically enhances with contrast. Mild edema and/or mass effect may be noted. Tuberculous or fungal abscesses cause ring-enhancing lesions with surrounding edema.
Management

GENERAL MEASURES

Antiretroviral therapy should be maximized, if possible (i.e., zidovudine, HAART). Nutritional and metabolic deficiencies should be corrected, especially those that might impact on neurologic function (e.g., hyponatremia). All systemic infections should be diagnosed and treated.

SURGICAL MEASURES

Biopsy may be required in rare cases to differentiate HIV dementia from other focal intracranial processes.

SYMPTOMATIC TREATMENT

Patients with HIV dementia may stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART). Muscle relaxants such as baclofen may be helpful in reducing spasticity in patients with advanced motor complications.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Patients are generally admitted for acute neurologic changes such as altered level of consciousness, confusion, focal or generalized weakness, seizure activity, headache, and focal neurologic deficits (e.g., dysphasia, hemianopsia). Patients with persistent neurologic deficits should be considered for rehabilitation.

Follow-Up

PATIENT MONITORING

Follow-up of neurologic status is required, especially as patients enter more advanced stages of HIV dementia.

EXPECTED COURSE AND PROGNOSIS

The course and prognosis for HIV dementia is quite poor, since it occurs in patients with low CD4 counts and advanced disease. The 6-month cumulative mortality rate for stages 2 to 4 of HIV dementia is 67%. However, the number of patients developing late-stage HIV dementia appears to be slowing with widespread use of HAART.

Medications

DRUG(S) OF CHOICE

All patients should be evaluated for zidovudine or HAART, since this may delay the onset or reduce the severity of HIV dementia. HAART usually consists of a combination of two nucleoside reverse transcriptase inhibitors (e.g., zidovudine, didanosine, lamivudine) plus one protease inhibitor (e.g., indinavir, saquinavir). Several randomized, placebo-controlled trials have shown benefit of single-agent zidovudine (1,000 or 2,000 mg/d) for delaying the onset of HIV dementia, or improving neuropsychological test performance in affected patients. More recently, a study by Chang et al. demonstrated that treatment with HAART can induce an improvement in clinical grading of HIV dementia, as well as reduce brain metabolite abnormalities as shown by magnetic resonance spectroscopy. In addition, HAART may prevent or reduce the risk of opportunistic infectious and neoplastic complications.

ALTERNATIVE DRUGS

Nimodipine (calcium channel blocker) was evaluated in a placebo-controlled clinical trial. Although the results did show a trend toward an effect for nimodipine, it was not statistically significant. Similar results have been noted in clinical trials of deprenyl (monoamine oxidase B inhibitor and antidepressant agent) and lerepafant (platelet-activating factor inhibitor). A new promising agent is memantine, which blocks ion channels associated with NMDA receptors and inhibits gp 120–associated neuronal injury in vitro. Clinical trials using memantine in patients with HIV dementia are currently ongoing.

SPECIAL TESTS

Lumbar puncture is often helpful and should at least include routine CSF studies, bacterial/fungal antigens, cytology, CSF/bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL. In addition, surrogate markers of immune activation should be ordered, such as fcy-microglobulin, quinolinic acid, and neopterin. EGG can rule out subclinical seizure activity as a cause for cognitive deterioration. Neuropsychological testing can establish a pattern of memory loss and cognitive dysfunction, and provide a baseline for subsequent follow-up testing.

References

Author(s) : Herbert B. Newton, MD

References

Author(s) : Herbert B. Newton, MD
Acquired Immunodeficiency Syndrome: Focal Brain Lesions

**DESCRIPTION**

CMS complications are frequent in patients with HIV infection and often manifest as enhanced or nonenhancing focal lesions of the brain. The most common focal brain lesions in HIV-infected patients are cerebral toxoplasmosis, primary CNS lymphoma (PCNSL), and progressive multifocal leukoencephalopathy (PML). Although the etiology of the focal lesion may vary, the various clinical presentations are often very similar, with signs and symptoms of elevated intracranial pressure, alterations of memory and cognition, and focal neurologic deficits. If patients don't respond to an empiric trial of antitoxoplasmosis therapy, surgical biopsy is required for a definitive histologic diagnosis.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Exact incidence and prevalence figures are not available. Recent estimates suggest an overall incidence of intracranial mass lesions in roughly 10% of HIV-infected individuals. Cerebral toxoplasmosis occurs in approximately 5% to 12% of all AIDS patients. Primary CNS lymphoma is noted in 3% to 5% of all AIDS patients; the incidence of PCNSL may be increasing. PML occurs in 2% to 4% of all AIDS patients. HIV dementia is estimated to have an incidence of 7.5% to 20% in retrospective studies. The overall incidence of focal brain lesions may be decreasing due to widespread use of highly active antiretroviral therapy (HAART).

Neuroimaging and autopsy studies demonstrate that cerebral toxoplasmosis accounts for 50% to 60% of all intracranial mass lesions, while another 20% to 30% are caused by PCNSL and 10% to 20% arise from PML.

All races affected; most common in Caucasians and blacks.

**Age**

Any age can be affected; most common 20 to 40 years of age.

**Sex**

Both sexes can be affected; most often diagnosed in males.

**ETIOLOGY**

Intracranial mass lesions usually develop in end-stage AIDS patients with CD4 counts below 200/μL. In rare patients, mass lesions can be the presenting manifestation of HIV infection. Cerebral toxoplasmosis is caused by reactivation of an endogenous infection by Toxoplasma gondii, an obligate intracellular parasite. The parasite usually reaches the brain by hematogenous spread from infected systemic organs. Pathologically, the abscesses demonstrate regions of necrosis with mild inflammation and Toxoplasma cysts, endarteritis, lipid-laden macrophages, extracellular tachyzoites, and encysted bradyzoites. Primary CNS lymphoma develops from neoplastic lymphocytes (usually B cells). Epstein-Barr virus DNA is present in many of the tumors. Pathologically, the tumors show densely packed neoplastic lymphocytes with diffuse infiltration into surrounding brain, regions of necrosis, and a tendency to spread along perivascular spaces. PML is caused by reactivation of the JC papovavirus. Once reactivated, the JC virus infects oligodendrocytes, causing progressive demyelination throughout the subcortical and periventricular white matter, cerebellum, and brainstem. Histologically, swelling and degeneration of oligodendrocytes are noted, with minimal inflammation. Viral inclusion bodies may be present within infected cells. Less common causes of intracranial mass lesions include abscess from other parasites (cytomegalovirus, fungi [Cryptococcus neoformans], and bacteria [Mycobacterium tuberculosis]); focal viral infections (e.g., cytomegalovirus herpes simplex virus); gliomas; metastatic brain tumors (e.g., Kaposi’s sarcoma, systemic lymphoma); and cerebrovascular disease. For a detailed discussion of the etiology of AIDS HIV dementia, see that specific chapter.

**Genetics**

Genetic factors have not been identified.

**RISK FACTORS**

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 200/μL), and advanced stage of disease, and lack of antiretroviral therapy.

**PREGNANCY**

Pregnancy has not been shown to affect the course of focal brain lesions in HIV patients.

**ASSOCIATED CONDITIONS**

N/A

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis is extensive and includes any non-HIV-related diseases that can present as a focal lesion within the brain. See chapters on Brain Tumors, Primary; Brain Tumor, Metastatic; and brain abscess for a more detailed differential diagnosis.

**SIGNS AND SYMPTOMS**

The temporal profile of cerebral toxoplasmosis is more acute than either PC NSL or PML, with symptoms evolving over several days to a week. The initial symptoms are typically headache and confusion, which develop in over half of all patients. Other frequent symptoms include lethargy, low-grade fever, seizures, and focal neurologic deficits (e.g., hemiparesis, dysphasia, ataxic gait, hemianopia, sensory loss).

Patients with PCNSL usually develop symptoms that evolve over 1 week to several weeks. The most common symptoms are headache, confusion, lethargy, personality changes, seizures, and memory loss. Focal neurologic signs and symptoms are frequent and similar to that noted above. Fever and other constitutional symptoms are generally absent. PML is the most indolent of the common focal intracranial lesions and evolves over several weeks or more. Signs and symptoms of elevated intracranial pressure, fever, and constitutional symptoms are absent. Patients complain of slowly progressive deterioration of memory and higher cognitive functions, as well as focal neurologic deficits as listed above.

HIV dementia causes progressive impairment of short-term memory, cognition, concentration, and motivation. Associated motor abnormalities include unsteady gait, leg weakness, tremor, and incoordination.

Less common causes of focal intracranial mass lesions present in a similar fashion.

**LABORATORY PROCEDURES**

The most important tests consist of blood counts (including CD4 counts, to determine stage of HIV infection), toxoplasmosis serology, and serum antibody titers of other infectious agents.

**IMAGING STUDIES**

MRI, with contrast, is the most sensitive technique to evaluate for a focal intracranial mass lesion. Cerebral toxoplasmosis usually demonstrates multiple ring-enhancing lesions with surrounding edema, present in the gray matter of the diencephalon and cortex. PCNSL presents as solitary or multifocal lesions within the deep periventricular white matter that enhance diffusely. Mild edema and/or mass effect may be noted. PML presents with patchy, nonenhancing, white matter lesions that slowly enlarge and coalesce. The lesions often begin adjacent to the cortex (i.e., affect subcortical fibers) and do not cause mass effect or edema. HIV dementia may demonstrate atrophy or scattered, nonenhancing, white matter lesions that usually spare the subcortical fibers. Focal viral encephalitis may produce mass lesions with minimal enhancement.

For patients without access to an MRI facility, cerebral CT is still an excellent alternative, especially with double-dose iodinated contrast. If available, thallium 201 single photon emission computed tomography (SPELT) or fluorodeoxyglucose positron emission tomography (PET) should be obtained. A positive result is suspicious for PCNSL.
Acquired Immunodeficiency Syndrome: Focal Brain Lesions

**SPECIAL TESTS**

Lumbar puncture may be helpful in selected patients (i.e., those who do not undergo immediate surgical biopsy and are not precluded by excessive intracranial pressure and/or mass effect) to differentiate the etiology of focal brain lesions, and should include at least routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL.

**Management**

**GENERAL MEASURES**

Antiretroviral therapy should be maximized, if possible (i.e., HAART). Corticosteroids should be avoided unless brain herniation is suspected.

**SURGICAL MEASURES**

All large lesions with mass effect and impending herniation require biopsy with decompression. Biopsy is also warranted for patients with positive SPECT or PET studies, those with a single lesion and negative toxoplasma serology, and all patients that have failed an empiric trial of antitoxoplasmosis therapy. Biopsy is accurate for diagnosis in 85% to 90% of cases.

**SYMPTOMATIC TREATMENT**

All patients, except those listed above, require an empiric trial of antitoxoplasmosis therapy: pyrimethamine (loading dose of 100 to 200 mg, then 25 to 50 mg/d), sulfadiazine (6 to 8 g/d in divided doses) and leucovorin (5 to 10 mg/d). Clinical and radiologic improvement in 10 to 14 days confirms the diagnosis. Patients with PCNSL should receive whole brain irradiation (4, 000-5,000 cGy), although chemotherapy (e.g., methotrexate or PCV, procarbazine, CCNU, vincristine) can be beneficial in selected patients with good performance status. Dexamethasone has ctitotoxic effects against PCNSL and often reduces tumor size and edema. Although there are no proven beneficial therapies for PML, occasional patients may stabilize or improve with HAART or intravenous cytaraebine therapy. HIV dementia may also stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART).

**ADJUNCTIVE TREATMENTS**

N/A

**ADMISSION/DISCHARGE CRITERIA**

Patients are admitted for acute neurologic changes related to the focal brain lesion, such as altered level of consciousness, confusion, seizure activity, headache, and focal neurologic deficits. Patients with persistent neurologic deficits should be considered for rehabilitation.

**Medications**

**DRUGS OF CHOICE**

All patients should be evaluated for HAART, since this may prevent or reduce the risk of opportunistic infectious and neoplastic complications. All other drug decisions have to be individualized to the neurologic complications of each specific focal mass lesion.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

Follow-up of neurologic status is required; particularly for focal lesions that need long-term therapy and serial MRI scans (e.g., PCNSL, toxoplasmosis). Patients with cerebral toxoplasmosis require lifelong maintenance therapy with pyrimethamine (25 to 50 mg/d) and sulfadiazine (2 g/d) to prevent relapses.

**EXPECTED COURSE AND PROGNOSIS**

The course and prognosis for HIV patients with focal intracranial mass lesions is quite poor, since most occur in patients with advanced disease. However, overall survival may be improving for this group because of the use of HAART. The 6-month cumulative mortalit y rate for cerebral toxoplasmosis is 51%, although many patients do respond to treatment with improvement of neurologic symptoms and MRI scans. Patients with PCNSL have a median survival of 1 month if untreated and 4 to 6 months following radiation therapy. The median survival for patients with PML is 2 to 4 months. The 6-month cumulative mortalit y rate for stages 2 to 4 of HIV dementia is 67%. Some focal infectious complications caused by specific agents may respond to appropriate therapy, such as CMV encephalitis.

**PATIENT EDUCATION**


**Miscellaneous**

**SYNONYMS**

N/A

ICD-9-CM: 323.9 Encephalitis, cause unspecified; 046.3 Progressive multifocal leukoencephalopathy; 191.9 Malignant neoplasm of brain, unspecified (PCNSL); 331.9 Cerebral degeneration, unspecified (HIV dementia)

SEE ALSO: ACQUIRED IMMUNODEFICIENCY SYNDROME: OVERVIEW OF NEUROLOGIC COMPLICATIONS; ACQUIRED IMMUNODEFICIENCY SYNDROME: DEMENTIA COMPLEX; ACQUIRED IMMUNODEFICIENCY SYNDROME: NEUROMUSCULAR COMPLICATIONS.

**REFERENCES**


Author(s): Herbert B. Newton, MD
Acquired Immunodeficiency Syndrome: Neuromuscular Complications

**Basics**

**DESCRIPTION**
Neuromuscular complications are common in patients with HIV infection and AIDS, potentially affecting nerve roots, peripheral nerves, and muscles. The etiology of these disorders is variable and may result from direct effects of HIV infection, damage from inflammatory processes and cytokine production, opportunistic infections and neoplasms, metabolic abnormalities, and toxic effects of HIV therapy.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
Exact incidence and prevalence figures are not available. Approximately 10% to 40% of patients with HIV-1 and AIDS develop some form of neuromuscular complication. The most common complication is a distal symmetric polyneuropathy (DSP), which is diagnosed in 22% to 30% of patients. Asymptomatic HIV-1-infected patients can also be affected and have an incidence between 2% and 26%, as shown by detai led neurophysiological testing. More recently, the incidence of neuromuscular complications appears to be decreasing, most likely due to widespread use of highly active antiretroviral therapy (HAART).

**Race**
All races affected; most common in Caucasians and blacks.

**Age**
Any age can be affected; most common 20 to 40 years of age.

**Sex**
Both sexes can be affected; most often diagnosed in males.

**ETIOLOGY**
The etiology is variable and depends on the stage of disease and the specific process involving the peripheral nerves and/or muscles. In early stages of HIV-1 infection, neuromuscular complications are caused by immune dysregulation. Acte and chronic forms of inflammatory demyelinating polyradiculoneuropathy (AIDP, CIDP) and vasculitic neuropathy are thought to occur by this mechanism. In AIDP and CIDP, an autoimmune process develops that results in damage to peripheral nerve myelin (i.e., myelin antibodies). Vasculitic neuropathy appears to be caused by deposition of HIV-1 antibody/antigen immune complexes into blood vessel walls. DSP and autonomic neuropathy usually occur in the middle and late stages of HIV-1 infection. Although the etiology of DSP remains unclear, it does not appear to be caused by direct infection of nerves by HIV-1. Instead, nerve damage occurs through indirect means initiated by productive systemic HIV-1 infection. The suspected mediators of this peripheral nerve damage are whole or fragmented gp 120 envelope glycoprotein and cytokines such as tumor necrosis factor-a, interleukin-1Q, interleukin-6, transforming growth factor-a, and nitric oxide. Concurrent infections (i.e., cytomegalovirus (CMV)) and malnutrition (e.g., vitamin B12) may also contribute to the clinical manifestations of DSP. During late stages, opportunistic infections and neoplasms can directly involve nerve roots and peripheral nerves. The most common infection is CMV, which can involve the nerve roots (i.e., polyradiculopathy) and/or peripheral nerves (i.e., mononeuropathy multiplex). Other less common infections include herpes zoster ganglionsitis, syphilitic radiculopathy, and tuberculotic polyradiculopathy. Lymphoma can directly invade nerve roots and cause polyradiculopathy after spreading to the spinal meninges. Infrequently, neuropathies can develop in patients with vitamin B6 and/or vitamin B12 deficiencies. Toxic neuropathies can arise in a dose-dependent manner from therapy for HIV-1, in particular the antiretroviral dideoxynucleotide analogues didanosine (ddI), zalcitabine (ddC), and stavudine (d4T). The neuropathy may result from damage to cellular mitochondria caused by inhibition of mitochondrial DNA-α polymerase. Myopathies can develop as a result of HIV-1 infection or from toxicity of antiretroviral therapy. Productive HIV-1 infection has not been demonstrated in myofibers. Rather, indirect mediators of myofiber damage are suspected, such as gp 120 mediated inflammatory cytokines. Zidovudine is also implicated as a cause of myopathy and appears to damage myofiber mitochondria, resulting in “ragged-red fibers” and other evidence of dysfunction. The mechanism is through inhibition of mitochondrial DNA-α polymerase. Rarely, opportunistic infections can directly involve muscle and present as a myopathy, such as toxoplasmosis or CMV.

**Genetics**
Genetic factors have not been identified.

**RISK FACTORS**
No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 100/µL) and a lack of antiretroviral therapy.

**PREGNANCY**
Pregnancy has not been shown to affect the course of neuromuscular complications of HIV.

**ASSOCIATED CONDITIONS**
N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
The differential diagnosis is extensive and includes any non-HIV-related disease with a similar presentation affecting the nerve roots, peripheral nerves, or muscles. See chapters on Guillain-Barra Syndrome; Myopathy; and Neuropathy, Peripheral for a more detailed differential diagnosis.

**SIGNS AND SYMPTOMS**
Patients with DSP usually complain of distal, symmetric numbness, paresthesias, and dysesthesia of the legs and feet that develops over weeks to months; upper extremities can become affected in late stages of disease. Typically, the pain is most severe on the soles of the feet. Light touch and pressure often exacerbate the pain. On examination, most patients have loss of reflexes at the ankles and a distal-to-proximal gradient to pinprick, cold, and vibration; muscle weakness and atrophy is usually mild or absent. Toxic neuropathies from HIV-1 therapy have signs and symptoms similar to DSP. HIV-1-related AIDP and CIDP have a similar clinical presentation to the idiopathic neuropathies. The patient notes either a rapid (i.e., weeks, for AIDP) or slow (i.e., months, for CIDP) onset of progressive weakness in two or more limbs, generalized areflexia, and mild sensory loss. Muscle atrophy may be noted in patients with long-standing disease. Patients with autonomic neuropathy complain of fainting, orthostatic dizziness, impotence, diminished sweating, diarrhea, and urinary dysfunction. In addition, cardiac conduction abnormalities may occur. The various forms of polyradiculopathy present with progressive lower extremity and sacral paresthesias, fascicul paraparesis, areflexia, sensory loss, and urinary dysfunction. Mononeuropathy multiplex is characterized by multifocal, asymmetric, dysfunction of cranial nerves, mixed nerves, and nerve roots that often presents with wrist drop, foot drop, facial palsy, and other focal neuropathic signs. Reflexes are preserved in asymptomatic nerve distributions. Patients with myopathy complain of slowly progressive, generalized proximal muscle weakness that initially affects activities such as rising from a chair or climbing stairs. Myalgias are noted in 25% to 50% of patients. Reflexes are preserved and sensory function remains intact.

**LABORATORY PROCEDURES**
The most important tests consist of blood counts (including CD4 counts, to determine stage of HIV infection), infectious cultures of appropriate tissues (e.g., CMV), and serum antibody titers of various infectious agents. Serum creatine kinase levels are moderately elevated (450 to 500 U/L) in patients with
myopathy. Other specific tests may be helpful in certain cases, such as VDRL, vitamin B₁₂, and vitamin B₆ Levels.

IMAGING STUDIES
MRT and CT have limited diagnostic value.

SPECIAL TESTS
Lumbar puncture is often helpful and sh ould at least include routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL. The CSF cell count always demonstrates a pleocytosis (≥250 mononuclear cells) in patients with HIV-1-related AIDP and CIDP (usually hypocellular in HIV negative cases). Patients with CMV mononeuropathy multiplex and polyradiculopathy have an elevated CSF protein and mononuclear cell pleocytosis. Electromyography and nerve conduction testing are helpful for diagnosis. In cell pleocytosis. Electromyography and nerve conduction velocities consistent with AIDP and CIDP demonstrate slowed motor nerve function testing may be helpful to define the presence and extent of autonomic neuropathy.

Management

GENERAL MEASURES
Antiretroviral therapy should be maximized, if possible (i.e., HAART). All systemic infections should be diagnosed and treated. Medications that could contribute to a myopathic or neuropathic process (e.g., zidovudine, dDC) should be reviewed and possibly discontinued as a therapeutic trial.

SURGICAL MEASURES
Biopsy of involved nerve roots, peripheral nerves, or muscles may be helpful for definitive diagnosis.

SYMPTOMATIC TREATMENT
Treatment for DSP is symptomatic and consists of a combination of tricyclic antidepressants, selected serotonin reuptake inhibitors, carbamazepine, gabapentin, lamotrigine, and topical agents (i.e., capsaicin).

Toxic neuropathies receive similar treatment to DSP and may improve after cessation of the offending drug. Patients with AIDP and CIDP may respond to plasmapheresis or IVIG, similar to HIV-negative patients. Therapy for autonomic neuropathy consists of fludrocortisone, antiarhythmic agents, and management of fluids and electrolytes. CMV polyradiculopathy and mononeuropathy multiplex may respond to ganciclovir. HIV myopathy may respond to a course of prednisone (60 mg/d). Zidovudine myopathy should be treated with reduced dosage or cessation of the drug.

ADJUNCTIVE TREATMENTS
N/A

ADMISSION/DISCHARGE CRITERIA
Patients are generally admitted for acute neurologic changes related to the specific neuropathic or myopathic process. The most common causes for admission include focal extremity weakness, generalized weakness, progressive proximal weakness, and exacerbation of extremity pain. Patients with persistent neurologic deficits should be considered for rehabilitation.

Follow-Up

PATIENT MONITORING
Follow-up of neurologic status is required. This is particularly true for conditions that require long-term therapy, such as distal painful neuropathy or infectious neuromuscular complications (e.g., CMV).

EXPECTED COURSE AND PROGNOSIS
The course and prognosis for many of the neuropathies and myopathies mentioned above is quite poor, since the majority occur in patients with low CD4 counts and advanced disease. However, in some cases treatment may lead to stabilization or improvement. Infectious complications caused by spheroidal agents may respond to appropriate therapy, such as CMV polyradiculopathy or mononeuropathy multiplex, syphilitic radiculopathy, or tuberculous polyradiculopathy. Toxic myopathies and neuropathies may improve if the offending agent is discontinued at an early stage.

PATIENT EDUCATION
AIDS Daily Summary: [www.cdcnpin.org](http://www.cdcnpin.org).
Centers for Disease Control (CDC) AIDS Information: [www.cdcnpin.org](http://www.cdcnpin.org).
International Association of Physicians in AIDS Care: [www.iapac.org](http://www.iapac.org).

Miscellaneous

SYNONYMS
N/A

ICD-9-CM: 357.9 Polyneuropathy, unspecified; 359.9 Myopathy, unspecified

SEE ALSO: ACQUIRED IMMUNODEFICIENCY SYNDROME: OVERVIEW OF NEUROLOGIC COMPLICATIONS; ACQUIRED IMMUNODEFICIENCY SYNDROME: DEMENTIA COMPLICATIONS; ACQUIRED IMMUNODEFICIENCY SYNDROME: FOCAL BRAIN LESIONS

REFERENCES

Author(s) Herbert B. Newt on, MD
Alcohol Abuse, Neurologic Complications

**DESCRIPTION**

Alcohol addiction is a major public health problem, accounting for an estimated $117 billion in annual cost in the United States in health expenses and lost productivity. Ethanol-related neurologic complications are diverse and can affect any level of the neuraxis, including brain, spinal cord, cranial and peripheral nerves, and muscle.

**ETIOLOGY**

Both sexes can be affected; most commonly diagnosed between 30 to 50 years of age. Sex

- Both sexes can be affected; most often diagnosed in males.

**RACE**

All races affected; most common in Caucasians and blacks.

**AGE**

Adults and adolescents can be affected; most commonly diagnosed between 30 to 50 years of age.

**ETIOLOGY**

- After ingestion of only 2 oz of 100% ethanol, the blood ethanol level will be 100 mg/dL requiring 6 hours to be metabolized. Blood ethanol levels of 100 mg/dL and higher result in symptoms of impaired concentration, poor judgment, reduced inhibitions, slurred speech, nystagmus, ataxic gait, and labile mood; levels of 300-400 mg/dL induce stupor and coma.

- Ethanol interacts with nervous system tissues in several ways, including intercalation into cell membranes, increasing membrane fluidity, and perturbing hydrophobic regions of membrane lipids and proteins; ethanol interacts directly with specific neurotransmitter receptors and ion channels in the brain. GABA<sub>A</sub> receptors, which regulate potassium and calcium channels, are modulated by ethanol; similarly, it is theorized that ethanol modulates GABA<sub>B</sub> receptors by augmenting their response to MBA, excitatory amino acid receptors are also affected by ethanol; ethanol inhibits NMDA-activated Ca<sup>2+</sup> currents and cellular responses to NMDA receptor activation; chronic ethanol exposure causes increased expression of glutamate receptors, which may contribute to the generation of alcohol withdrawal seizures.

- Chronic alcohol intake leads to poor dietary intake and deficiencies of protein, thiamine, riboflavin, and niacin; in addition, chronic ethanol intake can lead to accumulation of potentially toxic substances (e.g., acetaldehyde).

- Wernicke's encephalopathy results from thiamine deficiency, causing demyelination, necrosis, gliosis, and vascular proliferation in the mammillary bodies, superior vermis, hypothalamic nuclei, and diencephalon. Korsakoff's syndrome is also due to thiamine deficiency, causing lesions of the dorsal medial nuclei of the thalamus. Alcoholic cerebellar degeneration may also be related to thiamine deficiency, in addition to electrolyte derangements and direct neurotoxic effects. Pellagra is caused by niacin deficiency, which induces chromatolysis of neurons in the motor cortex and basal ganglia; alcoholic dementia is multifactorial and can be related to thiamine deficiency, pellagra, hepato cerebral degeneration, Marchiafava-Bignami disease, and direct neurotoxic effects of ethanol; alcoholic polyneuropathy is most likely from niacin deficiency (thiamine?); alcoholic myopathy is probably due to direct toxic effects of ethanol; the causes of Marchiafava-Bignami disease and central pontine myelinolysis (CPM) remain unknown; CPM usually occurs after overly aggressive correction of hypotension, with demyelination of the basis pontis.

**GENETICS**

Alcoholism is seven times more frequent in first-degree relatives of alcoholics than in the general population; 16% to 26% of fathers and 2% to 6% of mothers of alcoholics are alcohol abusers; identical twins have a significantly higher concordance rate for alcoholism than fraternal twins. No consistent genetic locus has been identified.

**RISK FACTORS**

The risk of developing neurologic complications is related to genetic factors and the duration and severity of the patient's alcoholism.

**PREGNANCY**

Pregnancy does not affect the course of neurologic complications of alcohol abuse; alcohol abuse during pregnancy may cause the fetal alcohol syndrome (mental retardation, microcephaly, hypotonia, poor coordination, impaired growth, abnormal facies).

**DIAGNOSIS**

The differential diagnosis is extensive and includes any non-ethanol-related diseases that can have a similar presentation to encephalopathy, seizure activity, dementia, polyneuropathy, myopathy, or cerebellar degeneration.

**SIGNS AND SYMPTOMS**

- Patients with minor alcohol withdrawal present with tremulousness, insomnia, agitation, flushing, sweating, nausea and emesis, tachypnea, tachycardia, and increased blood pressure. Hallucinations and seizures may also occur; seizures are generally tonic-clonic and occur within 48 hours of abstinence; some patients may progress to delirium tremens, which has similar but more severe symptoms compared to simple withdrawal, as well as fever, delusions, hallucinations, and severe encephalopathy.

- Patients with Wernicke's encephalopathy present with an acute confusional state, ophthalmoplegia, and gait ataxia; ocular findings include nystagmus, unilateral or bilateral lateral rectus palsy, and conjugate gaze palsies; other findings may include hypopitresis, hypothermia, polyneuropathy, and somnolence; Korsakoff's syndrome often develops after Wernicke's and is characterized by severe anterograde and short-term retrograde amnesia, lack of concern and insight, and confabulation.

- Alcoholic cerebellar degeneration presents with gait ataxia and less severe limb ataxia; symptoms affect the legs more than the arms; dysarthria may occur; usually gradual in onset.

- Alcoholic dementia presents as progressive cognitive decline; in patients without a niacin deficiency or other cause, it is often mild, with anterograde and retrograde memory deficits; on occasion, symptoms can be severe.

- Alcoholic polyneuropathy presents with paresthesias, pain, and weakness of the distal lower extremities; gait may be affected; pain and temperature sensation are reduced; distal atrophy and hyporeflexia are often present.

- Chronic alcoholic myopathy presents with intermittent cramps and painless, progressive proximal weakness of variable severity; atrophy may be present; acute alcoholic myopathy is a necrotizing process, often noted during alcoholic binges, that presents with pain, tenderness, weakness, muscle swelling, myoglobinuria, and cardiac arrhythmias.

- Pellagra presents with an acute confusional state, rigidity, and myoclonus; other signs may include hallucinations, seizures, pyramidal signs, ataxia, and neuropathy.
Alcohol Abuse, Neurologic Complications

- Marchiafava-Bignami disease presents with a progressive, subacute confusional state, dementia, seizures, dysarthria, pyramidal signs, and incontinence; stupor and coma may occur.
- CPM presents with acute confusion or coma, spastic paraparesis or quadriplegia, dysarthria, and dysphagia; locked-in syndrome may occur.

LABORATORY PROCEDURES
Patients should be screened for thiamine, niacin, and other vitamin levels, transketolase level, liver panel, ammonia, electrolytes, glucose, renal panel, calcium, and magnesium; ethanol level, toxicology screen, and infectious workup may be of benefit.

IMAGING STUDIES
MRI or CT, with and without contrast, are helpful for patients with neuropathy and/or myopathy.

Management

GENERAL MEASURES
Administration of thiamine, niacin, and multivitamins; correction of electrolyte, glucose, and fluid imbalances; hyponatremia should be corrected slowly (i.e., <10-12 mmol/L/d); monitoring of heart rhythm; calming environment; seizure precautions; treatment of general medical complications and infections as appropriate.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
• Treatment of early alcohol withdrawal consists of oral diazepam (10-40 mg) or chlordiazepoxide (25-100 mg) every 2-4 h; the addition of atenolol (50 mg qd or bid) or clonidine (0.3 mg bid) may be of benefit. Treatment of delirium tremens consists of intravenous (IV) diazepam (10-40 mg) every 5 to 10 min, titrated to clinical effect; maintenance doses of 5-20 mg every 1-4 h; oral atenolol (50 mg qd or bid) should be considered; hydration, electrolyte replacement, and cooling as needed; withdrawal-related seizures are typically self-limited once treatment has begun; persistent seizures or status epilepticus require IV diazepam or lorazepam and IV phenytoin, similar to non-ethanol-related seizures.
• Wernicke encephalopathy should be treated with thiamine 100 mg IV, converting to oral therapy at discharge; Korsakoff's syndrome should be treated with thiamine, although it typically does not improve; pellagra respondents to multivitamin and niacin (nicotinic acid) replacement; alcoholic polyneuropathy may respond to thiamine and multivitamin in replacement.
• There is no specific therapy for alcoholic cerebellar degeneration, it may improve with thiamine and multivitamin ins; there is no treatment for Marchiafava-Bignami disease or CPM; alcoholic myopathy usually improves with abstinence and supportive care.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
Seizure activity, mental status alterations, and focal neurologic deficits are the most common cause for admission; alcohol withdrawal and delirium tremens usually occur after admission and cessation of alcohol intake. Discharge is appropriate when symptoms of withdrawal, seizures, and other neurologic and medical complications have either stabilized or resolved.

N/A

Follow-Up

PATIENT MONITORING
Neurologic follow-up is required; monitoring of abstinence, nrtt, ional status and compliance with thiamine, multivitamin ins, and other medications is critical.

EXPECTED COURSE AND PROGNOSIS
The course and prognosis for early alcohol withdrawal is favorable, but becomes more guarded with delirium tremens, due to frequent medical complications. Patients with Wernicke's encephalopathy and Korsakoff's syndrome often have residual neurologic dysfunction (dementia, ataxia). Alcoholic cerebellar degeneration and polyneuropathy usually improve with abstinence and nrtt ional therapy; recovery from pellagra is excellent with treatment; recovery of myopathy is excellent with abstinence; recovery from Marchiafava-Bignami disease and CPM is poor.

PATIENT EDUCATION
• National Institute on Alcohol Abuse and Alcoholism: www.niaaa.nih.gov.
• Medical Council on Alcohol: www.medicalcouncilalcoholism.co.uk.
• Alcoholism/Treatment: www.alcoholismtreatment.org.
• American Council on Alcoholism: www.nca-usa.org.
• Alcoholics Anonymous: www.aa.org.

SYNONYMS
ICD-9-CM: 291.1 Alcohol amnestic syndrome (Korsakoff's, Wernicke-Korsakoff's); 291.2 Other alcoholic dementia; 291.3 Alcohol withdrawal hallucinosis; 303.0; 334.4 Cerebellar ataxia secondary to alcoholism; 357.5 Alcoholic polyneuropathy; 359.9 Myopathy, unspecified

SEE ALSO: ENCEPHALOPATHY, NEUROPATHY, MYOPATHY

REFERENCES

Author(s) Herbert B. Newt on, MD
### Basics

**DESCRIPTION**
- Transient global amnesia (TGA), as its name implies, is a self-limited loss of the ability to create new memory. It presents as sudden onset of confusion, best characterized as "bewildernent," on the part of the patient due to the inability to learn new material.

**EPIDEMIOLOGY**
- Incidence of about 5/100,000 annually
- Usually affects people age >50 years
- No clear sex differences

**ETIOLOGY**
- No cause of TGA is known. Speculation has revolved around cerebral ischemia, seizure, and migraine; however, it does not appear to herald an increased risk for strokes, transient ischemic attacks, or seizures.

**RISK FACTORS**
- Many TGA patients have a previous history of migraine
- Some studies suggest an increased presence of patent foramen ovale among TGA patients
- Precipitated by Valsalva
  - Exertion
  - Emotional excitement
  - Minor medical procedures (angiography, endoscopy)
  - Cold water

**PREGNANCY**
N/A

**ASSOCIATED CONDITIONS**
N/A

### Diagnosis

**DIFFERENTIAL DIAGNOSIS**
- Closed head trauma
  - Concussion
- Bitemporal cerebral contusions
- Drug effects
  - Benzodiazepines
  - Other sedative/hypnotic agents
  - Alcohol ("blackouts" or delirium tremens)
  - Hallucinogens
- Thiamine deficiency (Wernicke-Korsakoff syndrome) should be considered, especially if there is evidence of ophthalmoparesis or ataxia
  - Thiamine deficiency can occur without alcoholism
- Status epilepticus should be considered in patients with a history of epilepsy
- Encephalitis, especially herpes simplex encephalitis
  - Associated with decreased alertness, headache, or fever
- Psychogenic
  - Psychogenic amnesia produces loss of personal identity ("Who am I?"), but the ability to learn new material is retained. This is in direct contrast to organic amnesia, wherein personal identity is retained, but the patient is unable to learn.

**SIGNS AND SYMPTOMS**
- Abrupt onset of memory loss, usually including the last few hours, and inability to learn new material
  - Produces bewilderment in the patient who senses something is amiss but cannot recall previous reassurances
  - The patient often will repeatedly ask the same question or perform the same task
- Retained ability to repeat ("immediate memory")
- Retained ability to recall remote memories, including personal identity
- Preserved alertness and other cognitive functions, except for amnesia
- Normal neurologic examination except for amnesia

**LABORATORY PROCEDURES**
- Consider urine drug screen for benzodiazepines
- There are no laboratory studies for TGA

**IMAGING STUDIES**
- Consider CT of the head in cases of possible head trauma
- Diffusion-weighted MRI of the brain may show transient abnormalities
- There are no imaging studies for TGA
Follow-Up

PATIENT MONITORING
• Check for evidence of altered alertness that would suggest one of the differential diagnoses

EXPECTED COURSE AND PROGNOSIS
• Gradual return of the ability to learn new material, usually within 12 hours
• The patient will not recall events that occur while amnestic
• Recurs in <20% of patients
• Does not convey any increased risk for stroke or seizure

PATIENT EDUCATION
• TGA may recur in a minority of patients
• TGA does not herald an increased risk of stroke or seizures
• TGA is not a psychogenic reaction to stress
• No modification of lifestyle is required by the diagnosis of TGA per se

Miscellaneous

SYNONYMS
• TGA

ICD-9-CM: 294.8 Amnestic disorder not otherwise specified

SEE ALSO: WERNICKE-KORSAKOFF SYNDROME

REFERENCES

Author(s): Daniel W. Giang, MD-
Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

DESCRIPTION

- Amyotrophic lateral sclerosis (ALS) is an idiopathic, progressive CNS disease resulting in death of brain upper motor neurons (UMN), pyramidal tracts, and spinal cord lower motor neurons (LMN), and causing weakness of corticobulbar and corticospinal innervated muscles. ALS starts focally in a bulbar or limb muscle and spreads, resulting in death, usually by respiratory failure.

Epidemiology

Incidence
- 2/100,000/year

Age
- All ages, highest between 50 and 70 years, mean 58, uncommon <40

Sex
- Slight male predominance of 1.3:1, especially in younger ages; 1:1 <65

Race
- Fairly uniform geographic and ethnic distribution

Prevalence
- 6/100,000

Etiology

- Unknown; theories include apoptosis, autoimmunity, excitotoxicity, free-radical formation, mitochondrial dysfunction, paraneoplastic, viral infection

Genetics

- Familial ALS (about 10% of all ALS): younger age onset, mean 45.
- Multiple gene mutations: most are autosomal dominant; 20–40% of ALS
- Multiple gene mutations, with most being autosomal recessive
- FALS: genetic test available for prenatal testing

Pregnancy

- SOD, gene test available for prenatal testing (covers 1% of all ALS)

Associated Conditions

- N/A

Diagnosis

Differential Diagnosis

ALS Phenotype
- Familial ALS
- ALS with lymphoproliferative disease
- ALS with monoclonal gammopathy, or other malignancy
- ALS-like disease with HIV infection
- ALS-parkinsonism-dementia complex of Guam

LMN Disorders
- Spinal muscular atrophy (SMA): most are autosomal recessive (5q11.2-13.3); onset birth to young adult
- Spinal bulbar muscular atrophy (SBMA, Kennedy's disease): X-linked, CAG trinucleotide repeat in androgen receptor gene; adolescence or older; slow, proximal > distal LMN; chin fasciculations, dysarthria, dysphagia; normal EMG; slower than ALS, but "PMA" LMN onset frequently turns to ALS
- Viral: poliomyelitis, other enteroviruses

UMN Disorders
- Primary lateral sclerosis (PLS): adult onset; rare, sporadic
- Hereditary spastic paraplegia (HSP)
- Viral myelopathy; HTLV-1 (tropical spastic paraparesis) and HIV
- Other CNS: Creutzfeld-Jakob, progressive supranuclear palsy, corticobasal degeneration, diffuse Lewy body disease, multiple systems atrophy, syphilis

Disorders That May Be Confused with ALS
- Cervical myelopathy: spondylotic, Chiari malformation, tumor, syringomyelia
- Lumbar-sacral spinal stenosis
- Subacute combined degeneration
- Inclusion-body myositis (IBM): older male predominance; slowly progressive distal arm weakness; hip flexor weakness; dysphagia
- Multifocal motor neuropathy (MMN): sporadic LMN syndrome; middle age and older; male predominance; weakness without npt bne s os of pro port. ion to atrophy, fasciculations; antibody-mediated multifocal demyelinating motor neuropathy; confirm via NCS, motor conduction blocks, high-liter anti-GN, ganglioside antibody (30%)
- Chronic inflammatory demyelinating polyneuropathy
- Amyotrophy (diabetic or monomelic)
- Stroke
- Multiple sclerosis
- Myasthenia gravis
- Heavy metal intoxication
- Hyperthyroidism, hyperparathyroidism
- Benign cramp-fasciculation syndrome

Signs and Symptoms

- UMN signs: spasticity, hyperreflexia, Babinski and Hoffman signs, emotional lability (pseudobulbar)
- LMN signs: weakness and atrophy, fasciculations, hyporeflexia, facial weakness, muscle cramps; widespread fasciculations are sensitive but not specific, seen especially in tongue, upper chest, proximal limbs
- Bulbar: tongue atrophy and fasciculations, dysarthria (flaccid or spastic), jaw jerk/gag reduced or hyperactive, dysphagia, laryngospasm, saliorhea
- Respiratory: exertional dyspnea, orthopnea
  — Chronic ventilatory insufficiency: heralded by fitful sleep, awakenings, or change in snoring quality, orthopnea, nightmares, morning headache, excessive daytime somnolence
- Cognitive dysfunction (5%-10% of cases)
- El Escorial Criteria (World Federation of Neurology): requires progressive motor weakness; no alternative explanation; "regions" defined as bulbar, cervical myotomes, thoracic myotomes, and lumbar-sacral myotomes
- Definite ALS/UMN and LMN signs in 3 regions (bulbar + 2 spinal, or 3 spinal)
- Probable ALS/UMN and LMN signs in 2 regions, some UMN rostral to LMN
- Possible ALS/UMN and LMN signs in 1 region

Laboratory Procedures

- No serologic confirmatory test
- EMG/nerve conductions: single most useful test
  — For at least 3-limb acte and chronic denervation and reinnervation — Helpful in showing widespread LMN involvement if clinically unclear
- Laboratory tests to evaluate differential diagnosis:
  - CBC, ESR
  - CK (in ALS, normal or mild to moderately elevated)
  - TSH
  - Vitamin B12 (methylmalonic acid)
  - SII/SIIFX, U1EP/UFIX (exclude monoclonal)
  - ANA, rheumatoid factor
  - Lyme, HIV titers (depending on risk), RPR
  - Urine heavy metals (lead, mercaptane)
  - Acetylcholine receptor antibody
  - GM, ganglioside antibody (40%-60% MMN cases with high titer)
  - Hexosaminidase A
  - Gene tests: FALS, SBA, SMA

Imaging Studies

- Cervical MRI (to exclude cervical stenosis, especially if both UMN and LMN signs in upper extremities)
- Brain, thoracic, lumbar-sacral MRI (depending on presentation)
Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

**SPECIAL TESTS**
- Muscle biopsy (ALS shows nonspecific "neurogenic" changes); exclude inclusion-body myositis, dystrophy
- Cerebrospinal fluid if atypical presentation; exclude meningeval carcinomatosis

**Management**

**GENERAL MEASURES**
- Accurate diagnosis by ALExperienced neurologist is essential to enable patient and family to come to terms and to rationally choose among options
- Earliest feasible diagnosis helps avert unnecessary operations
- Encourage second diagnostic opinion if uncertain, or to facilitate "cure"
- Choice of ALS center for principal neurologic care requires a specialized neurologist and multidisciplinary care setting
- Compassion in "breaking the news"
- Discuss early and periodically review end-of-life wishes, advance directives, and durable power of attorney (health care); have non-rushed talks *let the need*
- Respite care and psychological support for the spouse or caregiver
- Deep vein thrombosis (DVT) prophylaxis
- Keep vaccinations current

**SURGICAL MEASURES**
- PEG: elective, most safely performed when forced vital capacity (FVC) >50%
- Tracheostomy: airway protection; enable long-term ventilation (if desired)

**SYMPTOMATIC TREATMENT**
- Dyspnea
  - Indications for respiratory support: dyspnea, excessive daytime sleepiness, morning headaches, frequent nocturnal awakenings
  - Nocturnal bi-PAP is treatment of choice for nocturnal ventilation; nasal O2 less effective, may cause hypoxemia drive in hypercapnia
  - Elevate head of bed
  - Aggressive early treatment of respiratory infections
  - Establish wishes regarding intubation, short- and long-term ventilation
  - Terminal care to prevent air hunger for patients declining ventilator
- Speech: as dysarthria progresses, low tech (notepads, letter boards) to hightech (computer voice synthesizers, head-set laser pointer)
- Salivation: sialorhea—glycopyrrole, hyoscine (Levinsi), tricyclics, hyoscamine, scopolamine patches; suction and quarterly botulinum toxin type A (Botox) parotid

**ADMITTANCE/DISCHARGE CRITERIA**
- Avoid hospitalizations, "elective" spinal surgery
- PEG placement
- Pneumonia

**ADJUNCTIVE TREATMENT**
- Physical and occupational therapy
- Durable goods: ankle-foot orthoses, cane, walker, wheelchair scooter, head support, hospital beds
- Domestic modifications: wheelchair ramps and vans, grab bars, lift devices
- Meticulous symptom management and palliative care at end of life

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**PATIENT MONITORING**
- Expected course and prognosis
- Patient with amyotrophic lateral sclerosis
- Palliative care at end of life
- Other laxatives
- Acid suppressants
- Calcium/magnesium/zinc, vitamin E, gabapentin
- Pain control
- Spasticity: baclofen, tizanidine, diazepam
- Cramps and myalgias: quinine, calcium/magnesium/zinc, vitamin E, gabapentin
- Jaw clenching: clonazepam, diazepam, botulinum toxin
- Cognitive impairment: consider trial of donepezil
- Depression and anxiety; medications, counseling, psychology/psychiatry liaison, support gr ops, respite
- Pseudobulbar affect: amitriptyline, carbamazepine, fluoxetine, paroxetine
- Sleep disturbance: consider change in nocturnal breathing, possible nocturnal hypoventilation, sleep apnea: other causes are depression, anxiety, pain
- Constipation: stool softener, bulk, sorbitol, other laxatives

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**CONTRAINDICATIONS**
- Caution with impaired hepatic and renal function, hypertension, history of neutropenia, hypersensitivity to drug class

**PRECAUTIONS**
- Monitor LFTs monthly for first 3 months, then every 3 months

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**MISCELLANEOUS**

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**MISCELLANEOUS**

**REFERENCES**
Antiphospholipid Antibody Syndrome, Neurologic Complications

Genetics
Familial aPL positivity has been linked to human leukocyte antigens (HLAs) DR7, DR4, DQw7, and DRw53. Familial coexistence has been linked to factor V Leiden mutation.

RISK FACTORS

PRENATIVITY
Antiphospholipid antibodies can cause spontaneous abortion.

ASSOCIATED CONDITIONS
- SLE
- Sneddon’s syndrome (livedo reticularis and stroke)
- Sjogren’s syndrome
- Primary inflammatory vasculitis
- Rheumatoid arthritis
- Bödd-Chian syndrome
- Addison’s disease
- Degas syndrome (malignant atrophic papulosis)
- Cerebral atrophy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
APS should be considered in patients with stroke, especially in the absence of recognized risk factors. Other causes of unexplained arterial or venous thrombosis should be excluded:
- Protein C or S deficiency
- Homocystinuria
- Antithrombin III deficiency
- CNS vasculitis
- Coagulation factors disorders
- Factor V Leiden mutation
- Sickle cell disease
- Underlying malignancy with hypercoagulability
- Conditions associated with transient elevation of aPL, such as AIDS, neuroleptic agents (in particular phenothiazines), recombinant tissue plasminogen activator (rt-PA), aging (50% of patients over 80 are aPL positive), and insulin-dependent diabetes mellitus.

SIGNS AND SYMPTOMS

Neuropsychiatric Manifestations
- Cerebral infarct: arterial infarct (thrombotic, cardioembolic); venous infarct
- TIA
- Transient global amnesia
- Headache: migraine-like headaches or auras; benign intracranial hypertension
- Seizures
- Dementia, including vascular dementia
- Encephalopathy

Non-Neurologic Manifestations
- Recurrent miscarriages
- Cutaneous manifestations: livedo reticularis; necrotizing vasculitis; livedoid vasculitis; thrombophlebitis; claustralgia; ulceration and necrosis; erythematous macules; purpura; ecchymoses; painful skin nodules; subungal splinter hemorrhages; pyoderma gangrenosum
- Ocular manifestations: retinal vein thrombosis; central retinal artery occlusion; ischemic optic neuropathy
- Cardiac valvular abnormalities
- Pulmonary hypertension/embolism
- Deep venous thrombosis
- Renal vein thrombosis
- Addison’s disease
- Adult respiratory distress syndrome
- Multiple organ failure
- Hematologic disorders: hemolytic anemia; autoimmune thrombocytopenic purpura; hemolytic-uremic syndrome

LABORATORY PROCEDURES
The presence of one or both of the circulating aPLs (LA or IgG-aCL) in the blood of patients with signs and symptoms of recurrent venous thrombosis is suggestive of the diagnosis of APS. Hematologic abnormalities that may be associated with APS include:
- Thrombocytopenia (26%-31%)
- Prolonged aPTT (50%)
- Positive Coombs test
- False-positive VDRL
- Neutropenia
- Lymphopenia
- Decreased G0 levels

IMAGING STUDIES
- CT and MRI findings are nonspecific. At least 50% of patients with APS will show a single lesion on CT, and about half this number will have multiple lesions in in the basal ganglia. Less common findings include white matter abnormalities, cortical atrophy, and sinus thrombosis.
- Conventional cerebral angiography or MRA may show evidence of intracranial stenosis in 40% of patients, half of which are in the MCA branches. Only 22% of patients may show extracranial lesions. Dural sinus thrombosis is a common finding. Rarely, the angio gram picture may be suggestive of vasculitis.

SPECIAL TESTS
None

Characteristics of aPL syndrome
- Antiphospholipid syndrome: thromboembolic events
- Thrombosis
- Pregnancy complications
- Thrombocytopenia
- Hypercoagulability
- Lupus
- Anticardiolipin antibodies (aCL)
- Plasma protein with high affinity to anionic phospholipids
- Antibody binding to citrine
- Immune complex formation
- Prothrombotic state
- APL: Antiphospholipid antibody syndrome
- APS: Antiphospholipid syndrome
- aCL: Anticardiolipin antibody
- LA: Anticardiolipin antibody
- Ig: Immunoglobulin
- HLA: Human leukocyte antigen
- G0: White blood cell count
- D-dimer: Dimeric fibrinogen fragment
- CEA: Carcinoembryonic antigen
- TIA: Transient ischemic attack
- VDRL: Venereal disease research laboratory test
- MRA: Magnetic resonance angiography
Management

GENERAL MEASURES

There are no good prospective studies to support any particular mode of therapy. Different therapeutic strategies include the use of antiplatelet agents, anticoagulants and immunomodulators individually or in combination. Multicenter collaborative trials are studying the usefulness of aspirin-warfarin in APS.

Control of Risk Factors
- Avoid smoking, excessive alcohol intake, and oral contraceptive pills.
- Management of blood pressure.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

Varies widely with symptoms.

ADJUNCTIVE TREATMENT

Varies widely with symptoms.

ADMISSION/DISCHARGE CRITERIA

Admission is required for management of acute thrombosis.

MEDICATIONS

DRUGS OF CHOICE

Antplatelet Agents
- Aspirin: aspirin reduces the risk of stroke recurrence by inhibiting platelet aggregation through inhibition of endothelial prostacyclin synthesis. Although it has been widely used as a prophylactic agent for stroke, the efficacy of aspirin in APS is uncertain. Aspirin can be used in variable doses of 81 to 1,300 mg, in patients with a single thromboembolic event and positive aCLs.
- Other antplatelet agents: ticlopidine, clopidogrel, and dipyridamole have not been studied in the aCL-positive sbgr op of str oke patients.

Anticoagulants
- Warfarin is an effective therapy for recurrent thromboembolic events, with an international normalized ratio (INR) aim of >3. Abrupt discontinuation of the medication may increase the probability of recurrent thrombosis. A combination of aspirin and warfarin has been used for patients who continue to have recurrent events on warfarin alone.
- Heparin: high doses of unfractionated heparin or low molecular weight heparin appear to be efficacious in protecting against recurrent thrombosis.

Thrombolytics
- Alteplase rtPA has been successfully used in few patients with APS, and can be used in selective patients with acute stroke.

Plasma Exchange
- Plasma exchange may lower the level of circulating antibodies; repeated exchanges may be required to avoid a rapid rise in aPL titers.

Steroids
- There is no conclusive evidence for a positive role for steroids in aCL-positive stroke patients. Its use in pregnant women was associated with decrease incidence of fetal loss, especially in patients with SLE.

Immunoglobulin Therapy
- The role of intravenous immunoglobulin (IVIG) in APS is not well undertaken. but is thought to bind to receptors on the endothelial cells prohibiting the interaction of aPL with receptors. Immunoglobulin therapy may cause thrombosis especially in elderly patients and in patients with other risk factors for thrombosis.

Immunosuppressive Agents
- Azathioprine, cyclophosphamide, and methotrexate, with or without corticosteroids, have been used in refractory APS, with remarkable decrease of aCL titers and LA activity.

Contraindications
- Known hypersensitivity reactions for any of the above drugs. Warfarin is contraindicated in those with active or potential sources of bleeding or frequent falls.

PRECAUTIONS

N/A

ALTERNATIVE DRUGS

Fish oil derivatives may help in preventing recurrent miscarriage in APS women.

Follow-Up

PATIENT MONITORING
- Patients should be reevaluated for new neurologic complaints. Those on warfarin require routine monitoring of coagulation parameters.

EXPECTED COURSE AND PROGNOSIS
- The disease duration is thought to be longer in secondary APS, after the initial manifestations or after the detection of circulating aCLs. The rate of recurrence of stroke or TIA in patients with APS is 35% to 50%.

PATIENT EDUCATION

N/A

Miscellaneous

SYNONYMS
- Hughes’ syndrome

ICD-9-CM: 795.79 Anticardiolipin antibody syndrome and antiphospholipid syndrome, with the code given for nonspecific immunologic findings, should be used in conjunction with codes for the specific symptoms/disorders associated with the presence of circulating aPLs: 436 Stroke; 435 TIA; 362.31 Central retinal artery occlusion; 363.5 Central retinal vein occlusion; 362.34 Amaurosis fugax; 695.4 Lupus

SEE ALSO/N/A

REFERENCES

Author(s) Rima M. Dafer, MD; Gretchen E. Tietjen, MD

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Arachnoiditis

Basics

DESCRIPTION
• Arachnoiditis is a nonspecific inflammatory process of the arachnoid (middle) layer of the meninges, classically the result of an insult to the membrane by an irritant, infection, or other foreign body introduced into the subarachnoid space of the spinal cord. The disease process of lumbosacral arachnoiditis is perhaps best viewed on a continuum, ranging from a mild thickening of the arachnoid membranes that is clinically asymptomatic to the progressive heavy scarring of adhesive arachnoiditis. In the most severe cases, spinal cord roots may be compressed by bands of collagen scar tissue and lead to a clinically debilitating myeloradiculopathy with weakness and paraesthesias of the lower limbs.

EPIDEMIOLOGY
Incidence/Prevalence
• Clinically significant arachnoiditis is much less common than radiographic evidence of the disease. The incidence is 1.8% of patients with a history of an iodophendylate (Pantopaque or Myodil) myelogram, an oil-based intrathecal contrast agent that was used in the United States until the 1980s.

Race
• No demonstrated ethnic predominance

Age
• Adults of all ages are at risk for arachnoiditis; risk is increased for older patients because of the increased frequency of lumbar disc disease; 25- to 65-year-old patients are at highest risk.

Sex
• May affect men more frequently than women.

ETIOLOGY
• Arachnoiditis is classically caused by a local inflammatory reaction of the arachnoid matter covering the nerve roots of the spinal cord in response to the presence of irritants, infections, or foreign bodies. The inflammatory process may be contained to a minimal/self-limited local response without clinical significance, or it can progress to complete obliteration of the subarachnoid space by swollen arachnoid sheaths. A more chronic phase is characterized by the deposition of scar tissue, causing the protective layers and the nerve roots to adhere to one another. In a small percentage of patients, this will calcify. Common causes include local spinal trauma from postsurgical procedures, lumbar puncture, spinal anesthesia, postoperative infection (after spine surgery), and, most commonly in modern western cultures, myelography, especially with oil-based contrast agents. Other known etiologies include herniated spinal disc, primary spinal stenosis, intrathecal blood or subarachnoid hemorrhage, intrathecal steroids, or chemotherapeutic agents. Although arachnoiditis classically involves the lumbosacral roots of the cauda equina, it can involve the arachnoid membrane in any part of the CNS.

Genetics
N/A

RISK FACTORS
• There are several well-known risk factors, including previous myelography, especially with oil-based intrathecal radiographic contrast materials with risk increasing for multiple or traumatic myelograms. A significant span of time may elapse between administration and clinical presentation (as long as decades). Although most commonly associated with intrathecal contrast agents, there are other, less frequently associated risk factors, including postoperative wound infections in the lumbar region after spinal surgery, previous spinal surgery, repeated lumbar procedures (particularly failed back syndrome), primary spinal stenosis, and intrathecal or epidural administration of therapeutic agents, including spinal anesthesia.

PREGNANCY
• There are no well-reported complications with pregnancy.

ASSOCIATED CONDITIONS
• Arachnoiditis can be seen in association with failed back syndrome (11% of patients). Other disease associations include sarcoidosis, spinal stenosis, ankylosing spondylitis, and fibromyalgia.

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Herniated disc
• Degenerative joint/disc disease
• Chronic back pain
• Infection
• Muscle or ligament strain
• Metastatic bone disease
• Osteoporotic states
• Paget's disease
• Structural congenital abnormalities
• Referred pain
• Multiple myeloma
• Psychogenic
• Other

SIGNS AND SYMPTOMS
• An alternative diagnosis to arachnoiditis should be considered if there is sudden pain following an intraspinal procedure or if the presentation is acute. Development of arachnoiditis depends on the etiology and can present months after a failed back surgery or as long as decades after myelography. Arachnoiditis represents a nonspecific, sometimes confusing, clinical picture. It can present with burning pain in one or both legs and/or the lower back; back pain made worse with activity; sciatica; positive straight-leg raise; tenderness at the sciatic notch; muscle spasm and leg cramps; limited trunk movement/limb stiffness; or motor, sensory, and/or reflex changes that occur bilaterally in as many as two thirds of selected patient groups. Such changes can involve only one root or can be more widespread, involving many roots. This can progress to monoparesis or paraparesis. Urinary frequency, urgency, or incontinence sometimes is seen.

LABORATORY PROCEDURES
• There are no reliable blood or CSF tests to help diagnose arachnoiditis.

IMAGING STUDIES
• MRI is the primary imaging modality for arachnoiditis. Findings include abnormal position and/or morphology of nerve roots, often with adhesion to the surrounding arachnoid membranes. Radiographic evidence of arachnoiditis occurs frequently in asymptomatic patients. Arachnoiditis tends to coexist with additional pathology; this pathology is important in treatment planning because it can represent potential curative aspects of the disease. Myelography often is avoided because of the success of less invasive imaging studies.

SPECIAL TESTS
• Infectious etiologies can be evaluated with CSF analysis.

Management

GENERAL MEASURES
• Despite many promising treatment possibilities, arachnoiditis generally responds poorly to treatment and is considered a permanent condition by some clinicians, with therapy related only to symptomatic care. Prevention is an important component of arachnoiditis. Specific treatment should be given if any underlying pathology is detected, such as a herniated lumbar disc or focus of infection, such as tuberculosis arachnoiditis.
Admission/Discharge Criteria

- Patients generally are evaluated and treated as outpatients. Admission may be indicated for patients with intractable pain or with acute changes in neurologic status.

Surgical Measures

- Correlation between clinical and radiologic findings may be difficult because of the frequency of asymptomatic radiographic findings on imaging studies. Clinical presentation and a history of classic etiologies with associated MRI findings may provide the most accurate means of evaluation. Surgical intervention is controversial. Exploratory surgery in the absence of progressive neurologic deficit or with well-controlled pain usually is not indicated. Surgical intervention with the presence of potentially cable pathology, including disc disease or other focal abnormality, is reasonable. In selected patients with progressive neurologic deficits, surgical neural micro-decompression with lysis of arachnoid scarring may be considered.

- Initial operative success may be tempered by conservative care includes symptomatic relief.

- Definitive treatment for arachnoiditis is limited to cases of arachnoiditis.

- Cordotomies usually are not recommended.

Adjunctive Treatment

- Several different adjunctive treatments can be considered, including dorsal column stimulators, transcutaneous electrical nerve stimulators for pain control, or intrathecal morphine or baclofen. Use of epidural steroids is controversial, because some investigators have related this treatment to actually causing arachnoiditis. Intrathecal hyaluronidase in spinal arachnoiditis caused by tuber culosis meningitis has been reported as successful, although preservative-free hyaluronidase is not FDA approved for use in the United States. Cordotomies usually are not recommended.

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Symptomatic Treatment

- Definitive treatment for arachnoiditis is limited to eliminating possible sources of irritants through prevention, medical therapy, or surgical intervention.

- Conservative care includes symptomatic relief with antiinflammatory and pain medications, patient education, and behavioral control.

Adjunctive Treatment

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Follow-Up

- Arachnoiditis is a chronic disease with the usual associated patient and caretaker issues. Regular scheduled follow-up is important. Although serial imaging studies are not customarily needed, any changes in neurologic or pain status should prompt a more complete workup. No regular patient monitoring of laboratory tests or imaging studies are required once a firm diagnosis is made. However, proper attention to changes in neurologic or pain status should prompt workup to rule out additional pathology.

Expected Course and Prognosis

- There is no cure for arachnoiditis. There is a wide spectrum of clinical disease ranging from mild to very severe. In one study with long-range follow-up, pain and functional disability tended to remain the same as they were at the time of diagnosis. Although most patients were able to walk and drive a car, their ability to return to full-time work was limited. This study also noted that a majority of subjects depended on daily narcotic analgesics.

Medications

- For pain control, consider gabapentin (Neurontin), start 300 mg PO qhs, increase by 300 mg/day over several days, maximum dose of 3,600 mg/day; or amitriptyline, start 10-25 mg PO qhs, gradually increase to effective dose of 100 mg/day.

- Amitriptyline should not be used in conjunction with monoamine oxidase inhibitors. Adjunctive pain control medication and referral to a pain management specialist can be considered in patients with intractable pain.

- Gabapentin: Decrease dose in renal impairment; not FDA approved for neuropathic pain.

- Amoxicillin and noroxitryline: Orthostatic hypotension, arrhythmias, and anticholinergic side effects; not FDA approved for chronic pain.

- Muscle relaxants on a short-term basis may provide relief in selected patients.

Patient Education

- National Organization for Rare Disorders, Inc. (NORD), P.O. Box 8923, New Fairfield, CT 06812-8923. Website: www.nord-nhid.com

- NIH/National Institute of Neurological Disorders and Stroke, 31 Center Drive, MSC 2540, Building 31, Room 8A16, Bethesda, MD 20892. Website: www.ninds.nih.gov

References


Author(s): L. Mervis, MD; Alexander M. Mason, MD
Arsenic Poisoning

**Basics**

**DESCRIPTION**
- Arsenic neuropathy is part of a systemic illness due to excessive exposure to this toxic metalloid. Arsenic is easily obtained because it is commonly used as a rodenticide, herbicide, and insecticide. It has a long history of medicinal applications, but it is also a notorious homicidal or suicidal agent. The neurologic consequences of recent or chronic intoxication are similar to those of acute intoxication.

**EPIDEMIOLOGY**
**Incidence**
- Little information exists, but its presence undoubtedly exceeds its recognition. There is no known predilection for individuals of any race, age, or sex.

**ETIOLOGY**
- Homicidal and suicidal applications account for most cases of acute intoxication. Other considerations include iatrogenic medicinal exposures (usually folk medicines) and inadvertent exposure to contaminated foods, beverages, water, or combustion fumes. Arsenic is a general protoplasmic poison that interferes with cellular energy metabolism.

**Risk Factors**
- The primary risk factor is excessive arsenic exposure from any source.

**PREGNANCY**
- There is no known relationship with pregnancy. Arsenic is not known to present any particular danger to the fetus at typical environmental concentrations.

**ASSOCIATED CONDITIONS**
- In addition to neuropathy, associated conditions are toxic encephalopathy, chemical hepatitis, pancytopenia, renal tubular necrosis, dermatitis with hyperkeratosis, pancreatitis, and cardiomyopathy. Inorganic arsenic compounds are human carcinogens associated with hepatic angiosarcoma and skin cancer.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Guillain-Barre syndrome (GBS), acute porphyric neuropathy, HIV-associated neuropathy, confluent va scular mononeuritis multiplex, chronic inflammatory demyelinating polyneuropathy, other dyssynaptic neuropathies associated with plasma cell dyscrasias (Waldenstrom's macroglobulinemia, y heavy-chain disease, cryoglobulinemia, systemic lupus erythematosus, Castleman's disease), lymphoma or occult malignancy, other toxic neuropathies (amiodarone, carbon disulfide, cytotoxic arabinoside, methyl-n-butyl ketone, n-hexane)

**SIGNS AND SYMPTOMS**
- After acute exposure, symptoms of transient nausea, vomiting, and diarrhea, followed 5 to 10 days later by distal numbness and tingling, intense paresthesias, and burning pain, muscle tenderness, and weakness
- Neurologic signs include profound length-dependent sensory loss, weakness (sometimes progressing to quadriplegia with respiratory failure), areflexia, and dysautonomia. CNS signs include drowsiness, confusion, stupor, and coma. Signs reflect the magnitude of exposure and typically progress over several weeks after a single exposure.
- Additional signs include Mees lines (transverse bands in all nails) and pigmented dermatitis. Mees lines do not appear until about 1 month after acute ingestion, which limits their usefulness when the diagnosis is in question.

**LABORATORY PROCEDURES**
- Arsenic is readily absorbed and rapidly excreted in the urine (half-life in blood of about 60 hours). The amount of urinary excretion reflects the magnitude of exposure. A 24-hour collection is most reliable for establishing exposure. Abnormal excretion documents potential exposure, not intoxication. Transient increases are common after ingestion of some seafood items (the organic form of arsenic contained in seafood is not neurotoxic).
- Arsenic is rapidly cleared from the blood, so blood levels are helpful only when the blood is collected within several days of acute poisoning.
- Arsenic is bound to keratin, and remote exposures can be documented by the amount of arsenic present in hair or nails.
- CSF protein is elevated (150-300 mg/dL) early in the course of neuropathy.
- Other laboratory abnormalities reflect systemic involvement and include abnormal liver function studies, pancytopenia, and basophilic stippling of RBCs (a nonspecific but important indication of a toxic exposure).

**IMAGING STUDIES**
- There are no specific imaging abnormalities. Chest x-ray film may demonstrate cardiomegaly.

**SPECIAL TESTS**
- Nerve conduction studies (NCSs) at onset may suggest the presence of an acquired demyelinating neuropathy, with motor nerve evidence of abnormal temporal dispersion, partial conduction block, slowed conduction velocity, and prolonged distal latency. Sensory nerve responses may be of low amplitude or unobtainable.
- NCS and needle EMG findings progress to those of an axonal sensorimotor neuropathy, often with loss of distal responses and profuse fibrillation potentials.
- Sural nerve biopsy occasionally is required to exclude other considerations, such as vasculitis. Biopsy results in arsenic neuropathy are nonspecific and include a decreased number of myelinated fibers, with axons in varying stages of axonal degeneration.
- Toxicologic examination at autopsy (e.g., liver or kidney) can establish intoxication.

**Management**

**GENERAL MEASURES**
- Establish the diagnosis and remove the patient from exposure, although removal from exposure frequently is impossible because most cases involve single massive exposures.
- The treatment of acute arsenic poisoning is beyond the scope of this section but may include gastric lavage, hemodialysis, and chelation to increase arsenic excretion.
- Arsenic neurotoxicity progresses for weeks after a single toxic exposure. By the time neurologic signs develop, it is questionable whether chelation or related treatments, such as hemodialysis, influence the rate or extent of neurologic progression or recovery.

**SURGICAL MEASURES**
- Not applicable, other than sural nerve biopsy

**SYMPTOMATIC TREATMENT**
- Painful paresthesia may require symptomatic analgesic treatment.
**Chelation agents used for treatment of**  
**Autonomic dysfunction may require**  
**The decision to proceed with chelation**  
**Precautions**  
- Impaired renal or liver function, pregnancy, hypertension, prior hypersensitivity, or allergic reaction

**Follow-Up**

**PATIENT MONITORING**

- Arsenic neuropathy may progress for many weeks after removal from exposure, so it is necessary to monitor patients for development of respiratory distress or dysautonomia until a plateau is reached or improvement is documented. Respiratory function should be monitored with interval measurement of FVC. Arterial blood gases are poor indicators of impending respiratory failure. Autonomic dysfunction requires monitoring of vital signs for hypotension or cardiac dysrhythmia. Systemic manifestations, such as renal failure or hepatic dysfunction, usually appear early in the course of intoxication, shortly after resolution of the acute gastrointestinal syndrome.

**EXPECTED COURSE AND PROGNOSIS**

- For patients who survive the acute systemic illness, including the complications of respiratory support, the prognosis for recovery is good. The systemic features of bone marrow suppression resolve rapidly, as do the chemical hepatitis and other non-neurologic features. The neuropathy becomes the most feared residual manifestation. The degree of axonal degeneration may be severe, and recovery typically is protracted. Patients who remain respiratory dependent and nonambulatory for months require long-term rehabilitation. Neurologic improvement occurs over many years, but residual distal sensory and motor deficits, similar to those observed among patients with severe GBS or other forms of nonprogressive neuropathy, are common.

**PATIENT EDUCATION**

N/A

**ADJUNCTIVE TREATMENT**

- Supportive care includes monitoring and management of respiratory function and prevention or treatment of infection, circulatory failure, and thromboembolism.
- Intubation is generally required when the forced vital capacity (FVC) approaches 15 mL/kg, but elective intubation should be considered when there is a rapid decline in FVC, independent of the absolute level.
- Autonomic dysfunction may require management of hypotension or cardiac dysrhythmia.
- Acute renal failure may require hemodialysis.
- Anecdotal reports suggest that therapeutic plasma exchange does not influence the course of neuropathy.

**ADMISSION/DISCHARGE CRITERIA**

- Admission criteria reflect the type and severity of the systemic involvement, as well as the magnitude and rate of progression of the neuropathy. All patients with progressive quadripareisis, respiratory decline, or evidence of dysautonomia require hospitalization and monitoring for progression.
- Discharge of patients with arsenic neuropathy is usually to a rehabilitation facility, depending on the magnitude of the residual impairment and deconditioning.

**DRUG(S) OF CHOICE**

- Despite a lack of evidence that chelation treatment influences the rate or extent of neurologic progression or recovery, standard treatment is chelation administration early in the course of the systemic intoxication.
- Chelation agents used for treatment of acute arsenic poisoning include DMPS (2,3-dimercaptopropanesulfonic acid), succimer (meso 2,3-dimercaptosuccinic acid, DMSA), and dimercaprol (British Anti-Lewisite, BAL) DMPS is preferred by some, but it is not widely available and is not FDA approved, which necessitates use of other agents in some cases. Succimer is the agent of choice for patients who can take PO medications. For those who cannot take PO succimer, BAL is recommended. Contraindications
  - Impaired renal or liver function, pregnancy, hypertension, prior hypersensitivity, or allergic reaction

**PRECAUTIONS**

- The decision to proceed with chelation should be approached cautiously if treatment is being given only to treat the neurologic impairment (because of the lack of demonstrable efficacy).

**ALTERNATIVE DRUGS**

- Other chelating agents are available, but the relative advantages and risks are unspecified.

**PATIENT MONITORING**

- Arsenic neuropathy may progress for many weeks after removal from exposure, so it is necessary to monitor patients for development of respiratory distress or dysautonomia until a plateau is reached or improvement is documented. Respiratory function should be monitored with interval measurement of FVC. Arterial blood gases are poor indicators of impending respiratory failure. Autonomic dysfunction requires monitoring of vital signs for hypotension or cardiac dysrhythmia. Systemic manifestations, such as renal failure or hepatic dysfunction, usually appear early in the course of intoxication, shortly after resolution of the acute gastrointestinal syndrome.

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**PATIENT EDUCATION**

N/A

**REFERENCES**


**SYNONYMS**

- Toxic neuropathy, arsenical polyneuropathy, neuropathy due to arsenic

**ICD-9-CM**

357.7 Polyneuropathy, arsenical

**SEE ALSO**

N/A

**ADJUNCTIVE TREATMENT**

- Supportive care includes monitoring and management of respiratory function and prevention or treatment of infection, circulatory failure, and thromboembolism.
- Intubation is generally required when the forced vital capacity (FVC) approaches 15 mL/kg, but elective intubation should be considered when there is a rapid decline in FVC, independent of the absolute level.
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  - Impaired renal or liver function, pregnancy, hypertension, prior hypersensitivity, or allergic reaction

**PRECAUTIONS**

- The decision to proceed with chelation should be approached cautiously if treatment is being given only to treat the neurologic impairment (because of the lack of demonstrable efficacy).
Attention Deficit Hyperactivity Disorder

**Description**

- Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental syndrome with symptom onset typically by age 7, most often between ages 3 and 5. It is primarily characterized by two symptoms: (i) inattention, and (ii) hyperactive and impulsive behaviors. The DSM-IV (1994) categorizes ADHD into three major subtypes: (i) predominantly inattentive type, (ii) predominantly hyperactive-impulsive type, and (iii) combined type.

**Epidemiology**

- Majority of studies report rates of 2%-5% within a school-aged population; therefore, 1-3 million children in the United States meet DSM-IV criteria for ADHD. ADHD occurs across cultures and genders. Boys seem to be affected at least three times more often than girls, and some statistics show the rates of boys to girls as high as 9:1. However, a recent epidemiologic study shows that girls are underdiagnosed and are diagnosed at a later age than boys. Differences in symptom expression may partially account for this. Boys tend to exhibit the more observable symptoms of hyperactivity and impulsivity, whereas girls tend to have the less obvious symptoms of inattention. About 60% of children will have residual symptoms into adulthood. In adulthood, the gender ratio of ADHD is 1:1.

**Etiology**

- Exact etiology of ADHD is not yet known, but recent research implicates both genetic and environmental factors. Growing evidence suggests that ADHD is genetically determined and primarily affects dopaminergic functions in the prefrontal cortex. Functional differences in the brains of ADHD patients are characterized by decreased prefrontal cortex dopaminergic activity and cerebral blood flow. Several twin studies demonstrate strong heritability. However, environmental contributions, such as premature birth, in utero exposure to substances, lead exposure, and psychosocial adversity, also are associated with ADHD symptoms in about 20%-30% of cases.

**Risk Factors**

- Family history of ADHD
- Significant environmental factors such as premature birth, in utero exposure to substances, lead exposure, and psychosocial adversity
- Traumatic brain injury
- Neurological disorders such as Tourette's syndrome and seizure disorder

**Pregnancy**

- Pregnant women who smoke, ingest alcohol or other illicit substances, or deliver prematurely are at higher risk for having a child with AND.

**Associated Conditions**

- Approximately 65% of children with ADHD will have a comorbid psychiatric condition. Most common are oppositional-defiant disorder (40%-50%; predominantly boys); anxiety and mood disorders (10%-35%; predominantly girls); learning disabilities (30%-40%), and conduct disorder (10%). Children with untreated ADHD are at high risk for developing significant comorbidities as they age. Children with seizure disorder (30%) and Tourette's syndrome (40%-70%) can have comorbid ADHD symptoms that warrant treatment.

**Diagnosis**

**Differential Diagnosis**

- Because disruption of attention is a final common pathway affected by many psychiatric and neurological disorders, the diagnosis of ADHD must be made in exclusion of other disorders that can account for the symptoms. Therefore, it is essential to rule out other psychiatric conditions, such as pervasive developmental disorders, obsessive-compulsive disorder, and other anxiety and mood disorders, especially bipolar disorder. Neurological conditions, such as seizure disorder, head trauma, birth trauma, mental retardation, and Tourette's syndrome, must also be taken into consideration. The DSM-IV has very specific criteria for diagnosing ADHD, including symptom descriptions, time of symptom onset, symptom duration, and impairment criteria.

**Signs and Symptoms**

- The first signs of ADHD often are observed in a school setting, with teacher complaints initiating a referral. Children with ADHD can be excessively active, unable to sit still, disruptive to others, loud, inattentive, distractible, unable to focus on a task at hand, and impulsive. Due to these behaviors, academic performance often is below expected for their age and IQ. Peer and interpersonal interactions also are impaired. Depending upon the subtype and severity of ADHD in a particular child, a physician may not always be able to observe the symptoms in a brief office visit, and observational data from outside sources (e.g., teachers) are necessary for accurate diagnosis.

**Symptomatic Treatment**

- The most effective treatment of ADHD is multimed and includes medication, academic accommodations, and behavioral interventions. The recent MTA (Multimodal Treatment Study of Children with ADHD) demonstrated that when a multimodal approach to ADHD treatment was implemented, 68% of the subjects attained a normalized behavior. Educational accommodations are necessary and implemented via the school system. For the vast majority of cases, drug "holidays" are neither necessary nor advisable.

**Adjunctive Treatment**

- Cognitive behavioral therapy, parent training, social skills groups, occupational and physical therapy, and academic interventions may be needed depending, upon the specifics of the case.

**Laboratory Procedures**

- N/A

**Imaging Studies**

- N/A

**Special Tests**

- N/A

**General Measures**

- Educational accommodations are almost always required in addition to medication management of symptoms. Psychoeducational evaluations and individual education programs should be pursued via the school system. Although behavioral therapy alone typically is not effective in fully controlling ADHD symptoms, behavioral treatments are a powerful adjunct to management with medication.

**Surgical Measures**

- N/A

**Management**

- N/A
ADMISSION/DISCHARGE CRITERIA

- Admission for evaluation of ADHD is rarely needed, unless a comorbid neurologic or psychiatric condition requires inpatient evaluation.

Medications

**DRUG(S) OF CHOICE**

- Stimulants are considered first-line therapy, with methylphenidate (MPH) therapies most commonly prescribed, followed by amphetamine-based therapies. Approximately 70% of children with ADHD will have a therapeutic response to stimulant treatment. Of the 30% who do not get a good response, switching to a different stimulant often will result in efficacy. Studies also demonstrate that, for the majority of ADHD patients, efficacy from stimulant therapy is not achieved until reaching a MPH dose of at least 15-20 mg/day.

- Long-acting methylphenidate products are now the treatment of choice and include Concerta (18-72 mg/day) and Metadate CD (240 mg/day). These medications are given once daily in the morning and last up to 9 h (Metadate CD) to 12 h (Concerta). The short-acting methylphenidate Ritalin (5-60 mg/day) is highly effective but wears off in 3-4 h, necessitating multiple dosing and possibly causing rebound of symptoms during wear-off. A newer short-acting form of MPH, d-MPH, is now available under the name Focalin*. Focalin is MPH minus the isomer and is purported to have fewer side effects than d-MPH. Ritalin SR was developed as a longer-acting form but has variable absorption and is not a preferred treatment. Ritalin LA, reportedly an improved version, will be available soon. Another form of MPH that will be available in the near future is the MethyPatch.

- Adderall (2.5-40 mg/day) and Adderall XR (10-40 mg/day), which are mixed-amphetamine salts compounds, are also commonly used long-acting stimulant therapies and last about 6 h (Adderra II) to 10 or more hours (Adderra II XR). The side effect profile for amphetamines, including Adderall, is higher than for MPH. Because of this, the amphetamine-based compounds Dexedrine and Dextrostat are rarely used minimally.

- For children with comorbidities, combination pharmacotherapy often is necessary. Selective serotonin reuptake inhibitors, antidepressants, mood stabilizers, and a-adrenergic agonists are all commonly used in conjunction with stimulants to treat ADHD and a associated comorbid conditions.

**Contraindications**

- Stimulants are contraindicated in children with a history of mania or bipolar disorder, psychosis and/or thought disorder, marked anxiety, high blood pressure, or glaucoma. Stimulants are not used in conjunction with monoamine oxidase inhibitors. Use with antiepileptic agents and anticoagulants must be closely monitored.

- Although MPH was once thought to be contraindicated in children with Tourette’s syndrome and comorbid ADHD, a recent study demonstrated that this contraindication is not warranted.

**Precautions**

- The most common side effects of stimulants include loss of appetite, insomnia, headache, nausea, irritability, and depression. In general, stimulants are well tolerated, and side effects tend to be mild and wane over a few days after initiating treatment. Sleep disturbance and appetite loss should be carefully monitored and managed clinically if necessary (note: many children with ADHD have preexisting sleep disturbance unrelated to medication therapy). Little is known about treatment response of preschoolers with ADHD. Long-term effects of stimulants are not well established. Abuse potential is limited with longer-acting agents.

**ALTERNATIVE DRUGS**

- a-Adrenergic agonists (clonidine, ganfena cine) are second-line therapies that have a synergistic effect when used in conjunction with stimulants. Bupropion (Wellbutrin) has been touted as a treatment for ADHD, but data supporting its efficacy are limited. Imipramine and other tricyclics have been used in the past with modest efficacy, but use has been limited by concerns about cardiac toxicity and other side effects. Other alternative therapies are currently in development (e.g., atomoxetine).

**Follow-Up**

**PATIENT MONITORING**

- Patients should be monitored closely for side effects. The CTRS and CPRS can be used to monitor symptom response during treatment. Medication dosage can be titrated higher as long as the child is obtaining benefit without problematic side effects.

**EXPECTED COURSE AND PROGNOSIS**

- Highly variable, depending upon severity of comorbidities, environmental surroundings, and treatment compliance. For children with ADHD and minimal comorbidities, the prognosis with treatment is very good. For children with severe psychiatric or neurologic comorbidities, the prognosis is guarded. For children with ADHD who do not receive treatment, the prognosis is quite poor, and they are at risk for developing more severe psychiatric and behavioral problems, becoming abusers, drop outs of school, being unemployed, and having unstable relationships.

**PATIENT EDUCATION**

- CHADD: National organization for children and adults with ADHD, providing educational materials, research updates, and national conferences. Website: www.chadd.org

- NIH/NIMH has a web page devoted to diagnosis and treatment of ADHD. Website: www.nimh.nih.gov

**Miscellaneous**

**SYNONYMS**

N/A

ICD-9-CM: 314.0 Attention deficit disorder; 314.00 ADD without hyperactivity; 314.01 ADD with hyperactivity

**REFERENCES**


Author(s): Donna Palumbo, PhD; Roger Kurlan, MD
**DESCRIPTION**

- Autism is a condition characterized by delayed language, impaired social interaction, and stereotyped behavior with onset before age 3 years.

**EPIDEMIOLOGY**

- The incidence of autism is 2-5 cases per 10,000. There is no racial predilection known for autism, and the age of onset, by definition, is before age 3 years. There are 4-5 times as many males as females with autism.
- The incidence of autism is increased when a first-degree relative is affected. A small percentage has an inverted duplication on the proximal long arm of chromosome 15 (15g11-q13) that usually is maternally inherited.

**RISK FACTORS**

- Patients with fragile X syndrome or tuberous sclerosis have an increased incidence of autism. Otherwise, there is no confirmed risk factor for autism, although preliminary evidence suggests perinatal stressors may be a risk factor.

**PREGNANCY**

- There are no known issues specific to managing autism during pregnancy.

**ASSOCIATED CONDITIONS**

- There is a 75% incidence of mental retardation with autism. There is also an increased incidence of seizures in patients with autism. A variety of behavioral disturbances are also associated with autism. Although frank macrocephaly is uncommon, there is a tendency toward a larger head size in autism.

**DIFFERENTIAL DIAGNOSIS**

- Asperger’s syndrome resembles autism with relatively preserved language.
- Pervasive developmental disorder—not otherwise specified (PDD-NOS) describes the condition where features of autism are present but the criteria for autism or Asperger syndrome are not met.
- Collectively, the related conditions of autism, Asperger’s syndrome, and PDD-NOS are referred to by some specialists as “autism spectrum disorder.”
- Rett’s disorder consists of normal development for the first 5-48 months, followed by deceleration of head growth, stereotyped movements (typically midline hand movements) axial incoordination, loss of language skills, and retardation. Only females are affected.
- Fragile X syndrome is a genetic disorder that often can present with some autistic features.
- Landau-Kleffner syndrome consists of seizures originating in the language area, and occasionally this can resemble autism.
- Childhood-onset schizophrenia is characterized by early normal development followed by the development of schizophrenia, and can sometimes resemble autism.
- Mental retardation sometimes can be difficult to distinguish from autism with mental retardation when retardation is sufficiently severe.

**SIGNS AND SYMPTOMS**

- Signs and symptoms of autism develop by age 3 years, usually without a period of normal development previously (except in occasional patients in whom development is normal in the first 1-2 years), in three domains:
  - Impaired social interaction: There is a lack of eye-to-eye gaze, blunted or abnormal facial expression, impaired use of social gesture, poor development of peer relationships (either lack of interest or lack of ability), lack of sharing enjoyment or interests with others, lack of social reciprocity, and inappropriate response to others’ needs or distress.
Management

GENERAL MEASURES
• Early and intensive behavioral intervention appears to be critical to optimizing development of functional ability in autism. This should be initiated as soon as possible after diagnosis and continued throughout schooling.
• Appropriate vocational rehabilitation services would be needed for those with sufficient cognitive ability to handle work.
• Medical treatment is directed at specific neuropsychiatric disturbances, such as obsessive-compulsive disorder, depression, agitation management, self-injurious behavior, anxiety, and sleep and eating disorders.
• No specific treatment for autism exists, but research on several agents is ongoing.

SURGICAL MEASURES
• There are no surgical measures specific to autism.

SYMPTOMATIC TREATMENT
• Behavioral therapy, sensory integration occupational therapy, auditory integration therapy, speech therapy, and cognitive therapy are options, as is vocational rehabilitation for older and higher functioning individuals.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• There are no admission/discharge criteria specific to autism, other than to ensure that the environment is safe and appropriate to the patient’s level of functioning.

Medications

DRUG(S) OF CHOICE
• As of yet, there is no specific drug for autism (see Management—General Measures)

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
• Monitoring should include follow-up visits to monitor effects of drugs used to treat neuropsychiatric conditions associated with autism and to monitor for adequacy of behavioral intervention strategies.

EXPECTED COURSE AND PROGNOSIS
• Individuals with autism often slowly improve with regard to their impairments as they develop through school years and adolescence, but seldom improve to the point of independent functioning. Occasional patients will have a behavioral decline during adolescence, often associated with difficulty handling the increase in complexity of social interaction in adolescence. Improvement is greatest in individuals with better language skills and higher overall intelligence.

PATIENT EDUCATION
• Families should be informed of the importance of early intervention and should be given information on regional chapters of the Autism Society of America to help them locate other appropriate resources and support.
• Autism Society of America, 7910 Woodmont Avenue, Suite 300, Bethesda, MD 20814-3015. Phone: 1-800-3AUTISM, website: www.autism-society.org

Miscellaneous

SYNONYMS
• Infantile autism
• Kanner’s syndrome

ICD-9-CM: 299.00 Infantile autism current or active state
SEE ALSO: N/A

REFERENCES
Author(s): David Q. Beversdorf, MD
Back Pain, Spondylosis, Lumbar Canal Stenosis

Basics

DESCRIPTION
- Lumbar spondylosis (LS) refers to degenerative changes including disc disease, osteophyte formation, facet joint disease, and ligamentous laxity, which can cause stenosis, segmental instability, and/or neurologic deficits. Lumbar canal stenosis (LCS) refers to a decrease in total area of spinal canal, lateral recess, or neural foramen. Other commonly used terms are spondylolisthesis (forward movement of one vertebral body in relation to the vertebral body below it) and spondylosis (congenital or degenerative/posttraumatic absence of the pars interarticularis between the vertebral body and posterior bony spinal elements, frequently associated with spondylolisthesis).

ETIOLOGY
- Approximately 80% of the adult population suffers from low back pain at some point during their lifetime. LS is one of the most frequent causes of low back and/or leg pain. The prevalence of LS by MRI studies ranges from 33% at age 20 to 95% in women >70. About 95% of males and 80% of females >65 show MRI evidence of LS. Plain radiographic evidence of LS is seen in about 80% of patients >65.

Spondylosis is most frequent in the cervical and lumbar spine, the most mobile regions of the spinal column.

LCS most commonly involves the L4-5 level, followed by L3-4, L2-3, L5-S1, and L1-2.

Age
- Both LS and LCS are seen with increasing frequency after the fifth decade of life. Sex
- Males are affected more often than females.

ETIOLOGY
- LS results from a complex process of disc degeneration, bilateral facet joint arthropathy, and osteophyte formation. Facet joint cartilage destruction and capsular laxity lead to subluxation and segmental lumbar instability.

LCS:
- Congenital: idiopathic/achondroplastic
- Acquired: degenerative stenosis
- Iatrogenic: post lumbosacral fusion stenosis
- Metabolic: Paget's disease, fluorosis
- Posttraumatic
- Location of LCS: central canal/lateral recess/fornaminal stenosis or foraminal stenosis (compression between L5 transverse process and sacral ala)

• Narrowing of spinal canal diameter in extension by hypertrophied facets, buckling of ligamentum flavum, and protruding intervertebral disc aggravates symptoms, which are relieved by flexion
• Etiology of neurogenic claudication: narrowed canal prevents vaso dilatation of blood vessels with activity, causing ischemic neuritis of the nerves

Genetics

N/A

RISK FACTORS
- Trauma

PREGNANCY
- Back pain is frequent during the third trimester of pregnancy (due to additional abdominal weight) and usually resolves postpartum.

ASSOCIATED CONDITIONS
- Cervical canal stenosis

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Vascular claudication
- Referred pain from leg, hip joint disease
- Lumbar disc disease
- Peripheral neuropathy (e.g., diabetes)
- Vertebral osteomyleitis
- Spinal tumors (bone tumors/metastasis)
- Myofascial syndromes

SIGNS AND SYMPTOMS
- Pain: midline low back pain (lumbar instability, paraspinous muscle spasm); radiculopathy (with lateral recess and foraminal stenosis); neurogenic claudication (pain; sensory and/or motor changes on standing and walking, relieved with rest and/or flexion)
- Absent or minimal neural signs. Neural deficits are reproducible with walking in LCS.
- Patients usually stoop forward to relieve symptoms (stoop sign) and may use a shopping cart to maintain flexion. Extension is limited and painful
- Walking down stairs (i.e., extension) is more painful in LCS/neurogenic claudication; walking up stairs (i.e., flexion, exertion) is more painful in vascular claudication.
- Patients tend to walk with slight hip and knee flexion (simian stance)
- Straight-leg raising test usually is negative.

• Loss of lumbar lordosis is common.
• Examination of hip joints, abdomen, and peripheral vessels should be performed to rule out other etiologies or coexisting pathologies.

LABORATORY PROCEDURES
- CBC and differential; sedimentation rate; C-reactive protein to rule out infection or inflammatory process

IMAGING STUDIES
- Plain radiographs: Sagittal diameter of lumbar canal (normal 15-25 mm) is reduced below 12 mm in most patients with LCS. Lateral recess diameter (normal 3-5 mm) is reduced below 3 mm in patients with lateral recess stenosis. Foraminal height is reduced below 15 mm in patients with foraminal stenosis. Flexion-extension dynamic x-ray films may show subluxation of the involved spinal segments. Findings in LS include disc space narrowing, facet joint hypertrophy, LCS, foraminal stenosis, subluxation, and scoliosis.
- Myelography often reveals multiple areas of contrast compression (hourglass constriction). With lateral recess stenosis, myelography shows root sleeve claudication.
- Complete block produces a characteristic paint brush appearance.
- CT with or without contrast provides details of the bony anatomy and may provide information necessary for complex cases. Patients with previous lumbar instrumentation may show less artifact on CT than MRI; those with implanted devices (e.g., cardiac pacemakers) may be limited to CT.
- MRI is the preferred imaging modality. It is noninvasive, highly sensitive, provides excellent soft-tissue resolution, and shows the extent of neural compression without risk of radiation. Asymptomatic degenerative changes may be seen in 60% of patients on MRI. Hypertrophied bone is low signal on T1 and T2 images, whereas hypertrophied ligamentum flavum is intermediate signal on T1 and T2 images.

SPECIAL TESTS
- Neurophysiologic studies (EMG and nerve conduction velocity [NCV]) can be very helpful in difficult cases of suspected peripheral neuropathy, nerve root compression, or paraspinal muscle syndromes. Somatosensory evoked potential recording also can be helpful, especially when performed before and after a walking stress test.
Management

GENERAL MEASURES

• Conservative measures are helpful in most patients with LS and about 50% of patients with LCS. Physical therapy (spinal exercises, traction, heat or cold pack application), weight reduction, or spinal epidural/or foraminal injections can be tried in patients with LS or LCS. Flexion spinal exercises, which decrease lumbar lordosis, can be useful in patients with LCS. In LS patients with facet joint pain, facet joint injections are a useful option. A well-fitted lumbosacral corset can be helpful for low back pain secondary to instability.

SURGICAL MEASURES

• Indications for surgery include cauda equina syndrome, progressive neurologic deficits, and severe unrelenting pain. The onset of bowel or bladder dysfunction (incontinence or retention) is a surgical emergency, because permanent impairment in bowel or bladder function can quickly ensue. Surgery often is required in the presence of severe canal stenosis or segmental instability. Decompressive surgery (laminectomy, laminoforaminotomy, window laminotomy) of the stenotic segments by either open or endoscopic techniques is effective in most cases. Fusion should be considered for severe unrelenting back pain due to lumbar instability, or when stenosis requires complete excision of more than one facet joint at a particular level.

SYMPTOMATIC TREATMENT

• See General Measures

ADJUNCTIVE TREATMENT

• See General Measures and Surgical Measures

ADMISSION/DISCHARGE CRITERIA

• Emergent admission (and usually surgical treatment) is indicated for bowel or bladder dysfunction, sudden or progressive neurologic deficits, or cauda equina syndrome.

Medications

DRUGS OF CHOICE

• Nonsteroidal antiinflammatory drugs: ibuprofen, naproxen, celecoxib, rofecoxib

Contraindications

• Known history of gastrointestinal bleeding, hypersensitivity reaction to nonsteroidal antiinflammatory drugs, bronchial asthma

Precautions

• History of peptic ulcer, or renal, hepatic, or hematologic disease

ALTERNATIVE DRUGS

• Narcotic medications can be helpful for severe pain, and muscle relaxants for muscle spasms.

Follow-Up

PATIENT MONITORING

• Patients should be encouraged to keep a journal of activities performed and medication taken in order to have objective evidence of trends toward improvement or deterioration. Follow-up neurologic assessment should include, in addition to the standard motor and sensory examinations, the claudication distance in cases of LCS to assess progression of disease in functional terms. Serial EMG and/or NCV studies can be helpful to assess progression or improvement in selected cases.

EXPECTED COURSE AND PROGNOSIS

• About 50% of cases experience progressive worsening; 50% tend to be stationary or improve. About 80% of patients will have a satisfactory outcome after surgery; limited decompressive procedures (e.g., window laminotomy) have a quicker recovery time than more extensive decompressive surgery and/or fusion procedures. Operative morbidity ranges from 1%-2% up to 15%, depending upon the extensiveness of the procedure performed, initial versus reoperation, and the surgical risk status of the patient (e.g., age, medical conditions).

PATIENT EDUCATION

• Physical therapy can be very helpful in educating the patient about low back care, activities of daily living, risk avoidance, and use of walkers and other aids.

REFERENCES


Author(s): Raju S.V. Balabhadra, MD; Russell J. Andrews, MD

SYNONYMS

• Degenerative disc disease ICD-9-CM: 724.02 Lumbar stenosis

SEE ALSO: N/A

Miscellaneous
**Bell's Palsy/Facial Palsy**

**Basics**

**DESCRIPTION**
- Facial palsy is a syndrome of weakness of the facial musculature that may be due to a number of causes. Bell's palsy was traditionally considered to be idiopathic.

**EPIDEMIOLOGY**
- Facial palsy is the most common of the cranial neuropathies. The majority of cases are Bell's palsy.
- The incidence of Bell's palsy is estimated to be 23 per 100,000 annually. This disorder affects men and women equally. No differences in racial prevalence are known.

**Etiology**
- Significant evidence demonstrates that Bell's palsy is not idiopathic but rather due to infection with herpes simplex virus.

**RISK FACTORS**
- Diabetes mellitus
- Pregnancy

**PREGNANCY**
- Some studies show an increase in the incidence of Bell's palsy in the peripartum period.

**ASSOCIATED CONDITIONS**
- See Differential Diagnosis

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- The differential diagnosis of idiopathic facial palsy includes the numerous diseases that can injure the facial nerve by inflammation, infection, infiltration, compression, or trauma.
  - Neoplastic - Carcinomatous meningitis
  - Leukemic meningitis
  - Tumors (primary and metastatic) of the base of the skull
  - Parotid gland tumors
  - Cranial nerve VII (facial) neurinoma or cranial nerve VIII (acoustic) Schwannoma
  - Inflammatory or demyelinating
    - Sarcoidosis - Guillain-Barre syndrome
    - Malignant lymphoma
    - Infectious
      - HIV infection
      - Ramsay-Hunt syndrome (due to varicella-zoster infection)
      - Lyme disease
  - Idiopathic
    - Melkerson-Rosenthal syndrome (recurrent facial paralysis with facial edema, especially labial)
    - Idiopathic cranial polyneuropathy
  - Mobius syndrome
  - Trauma
  - Facial injuries
  - Basal skull fractures
  - Birth trauma
  - Metabolic
    - Diabetes mellitus
  - Pregnancy
  - Supranuclear facial palsy
  - Cerebrovascular accident
  - Pontine mass lesion

**SIGNS AND SYMPTOMS**
- Acute or subacute onset, often preceded by retroauricular pain and/or dysgeusia (impairment of taste)
- Half of patients reach maximal paralysis 48 hours after onset; the vast majority of cases by 5 days
- Followed by ipsilateral unilateral paralysis of facial muscles, partial or complete
- Subjective "numbness" or hypesthesia is present in branches of the trigeminal nerve on the same side
- Ipsilateral excess tearing or insensate tearing
- Ipsilateral hyperacusis or distortion of sound indicating paralysis of the stapedius muscle (one third to one half)

**Management**

**GENERAL MEASURES**
- General treatment includes treatment with a brief course of oral corticosteroids and oral acyclovir, reassurance regarding the generally favorable prognosis, and protection of the eye from drying and corneal exposure when eye closure is incomplete.

**SURGICAL MEASURES**
- Surgical decompression of the facial nerve is a standard approach to traumatic paralysis. Some recommend surgical exploration and decompression for idiopathic facial nerve palsy that does not improve after 3 months, but this is controversial and not well supported by evidence-based medicine.

**SYMPTOMATIC TREATMENT**
- Protection of the eye with lubricating agents and patching

**ADJUNCTIVE TREATMENT**
- N/A

**ADMISSION/DISCHARGE CRITERIA**
- N/A

**LABORATORY PROCEDURES**
- Complete blood count when infection is suspected
- Fasting blood glucose in the elderly population to screen for diabetes mellitus
- Lyme serology if history of tick bite, erythema migrans, or arthralgias

**IMAGING STUDIES**
- Routine imaging studies are not indicated for typical facial palsy with a normal otologic examination. CT and MRI of the temporal bone and posterior fossa should be considered in case of trauma, recurrent facial palsy, slowly progressive facial palsy, abnormal examination, or failure to show any improvement of paresis within 3 months.

**SPECIAL TESTS**
- Nerve conduction studies and EMG may help to distinguish temporary conduction defect from denervation from axonal injury and may be useful in prognosis.
Bell's Palsy/Facial Palsy

**Medications**

**DRUG(S) OF CHOICE**

- Corticosteroids: prednisone. Several different regimens proposed, all similar. May give 80 mg daily tapering in 20 mg increments over 10-12 days. Should be given in first 4 days but still is helpful after this time for relief of retroauricular pain.

- Acyclovir recommended at 400 mg five times per day for 10 days.

**Contraindications**

- Prednisone in known disseminated tuberculosis or fungal infections

**Precautions**

- Monitor blood glucose with prednisone use in diabetics; caution with acyclovir use in renal impairment or pregnancy.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

- Recheck after 1 month. Severe cases with poor eyelid closure should be seen monthly for 6-12 months to look for corneal abrasions.

**EXPECTED COURSE AND PROGNOSIS**

- High rate of spontaneous recovery (full, approximately 66%; moderate, 10%-12%; poor, 5%). Recovery typically begins in 3 weeks, may continue 6-9 months. Early recovery of some motor function within the first week is a very favorable prognostic sign.

- Better prognosis associated with incomplete paralysis, younger age group, nondiabetic

- Presence of pain has no prognostic value, but severe pain associated with Ramsay-Hunt syndrome

- Complications include facial weakness, aberrant regeneration with synkinesis, corneal abrasion, facial contractures, postparalytic hemifacial spasm (rare), tearing problems

**PATIENT EDUCATION**

- Eye protection

- Website: [www.ninds.nih.gov/patients/disorder/bells.htm](http://www.ninds.nih.gov/patients/disorder/bells.htm)

**Miscellaneous**

**SYNONYMS**

- Idiopathic facial palsy (questionable term now that there is significant evidence of viral causation)

ICD-9-CM: 351.0 Bell's

**SEE ALSO:** N/A

**REFERENCES**


Author(s): Ronnie Bergen, MD
Botulism

Basics

DESCRIPTION
• Botulism is an acute paralytic condition resulting from intoxication with a neuromuscular blocking agent that is produced by the anaerobic bacterium Clostridium botulinum. Currently, five clinical forms are recognized:
  — Foodborne (adult)
  — Infant
  — Wound
  — Hidden
  — Inadvertent

ETIOLOGY
• Between 1973 and 1996, an annual median number of 24 cases of foodborne botulism, 3 cases of wound botulism, and 71 cases of infant botulism were reported to the CDC. Over the past decade, an increase in wound botulism has appeared among IV drug users. The numbers of cases of hidden and inadvertent botulism secondary to botulinum toxin injections remain very small.

DIAGNOSIS
• There is no evidence that maternal botulism can be transmitted to the fetus. The high molecular weight of botulinum molecule prevents it from diffusing across the placenta. The reported cases of maternal botulism did not indicate that the condition appeared in the fetus. Additionally, in reported cases of mothers who were given therapeutic injections of purified botulinum toxin there were no adverse effects on the fetus. It is not clear whether breast-feeding has a protective effect in cases of infant botulism.

ASSOCIATED CONDITIONS
N/A

RISK FACTORS
• Foodborne
  — Ingestion of foods that contain preformed toxin
  — Low-acid foods with anaerobic environment, e.g., poorly preserved meat, fish, potatoes, or vegetables
  — Toxin is heat labile, but spores are heat resistant
• Wound
  — Germination of spores and toxin formation in anaerobic wound environment
  — Toxin may be absorbed through mucous membranes or inhalation
• Infant
  — Immature infant GI tract can allow spores to germinate and produce toxin
  — Honey often harbors C. botulinum spores
• Hidden botulism
  — Occurs in adults with GI tract abnormality, e.g., achlorhydria or Crohn’s disease
  — Abnormal GI environment allows germination of spores and formation of toxin

PREGNANCY
• There is no evidence that maternal botulism can be transmitted to the fetus. The high molecular weight of botulinum molecule prevents it from diffusing across the placenta. The reported cases of maternal botulism did not indicate that the condition appeared in the fetus. Additionally, in reported cases of mothers who were given therapeutic injections of purified botulinum toxin there were no adverse effects on the fetus. It is not clear whether breast-feeding has a protective effect in cases of infant botulism.

ASSOCIATED CONDITIONS
N/A

Genetics
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Myasthenia gravis
• Landry-Guillain-Barre (LGB) syndrome
• Polio
• Tick bite paralysis
• Diphtheric neuropathy
• Lambert-Eaton syndrome
• Hypokalemic periodic paralysis
• The clinical picture usually serves to differentiate among these disorders.

Foodborne botulism is almost invariably preceded by prominent GI symptoms that are an important diagnostic clue. Botulism may be differentiated from LGB syndrome by the relative preservation of deep tendon reflexes and normal CSF in the former. Diphtheric neuropathy occurs in the setting of a history of signs and symptoms of diphtheria, i.e., pharyngitis and tonsillar exudate. Both myasthenia and Lambert-Eaton syndrome are associated with autoimmune antibodies that can be assayed. Additionally, an edrophonium hydrochloride test in patients with botulism usually is negative. Poliomyelitis tends to present as an acute febrile syndrome with headache and meningismus.

SIGNS AND SYMPTOMS
• Incubation period several hours to 8 days
• Peak onset 18-36 hours after ingestion

GI Symptoms
• Nausea, vomiting
• Cramps, diarrhea
• Constipation is a later manifestation

Neurologic Symptoms
• Diplopia
• Ptosis
• Dysarthria
• Dysphagia
• Dysphonia
• Descending weakness
• Respiratory compromise
• Autonomic (xerostomia, pupillary dysfunction, postural hypotension, urinary retention)
• Neurologic presentation of wound botulism or hidden botulism is similar to that of foodborne botulism, except there is no prominent GI prodrome or history of ingestion of contaminated food. The incubation period for wound botulism is longer than that of foodborne intoxication, ranging from a few days to 2 weeks.

Infant Botulism
• Usually occurs in infants <6 months of age
• Early signs are constipation, weak cry, and poor sucking or feeding
• Progression to loss of head control, limb and bulbar weakness, respiratory distress
• Patients who develop inadvertent botulism from therapeutic injections of purified botulinum toxin can manifest generalized weakness and/or autonomic dysfunction similar to that seen in foodborne botulism.

LABORATORY PROCEDURES
• Clinical diagnosis is confirmed by the presence of botulinum toxin in the patient’s blood, stool, or wound exudate. This is done via the mouse inoculation test, in which mice that received injections of samples of stools or foods, body fluids) thought to contain toxin are inoculated with type-specific botulinum antibodies. Clinical signs of botulism then develop in mice in which the toxin is not neutralized. Additionally, C. botulinum organisms may be isolated from the stool of about 60% of patients with botulism. In cases of foodborne botulism, toxin may be recovered from the contaminated food.
IMAGING STUDIES

- Neuroimaging studies in cases of botulism should be normal and help to differentiate from other causes of bulbar symptoms, such as brainstem stroke.

SPECIAL TESTS

- The most common EMG abnormality seen in muscles affected by botulism is a small muscle action potential in response to a single supramaximal nerve stimulus. The amplitude of the muscle action potential is reduced, but conduction velocities are normal. Some degree of posttetanic facilitation may be present, but not to the same degree as is seen in Lambert-Eaton syndrome. CSF analysis should be normal.

GENERAL MEASURES

- Supportive treatment
- ICU monitoring until respiratory function is stable
- Assisted ventilation may be needed for several months, but usually only for a few weeks
- Gastric lavage may be useful if toxin ingestion was recent
- Pulmonary toilet
- Skin care
- Bowel and bladder protocol
- Report to state health agency and CDC (phone: 404-639-2206)

SURGICAL MEASURES

- Debride wound
- Antibiotics as needed

SYMPTOMATIC TREATMENT

- Dysphagia
  - Tube feedings
  - Swallowing therapy
  - Special diets
- Urinary retention and constipation
  - Intermittent straight catheterization
  - Stool softeners
- Timed evacuation

ADJUNCTIVE TREATMENT

- May need to turn and position the patient frequently to prevent skin breakdown, and use decubitus-preventing mattresses or circulating fluid beds. Physical and occupational therapy should be instituted as early as possible to prevent contractures, promote mobility, and maximize function in activities of daily living.

ADMISSION/DISCHARGE CRITERIA

- All patients with suspected botulism should be admitted and monitored closely, particularly those with recent onset of symptoms. Patients may be discharged to home or a long-term care facility, depending upon degree of residual motor and/or respiratory deficit.

Medications

DRUG(S) OF CHOICE

- The only specific medications for treatment of botulism are antitoxins. Two botulinum antitoxins currently are available for treatment of adult botulism. The trivalent form has antibodies to toxin types A, B, and E; the bivalent only to types A and B. The antitoxin only neutralizes circulating toxin that has not yet bound to nerve terminals; thus, it is most effective when given as early as possible in the course of the illness. Current recommended dose is one vial of bivalent or trivalent antitoxin administered IV, with additional doses as needed. One vial also may be given intramuscularly to provide a reservoir of antitoxin. Antitoxin is distributed by the CDC through regional distribution stations. The bivalent and trivalent antitoxins are equine-derived products and are not recommended for treatment of infant botulism because of concerns with hypersensitivity reactions. A human-derived immune globulin is available from the California Department of Health Services (510-540-2646) for treatment of infant botulism.

Contraindications

- Antitoxin should not be administered to persons with known hypersensitivity to equine-derived products.

Precations

- All patients should undergo skin or eye testing for hypersensitivity reactions prior to administration of antitoxin. Epinephrine solution should be available for immediate injection.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

- Patients should be monitored in an ICU setting until respiratory function has stabilized. Respiratory care and rehabilitation in a long-term care facility may be required.

EXPECTED COURSE AND PROGNOSIS

- The majority of patients with botulism make a full functional recovery, but this may take several weeks to months, as recovery depends on the formation of new motor end plates at the neuromuscular junction. Current mortality rates are 5%-10%. Studies have reported shorter hospital stays and decreased mortality for patients who received botulinum antitoxin within the first 24 hours of symptom onset, compared to patients who received later administration or no antitoxin.

PATIENT EDUCATION

N/A

Miscellaneous

SYNONYMS

N/A

ICD-9-CM: 005.1 Botulism

SEE ALSO: N/A

REFERENCES


Author(s): Barbara S. Giesser, MD
Brain Abscess

**Basics**

**DESCRIPTION**
- Brain abscesses begin as a localized area of cerebritis that develops into a focal parenchymal infection characterized by a capsularized collection of pus.

**EPIDEMIOLOGY**
- There are 1,500–2,500 cases diagnosed annually in the United States, with slight male predilection and median age of 30–40.

**ETIOLOGY**
- Brain abscesses arise by three main etiologies: local contiguous spread, hematogenous dissemination, and traumatic injury. The most common causes of brain abscesses are related to uncontrolled infections of the paranasal sinuses, middle ear, mastoid cells, and teeth. The cause is cryptogenic in 20%–30% of cases.
- For patients with a sinus source, aerobic and anaerobic streptococci, as well as Haemophilus sp, Bacteroides spp, and Fusobacterium sp, would be suspected. Prior otitis media or mastoiditis suggests Bacteroides sp, streptococci, Pseudomonaceae, or Enterobacteriaceae. Dental infections often predispose to brain abscesses with Fusobacterium, Prevotella, and Bacteroides spp and streptococci. Prior neurosurgery or penetrating head trauma would suggest Staphylococci, Enterobacteriaceae, Clostridium sp, or Pseudomonaceae.

**Genetics**
N/A

**RISK FACTORS**
- Risk factors include penetrating head trauma, neurosurgery, untreated bacterial otitis media or sinusitis, dental infection, cyanotic congenital heart disease, and immunosuppression.

**PREGNANCY**
N/A

**ASSOCIATED CONDITIONS**
- Immunocompromised patients have a broadened differential diagnosis, including bacteria, fungi, protozoa, and helminths.
- Mucormycosis is classically seen in diabetics with aci demia who are severely systemically ill. Nocardia is associated with defects in cell-mediated immunity. Fungal infections are found more commonly in people who are immunosuppressed, taking corticosteroids, or have received broad-spectrum antibiotics. Pseudallescheria boydii or Scedosporium apiospermum often occurs after a near drowning. Mycobacteria tuberculosis brain abscesses occur in individuals with disseminated TB or those from endemic areas. Aspergillus brain abscesses may present as an acute cerebrovascular accident in an immunocompromised host. The most common cause of brain abscess in AIDS patients is toxoplasmosis.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Conditions that mimic brain abscess include:
  - Neopla sm
  - Cerebral hemorrhage
  - Acte cerebrovascular accident

**SIGNS AND SYMPTOMS**
- The classic triad includes fever, headache, and focal neurologic deficit however, it is present in <50% of patients. Presenting symptoms in order of decreasing frequency include:
  - Headache
  - Mental status changes (disorientation, confusion, lethargy, neuropsychiatric complaints)
  - Focal neurologic deficits, depending upon the location of the abscess (motor, sensory or speech disorders, visual field defects, ataxia)
  - Fever
  - Seizures, focal and generalized
  - Nausea and vomiting
  - Nuchal rigidity
  - Papilledema
- Sudden worsening of a preexisting headache or new-onset meningismus may signal rupture of the abscess into the ventricles, an often fatal complication. Immunocompromised patients may have an occult presentation due to a decreased inflammatory response.

**LABORATORY PROCEDURES**
- Abscess aspirate should be sent for:
  - Gram stain
  - Aerobic and anaerobic culture
  - Fungal stain and cultures
  - Acid-fast stain and culture
  - Modified acid-fast stain (Nocardia)
- Serum toxoplasmosis IgG titer should be obtained in immunocompromised patients. Routine blood cultures are infrequently positive but may be the only diagnostic data in patients requiring urgent antibiotics. Lumbar puncture is of low yield and risks brain herniation.

**IMAGING STUDIES**
- Imaging has improved the diagnosis of, and decreased the mortality from, brain abscesses. CT shows ring-enhancing lesion(s) with variable surrounding edema. Contrast-enhanced MRI is more sensitive and can differentiate abscess from early cerebritis. Radionuclide scans are sometimes of benefit when CT or MRI is inconclusive. PET scanning may be able to differentiate neoplasm from infection.

**SPECIAL TESTS**
- Sterotactic brain biopsy, aspiration, or excision may be necessary. The source of the brain abscess should be sought. Appropriate workup includes a thorough physical examination, with special attention to ears, mastoids, sinuses, and teeth. Consideration should be given to sinus imaging, chest x-ray film, dental x-ray film, or possibly echocardiography.
Brain Abscess

**Management**

**GENERAL MEASURES**

- Antimicrobial treatment is chosen to cover for predisposing conditions, presumed source, and gram stain. Therapy is then adjusted for culture data.

**SURGICAL MEASURES**

- Neurosurgical consultation should be obtained. Potential needs include radiographically guided aspiration, burr hole placement and aspiration, or craniotomy and excision (especially if the abscess is >2.5 cm).

**SYMPTOMATIC TREATMENT**

- Patients may require pain management and seizure precautions. Some experts recommend routine antiepileptic medications.

**ADJUNCTIVE TREATMENT**

- Steroids (e.g., dexamethasone 6-12 mg q8h) are indicated if the patient has significant edema or mass effect. Steroids may decrease response to antimicrobial treatment and should be tapered as soon as feasible. Elevated intracranial pressure may additionally require IV mannitol or induced hyperventilation.

**ADMISSION/DISCHARGE CRITERIA**

- The majority of patients with brain abscess will require inpatient admission for definitive diagnosis and initial treatment. Discharge is possible when the diagnosis is secure, the patient is stable or improving, and a plan for outpatient treatment has been formulated (i.e., IV or PO antimicrobials).

**Medications**

**DRUG(S) OF CHOICE**

- Treatment depends on the likely causative agent. In a bacterial abscess of unclear etiology, a third-generation cephalosporin (e.g., ceftriaxone 2 g IV q24h) and metronidazole (500 mg IV q8h) would be appropriate empiric therapy. Cefazidime or ceftepime would be used instead of ceftriaxone if *Pseudomonas aeruginosa* was suspected. Initial therapy in an immunocompromised patient should be chosen in consultation with an infectious disease specialist.

- Other predisposing conditions and suggested initial antibiotic regimens include:
  - Otitis media, mastoiditis, or sinusitis: metronidazole and a third-generation cephalosporin
  - Dental source: penicillin (2-4 million units q8h) and metronidazole
  - Penetrating trauma or neurosurgery: vancomycin (1 g q12h with dose adjustment to serum levels) and third-generation cephalosporin + metronidazole

**CONTRAINDICATIONS**

- Known hypersensitivity to a particular antibiotic
- Fluoroquinolones are not recommended due to a lack of data. Antimicrobials administered should penetrate the blood-brain barrier.

**PRECAUTIONS**

- Use caution in choosing empiric therapy that may lower the seizure threshold (e.g., high-dose Q-lactams).

**ALTERNATIVE DRUGS**

- Trimethoprim-sulfamethoxazole 15 mg/kg divided tid would be added for a patient with concomitant lung pathology and suspected *Nocardia* sp infection.

**Follow-Up**

**PATIENT MONITORING**

- Serial monitoring is necessary to monitor for improvement or progression. Serial laboratory monitoring is determined by the specific toxicities of the antimicrobial agents chosen.

**EXPECTED COURSE AND PROGNOSIS**

- Prognosis depends on the rapidity of diagnosis and appropriate treatment, as well as the mental status of the patient upon presentation. If treatment is initiated while the patient is alert, expected mortality is 5%-10%. Mortality rises significantly to >50% if the patient is comatose when treatment is initiated. Approximately 30% of surviving patients have residual neurologic deficits such as focal epilepsy.

**PATIENT EDUCATION**

- Some experts recommend at least 3 months of antiepileptic therapy with a normal EEG prior to discontinuation. Driving may be affected.

**Miscellaneous**

**SYNONYMS**

N/A

**ICD-9-CM:** 324.0 Brain abscess

**SEE ALSO:** N/A

**REFERENCES**


Author(s) Ruth M Ullowney-Agra, MD
### Brain Death

#### Basics

**DESCRIPTION**

- Brain death is defined as the irreversible loss of function of the entire brain, including the brainstem. Brain death was first proposed as a criterion of death in 1968 and was endorsed in 1981 by the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. In the United States, properly documented brain death meets the legal standard for the declaration of death.

**EPIDEMIOLOGY**

- **Indidence/Prevalence**
  - Unknown
  - Race
  - No ethnic predominance

- **Age**
  - May occur at any age. Special criteria for determining brain death in children under 5 years have been published.

- **Sex**
  - Nondifferential in males or females

**ETIOLOGY**

- Brain death resulting from a primary neurologic disease is most often caused by severe head trauma, hemorrhage, or ischemic strokes causing herniation. Infectious causes include severe cases of meningitis and abscesses resulting in herniation. The most common non-neurologic etiology is hypoxic-ischemic coma due to cardiorespiratory arrest, although other causes of severe encephalopathy, such as fulminant hepatic encephalopathy, also may cause brain death.

**Genetics**

- N/A

**RISK FACTORS**

- N/A

**PREGNANCY**

- Brain death occurring during pregnancy is a complex and controversial issue. There is a general consensus that attempts to maintain the brain-dead maternal body are appropriate if there is a reasonable possibility of delivering a healthy fetus. Who should make medical decisions is less clear: if the patient is married, the husband is generally considered the most appropriate surrogate decision maker; if unmarried, both the father of the fetus (identified and involved) and the mother’s immediate family should be included in the decision-making process. The basis for decision making also is controversial: many consider the interests of the fetus to be paramount, but others believe that the mother’s interests are equally important.

**ASSOCIATED CONDITIONS**

- N/A

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td><strong>DIFFERENTIAL DIAGNOSIS</strong></td>
</tr>
<tr>
<td>- Conditions that resemble brain death</td>
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<tr>
<td>— Severe coma with minimal residual cortical or brainstem function</td>
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<tr>
<td>- Conditions that may interfere with diagnosing brain death</td>
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<tr>
<td>— Hypothermia (core temperature &lt;32°C)</td>
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<tr>
<td>— Drug intoxication, poisoning, or severe metabolic derangements</td>
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<tr>
<td>- Conditions that interfere with the clinical diagnosis of brain death</td>
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<tr>
<td>— Severe facial trauma or preexisting pupillary abnormalities</td>
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<td>— Sleep apnea or severe pulmonary disease; may preclude apnea testing</td>
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**SIGNS AND SYMPTOMS**

- Brain death is a clinical diagnosis. Confirmatory tests are optional unless the full clinical examination cannot be performed or provides ambiguous information, in which case the diagnosis will depend on appropriate confirmatory tests.

- Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible. The diagnosis can be made only when the following are present:
  - Clinical or neuroimaging evidence of an acute CNS catastrophe compatible with the diagnosis of brain death
  - Exclusion of the following conditions - Severe metabolic disturbances that may confound clinical assessment - Drug intoxication or poisoning - Hypothermia

- The three cardinal clinical findings in brain death are
  - Unresponsiveness, including the absence of cerebral motor response to painful stimulation
  - Absence of all brainstem reflexes, including pupillary response to bright light, oculocephalic and oculovestibular responses, corneal reflexes, jaw jerk, facial grimacing, gag reflex, and cough reflex to deep suctioning

- Apnea testing should be performed according to the AAN statement (Neurology 1995;45:1012-1014).

- The diagnosis of brain death requires two complete examinations consistent with brain death performed approximately 6 hours apart. The interval between examinations may be adjusted depending on the clinical situation.

**LABORATORY PROCEDURES**

- Blood and urine tests to exclude potentially reversible toxic/metabolic causes of severely diminished brain function
  - Blood and urine toxicology screens
  - Electrolytes, BUN, creatinine, glucose, liver function tests

- Additional laboratory tests may be appropriate when the etiology of coma is unclear after initial workup.

**IMAGING STUDIES**

- Imaging studies to document the absence of intracerebral blood flow may be used to confirm the diagnosis of brain death.

- Cerebral radionuclide angiography demonstration of absence of intracerebral blood flow confirms the diagnosis. Conversely, the presence of intracerebral blood flow indicates that the individual is not brain dead. Minimal blood flow in a patient who meets clinical brain death criteria usually will disappear within 12-24 hours, so repeated testing may be appropriate.

- Conventional angiography: In brain death, intracerebral arterial blood flow will be absent, whereas external carotid circulation remains patent.

**SPECIAL TESTS**

- EEG documenting electroencephalographic silence (ECS), i.e., a “flat EEG,” for a minimum of 30 minutes utilizing appropriate recording technique as adopted by the American Electroencephalographic Society (AES) is consistent with the diagnosis of brain death. Because ECS may also be seen in patients with sedative overdose, hypothermia, or severe cerebral injury with residual brainstem function, the EEG must be interpreted in the context of the clinical evaluation.

- Transcranial Doppler ultrasonography may provide support for the diagnosis of brain death, but excellent technique and significant experience are required.

- Somatosensory evoked potentials (SSEPs) demonstrating bilateral absence of N20-P22 response with median nerve stimulation supports the diagnosis of brain death; however, the clinical value of SSEPs remains limited.
Management

GENERAL MEASURES

- Management must be separated into two phases: management of a patient who is being evaluated for possible brain death, but not yet declared brain dead; and management of a patient who has been declared brain dead. If the patient is a pregnant woman, this will influence the management of the patient.
- A pregnant woman who may be brain dead should be evaluated by an obstetrician to assess the gestational age, viability, and health of the fetus. Aggressive treatment should be continued while a decision is made as to how to manage the pregnancy. The involvement of a medical intensivist, an obstetrician, a neurologist, and ethics consultant in the decision-making process is recommended.
- Nonpregnant patients being evaluated for possible brain death should be managed according to standard practice for their underlying neurologic or medical problems.
- Decisions about the aggressiveness of treatment, including establishing do-not-resuscitate (DNR) status, should be made according to standard practice.
- The family should be informed when brain death evaluation is initiated. They should be advised of the severity of the neurologic injury, the possibility that the patient may be brain dead, and the fact that brain death is a legal definition of death throughout the United States.
- In certain states (e.g., New York, New Jersey), if a family has a religious objection to using brain death criteria to determine death (e.g., some Orthodox Jews), the physician is legally obligated to respect this decision and use only the traditional cardiopulmonary criteria to determine death for such patients. In most states, although religious objections to brain death do not have legal support, sensitivity to these issues is important, and pastoral and ethics consultation should be obtained if the family indicates they have such an objection.
- The possibility that a patient may qualify as an organ donor should not alter the medical care or decision-making process of the medical personnel.
- Nevertheless, some families may strongly desire that their loved one, if brain dead, become an organ donor, and this may influence their decision-making process (e.g., continuing "futile" care to permit a nearly brain-dead patient to become brain dead).

Brain death determination itself should generally be performed by, or in consultation with, a physician experienced in the matter, usually a neurologist, neurosurgeon, or intensivist.
- Pastoral care to provide support for the family often is helpful.
- Ethics consultation may be beneficial if there are conflicts or disagreements between the family and the medical team.
- Hospitals must contact their designated organ procurement organization (OPO) in a timely manner about individuals who die or whose death is imminent. It is optimal to contact the OPO when brain death evaluation is initiated or when the first examination is consistent with brain death.
- The time of death is the time of the second brain death evaluation.
- The family should be immediately informed of the diagnosis.
- Hospitals must collaborate with the OPO to ensure that the family of every potential donor is informed of the option to donate organs or tissues.
- If the family declines organ donation, all medical treatments should be discontinued and the patient should be extubated. It is not appropriate to ask the family’s consent to discontinue treatment.
- If the family consents to organ donation, medical treatment of the patient should continue according to the standard hospital protocol for an organ donor until the organs can be harvested.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

N/A

ADJUNCTIVE TREATMENTS

N/A

ADMISSION/DISCHARGE CRITERIA

- Brain death evaluation is generally performed in hospitalized patients.
- The time of death is the time of the second brain death evaluation.
- The family should be immediately informed of the diagnosis.
- Hospitals must collaborate with the OPO to ensure that the family of every potential donor is informed of the option to donate organs or tissues.
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- If the family consents to organ donation, medical treatment of the patient should continue according to the standard hospital protocol for an organ donor until the organs can be harvested.

Medications

DRUG(S) OF CHOICE N/A

ALTERNATIVE DRUGS

N/A

Follow-up

PATIENT MONITORING

N/A

EXPECTED COURSE AND PROGNOSIS

N/A

PATIENT EDUCATION

- Website: www.organdonor.gov/

Miscellaneous

SYNONYMS

N/A

ICD-9-CM: N/A. The diagnosis should be coded according to the underlying process resulting in brain death.

REFERENCES


Author(s): Robert M. Taylor, MD
Brain Tumor, Acoustic Schwannoma

Basics

DESCRIPTION
- Acoustic schwannomas are extraxial benign neoplasms that arise from the vestibular branch of the eighth cranial nerve in the cerebellopontine angle (CPA) region, near the porus acusticus. They typically are slow growing, with a growth rate of 1-2 mm/year. In some cases, especially older patients, the tumor may remain dormant. There are three stages of growth: canalicular, cisternal, and brainstem compressive. In late stages of growth, the seventh cranial nerve becomes draped over the mass as it grows into the cistern toward the brainstem.

EPIDEMIOLOGY

INcidence/Prevalence
- Schwannomas account for 6%-8% of all primary brain tumors. The majority of schwannomas (85%-90%) are of the acoustic type and usually are unilateral (95%). The annual incidence is 1 per 100,000 persons. Bilateral tumors occur in patients with neurofibromatosis (NF) type II.

SEX
- All races and ethnic groups equally affected.

AGE
- Typical presentation is between 44 and 64 years.

SEX
- Females have a higher incidence than males (1.5:1).

ETIOLOGY
- The cells of origin of acoustic schwannomas are transformed Schwann cells from the eighth cranial nerve. In most cases, the initial genesis of transformation is unknown. The tumor appears as a discrete, rounded, encapsulated mass of a milky white color, arising from a nerve fascicle. Microscopically, schwannomas have biphasic architecture, with Antoni A and B regions. Antoni A is most common, with features of dense compact rows of elongated spindle-shaped cells; Antoni B regions demonstrate loosely organized areas of stellate cells, lipid, and microcystic change. Mitoses and nuclear pleomorphism may be seen. Abnormalities of chromosome 22 are common, including monosomy and alterations of the long arm (i.e., deletions, inversions, translocations).

Genetics
- The majority of acoustic schwannomas are sporadic and unilateral. Approximately 5% can develop in association with NF type I or II. In all NF-related tumors and between 65% and 70% of sporadic tumors, there are mutations of a tumor suppressor gene located at 22q12, the NF2 gene, which codes for a protein, schwannomin, which interacts with cytoskeletal proteins involved in regulation of cell adhesion and proliferation.

RISK FACTORS
- There are no known risk factors for acoustic schwannomas except for NF types I and II. Prior cranial radiation may be causally related in rare cases.

PREGNANCY
- Pregnancy has not been shown to affect the clinical course of acoustic schwannomas.

ASSOCIATED CONDITIONS
- NF type I, NF type II

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Acoustic schwannomas account for 80% of tumors in the CPA region. Differential diagnosis includes other masses or processes that can cause a progressive syndrome in the CPA: meningioma, epidermoid cyst, exophytic brainstem glioma, ependymoma, choroid plexus papilloma, schwannomas of other cranial nerves (V, VII, IX, X, XI), jugular foramen paraganglioma, metastatic tumor, vascular processes (aneurysm, arteriovenous malformation), and abscess.

SIGNS AND SYMPTOMS
- Common symptoms include unilateral sensory hearing loss (96%), unsteadiness (77%), tinnitus (71%), headache (29%), mastoid pain or otalgia (28%), facial numbness, diplopia, and vertigo. Mean time from onset of symptoms to diagnosis is 3.7 years. Loss of hearing and balance is slow and gradual in most cases. Tinnitus typically is unilateral, mild, and constant.

- Common neurologic signs include unilateral sensorineural hearing loss in 90%-95% of patients. Preserved hearing suggests the tumor will be <1.5 cm. In 50% of patients at presentation, hearing loss is the solitary neurologic sign. Gait is either normal or only mildly affected. Large tumors (>3 cm) can cause gait ataxia, dysmetria, nystagmus, facial hypertension, and papilledema.

LABORATORY PROCEDURES
- Screening tests that are sometimes used before MRI or CT in patients with hearing loss include pure tone audiometry, speech discrimination assessment, and auditory evoked brainstem responses (AEBR). In 60%-70% of patients, high-frequency loss is present on audiometry. Speech discrimination is abnormal in 45%-80% of cases. AEBR is the most sensitive nonimaging test and shows delayed latency or loss of wave V in approximately 95% of patients.

IMAGING STUDIES
- MRI, with and without gadolinium contrast, is the most critical diagnostic test; axial and coronal enhanced images should be obtained. MRI is more sensitive than CT for small intracanalicular tumors and vascular stenoses, although both modalities properly visualize large masses. The tumor usually is isointense to brain on T1 images but hyperintense on T2 images. Schwannomas enhance densely after administration of gadolinium. An MRI negative for an enhancing mass in the internal auditory canal rules out an acoustic schwannoma.

SPECIAL TESTS
- Intraoperative monitoring of cranial nerves V, VII, and XI during surgical resection is an excellent method for reducing morbidity of these nerves. Monitoring of cranial nerve VIII remains controversial; it may reduce morbidity during resection of tumors <2 cm.

Management

GENERAL MEASURES
- In certain patient cohorts, tumors are followed conservatively after diagnosis, including patients in poor health, elderly patients with small lesions (<10 mm) or who are reluctant to proceed to surgery, and any patient with poor hearing in the contralateral ear. Tumors are likely to remain quiescent if they remain stable during the initial observation period (usually 6 months). Conservative approaches are unmodified in most young patients due to accelerated growth rates.

SURGICAL MEASURES
- Complete surgical resection is the treatment of choice in most patients. Tumors <1 cm in diameter are most likely to be completely resected while preserving cranial nerve function. Three surgical approaches are commonly used, the choice of technique depends on tumor size, depth of internal auditory canal penetration, hearing status, exposure of the facial nerve, and patient age.
The suboccipital or retrosigmoid approach allows for excellent exposure of the tumor and the CPA, and hearing may be preserved; this approach is excellent for large tumors. The translabyrinthine or anterolabyrinthine approach allows for good exposure of the internal auditory canal, CPA, and course of the facial nerve; although postoperative complications are reduced (especially facial nerve paralysis), hearing is abolished. The middle fossa or retrolabyrinthine approach does not give good exposure of the CPA, but it does allow for removal of intracanalicular or small cisternal tumors while sparing hearing and minimizing complications. Traction of the cerebellum during the suboccipital approach can cause dysmetria; traction of the temporal lobe during the middle fossa approach can cause epilepsy or dysphasia.

SYMPTOMATIC TREATMENT
- Rates range from 90%-95%, with variable fraction to the 50% isodose line; local control and minimizing complications.

ADJUNCTIVE TREATMENTS
- Conventional external beam radiotherapy (RT)
- Adjunctive or alternative forms of treatment in selected patients.

ADJUNCTIVE TREATMENTS
- Conventional external beam radiotherapy (RT) and stereotactic radiosurgery (linear accelerator, proton beam, gamma knife) can be adjunctive or alternative forms of treatment in selected patients. RT (30-50 Gy) should be considered in patients with large residual tumors after surgery, patients with large recurrent tumors, and patients with large tumors that are poor surgical candidates. RT can lengthen progression-free survival. Patients most appropriate for radiosurgery include those who are medically unstable, elderly (>85 years), contralaterally deaf, have failed previous surgery, or refuse use surgical intervention; tumors <3 cm in diameter are most suitable. Dosing usually is between 16 and 18 Gy in a single fraction to the 50% isodose line; local control rates range from 90%-95%, with variable amounts of tumor shrinkage. Complications of radiosurgery include hearing loss, nausea and emesis, headaches, and delayed facial neuropathy.
- Currently, there is no role for chemotherapy in the treatment of acoustic schwannomas.

ADMISSION/DISCHARGE CRITERIA
- Admission is generally reserved for presurgical evaluation and surgical resection. Angiography may be included in the workup to assess regional vascular anatomy and rule out aneurysms and vascular malformations of the CPA. Patients with brainstem compression might benefit from admission for intravenous dexamethasone.

Brain Tumor, Acoustic Schwannoma

Medications

**DRUG(S) OF CHOICE**
- Dexamethasone 8-16 mg/day may be of benefit to reduce edema and swelling for patients in the brainstem compressive stage of growth. It also may improve transient symptoms of pressure and swelling after RT or radiosurgery.

**Contraindications**
- N/A

**Precautions**
- All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

**ALTERNATIVE DRUGS**
- N/A

Follow-Up

**PATIENT MONITORING**
- Patients are followed with serial MRI scans and assessment of neurologic function every 6-12 months.

**EXPECTED COURSE AND PROGNOSIS**
- Overall prognosis for survival and neurologic function is good for sporadic tumors if diagnosed in the calunicular or cisternal phases. Recurrence rate after a gross total resection is 1%-2%. Surgical complications include mortality (0.5%-2%), hemorrhage, cerebellar injury, cranial nerve injury (V, VII, VIII, XI), headache, aseptic meningitis, and CSF leak. Incomplete resection will result in recurrent tumor with in 7 years in 44% of patients. Almost two thirds of patients are able to return to work within 4 months after surgical resection.
- Complications of acoustic schwannomas and their treatment include partial or complete hearing loss, facial weakness, vertigo, and dysmetria. Less common sequelae include impairment of other cranial nerves, ataxia, and hydrocephalus.

PATIENT EDUCATION
- Acoustic Neuroma Association. Website: www.anausa.org
- Brain tumors.com. Website: www.brain tumors.com
- Johns Hopkins Acoustic Neuroma Program-Textbook. Website: www.medichu.edu/radiosurgery/brain tumors/acoustic/textbook

SYNONYMS
- Acoustic neuroma
- Vestibular neuroma or schwannoma
- Neurilemmoma
- Perineural fibroblastoma

ICD-9-CM: 225A Acoustic schwannoma

SEE ALSO: NEUROFIBROMATOSIS TYPES I AND II

REFERENCES

Author(s) Herbert B. Newt on, MD
Brain Tumor, Ependymoma

Basics

**DESCRIPTION**
- Ependymomas are gliomas that arise from cells forming the ependymal surfaces of the ventricles. As with other gliomas, the primary symptoms associated with ependymomas primarily reflect local compressive effects. By arising from the ependymal surface, frequently in the fourth ventricle, these tumors are more often associated with hydrocephalus and subarachnoid metastases than most gliomas, although less often than medulloblastoma/primitive neuroectodermal tumor (PNET). Childhood ependymomas usually are intracranial tumors: 60%-70% occur in the fourth ventricle. Most of these are histologically low grade, yet irrespective of grade there is a strong tendency for recurrence. Ependymomas in adults also are intracranial but occur with a higher frequency in the lateral ventricles.
- PNET with ependymal differentiation, ependymoblastoma, has biologic and clinical features that relate it to the medulloblastoma/PNET group of neoplasms. The prognosis and treatment are distinct from that of ependymomas.

**EPIDEMIOLOGY**
- Ependymomas represent 21%–8% of all neuroepithelial tumors but account for a higher percentage in children. They occur at all ages, with peaks in early childhood and again in young adult life. They represent 8% of gliomas in patients <19 years but only 1.3% in patients >65 years.

**ETIOLOGY**
- The etiology is uncertain, but an association with exposure to simian vacuolating virus no. 40 (SV40) through contaminated vaccines has been suggested. The SV40 large T antigen has been demonstrated in tumor samples from patients exposed in utero.

**GENETICS**
- Ependymomas are observed with increased frequency in patients with neurofibromatosis (NF) type I and type II.

**RISK FACTORS**
- Family history of NF

**PREGNANCY**
- No specific relationship to pregnancy is known.

**ASSOCIATED CONDITIONS**
- Ependymomas are strongly associated with NF, especially type II, but they also can occur in NF type I.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- The differential diagnosis varies considerably based on site of the lesion and includes both neoplastic and progressive nonneoplastic disorders.
  - Astrocytoma
  - Medulloblastoma
  - Other mass lesions
  - Craniofacial junction anomalies and posterior fossa malformations

**SIGNS AND SYMPTOMS**
- Ataxia/dysequilibrium
- Headache
- Nausea and vomiting
- Rapidly increasing head circumference in children
- Diplopia, particularly related to cranial nerve (CN) VI patsies
- Cerebellopontine angle syndrome, including CN V, VII, and VIII
- Seizures
- Weakness

**LABORATORY PROCEDURES**
- CSF analysis for cytology is part of the extent of disease assessment in children. In adults this would be indicated only when clinical findings or neuroimaging studies suggested subarachnoid metastases.

**IMAGING STUDIES**
- MRI scanning usually demonstrates a well-demarcated, contrast-enhancing mass. Hydrocephalus is common with fourth ventricle ependymomas. In children, determining the extent of involvement by neoplasm (i.e., extent of disease or staging assessment) should include scanning the entire craniospinal axis to search for subarachnoid metastases. Rarely is this necessary for adults. If an ependymoma or other neoplasm with a propensity for subarachnoid dissemination (e.g., medulloblastoma/PNET) is suspected from the initial scans, it is preferable to perform the spine MRI studies prior to surgery because some postoperative artifacts may be difficult to distinguish from subarachnoidal metastases. For patients who cannot undergo MRI scanning, myelography performed after surgery is used as an alternative for assessment of the spinal axis.

**MANAGEMENT**

**GENERAL MEASURES**
- Initial measures are aimed at controlling rapidly progressive neurologic symptoms and elevated intracranial pressure. Both cerebral edema and hydrocephalus may contribute to the increased pressure. Dexamethasone (Decadron) and occasionally osmotic diuretics such as mannitol are required for cerebral edema. Urgent surgical measures for tumor-related mass effect or hydrocephalus are sometimes needed.

**SURGICAL MEASURES**
- Emergency ventriculostomy may be needed for rapidly progressive hydrocephalus usually related to fourth ventricle neoplasms. Many patients will not require permanent shunting once the tumor is removed. If elevated intracranial pressure or hydrocephalus persists after tumor resection, a ventriculoperitoneal shunt may be needed.

**SYMPTOMATIC TREATMENT**
- Corticosteroids are titrated to control symptoms arising from cerebral edema. Anticonvulsant therapy is used if seizures occur.

**DIFFERENTIAL DIAGNOSIS**
- CT scanning also is able to demonstrate intracranial ependymomas well, but MRI scanning tends to be more informative, particularly with regard to posterior fossa lesions and meningeal dissemination. Neither CT nor MRI scanning can distinguish ependymomas from other CNS neoplasms with sufficient certainty to be considered diagnostic.

**SPECIAL TESTS**
- N/A
ADJUNCTIVE TREATMENT
• In very young children, mutilagent chemotherapy is used and radiation is deferred to avoid the profound neurotoxicities associated with radiotherapy at this age. In older children, radiation therapy directed at the tumor bed is the main postoperative treatment. Craniospinal radiation is not advocated unless subarachnoid metastases are present. The addition of chemotherapy with radiation is not clearly beneficial but often is considered part of investigational protocols. In adults, radiation is used for incompletely resected ependymomas. Repeated resections and radiosurgery also are used for locally recurrent tumors. Chemotherapy is used as a second-line therapy for recurrence in adults.

ADMISSION/DISCHARGE CRITERIA
• Admit for signs of elevated intracranial pressure or rapidly progressive neurologic deficits.

Medications

DRUG(S) OF CHOICE
• Corticosteroids, most often dexamethasone, are used to treat cerebral edema.
• A large number of chemotherapy agents have been tried, usually in mutilagent combinations. Most of these are alkylating agents including the nitrosoureas (carmustine [BCNU], lomustine [CCNU]), platinum derivatives (cisplatin, carboplatin), and cyclophosphamide. Other agents including vincristine and etoposide are also commonly used.

Contraindications
• Chemotherapy is contraindicated in patients with persistent leukopenia (<2.0) or thrombocytopenia (<100,000).

Precautions
• Anticonvulsant therapy is indicated only when seizures have occurred. Perioperative prophylaxis is sometimes recommended, particularly if intracranial pressure is elevated. Anticonvulsants that are available in IV formulations are preferable, particularly in the perioperative period. Anticonvulsants with relatively common hematologic toxicities (carbamazepine, divalproex [Depakote]) should not be first-line choices for patients who will receive chemotherapy.
• Special care is required for sedation and pain control in patients suspected of having elevated intracranial pressure, especially if related to a posterior fossa mass where respiratory depression and loss of airway protection may rapidly develop.

• Severe encephalopathy and loss of brainstem reflexes may occur following resection of posterior fossa tumors in children. The exact cause is uncertain, but brainstem edema and ischemia due to vasospasm have been postulated. These symptoms may last for weeks or a few months, usually with slow improvement.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
• For children, MRI scans are obtained every 4 months during therapy and for the first year after, then every 6 months for 3–5 years. Less frequent scanning (every 6–12 months) is appropriate for histologically benign adult ependymomas.
• MRI scanning of the entire neuraxis may be required on a regular schedule for some patients. Clinical assessment must always include careful search for subarachnoid metastases, particularly spinal “drop metastases.” CSF evaluation for cytology may be needed.

EXPECTED COURSE AND PROGNOSIS
• There is a high likelihood of recurrence in children. The site of recurrence is local in 90% of patients, although some patients will have concurrent subarachnoid metastases. Recurrence in the subarachnoid space without local recurrence is much less common. Metastasis outside of the neuraxis is rare. The 5-year survival rate is 50% in children. The median survival is considerably longer in adults than in children.

PATIENT EDUCATION
• American Brain Tumor Association, 2720 River Road Suite 146, Des Plaines, IL 60018. Phone: 708-827-9918, 800-886-2282, website: www.abta.org
• National Brain Tumor Foundation, 414 13th Street, Suite 700, Oakland, CA 94612. Phone: 510-839-9777, fax: 510-839-9779, website: www.braintumormwr

Miscellaneous

SYNONYMS
• Ependymoma
• Anaplastic ependymoma

ICD-9-CM: 191.9 Malignant neoplasm of the brain, unspecified; 237.5 Neoplasm of uncertain behavior of brain and spinal cord

SEE ALSO: N/A

REFERENCES

Author(s): Paul L. Moots, MD
Brain Tumor, High-Grade Astrocytoma

Basics

DESCRIPTION

- High-grade astrocytomas (HGAs) are a group of malignant neoplasms that typically occur in middle-aged and older adults. They have a high growth potential and are more infiltrative than low-grade gliomas. Survival is limited in most patients and ranges between 1 and 5 years.

EPIDEMIOLOGY

Incidence/Prevalence

- HGAs comprise approximately 33%-45% of primary brain tumors in adults, which corresponds to roughly 7,500 new cases of HGA each year in North America; 50%-80% of HGAs are glioblastoma multiforme (GBM); 20%-40% are anaplastic astrocytoma (AA). Gliosarcoma and mixed anaplastic oligoastrocytoma (AOA) occur less frequently.

Race

- All races and ethnic groups are affected. Caucasians are affected more commonly than blacks, Latinos, and Asians.

Age

- Typical presentation is between 50 and 65 years of age for GBM and gliosarcoma patients and between 30 and 50 years of age for AA and mixed AOA patients.

Sex

- Incidence is slightly higher in males than females (1.5:1).

ETIOLOGY

- The World Health Organization (WHO) classifies AA as grade III, GBM as grade IV, gliosarcoma as grade IV, and mixed AOA as grade II.

- HGAs are derived from transformed astrocytes. Pathologic evaluation of HGA reveals significant heterogeneity, with high cellularity, cellular and nuclear atypia, moderate-to-high mitotic rate, endothelial proliferation, and necrosis (GBM and gliosarcoma only). Gliosarcomas show regions of sarcomatous differentiation admixed with separate areas of neoplastic glial cells. Staining for glial fibrillary acidic protein is more variable in HGA and typically less than that of low-grade gliomas.

- Molecular genetic studies of HGA reveal frequent loss or mutation of the tumor suppressor gene p53, and amplification of MDM2 or CDK2Delet ion or mutation of the tumor suppressor genes p16 and retinoblastoma may be present. Primary GBMs have amplification of epidermal growth factor receptors and/or deletion of the primitive neuroectodermal tumor (PNET) tumor suppressor gene. Deletion of 1p and 19q may be noted in mixed AOA and is associated with improved survival.

Genetics

- HGAs usually are sporadic and do not have an underlying genetic predilection. Rarely, HGAs can manifest as part of a genetically mediated syndrome (e.g., neurofibromatosis [NF]).

RISK FACTORS

- The only known risk factors for HGA are prior cranial radiation exposure and genetic diseases with a predilection for astrocytomas, such as Turcot's syndrome, NF types I and II, and Li-Fraumeni syndrome. Rarely, HGA can be familial.

PREGNANCY

- Pregnancy does not affect the clinical course of HGA.

ASSOCIATED CONDITIONS

- NF type I, NF type II, Turcot's syndrome, Li-Fraumeni syndrome. Rarely, HGA can be familial.

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Other mass Lesions that enhance should be considered, including mature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

SIGNS AND SYMPTOMS

- The median duration from onset of symptoms to diagnosis ranges from <6 months in GBM to 6-8 months for AA. The most common symptoms at presentation include headache (70%), seizure activity (54% overall; partial motor 23%; partial complex 9%), cognitive and personality changes (52%), focal weakness (43%), nausea and emesis (31%), speech disturbances (2%), and altered ions of consciousness (25%).

- Common findings on neurologic examination include hemiparesis (57%), cranial nerve palsies (54%), papilledema (53%), cognitive deficits and confusion (45%), depressed sensorium (37%), hemianopsia (29%), and dysphasia (25%).

LABORATORY PROCEDURES

- Molecular analysis of chromosome 1p and/or 19q loss may be of prognostic significance for patients with mixed AOA.

IMAGING STUDIES

- MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for HGAs that are small or within the posterior fossa. On T1 images, the tumor usually is infiltrative and appears hypointense or isointense compared to brain; on T2 images, the mass is hyperintense. With gadolinium administration, most HGAs show either diffuse or ring-like enhancement. Peritumoral edema and mass effect usually are moderate to severe. Hemorrhage and regions consistent with necrosis may be noted. CT demonstrates an ill-defined region of hypodensity with moderate-to-severe enhancement, edema, and mass effect.

SPECIAL TESTS

- Fluorodeoxyglucose positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of HGA to differentiate from nonneoplastic lesions and to maximize targeting for biopsy. HGAs typically appear hypermetabolic on PET imaging. Magnetic resonance spectroscopy (MRS) also can be used for metabolic screening to differentiate HGA from other lesions. MRS of HGA often reveals an elevated choline peak, severely reduced N-acetylaspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.

Management

GENERAL MEASURES

- The management of HGA requires a multi-modality approach to cytoreduction that includes surgery, radiotherapy, and chemotherapy. Input from neurosurgeons, neuro-oncologists, and radiation oncologists is necessary for optimal treatment.

SURGICAL MEASURES

- Surgery should be considered in all patients to make a histologic diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms. Maximal surgical resection is the treatment of choice for accessible HGA, preferably by computer-assisted volumetric resection techniques (e.g., Stealth apparatus). For patients with deep inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Some studies suggest that overall and 1-year survival are improved with complete or subtotal resection versus biopsy.
**Brain Tumor, High-Grade Astrocytoma**

**SYMPTOMATIC TREATMENT**
- Dexamethasone 4-16 mg/day IV may be of benefit to reduce peritumoral edema and swelling. In some patients, IV mannitol 12.5-25 g q3-6h may also be necessary to control severe edema, mass effect, and midline shift.

**ADJUNCTIVE TREATMENT**
- External beam radiation therapy (RT) should be considered for all HGAs after surgical resection. Phase I/II trials demonstrate that time to progression and overall survival are significantly improved with RT (overall survival 36 weeks with RT vs. 16 weeks with surgery alone). The recommended RT dose is 60 Gy over 6 weeks, in daily fractions of 180-200 cGy. Focal three-dimensional treatment planning and conformal techniques should be used whenever possible to minimize radiation exposure to normal brain, especially in younger patients. For elderly patients (>65 years) and those with poor Karnofsky performance status, a protracted course of RT may be appropriate: 30-40 Gy in 10 fractions over 3 weeks.
- Stereotactic radiosurgery (SRS) has been used for HGA, as a boost after initial RT and at recurrence, for tumors up to 4 cm in size; larger tumors will not benefit from SRS due to infiltration beyond the treatment field. Median doses range from 15-17 Gy in one fraction. SRS may improve survival in carefully selected patients with small HGA.
- Chemotherapy should be considered for all patients with HGA after RT and at recurrence. Clinical trials and meta-analyses suggest a modest survival benefit after RT (10%-15% extension in 1-year survival), especially in patients with AA and mixed AOA. For AA and GBM, the most active drugs and combinations include carmustine (BCNU), procarbazine, PCV (procarbazine, CCNU [lomustine], vincristine), cisplatin, carboplatin, temozolomide, and etoposide. Mixed AOA may respond well to chemotherapy with PCV or temozolomide if chromosome 1p and 19q deletions are noted. At recurrence, local chemotherapy with BCNU-impregnated wafers may add a modest survival benefit, as suggested by several phase I/II trials.

**ADMISSION/DISCHARGE CRITERIA**
- Patients with HGA often are admitted for seizure control or neurologic deterioration due to elevated intracranial pressure and tumor growth. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure are required before discharge.

**Follow-Up**
- Patients are followed with serial MRI scans and neurologic examinations every 4-8 weeks. Patients receiving chemotherapy may require more frequent follow-up. Anticonvulsant levels need to be monitored carefully.

**EXPECTED COURSE AND PROGNOSIS**
- Median survival after diagnosis of patients with HGA is 30-42 months for AA, 8-13 months for GBM and gliosarcoma, and 42-52 months for mixed AOA.
- Prognosis is improved with young age (<40 years) AOA or AA histology, and high Karnofsky performance status. Prognosis is worse with age >50 years, poor Karnofsky performance status, and GBM or gliosarcoma histology.

**PATIENT EDUCATION**
- BrainTumors.com.
- Website: [www.braintumors.com](http://www.braintumors.com)
- National Brain Tumor Foundation.
- Website: [www.braintumor.org](http://www.braintumor.org)
- American Brain Tumor Association.
- Website: [www.abta.org](http://www.abta.org)
- The Brain Tumor Society.
- Website: [www.bts.org](http://www.bts.org)
- Massachusetts General Hospital-Brain Tumor Center. Website: [brain.mgh.harvard.edu](http://brain.mgh.harvard.edu)
- Brain Tumor Treatment Options & Information. Website: [users.erols.com/collins/index.htm](http://users.erols.com/collins/index.htm)

**REFERENCES**

Author(s) Herbert B. Newt on, MD
Brain Tumor, Low-Grade Glioma

Basics

DESCRIPTION

- Low-grade gliomas (LGGs) are a diverse group of pathologically distinct neoplasms that usually occur in children and young adults. The most common LGGs are of astrocytic and oligodendroglial origin. These tumors have a reduced growth potential and often are less infiltrative compared to malignant gliomas. Survival typically is prolonged, >5 years in most patients.

ETIOLOGY

- Incidence is slightly higher in mates than females.

EPIDEMIOLOGY

Incidence/Prevalence

- LGGs comprise approximately 10%-15% of primary brain tumors in adults, which corresponds to roughly 1,900 new cases of LGG each year in North America. The majority of LGGs consist of grade I astrocytomas, oligodendrogliomas, and mixed tumors.

Race

- All races and ethnic groups are equally affected.

Age

- Typical presentation is between 30 and 45 years (mean 37).

Sex

- Incidence is slightly higher in mates than females.

ETIOLOGY

- LGGs are a heterogeneous group of neoplasms that include pilocytic astrocytoma (PCA; World Health Organization [WHO] grade I), diffuse astrocytoma (WHO grade II), WHO grade II oligodendroglioma, WHO grade II mixed oligoastrocytoma, subependymoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, central neurocytoma, and dysplastic neuroepithelial tumors.

- Cells of LGG origin are variable, depending on tumor type. Pathologic evaluation of LGG reveals mild-to-moderate cellularity without anaplasia or severe nuclear atypia, minimal mitotic activity and endothelial proliferation, and no necrosis. Tumor cells often stain for glial fibrillary acidic protein. Diffuse astrocytomas can undergo anaplastic degeneration in up to 75% of cases.

- Molecular genetic studies of LGG reveal frequent allelic deletions of chromosome 17p, often with loss or mutation of the tumor suppressor gene p53. Presence of abnormal p53 protein in LGG is associated with shorter survival. Amplification of MDM2 or CDK2 and deletion of the tumor suppressors p16 and retinoblastoma (Rb) may be present in some tumors. Deletion of 1p and 19q may be noted in oligodendrogliomas and is associated with chemosensitivity and extended survival.

Genetics

- LGGs usually are sporadic and do not have an underlying genetic predilection. Rarely, LGGs can manifest as part of a genetically mediated syndrome (i.e., neurofibromatosis [NF]).

RISK FACTORS

- The only known risk factors for LGGs are prior cranial radiation exposure and genetic diseases with a predilection for gliomas, such as Turcot’s syndrome, NF types I and II, Li-Fraumeni syndrome, basal cell nevus syndrome, and tuberous sclerosis. Rarely, LGGs can be familial.

PREGNANCY

- Pregnancy does not affect the clinical course of LGGs.

ASSOCIATED CONDITIONS

- NF type I, NF type II, Turcot’s syndrome, Li-Fraumeni syndrome, basal cell nevus syndrome, tuberous sclerosis

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Other mass lesions that may or may not enhance should be considered, including immature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

SIGNS AND SYMPTOMS

- The median duration from onset of symptoms to diagnosis ranges from 6-17 months. The most common symptom at presentation is seizure, which occurs in 60%-65% of patients. Focal seizures are more likely than generalized seizures. Headache and focal weakness each occurs in approximately one fourth of patients. Cognitive changes, speech deficits, and visual abnormalities are noted in <15% of patients.

- Neurologic examination is normal in about 50% of patients. Neurologic abnormalities may include focal motor deficits (45%), sensory alterations (40%), mental status alterations (25%), papilledema (20%), dysphasia (20%), and memory deficits (18%).

LABORATORY PROCEDURES

- Molecular analysis of chromosome 1p and/or 19q loss may be of diagnostic significance in patients with oligodendroglioma. EEG should be considered in patients with atypical or unusual seizures.

IMAGING STUDIES

- MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for tumors that are small or within the posterior fossa. On T1 images, the tumor usually is somewhat circumscribed and appears hypointense or isointense compared to brain; on T2 images, the mass is hyperintense. Cystic regions are often present in PCA. With gadolinium administration, most LGGs show minimal or no enhancement. PCA can show variable enhancement, often within a cyst-associated mural nodule. Peritumoral edema and mass effect are usually mild to moderate. Calcification may be noted. CT demonstrates an ill-defined region of hypodensity with minimal enhancement. More than one third of tumors that appear to be LGGs by MRI/CT criteria are higher-grade tumors, usually anaplastic astrocytoma.

GENERAL MEASURES

- The management of LGG remains controversial. Some authors recommend observation and serial MRI scans for proof of growth potential before initiation of treatment (i.e., surgery, irradiation); others suggest immediate tissue diagnosis with biopsy or resection, followed by irradiation or chemotherapy. Observation is most appropriate for small deep tumors that are asymptomatic except for seizure activity.
Brain Tumor, Low-Grade Glioma

SURGICAL MEASURES
- Surgery should be considered in all patients to make a histologic diagnosis and alleviate symptoms. Maximal surgical resection is the treatment of choice for accessible LGGs, preferably by computer-assisted volumetric resection techniques (e.g., Stealth apparatus). For patients with deep inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Some studies suggest that overall and 5-year survival are improved with complete or subtotal resect ion versus biopsy.

SYMPTOMATIC TREATMENT
- Dexamethasone 4-16 mg/day may be of benefit to reduce peritumoral edema and swelling.

ADJUNCTIVE TREATMENT
- External beam radiation therapy (RT) should be considered for all nonpilocytic LGG after incomplete surgical resection. Postoperative RT can be postponed for patients with PCA until growth potential is demonstrated. Retrospective studies suggest that time to progression and overall survival are improved with RT (5-year survival 32% with RT vs. 10% without surgery) alone. Timing of RT remains controversial; some authors advocate immediate postoperative treatment while others suggest waiting until the tumor progresses; however, the timing of RT does not appear to be critical, because overall survival is similar in the immediate and delayed treatment groups. RT for LGG is more beneficial for older patients (>40 years). Conformal techniques should be used whenever possible to minimize radiation exposure to normal brain. Recommended RT doses are 50-55 Gy over 6 weeks. Irradiation should be delayed postoperatively in young children until proof of growth by MRI and/or neurologic examination.
- Stereotactic radiosurgery is a more recent RT option. Several studies have used doses of 15-50 Gy for LGGs up to 40 mm. Objective responses have been noted in >50% of patients, although follow-up has been brief.
- Chemotherapy does not have a clear role in most patients with LGG. Young children may respond to cisplatin-based regimens in order to delay the need for RT. A Southwest Oncology Group phase III trial that of LGG in adults did not demonstrate a survival benefit for lomustine in combination with RT. Phase II studies suggest nitrosoureas (lomustine, carmustine), alone or in combination with platinum (cisplatin, carboplatin) drugs, may have benefit for patients with LGG. PCV (procarbazine, lomustine, vincristine) has demonstrated activity against LGG, especially oligodendrogliomas. Objective responses range from 30%-45% in some studies. Temozolomide has demonstrated activity similar to PCV against LGG in recent phase II studies. Progressive or recurrent PCA may respond to cisplatin-based multiagent chemotherapy regimens.

ADMISSION/DISCHARGE CRITERIA
- Patients with LGG are most often admitted for seizure control or to reduce elevated intracranial pressure. Maximizing anticonvulsant doses and resolving metabolic disturbances is required before discharge.

DRUG(S) OF CHOICE
- Seizures are a common problem in patients with LGG, so appropriate anticonvulsant choices and management are critical. Dexamethasone is used at the lowest dose able to control symptoms related to intracranial pressure.

Contraindications
- Patients on chemotherapy must meet appropriate hemodynamic parameters before proceeding with the next cycle. WBC should be >2.0, hemoglobin >10.0, and platelets >100,000.

Precautions
- All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
- Patients are followed with serial MRI scans and neurologic examinations every 4-6 months. Patients receiving chemotherapy will require more frequent follow-up; anticonvulsant levels will need to be monitored.

EXPECTED COURSE AND PROGNOSIS
- Median survival after diagnosis of patients with LGG is 4.7 years for diffuse astrocytomas, 7.1 years for mixed oligoastrocytomas, and 9.8 years for oligodendrogliomas. The 10-year survival in these cohorts is 17%, 33%, and 49%, respectively.
- Prognosis is improved with oligodendrogial or pilocytic histology, young age, and seizures at presentation. Prognosis is worse with age >40 years, poor performance status, and diffuse astrocytic histology.

PATIENT EDUCATION
- Brain tumors.com. Website: www.braintumors.com
- National Brain Tumor Foundation. Website: www.braintumor.org
- American Brain Tumor Association. Website: www.tbts.org
- The Brain Tumor Society. Website: www.tbts.org
- Massachusetts General Hospital-Brain Tumor Center. Website: brain.mgh.harvard.edu

SYNONYMS
- Low-grade astrocytoma
- Low-grade oligodendroglioma
- Pilocytic astrocytoma
- Subependymoma
- Subependymal giant-cell astrocytoma
- Low-grade mixed oligoastrocytoma
- Pleomorphic xanthoastrocytoma
- Ganglioglioma
- Central neurocytoma
- Dysembryoplastic neuroepithelial tumors

ICD-9-CM: 225.0 Benign neoplasm of brain

SEE ALSO: BRAIN TUMOR, OLIGODENDROGLIOMA

REFERENCES

Author(s) Herbert B. Newt on, MD
DESCRIPTION
• Medulloblastoma is the most common malignant primary brain tumor of childhood. It is an invasive embryonal neoplasm that arises in the midline cerebellum. Recent advances in multimodality treatment have led to significant improvements in local tumor control and survival.

EPIEMIOLOGY
Incidence/Prevalence
• Medulloblastoma comprises approximately 20°6-25% of all malignant primary brain tumors in children. The overall incidence in the United States is approximately 5 cases per million persons, which corresponds to roughly 350 new cases each year. Medulloblastoma is uncommon in adults, with an incidence of 1%. Adults account for 15%-20% of medulloblastoma cases.

Race
• All races and ethnic groups are affected. Caucasians are affected more commonly than blacks, Latinos, and Asians.

Age
• Typical presentation is between 7 and 9 years of age; 80% of patients present before age 20 years; a secondary peak occurs in adults between 26 and 30 years.

Sex
• Incidence in childhood is slightly higher in males than females (1.4-2.3:1). Males and females are equally affected in adulthood.

ETIOLOGY
• The World Health Organization classifies medulloblastoma as grade IV.

• The cell of origin of medulloblastoma remains controversial. The cells are derived from transformation of pluripotent cells that reside in either the external granular layer of the cerebellum or the ependymal matrix. In children they typically occur in the midline cerebellum, with variable extension into the brainstem; in adults, they are eccentrically located, with extension into one of the cerebellar hemispheres. Pathologic evaluation reveals a highly cellular tumor consisting of densely packed, small, poorly differentiated cells with hyperchromatic nuclei and scant cytoplasm, Homer-Wright rosettes, occasional ganglion cells, regions of necrosis, and frequent mitoses. Histologic variants include the desmoplastic, nodular, and large cell forms.

• have noted frequent deletions of chromosomes 17p, 1q, and 10q. Three separate pathways have been implicated in the transformation process: amplification of the N- and C-myc genes, mutation of the PTCH gene, and dysfunction of the sonic hedgehog/PTCH signaling pathway, and dysregulation of the Wnt/APC/β-catenin signaling pathway. High expression of TrkG is associated with extended survival.

Genetics
• Medulloblastomas usually are sporadic. Medulloblastoma can arise as a manifestation of heritable disorders such as Turcot's syndrome, Li-Fraumeni syndrome, ataxia-telangiectasia, nevoid basal cell carcinoma syndrome, and Coffin's syndrome. Rarely, medulloblastoma can be familial.

RISK FACTORS
• The only known risk factors for medulloblastoma are the above mentioned heritable syndromes and rare familial predispositions.

PREGNANCY
• Pregnancy does not affect the clinical course of medulloblastoma.

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Other mass lesions of the cerebellum that may or may not be associated with extracerebellar disease should be considered, including abscess, subacute infarct, tumefactive regions of demyelination, evolving hematoma, other primary brain tumors (e.g., astrocytoma), and metastasis.

SIGNS AND SYMPTOMS
• The median duration from onset of symptoms to diagnosis ranges from 3-6 months. Initial symptoms include irritability, loss of appetite, progressive headache, lethargy, and nausea and emesis (often in the morning). Later symptoms include double vision, truncal and/or limb ataxia, gait imbalance, neck stiffness, and dizziness.

Common findings on neurologic examination include lethargy, papilledema, gait ataxia, nystagmus and sixth nerve palsy. Less common findings include hemiparesis, internuclear ophthalmoplegia, dysphagia, and myelopathy.

• MRI, with and without contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for tumors within the posterior fossa and has the advantage of midsagittal formatting. On T1 images, the tumor is mildly to moderately infiltrative and appears hypointense or isointense compared to brain; on T2 images, the mass is hyperintense. With gadolinium, medulloblastoma demonstrates patchy or dense enhancement (90%). Edema and mass effect are mild to moderate, with frequent compression of the fourth ventricle. Leptomeningeal metastases are noted in one third of patients. CT demonstrates an ill-defined region of hypodensity that has variable enhancement, mild edema, and mass effect. Hydrocephalus is common (75%-85%).

SPECIAL TESTS
• All patients require an EODWU to screen for leptomeningeal metastases and allow stratification into low-risk and high-risk groups. The EODWU involves a contrast-enhanced MRI scan of the spine. Patients with normal or equivocal MRI results require a lumbar puncture to evaluate CSF. Patients suspected of having extraneural metastases require a skeletal survey and nuclear medicine scan.
Brain Tumor, Medulloblastoma

Management

GENERAL MEASURES
• Management of medulloblastoma involves a multimodality approach to cytoreduction that requires surgery, radiotherapy, and, in selected patients, chemotherapy.

SURGICAL MEASURES
• Surgery should be considered in all patients to make a histologic diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms. Maximal surgical resection is the treatment of choice for medulloblastoma, preferably by computer-assisted volumetric resection techniques. For patients with extensive infiltration of tumor into the brainstem or cerebellar hemispheres, an extensive subtotal resection should be performed. A ventriculoperitoneal shunt may be necessary if hydrocephalus persists after maximal tumor resection (35%-40%). Several studies suggest that overall and 5-year survival are improved with complete or subtotal resection versus biopsy. Postoperative CT or MRI should be performed within 24-72 hours to screen for residual tumor.

SYMPTOMATIC TREATMENT
• Dexamethasone 4-16 mg/day usually is necessary to reduce periocular edema, swelling, and mass effect.

ADJUNCTIVE TREATMENT
• External beam radiation therapy (RT) is recommended for all medulloblastoma patients. Standard RT involves treatment of the entire intracranial cavity and spine. RT to the posterior fossa consists of 50-55 Gy over 6-7 weeks in daily fractions of 180-200 cGy. RT to the brain and spinal neuraxis is administered concurrently. Dosing for the brain ranges from 40-45 Gy; dosing for the spine ranges from 33-36 Gy. Patients receiving <30 Gy to the spine are at increased risk for early relapse and shorter survival time. RT is the sole initial treatment for low-risk patients. Recent attempts to reduce RT toxicity in pediatric patients have included using reduced doses in combination with mutagen chemotherapy. Focal RT may be necessary for patients with extraneural metastases (e.g., bone lesions). The role of radiosurgery remains unclear.
• Chemotherapy should not be used for low-risk medulloblastoma patients. Phase III trials have demonstrated a survival advantage for chemotherapy in the high-risk patient cohorts only when used during and after RT. Chemotherapy should be considered for all high-risk patients and for any patient with recurrent disease. The most active single agents include cisplatin, carboplatin, lomustine (CCNU), etoposide, and cyclophosphamide. The most active combination regimens include CCNU and vincristine, MOPP (mustard, vincristine, prednisone, procarbazine), cyclophosphamide and vincristine, and platinum-based regimens (e.g., cisplatin, CCNU, vincristine). Adult medulloblastoma patients have chemotherapy response profiles similar to those of pediatric patients.

ADMISSION/DISCHARGE CRITERIA
• Patients with medulloblastoma are often admitted for neurologic deterioration due to elevated intracranial pressure, tumor growth, seizures, leptomeningeal metastases, or infections. Maximizing anticonvulsant doses, reducing intracranial pressure, and treating infections are required before discharge. Some patients may require the initiation of new cytotoxic treatment (e.g., intrathecal chemotherapy).

PRECAUTIONS
• Precautions are followed with serial MRI scans and neurologic examinations every 4-8 weeks. Patients receiving chemotherapy may require more frequent follow-up.

ALTERNATIVE DRUGS
N/A

Medications

DRUG(S) OF CHOICE
• Seizures occasionally can be a problem. Appropriate anticonvulsant choices (e.g., phenytoin, carbachazepine, levetiracetam) and management are critical.

Contraindications
• Patients on chemotherapy must meet appropriate hematologic parameters before proceeding with the next cycle: WBC >2.0, hemoglobin >10.0, and platelets >100,000.

Follow-Up

PATIENT MONITORING
• Patients are followed with serial MRI scans and neurologic examinations every 4-8 weeks. Patients receiving chemotherapy may require more frequent follow-up.

EXPECTED COURSE AND PROGNOSIS

• Low-risk patients (complete resection, intact neurologic function, negative EODWU) have 5- and 10-year survival rates of 85% and 50%, respectively. High-risk patients (subtotal resection, brainstem infiltration, focal neurologic dysfunction, positive EODWU) have 5- and 10-year survival rates of 50% and 30%, respectively. Long-term survivors often develop impairment of memory and cognition.

• Prognosis is improved with adult onset, complete surgical resection, negative EODWU, intact neurologic function, and the presence of high TrkC expression. Prognosis is worse with young age, incomplete surgical resection, positive EODWU, and focal neurologic dysfunction.

PATIENT EDUCATION

• Brain tumors.
  Website: www.braincancer.org

• American Brain Tumor Association.
  Website: www.abta.org

• National Cancer Institute: Childhood Medulloblastoma.
  Website: cancer.gov/clinicaltrial/mbf
  Website: www.abta.org
  Website: www.tbts.org

• The Brain Tumor Society.
  Website: www.tbts.org

REFERENCES

• Paulino AC. Radiotherapeutic management of medulloblastoma. Oncology (Huntingt) 1997;11: 813-823.

Author(s) Herbert B. Newton, MD
**Brain Tumor, Meningioma**

**Basics**

**DESCRIPTION**
- Meningiomas are extraxial tumors that arise from the meninges of the intracranial dura mater. They can develop in any location that has continuity with the meninges. The most common locations are the parasagittal region (25%), cerebral convexities (20%), sphenoid wing (17%), posterior fossa (8.7%), olfactory groove (8%), and middle fossa (4%). Less common locations include the optic nerve or chiasmal region, cerebellopontine angle, and within the ventricles.

**EPIDEMIOLOGY**
- Meningiomas comprise 18%-20% of all primary brain tumors in adults but only 2% in children. The incidence is 2-7 per 100,000 in women and 1-5 per 100,000 in men; this corresponds to approximately 3,500-4,500 newly diagnosed meningiomas in the United States each year.

**Race**
- All races and ethnic groups are equally affected.

**Age**
- Typical presentation is between 50 and 65 years of age.

**Sex**
- Females have a higher incidence than males (2:1).

**ETOLOGY**
- The World Health Organization (WHO) grades typical low-grade meningiomas (e.g., meningothelial, fibrous, transitional, pachymenomatous, angiomatous) as WHO grade I; intermediate tumors (e.g., atypical, clear cell, chordoid) as WHO grade II; and malignant tumors (e.g., rhabdoid, papillary, anaplastic) as WHO grade III. The majority of meningiomas are WHO grade I; grade II and III tumors are uncommon.

- The cells of origin of meningiomas are transformed arachnoidal cap cells from the outer layer of the arachnoid membrane. Typical low-grade tumors demonstrate uniform sheets of spindle-shaped cells, minimal cellular and nuclear atypia, whorl formation, psammoma bodies, and no evidence for mitotic activity or brain infiltration. Higher-grade tumors have higher cellularity, more prominent nucleoli, high mitotic activity, necrosis, and brain invasion.

- Molecular genetic studies reveal frequent deletions of chromosomes 22q and 1p. The NF2 gene (located at 22q12.3) is mutated in up to 60% of meningiomas, with dysfunction of the merlin protein. The majority of meningiomas are positive for estrogen and progesterone receptors. Other receptors of importance include the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors, both of which stimulate secretion of vascular endothelial growth factor. The ras signaling pathway is activated by stimulation by EGF and PDGF.

**Genetics**
- Meningiomas usually are sporadic tumors; less frequently, they can arise as part of a heritable syndrome such as neurofibromatosis (NF). In rare cases they can be familial.

**RISK FACTORS**
- Factors that increase the risk of meningioma include cranial radiation (>10 Gy), focal head trauma (especially with dural penetration), breast cancer, heritable disorders (e.g., NF), and rare familial clusters.

**PREGNANCY**
- In some women, pregnancy can accelerate the growth and increase the clinical symptoms of meningiomas.

**ASSOCIATED CONDITIONS**
- NF type I, NF type II

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Includes other extraxial enhancing masses, such as schwannoma, metastasis, choroid plexus papillomas, and abscess.

**SIGNS AND SYMPTOMS**
- Meningiomas are slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis typically is prolonged (i.e., months to years). The presentation varies with tumor location, rate of growth, and amount of peritumoral edema. Common symptoms at presentation include headache, seizure activity (often focal), personality changes, speech abnormalities, cranial nerve dysfunction (e.g., visual loss, facial numbness), visual field defects, and focal motor deficits. In some patients, meningiomas are asymptomatic at diagnosis.

- Common neurologic signs include monoparesis or hemiparesis, asymmetric reflexes, impairment of memory and cognition, visual loss (monocular or hemianopic), dysphasia, and cranial nerve palsies (i.e., V, VI, VII).

**LABORATORY PROCEDURES**
- N/A

**IMAGING STUDIES**
- MRI, with and without intravenous contrast, is the most critical diagnostic test; axial, coronal, and midsagittal enhanced images should be obtained. MRI is more sensitive than CT for small tumors and associated vascular structures, although both modalities properly visualize large masses. On T1 images, the tumor usually is isointense to brain; on T2 images, it is hyperintense. Meningiomas enhance densely after administration of gadolinium. On CT, meningiomas are isodense compared to brain and enhance densely with contrast. MRI and CT often demonstrate a site of dural attachment or a dural tail, as well as hyperostotic changes in nearby bone.

**SPECIAL TESTS**
- Angiography is performed in selected patients to assess vascular anatomy and collateral blood supply prior to surgery. It also may be useful in preoperative embolization (to minimize intraoperative bleeding) or postoperative vascular reconstruction.

**Management**

**GENERAL MEASURES**
- In certain patient cohorts, meningiomas are followed conservatively after diagnosis, including patients with poor health, elderly patients with small lesions or who are reluctant to proceed to surgery, and patients with small II tumors that do not correlate with symptoms. Observation should include an enhanced CT or MRI every 4-6 months to monitor for growth. Tumors may remain quiescent if they are stable during the initial observation period. Conservative approaches are unjustified in symptomatic patients and most young patients, especially if growth potential is demonstrated.

**SURGICAL MEASURES**
- Surgical resection is the treatment of choice for most symptomatic patients. The surgical approach will vary depending on the location of the tumor. Complete surgical extirpation is the goal whenever possible. Only subtotal removal is possible for tumors intimately associated with cranial nerves and/or vessels. After removal of the tumor, involved bone and dural attachments should also be resected, with a wide margin. Dural defects should be repaired with pericranium, temporalis fascia, or fascia lata grafts.
SYMPTOMATIC TREATMENT
• Consists of corticosteroids to control symptoms of intracranial pressure and anticonvulsants as required to control seizures.

ADJUNCTIVE TREATMENT
• Conventional external beam radiotherapy (RT) is of benefit for selected patients after subtotal removal, for recurrent or aggressive tumors, and for all patients with malignant pathology (WHO grade III). Clinical trials demonstrate a survival advantage for patients given RT after subtotal removal versus surgery alone. Recommended RT doses for typical low-grade tumors are 50-55 Gy over 6 weeks, with 180-200 cGy fractions per day. More aggressive RT doses of 55-60 Gy may be appropriate for malignant meningiomas. Three-dimensional conformal treatment planning or intensity-modulated techniques should be used to minimize irradiation of normal brain. RT is not necessary for completely resected meningiomas with low-grade pathology.
• Stereotactic radiosurgery (linear accelerator, gamma knife) can be an adjunctive form of treatment for meningiomas with low-grade pathology. Stereotactic radiosurgery is considered for patients who cannot undergo surgery or for patients who have failed previous surgery, or refuse surgical intervention; tumors <3 cm in diameter are most suitable. Dosing is usually between 16 and 18 Gy in a single fraction to the 50% isodense line. Local control rates range from 90%-95%, with variable amounts of tumor shrinkage. Standard single-dose radiosurgery may be unsuitable for tumors in close proximity to the optic chiasm or brainstorm. Fractionated radiosurgery (linear accelerator) may be a safer option for tumors near the optic apparatus or brainstorm.
• Currently, chemotherapy has a limited role in the treatment of meningiomas. It should be considered for patients who cannot undergo surgical resection and for tumors that recur despite surgery and/or RT. Traditional cytotoxic chemotherapy has limited activity against meningiomas. Drugs with modest activity in phase I-II trials include mifepristone (RU-486; antagonist to progesterone receptors), hydroxyurea (induces apoptosis in meningioma cells), and interferon-α-2b. When active, chemotherapy usually induces tumor stabilization; shrinkage is uncommon.

ADMISSION/DISCHARGE CRITERIA
• Admission is generally reserved for presurgical evaluation and surgical resection. Angiography may be included in the workup to assess regional vascular anatomy. Patients with severe brain or brainstem compression might benefit from admission for IV dexamethasone.

MEDICATIONS

DRUG(S) OF CHOICE
• Dexamethasone 2-8 mg/day may be of benefit to reduce edema and swelling for patients with brain compression. It may improve transient symptoms of pressure and swelling after RT or radiosurgery.

CONTRAINDICATIONS
N/A

PRECAUTIONS
• All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

ALTERNATIVE DRUGS
N/A

FOLLOW-UP

PATIENT MONITORING
• Patients are followed with serial MRI scans and assessment of neurologic function every 6-12 months.

EXPECTED COURSE AND PROGNOSIS
• The recurrence rate for completely resected tumors is 20% at 10 years. For incompletely resected tumors the rate is 55% at 10 years. For completely resected tumors the 5- and 10-year progression-free survival rates are 88% and 75%, respectively. For tumors that have undergone surgery plus RT, the 5- and 15-year progression-free survival rates are 95% and 86%, respectively. Survival is more limited for patients with malignant meningioma, with a 5-year survival rate of 63%.
• Factors that increase the probability for recurrence include incomplete removal of all dural attachments, invasion of bone, soft-tumor consistency, and malignant histology.

PATIENT EDUCATION

SYNONYMS
N/A

CD-9-CM: 225.2 Benign neoplasm of cerebral meninges; 192.1 Malignant neoplasm of cerebral meninges

SEE ALSO: NEUROFIBROMATOSIS TYPES I AND II

REFERENCES

Author(s) Herbert B. Newt on, MD
Brain Tumor, Metastases

DESCRIPTION

Basics

- Metastatic brain tumors (MBTs) are the most common complication of systemic cancer. MBTs most often arise from tumors of the lung (50%-60%), breast (15%-20%), melanoma (5%-10%), and GI tract (4%-6%); however, they can develop from any systemic malignancy, including primary tumors of the prostate, ovary, female reproductive system, kidney, esophagus, soft-tissue sarcoma, bladder, and thyroid. In children and young adults, MBTs most often arise from sarcomas (e.g., osteogenic, Ewing's), germ cell tumors, and neuroblastoma. Postmortem studies suggest that melanoma, renal carcinoma, and testicular carcinoma have the greatest propensity for spread to the brain. In 65%-75% of patients, MBTs will present as multiple lesions. Multiple MBTs are most common with lung carcinoma and melanoma. Single MBTs are noted most often in patients with breast, colon, and renal cell carcinoma.

Epidemiology

Incidence/Prevalence

- Brain metastases develop in 2%-40% of adults and 6%-10% of children with systemic cancer. The annual incidence is 3.4-8.3 per 100,000 population. This corresponds to an estimated 125,000-170,000 new cases of MBT each year in the United States.

Race

- All races and ethnic groups are equally affected.

Age

- Typical presentation is 45-70 years in adults and 8-14 years in children; 40%-45% of MBTs present in patients >65 years.

Sex

- Males have a higher incidence than females (1.36:1).

Etiology

- Systemic tumor cells usually travel to the brain by hematogenous spread through the arterial circulation, most often originating from the lungs (primary or lung metastasis). The distribution of MBT follows the relative volume of blood flow to each area so that 80% of tumors arise in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem. Tumor cells typically lodge in small vessels at the gray-white junction and then spread into the brain parenchyma, where the cells proliferate and induce their own blood supply. MBTs are histologically similar to the primary tumor of origin.

- Neurologic function is disrupted by MBT through several mechanisms, including direct displacement of brain structures, perilesional edema, irritation of overlying gray matter, and compression of arterial and venous vasculature.

- Tumor cells more likely to metastasize to the brain have a more aggressive phenotype, with increased cell motility and angiogenic capacity. These changes are mediated by scatter factor, autocrine motility factor, activation of the ras signal transduction pathway, amplification of oncogenes, and loss or mutation of metastasis-suppressor genes (e.g., nm23, KISS).

Genetics

- Brain metastases are sporadic tumors without any specific genetic influence.

Risk Factors

- Risk factors that increase the probability of MBT include lung carcinoma and other primary malignancies with a predilection for the brain (i.e., melanoma, renal carcinoma, testicular carcinoma) and widespread aggressive disease, especially lung metastases.

Comorbidities

- Common comorbidities of cancer patients, such as infection and sepsis, metabolic encephalopathy, carcinomatous meningitis, and epidural spinal cord compression.

Diagnosis

Differential Diagnosis

- Includes other enhancing solitary or multilocular masses, such as mature abscess or abscesses, primary brain tumor, acute infarct, and hemmorhage.

Signs and Symptoms

- Symptoms caused by MBT usually are progressive over days to weeks. Any symptom can arise from MBT, depending on tumor location. The most frequent symptoms include headache (25%-40%), alterations of thinking and memory (2%-25%), focal oculac weakness (20%-30%), and seizure activity (15%-25%). Less common symptoms consist of gait difficulty, visual loss, speech abnormalities, and sensory loss.

- Common neurologic signs include hemiparesis (55%-60%), impaired cognition (55%), papilledema (2%), dysphasia (15%-20%), gait disturbance (10%-20%), hemiweakness (5%), and hemisensory loss (5%).

Laboratory Procedures

N/A

Imaging Studies

- MRI, with and without contrast, is the most critical diagnostic test. Axial, coronal, and midsagittal enhanced images should be obtained. MBTs present as rounded, well-circumscribed, noninfiltrative masses surrounded by a large amount of edema. MRI is more sensitive than CT for small tumors and tumors in the posterior fossa and brainstem, although both modalities properly visualize large MBTs. Of the images, the tumor usually is hypointense or isointense compared to brain; on T2 images, it is hyperintense. MBTs enhance densely after administration of gadolinium. On CT, MBTs are hypodense or isodense compared to brain and enhance densely with contrast.

Special Tests

- Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of the suspected MBT to differentiate it from nonneoplastic lesions. MBT typically appear hypermetabolic on PET imaging. Magnetic resonance spectroscopy (MRS) also can be used for metabolic screening to differentiate MBTs from other lesions. MRS of MBT often reveals an elevated choline peak, reduced N-acetyl aspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.

General Measures

- Should include symptomatic treatment and consultation by radiation oncology, neurooncology, and neurosurgery for treatment evaluation.

Surgical Measures

- Surgical resection is used for carefully selected patients with symptomatic accessible MBT and limited systemic disease. It is applied most frequently to patients with solitary MBT. Phase I trials have demonstrated a survival advantage for surgical resection plus irradiation versus irradiation alone (40 vs. 15 weeks) for patients with solitary lesions. Patients with multiple MBT can also be considered for resection if one or two accessible tumors are responsible for the majority of symptoms.
Brain Tumor, Metastases

SYMPTOMATIC TREATMENT

• Consists of dexamethasone to control symptoms of intracranial pressure and anticonvulsants as required to control seizures. Anticonvulsants should not be used prophylactically; they should be implemented after documented seizure activity.

ADJUNCTIVE TREATMENT

• Conventional external beam radiotherapy (RT) to the whole brain is the most commonly used mode of treatment for patients with MBT. RT increases median survival to 12-24 weeks in most patients. RT is effective at palliation of neurologic symptoms (70%-80% rate of symptomatic improvement) and reduces the risk of death due to progression of MBT. Recommended RT doses are 30-45 Gy administered over 3-4 weeks, in fractions of 180-200 cGy. Addition of RT after surgical resection will prolong time to neurologic recurrence and reduce the risk of death from MBT.
• Stereotactic radiosurgery (linear accelerator, gamma knife) can be an adjunctive form of treatment in selected MBT patients. Although phase II trials have not been concluded, phase I/II data suggest that radiosurgery can extend survival and improve local tumor control. Appropriate patients have a good prognostic profile, including minimal neurologic dysfunction, three or fewer MBT that are <3 cm in size, stable systemic disease, and relatively young age. Recommended doses are 18-25 Gy in a single fraction.
• Chemotherapy has a limited role in the majority of patients with MBT. It is most beneficial for patients with stable systemic disease who have progressive MBT after RT or radiosurgery. Several approaches have been used (e.g., multiagent intravenous, intraarterial, oral) and demonstrated modest efficacy in phase I/II trials. The most active IV drugs are cisplatin, etoposide, and cyclophosphamide. Intraarterial carboplatin and oral temozolomide have been demonstrated modest efficacy in phase I/II trials. The most active IV drugs are cisplatin, etoposide, and cyclophosphamide. Intraarterial carboplatin and oral temozolomide have been effective in some patients.

ADMISSION/DISCHARGE CRITERIA

• Admission usually is for exacerbation of cerebral edema and intracranial pressure or for excessive seizure activity. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure are required before discharge.

ADMISSION/DISCHARGE CRITERIA

• Admission usually is for exacerbation of cerebral edema and intracranial pressure or for excessive seizure activity. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure are required before discharge.

DRUG(S) OF CHOICE

• Dexamethasone 4-16 mg/day is of benefit to reduce edema and swelling and may improve transient symptoms of pressure and swelling after RT or radiosurgery. Seizures are a common problem in patients with MBT. Appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management are critical.

Contraindications

• Patients on chemotherapy must meet appropriate hematologic parameters before proceeding with the next cycle. WBC >2.0, hemoglobin >10.0, and platelets >100,000.

Precautions

• All patients should be taken an H2-blocking drug while receiving chronic dexamethasone.

ALTERNATIVE DRUGS

N/A

PATIENT MONITORING

• Patients are followed with serial MRI scans and assessment of neurologic function every 2-4 months. Patients receiving chemotherapy may need more frequent monitoring of clinical and hematologic status. Anticonvulsant levels need to be monitored carefully.

EXPECTED COURSE AND PROGNOSIS

• Overall prognosis depends on the histologic tumor type, number and size of MBT, severity of neurologic dysfunction, and amount of systemic involvement. If left untreated, the expected survival of most patients with MBT is 4 weeks. Survival improves to 8 weeks with the addition of dexamethasone. Surgical resection and/or RT can extend survival another 8-20 weeks for most patients.
• The most important factors for extended survival are age <65 years, intact neurologic function, with a Karnofsky performance status >70, and well-controlled systemic disease. Patients with multiple MBTs have a reduced survival.

PATIENT EDUCATION

• Brain tumors.com.
  Website: www.brain tumors.com
• National Brain Tumor Foundation.
  Website: www.brain tumor.org
• American Brain Tumor Association.
  Website: www.abta.org
• The Brain Tumor Society.
  Website: www.brts.org
• Clinical Trials-Brain Metastases. Website:
  www.bttreatment.com/metstriah.htm
• National Cancer Institute CancerNet. Website:
  cancernet.nci.nih.gov/tcemet/103854.html

SYNONYMS

N/A

REFERENCES


Author(s) Herbert B. Newt on, MD
Brain Tumor, Oligodendroglioma

**Basics**

**DESCRIPTION**
- Oligodendrogliomas are an uncommon group of glial neoplasms that typically occur in young and middle-age adults. They have variable growth potential and can be quite infiltrative, depending on whether they are typical low-grade oligodendrogliomas (LGO) or the more aggressive anaplastic oligodendrogliomas (AO). Survival is prolonged in most patients and ranges between 4 and 10 years.

**Epidemiology**
- Incidence/Prevalence:
  - Oligodendrogliomas comprise approximately 410-5% of primary brain tumors in adults; this corresponds to roughly 700 new cases each year in North America. The incidences of LGO and AO are relatively equal, similar to the incidences of pure and mixed oligodendrogliomas.
- Race:
  - All races and ethnic groups are affected. Caucasians are affected more commonly than blacks, Latinos, and Asians.
- Age:
  - Typical presentation is between 40 and 50 years of age for all forms of oligodendrogliomas.
- Sex:
  - Incidence is slightly higher in males than females (1.5:1).

**Etiology**
- The World Health Organization classifies LGO as grade II, AO as grade III, and mixed anaplastic oligoastrocytoma (AOA) as grade III.
- Oligodendrogliomas are most likely derived from transformed oligodendrocytes. They have a predilection for the subcortical white matter of the cerebral hemispheres. Pathologic evaluation of LGO reveals a moderately cellular tumor with rounded homogeneous cells that have a “fried-egg appearance” on paraffin sections. Other features include microcalcifications, dense branching capillaries, mild nuclear atypia, and low-level mitotic activity. AO will have similar features with the addition of higher cellular density, cellular and nuclear atypia, high mitotic rate, endothelial proliferation, and necrosis.

**Diagnosis**

**Differential Diagnosis**
- Other mass lesions that may or may not enhance should be considered, including abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

**Signs and Symptoms**
- Median duration from onset of symptoms to diagnosis ranges from 6-12 months in AO and 18-30 months for LGO. The most common symptom at presentation is seizure activity (50%-70%). Seizures can be simple partial, complex partial, generalized tonic-clonic, or a combination. Other presenting symptoms include headache and other signs of increased intracranial pressure (e.g., nausea, emesis, diplopia), focal weakness, speech dysfunction, cognitive decline, and behavioral changes. Rarely, patients can have acute symptoms from intratumoral hemorrhage.

**Laboratory Procedures**
- Molecular analysis of chromosomes 1p and/or 19q loss is of prognostic significance in patients with AO and LGO.

**Imaging Studies**
- MRI, with and without contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for oligodendrogliomas that are small or within the posterior fossa. On T1 images, the tumor usually is infiltrative and appears hypointense or isointense compared to brain; on T2 images, the mass is hyperintense. Foci of hemorrhage or calcification may be noted. With gadolinium administration, most LGOs do not enhance, whereas AO/ABA show either patchy or ringlike enhancement. Peritumoral edema and mass effect usually are mild to moderate. CT demonstrates an ill-defined region of hypodensity with variable enhancement. Edema and mass effect are mild.

**Special Tests**
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of oligodendrogliomas to differentiate from nonneoplastic lesions and to maximize targeting for biopsy. On PET imaging, LGOs appear hypometabolic and AOs appear hypermetabolic. Magnetic resonance spectroscopy (MRS) also can be used for metabolic screening to differentiate oligodendrogliomas from other lesions. MRS reveals an elevated choline peak, moderately reduced N-acetylaspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.

**Management**

**General Measures**
- The management of LGO and AO requires a multimodal approach to cytoreduction that may require surgery, radiotherapy, and chemotherapy. Treatment must be individualized. Input from neurosurgeons, neuro-oncologists, and radiation oncologists is necessary for optimal therapy. Patients with small indolent tumors (i.e., presentation with seizures, normal neurologic examination, no evidence on CT/MRI of increased intracranial pressure) may be followed without treatment for evidence of growth.
Surgical Measures
- Surgery should be considered in all patients to make a histologic diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms. Maximal surgical resection is the treatment of choice for accessible LGO and AO, preferably by computer-assisted volumetric resection techniques (e.g., Stealth apparatus). For patients with deep inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Several studies suggest that median and 5-year survival of LGO and AO are improved with complete or subtotal resection versus biopsy.

Symptomatic Treatment
- Dexamethasone 4-16 mg/day may be of benefit to reduce peritumoral edema and swelling.

Adju nctive Treatment
- External beam radiation therapy (RT) should be considered for carefully selected oligodendroglioma patients after subtotal resection or at progression. It is appropriate to consider delaying RT for patients with clean postoperative margins on follow-up MRI. Most patients with AO should be considered for RT after surgery, although it may be delayed until after chemotherapy in patients with deletion of 1p and 19q. The majority of phase I clinical trial data suggest an extension of median and 5-year survival by RT after subtotal resection and at recurrence. The recommended RT dose is 50-60 Gy over 6 weeks, in daily fractions of 180-200 cGy. Focal three-dimensional treatment planning and conformal techniques should be used whenever possible to minimize radiation exposure to normal brain.
- Stereotactic radiosurgery (SRS) has recently been used for recurrent oligodendrogliomas <4 cm. Larger tumors will not benefit from SRS due to infiltration beyond the treatment field. Median doses range from 15-17 Gy in one fraction. SRS may improve survival in carefully selected patients with small oligodendrogliomas.
- Oligodendrogliomas are the most chemosensitive type of primary brain tumor. Use of chemotherapy should be delayed until after complete surgical resection. Chemotherapy should be considered first-line treatment for subtotal/rectangle LGO or AO with 1p/19q deletion status (100% response rate, survival >1.20 months) or 1p deletion/p53 mutation (100% response rate, survival >71 months) Patients with oligodendrogliomas that retain 1p and/or 19q may still respond to chemotherapy, but with lower response rates and shorter median survival. The most active regimens are PCV (procarbazine, CCNU [lomustine], vincristine), temozolomide, Carmustine (BCNU), and melphalan.

Admission/Discharge Criteria
- Patients with LGO and AO often are admitted for seizure control or neurologic deterioration due to elevated intracranial pressure and tumor growth. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure are required before discharge.

Medications

Drug(s) of Choice
- Seizures are a common problem for patients with LGO and AO. Appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management are critical. Dexamethasone is used at the lowest dose able to control symptoms related to intracranial pressure.

Contraindications
- Patients on chemotherapy must meet appropriate hematologic parameters before proceeding with the next cycle: WBC >2.0, hemoglobin >10.0, and platelets >100,000.

Precautions
- All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

Alternative Drugs
N/A

Follow-Up

Patient Monitoring
- Patients are followed with serial MRI scans and neurologic examinations every 4-6 months. Patients receiving chemotherapy may require more frequent follow-up. Anticonvulsant levels need to be monitored carefully.

Expected Course and Prognosis
- Median survival of patients with LGO is 6-10 years, with a 5-year survival rate of 75%. Median survival of patients with AO is 3-4 years. Survival of AO patients is affected by 1p and 19q status. Tumors with deletion of both 1p and 19q are very chemosensitive, with survival of 8-10 years. Tumors that maintain both 1p and 19q are treatment resistant, with survival of 2-5 years.
- Prognosis is improved with young age (<40 years) LGO histology, high Karnofsky performance status, and deletion of both 1p and/or 19q.

Follow-Up

Patient Education

- BrainTumors.com.
  Website: www.braintumors.com
- National Brain Tumor Foundation.
  Website: www.braintumor.org
- American Brain Tumor Association.
  Website: www.abta.org
- The Brain Tumor Society.
  Website: www.batba.org
- Massachusetts General Hospital-Brain Tumor Center.
  Website: brain.mgh.harvard.edu
- Brain Tumor Treatment Options & Information.
  Website: users.erin.com/colilla/index.htm

Synonyms
- Oligodendroglioma, anaplastic oligodendroglioma

ICD-9-CM: 191.8 Oligodendroglioma or anaplastic oligodendroglioma of brain

See also: Brain Tumor, High-Grade Astrocytoma; Brain Tumor, Low-Grade Glioma

References

Author(s) Herbert B. Newt on, MD
Brain Tumor, Pituitary

**Basics**

**DESCRIPTION**

- Pituitary tumors (adenomas) are benign mononucleolar neoplasms that originate from the adenohypophysis (anterior pituitary gland). They can be classified as functional (secrete endocrinologically active hormones) or nonfunctional (nonsecretors). Based on their size, they can either be microadenomas (<10 mm in greatest diameter) or macroadenomas (>10 mm).

**EPIDEMIOLOGY**

- **Incidence**
  - Pituitary adenomas are among the most common adult intracranial neoplasms and account for 10%-15% of adult intracranial tumors. Microadenomas are far more common than macroadenomas and are detected in up to 21% of pituitaries in postmortem studies.
  - Pituitary tumors usually occur in adults (third to fifth decade of life), with only <10% diagnosed in children (comprising <2% of pediatric intracranial tumors).
  - **Race**
    - There is no evidence of racial predisposition.

**ETIOLOGY**

- **Sex**
  - Prolactin-secreting and adrenocorticotropic hormone (ACTH)-secreting tumors are more common in females. Growth hormone-secreting and nonfunctioning adenomas predominate in males.

**RISK FACTORS**

- Multiple endocrine neoplasia (MEN) types I and II

**PREGNANCY**

- Pituitary adenomas can grow and become symptomatic during pregnancy. During pregnancy, the risk of symptomatic enlargement of a microadenoma is low (2%-4.5%) compared to the high risk (15%-25%) of symptomatic macroadenoma progression. For this reason, surgical debulking of pituitary macroadenomas is favored prior to conception, especially if they are nonfunctional.

**ASSOCIATED CONDITIONS**

- Cushing’s syndrome
- Acromegaly

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Pituitary hyperplasia
- Craniopharyngioma
- Empty sella syndrome
- Rathke cleft cyst
- Meningioma
- Germ cell tumors (germinoma)
- Chiasmatic/hypothalamic glioma
- Metastasis (lung, breast, prostate)
- Juxtasellar aneurysm
- Lymphocytic hypophysitis
- Hamartomas
- Chordomas
- Granulomas
- Langerhans’ cell histiocytosis
- Sarcoidosis

**SIGNS AND SYMPTOMS**

- Microadenomas usually cause symptoms related to hormonal hypersecretion, but they also can be asymptomatic. Macroadenomas usually present with mass effect. The most common complaints are headache (vague, dull, and usually bifrontal and behind the eyes) and visual abnormalities (chiasmal compression with bitemporal field defect, blurred vision, decreased visual acuity).
- Approximately 75% of patients with functioning pituitary adenomas present with an endocrinopathy consistent with their underlying pathology. Prolactinomas present with amenorrhea and galactorrhea in women and impotence in men. A growth hormone-secreting adenoma presents with gigantism in children and acromegaly in adults. In addition to the acral changes, they have systemic hypertension and impaired glucose tolerance. ACTH-secreting pituitary tumors (Cushing’s disease) typically present with Cushing’s syndrome. Clinical signs and symptoms include central obesity with abdominal striae, buffalo hump, and moon facies, as well as menstrual irregularity, hirsutism, hypertension, and diabetes.

- Pituitary apoplexy is a syndrome that occurs as a result of hemorrhage and/or infarction within a pituitary adenoma and leads to acute and severe headache, nausea/vomiting, ocular paresis, meningeval signs, and altered sensorium. It can mimic an acute subarachnoid hemorrhage.

**LABORATORY PROCEDURES**

- Serum prolactin level, growth hormone level, insulin growth factor type I, serum TSH, T4/T3 levels, serum luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol and testosterone serum levels. Stenosis of the pituitary gland is confirmed with an AM cortisol and an ACTH level. Draw basic electrolyte panel if diabetes insipidus is suspected.
- When checking the prolactin serum levels, it should be noted that occasionally in giant invasive prolactinomas the laboratory should be instructed to dilute the samples before measuring them, otherwise a false low prolactin level may appear. This has the risk of denying the patient medical treatment with dopamine agonists and favoring a surgical approach when it is not indicated.

**IMAGING STUDIES**

- MRI is the radiologic study of choice. Pituitary microadenomas typically are hypointense to surrounding tissue on T1-weighted images, and isointense or hyperintense on T2-weighted images. These tumors typically enhance more slowly than normal pituitary tissue. Cavernous sinus invasion is suspected when the tumor encases the cavernous portion of the internal carotid artery. Pituitary macroadenomas enhance with gadolinium and may show heterogeneity due to necrosis, hemorrhage, or cyst formation. CT may be used for delineating the bony structures of skull base, especially when dealing with invasive adenomas.

**Management**

**GENERAL MEASURES**

- The goals of treatment centers are —Removing mass effect and associated neural compression
  —Correcting any endocrinopathy — Reestablishing normal hormonal functions in a preserved pituitary gland
- The decision of whether to proceed with a surgical or medical treatment depends on the hormonal evaluation. Prolactin-secreting pituitary adenomas are best treated with medical therapy using dopamine agonists.
SURGICAL MEASURES
• Most pituitary adenomas can be approached via a transsphenoidal approach with low morbidity and mortality (complication rate 2%-4%). The sphenoid sinus is accessed via an endonasal or transanal approach, followed by removal of the tumor from the sellar region. The most common surgical complications include transient CSF rhinorrhea, hypopituitarism, and diabetes insipidus. A cranial approach may be indicated for patients with tumor extension into the anterior and/or middle cranial fossa.

RADIATION THERAPY
• Radiation is effective in treating pituitary adenomas. Risks include damage to the optic nerve/chiasm, hypothalamus and adjacent temporal lobe. Radiation therapy leads to permanent damage of the pituitary gland and hypopituitarism. Focused radiation therapy using radiosurgical techniques have the advantage of minimal exposure to radiation of the adjacent neural tissue and may be indicated in recurrent tumors that failed surgical resection.

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• Admission is warranted for surgical resection of adenomas.

Follow-Up

PATIENT MONITORING
• A neuroendocrine nurse can contact these patients during the first 2 weeks regarding hormone replacement therapy. Desmopressin acetate (DDAVP) spray or tablets can be given to patients with a prolonged diabetes insipidus state.
• Patients are informed to call a patient or to discuss signs of menigitis. Patients are then scheduled to come back to their first clinic visit in 4-6 weeks for follow-up MRI of the brain.

EXPECTED COURSE AND PROGNOSIS
• Prolactinomas: Surgical treatment of a prolactin-secreting microadenoma is very rewarding. Cure rates are estimated to be as high as 85%-90%. However, the medical treatment is as rewarding, and both options are excellent for patients with microadenomas. The cure rate is increased in patients with preoperative prolactin levels in the 200-300 range. The recurrence rate is as high as 10% over a 5- to 10-year period. Macroadenomas have lower cure rates with surgical treatment and respond optimally to medical therapy with dopamine agonists.
• Growth hormone-secreting adenomas: Up to 70% of patients with acromegaly are expected to achieve remission with surgical treatment (more common with microadenomas). The recurrence of these tumors is treated with either surgical exploration or medical therapy with octreotide. Radiation therapy also can be considered and is effective.
• ACTH-secreting adenomas: The ACTH-secreting adenomas are more likely to recur after remission is achieved by surgical removal. Approximately 70% of patients with a distinct microadenoma on MRI achieve remission. The recurrence rate of ACTH-producing adenomas is higher than the other secreting adenomas and occurs in up to 15%-25% of patients (40% following an initial resection).

PATIENT EDUCATION
• There are numerous support groups that provide assistance and information for patients and families with pituitary adenomas.
• Pituitary Tumor Network Association P.O. Box 1958 Thousand Oaks, CA 91358. Phone: (805) 499-9973. www.pituitary.com

Miscellaneous

SYNONYMS
• Pituitary tumors ICD-9-CM: 227.3 Benign neoplasm, pituitary

SEE ALSO: N/A

REFERENCES

Author(s) Said E Ishihabi, MD; Ali F. Kristht, MD
Brain Tumor, Primary Central Nervous System Lymphoma

**Basics**

**DESCRIPTION**
- Primary CNS Lymphoma (PCNSL) is a malignant non-Hodgkin's lymphoma limited to the cranial-spatial axis without systemic involvement. It originates in the brain and must be distinguished from metastatic systemic lymphoma. At the time of diagnosis, the leptomeninges (30%-35%) and eyes (25%) are frequently involved. PCNSL occurs most often in immunocompromised patients but also can arise in patients with intact immune function.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- The incidence of PCNSL is rising in immunocompetent patients and in those with HIV, with a 10-fold increase over the past 25 years. PCNSL now accounts for 2%-3% of all primary brain tumors in immunocompetent patients. For HIV patients, the lifetime incidence is in the range from 5%-10%. The annual incidence is currently 30 cases per 10 million persons.

**Race**
- All races and ethnic groups are affected. Caucasians are affected more commonly than blacks, Latinos, and Asians.

**Age**
- Typical presentation is between 50 and 55 years of age in immunocompetent patients and between 30 and 35 years in HIV patients.

**Sex**
- Incidence is slightly higher in males than females (3:2). HIV patients with PCNSL are predominantly male (7:3:1).

**ETOLOGY**
- PCNSL is classified as a stage IE non-Hodgkin’s lymphoma because the involvement is restricted to a single extranodal site—the brain. It is a clonal expansion of B cells in >97% of cases. T-cell PCNSL is uncommon (2%-3%). The World Health Organization does not have a specific classification scheme for PCNSL. Histologic subtyping of PCNSL suggests that diffuse large cell and diffuse large cell immunoblastic types are most common. However, subtyping has not been shown to have clinical relevance.
- It remains unclear how PCNSL arises in the brain, because the CNS is devoid of lymphoid tissue or lymphatics. Histologic evaluation reveals an angiocentric, diffusely infiltrative mass of neoplastic lymphoid cells, with extension into surrounding brain parenchyma. Isolated nodules of lymphoma can be observed at remote sites. Reactive astrocytosis and necrosis may be noted.
- Molecular genetic studies of PCNSL demonstrate clonal abnormalities of several chromosomes (1, 6, 7, 14) and translocations (e.g., 1;14, 6:14). Clonal rearrangements of the immunoglobulin and TCR genes are typically noted. The most common genetic alterations are mutations of the CDKN2A/p16 and CDKN2B/p15 tumor suppressor genes.

**Genetics**
- PCNSL are sporadic and do not have an elderly genetic predilection, except for genetically mediated immunodeficiency states.

**RISK FACTORS**
- The most important risk factor for PCNSL is immunosuppression, usually in patients with HIV or after organ transplantation, less often in congenital immunodeficiency states such as ataxia-telangiectasia and Wiskott-Aldrich syndrome. Epstein-Barr virus (EBV) is involved in the pathogenesis of >95% of PCNSL from HIV patients. EBV is implicated in <5% of PCNSL from immunocompetent patients.

**PREGNANCY**
- Pregnancy does not affect the clinical course of PCNSL.

**ASSOCIATED CONDITIONS**
- N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Other mass lesions that enhance should be considered, including other malignant brain tumors, mature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

**SIGNS AND SYMPTOMS**
- PCNSL is a highly aggressive tumor with a rapidly progressive course. Median time from onset of symptoms to diagnosis is only 4-12 weeks. The most common signs and symptoms at presentation include focal neurologic deficits (e.g., hemiparesis, dysphasia, cranial neuropathy; 50%-55%), mental status changes (e.g., reduced mentation, lethargy, confusion; 34%-50%), seizures (10%-25%), and evidence of increased intracranial pressure (e.g., headache, nausea, emesis, papilledema; 14%-30%). Patients with ocular involvement complain of blurred vision or floaters. Patients with spinal and/or leptomeningeal disease complain of neck or back pain, myelopathic weakness, and/or bowel and bladder dysfunction.

**LABORATORY PROCEDURES**
- Patients with suspected PCNSL require a lumbar puncture to assess CSF for cytology; HIV screening; CSF EBV DNA testing in AIDS patients, bone marrow evaluation for lymphomatous involvement

**IMAGING STUDIES**
- PCNSL usually presents in the periventricular region or among the deep nuclear structures. The tumor nodules are multifocal in 40% of cases (more so in HIV patients) MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. MRI images, the tumor usually is infiltrative and appears hypointense or isointense compared to brain. OTR images, the mass is hyperintense. With gadolinium administration, most PCNSLs show either diffuse or ringlike enhancement. Peritumoral edema and mass effect are usually mild to moderate. Hemorrhage and regions consistent with necrosis are occasionally noted. CT demonstrates an ill-defined region of hypodensity with variable enhancement, and mild-to-moderate edema and mass effect. Spinal MRI is indicated in patients with spinal symptoms to screen for involvement of the spinal cord or leptomeninges.
- Chest x-ray film and CT of the abdomen and pelvis are necessary to screen for systemic lymphoma.

**SPECIAL TESTS**
- Fluorodeoxyglucose-positron emission tomography (EBB-PET) may be of benefit to assess the metabolism of PCNSL to differentiate it from nonneoplastic lesions. PCNSL typically appears hypermetabolic on PET imaging, POG-PET is especially helpful in HIV patients to differentiate PCNSL from infection (i.e., toxoplasmosis). CSF evaluation reveals mild pleocytosis in 35%-60% of patients, with positive cytology in up to 30% of cases. Ophthalmologic evaluation (including slit-lamp testing) is necessary to screen for ocular lymphoma.

**Management**

**GENERAL MEASURES**
- Management of PCNSL requires a multimodal approach that involves input from neurosurgeons, neuro-oncologists, and radiation oncologists.
**SURGICAL MEASURES**
- Surgery should be considered in all patients to make a histologic diagnosis. Because extent of surgical resection has not been found to correlate with survival in PCNSL and most lesions are located deep in the brain, stereotactic biopsy is the recommended approach. Intracranial biopsy may be necessary to demonstrate lymphoma cells and justify ocular therapy. Ocular biopsy may be diagnostic of PCNSL in some patients.

**SYMPTOMATIC TREATMENT**
- Consists of reducing intracranial pressure, controlling seizures, and pain control. Corticosteroids should be used as sparingly as possible, because PCNSL may shrink transiently and make biopsy more difficult.

**ADJUNCTIVE TREATMENT**
- External beam radiation therapy (RT) should be considered, because PCNSL is radiosensitive in immunocompetent and HIV patients. Complete and partial responses can be noted; however, the responses are not durable, with relapse within 8-14 months. The recommended approach for immunocompetent patients is whole-brain RT, 45-50 Gy over 5 weeks in daily fractions of 180-cGy. HIV patients receive 40-45 Gy. Patients with ocular PCNSL may require RT to both orbits (40 Gy). Median survival with RT alone is 17 months in immunocompetent patients and 3 months in HIV patients. Lower-dose RT is sometimes combined with chemotherapy.
- Chemotherapy should be considered for all patients with PCNSL. The most active regimens use high-dose methotrexate (IV or intraarterial) in combination with other drugs (e.g., cyclophosphamide, etoposide, procarbazine, cytarabine). Intraarterial chemotherapy is combined with mannitol-induced blood-brain barrier disruption in some patients. Chemotherapy can be used alone (i.e., neoadjuvant) or in combination with RT. Younger patients with intact neurologic function and good performance status are the best candidates for neoadjuvant approaches. Median survival ranges from 40-45 months in patients treated with chemotherapy alone or in combination with RT. Intraarterial chemotherapy (methotrexate, cytarabine, cytarabine depofoam), preferably via an Ommaya reservoir, improves survival in PCNSL patients in combination with systemic chemotherapy. Intraocular chemotherapy (methotrexate) may be of benefit in selected patients with ocular PCNSL.

**ADMISSION/DISCHARGE CRITERIA**
- Patients with PCNSL often are admitted for seizure control, neurologic deterioration due to elevated intracranial pressure and tumor growth, or leptomeningeal metastases. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure are required before discharge. New therapeutic interventions may be necessary (e.g., intrathecal chemotherapy).

**MEDICATIONS**
- **DRUGS OF CHOICE**
  - Seizures are a common problem in patients with PCNSL. Appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical. Dexamethasone should be avoided, if possible, or used at the lowest dose able to control pressure-related symptoms.
  - **Precautions**
    - All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

**ALTERNATIVE DRUGS**
- N/A

**FOLLOW-UP**
- Patients are followed with serial MRI scans and neurologic examinations every 4-8 weeks. Patients receiving chemotherapy may require more frequent follow-up. Anticonvulsant levels need to be monitored carefully.

**EXPECTED COURSE AND PROGNOSIS**
- The natural history of PCNSL is death within 8-14 weeks without treatment. With RT plus chemotherapy or chemotherapy alone, median survival ranges from 25-45 months in immunocompetent patients. For HIV patients, median survival is 8-18 months with treatment.
- Prognosis is improved with young age (<60 years), intact neurologic function, good performance status, and male sex. Prognosis is worse with age >60 years, poor neurologic function, female sex, and tumor.
Carcinomatous Meningitis

Basics

DESCRIPTION
• Carcinomatous meningitis (CAM) is a common neurologic complication of systemic cancer that is associated with severe mortality and morbidity. CAM is caused by the spread of cancer cells into the subarachnoid space and CSF with subsequent access to the entire neuraxis. CAM has the capacity to affect every component of the CNS, including the brain, cranial nerves, spinal cord, spinal nerve roots, and cauda equina. It can develop in virtually any malignancy, but it is most common in leukemia, lymphoma, and solid tumors such as melanoma, breast carcinoma, and small cell lung carcinoma.

EPIDEMIOLOGY
Incidence/Prevalence
• The estimated incidence of CAM is 4%-15% of patients with solid tumors, 7%-15% of patients with lymphoma, 5%-15% of patients with leukemia, and 1%-2% of patients with primary brain tumors.

Race
• All races and ethnic groups are equally affected.

Age
• Typical presentation is between 45 and 60 years of age.

Sex
• Females have a higher incidence than males (1.6:1).

ETIOLOGY
• Systemic tumor cells gain access to the subarachnoid space and CSF through hematogenous spread to arachnoidal vessels, choroid plexus by direct extension from superficial regions of brain parenchyma, periventricular, or epidural metastases; and by perineural spread along spinal or cranial nerves. CAM is histologically similar to the primary neoplasm.

• Neurologic function is disrupted by CAM through several mechanisms, including elevation of intracranial pressure by the presence of diffuse tumor burden, direct invasion of neural tissues (brain, spinal cord, cranial and spinal nerves), ischemia due to obstruction of arterial blood flow, and regional metabolic alterations (e.g., lactic acidosis, low glucose concentration).

• Tumor cells most likely to metastasize to the CNS have a more aggressive and motile phenotype. These changes are mediated by scatter factor, autocrine motility factor, amplification of oncogenes, and mutation of metastasis-suppressor genes (e.g., nm23).

Genetics
• CAM is a sporadic process without a specific genetic influence.

RISK FACTORS
• Risk factors that increase the probability of CAM include tumor type (e.g., melanoma) and aggressive, widespread systemic disease.

PREGNANCY
• Pregnancy does not affect the clinical behavior of CAM.

ASSOCIATED CONDITIONS
• Include other common general and neurologic complications of cancer patients, such as infection and sepsis, metabolic encephalopathy, brain metastasis, and epidural spinal cord compression.

Diagnosis
DIFFERENTIAL DIAGNOSIS
• Includes other diseases that can involve the subarachnoid space, induce CSF inflammation, and cause enhancement of the leptomeninges on MRI, such as chronic bacterial or fungal meningitis, neurosarcoidosis, Guillain-Barre syndrome, and vasculitis.

SIGNS AND SYMPTOMS
• Symptoms and signs of CAM can involve any region of the neuraxis, including the brain, cranial nerves, and spine. The symptoms usually are progressive over days to weeks. In 30%-40% of patients, more than one region of the neuraxis will be involved. Cerebral signs and symptoms include headache (60%), mental status changes (50%), gait alterations (25%), nausea and emesis (22%), seizures (11%), and hemiparesis (3%). Cranial nerve signs and symptoms include diplopia and ocular motor pareses of III, IV, and VI (30%), facial weakness (2%), impaired hearing (13%), facial numbness (8%), visual loss and optic neuropathy (8%), facial numbness (8%), and tongue weakness (8%). Spinal signs and symptoms include reflex asymmetry (85%), leg weakness (70%), paresthesias (40%), sensory loss (30%), back/neck pain (30%), radicular pain (26%), and bowel/bladder dysfunction (15%).

LABORATORY PROCEDURES
• The single most useful diagnostic test is examination of the CSF by lumbar puncture (LP). The CSF is always abnormal, even when the cytology is negative. In most patients, there is mild-to-moderate pleocytosis, elevated protein, reduced glucose level, and elevated lactate level. Tumor markers (e.g., 8-glucuronidase, 8-microglobulin, carcinoembryonic antigen) are adjunctive tests that can improve diagnostic accuracy if elevated. 50% of patients with CAM will have a positive cytology after one LP and 90% will be positive after the third LP. CSF cytology can remain negative in some patients.

IMAGING STUDIES
• MRI of the brain and/or spinal cord, with and without gadolinium contrast, is the most sensitive imaging test; axial, coronal, and midsagittal enhanced images should be obtained. Abnormal enhancement is noted in 70% of patients with CAM, along the surface of the brain, ventricular ependyma, cranial nerves, spinal cord, and cauda equina. Nodules of enhancing and hydrocephalus are noted in 30% and 7% of patients, respectively. CT reveals similar enhancement patterns, but in only 40% of patients with CAM. MRI or CT evidence of CAM can be diagnostic if CSF cytology is negative. However, a negative MRI or CT does not rule out CAM. Myelography, with or without CT followthrough, also can be diagnostic if MRI is unavailable.

SPECIAL TESTS
• Flow cytometry of the CSF may be diagnostic of CAM from leukemia and lymphoma if it is able to demonstrate a monoclonal population of cells. It also may demonstrate the presence of neoplastic aneuploid DNA populations. For CAM patients with diffuse bulky disease, a radionuclide CSF flow study may be necessary to demonstrate patency of the CSF pathways before intrathecal (IT) chemotherapy is administered through an Ommaya reservoir.


**Carcinomatous Meningitis**

**Management**

**GENERAL MEASURES**
- Should include symptomatic treatment and consultation by radiation oncology, neuro-oncology, and neurosurgery for treatment evaluation.

**SURGICAL MEASURES**
- Surgical intervention is rarely necessary for treatment of CAM. Leptomeningeal biopsy may be of benefit in clinically suspicious patients with negative CSF and MRI testing. Ommaya reservoir placement should be considered for all patients receiving IT chemotherapy. Patients who develop hydrocephalus will require placement of a ventriculoperitoneal shunt. The shunt should contain an on/off valve to allow IT chemotherapy.

**SYMPTOMATIC TREATMENT**
- Consists of dexamethasone to control symptoms of intracranial pressure, anticonvulsants as required to control seizures, and pain control.

**ADJUNCTIVE TREATMENT**
- Conventional radiotherapy (RT) is of benefit to stabilize or palliate symptomatic regions of CAM. It is most often administered to the whole brain or to involved regions of the spinal axis with bulky disease. RT is more effective than IT chemotherapy for bulky disease, due to poor penetration of drug deeper than 2-3 mm. Pain-related symptoms often are improved with RT. Spinal neuraxis RT is generally avoided due to severe myelosuppression. The recommended dose to the brain or involved spine is 30 Gy in 10 fractions over 2 weeks. Patients with leukemic or lymphomatous CAM may improve neurologically after RT. Improvement is uncommon with CAM from solid tumors.
- Chemotherapy is the only therapeutic modality that can treat the whole neuroaxis. It is best administered by the IT route, either by LP or Ommaya reservoir. Drug distribution is more even throughout the neuroaxis when using the intraventricular route. Drugs that are approved for IT chemotherapy (usually once or twice weekly) include methotrexate, cytarabine, thiopeta, and depo-fomomycine. Systemic chemotherapy has not been as effective as IT, due to poor CSF penetration and low drug concentrations. High-dose intravenous methotrexate, cytarabine, and thiopeta have demonstrated modest efficacy in some patients.

**ADMISSION/DISCHARGE CRITERIA**
- Admission is usually for progression of neurologic dysfunction and/or seizure activity. Maximizing anticonvulsant doses and resolving metabolic disturbances are required before discharge. New modes of treatment may be required (e.g., RT, IT chemotherapy).

**Medications**

**DRUG(S) OF CHOICE**
- Dexamethasone 2-8 mg/day may be of benefit to reduce edema and swelling or to improve transient symptoms of pressure and swelling after RT. Seizures may be a problem in patients with CAM. Appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management are critical. Narcotic analgesics may be necessary for adequate amelioration of pain.

**Contraindications**
- Patients on chemotherapy must meet appropriate hematologic parameters before proceeding with the next cycle: WBC >2.0, hemoglobin >10.0, and platelets >100,000.

**Precautions**
- All patients should be taking an H2-blocking drug while receiving chronic dexamethasone.

**ALTERNATIVE DRUGS**
- N/A

**Follow-Up**

**IN-PATIENT MONITORING**
- Patients are followed with assessment of neurologic function and CSF evaluation every 4-8 weeks. MRI follow-up is required every 2-4 months. Patients receiving chemotherapy may need more frequent monitoring of clinical and hematologic status and anticonvulsant levels need to be monitored carefully.

**EXPECTED COURSE AND PROGNOSIS**
- CAM is a virulent complication of cancer with a natural history of death in 4-8 weeks without treatment. Median overall survival is poor and ranges from 4-6 months with treatment. Survival is most limited for patients with solid tumors, except for those with breast cancer, who may survive 6-12 months. Patients with leukemia and lymphoma may respond well to therapy.

**Patient Education**
- Carcinomatous neoplastic meningitis:
  - www.neuro-oncology.org/neomenl.htm
  - www.bt-treatment.com/neomenl.htm
  - www.scrnresearch.com/glossary/carcinomatous%20meningitis.htm
- Carcinomatous meningitis clinical resources.
  - Website: [www.dcnasonline.com](http://www.dcnasonline.com)
  - [www.scienceonline.com](http://www.scienceonline.com)
  - [mcpherson54.com](http://mcpherson54.com)

**References**

Author(s) Herbert B. Newt on, MD
Cardioembolic Stroke

**Basics**

**DESCRIPTION**
- Cardioembolic infarction is defined as rapidly developing clinical signs of focal or sometimes global disturbance of cerebral function lasting >24 hours caused by embolism originating from a cardiac source of thrombus.

**EPIDEMIOLOGY**
- **Incidence**
  - Frequency of cardiac embolism ranges from 15%–30% of all cases of stroke.
  - Affects all ages
  - Males and females equally affected
  - Race
- **ETIOLOGY**
  - Cardiac disorders that lead to the formation of a thrombus with subsequent brain embolism can be divided into six groups:
    - **Arrhythmias:** Atrial fibrillation is one of the most common cardiac disorders. It is more common as patients age. It accounts for approximately 70% of emboli of cardiac origin. Sick sinus syndrome is another condition that is associated with brain embolism.
    - **Valvular heart diseases:** This group especially includes mitral stenosis, prosthetic heart valves, infective endocarditis, and marantic endocarditis. Other valvular diseases shown to be associated with cardiac embolism include mitral valve prolapse, aortic valve disease, and mitral annulus calcification.
    - **Ventricular myocardial abnormalities related to coronary artery disease, myocardial infarction, or other dilated cardiomyopathy:**
      - Lesions within the cavity of the ventricles such as tumors (myxomas) or thrombi
      - Shunts: Intraatrial septal defects and patent foramen ovale (PFO) allow emboli formed in the peripheral veins to enter the systemic circulation causing paradoxical embolism.
      - Atrial lesions such as dilated atia, atrial infarcts and thrombi, and atrial septal aneurysms.
    - **Many times the development of thrombi within the heart is triggered by a spasm or cesed hypercoagulable state.**

**ASSOCIATED CONDITIONS**
- See Etiology

**Differential Diagnosis**
- Large artery atherosclerosis with in situ thrombosis and occlusion or artery-to-artery emboli
- Arterial dissection with occlusion or artery-to-artery emboli
- Vasculitis
- Fat, air, tumor, or foreign body embolism

**Signs and Symptoms**
- The neurologic picture depends on the area infarcted. The most common and most characteristic time course in patients with cardiac embolism to the brain is the sudden onset of neurologic signs that are maximal at onset without warning episodes.
- Another pattern quite characteristic of brain embolism has been called the spectacular shrinking deficit, which is described as sudden, complete or nearly complete clearing of the neurologic deficit.
- Transient ischemic attacks do occur in some patients with brain embolism. Headache is common. Seizures are uncommon; however, they are more frequent in cardiac origin embolism compared to nonembolic causes of ischemic stroke.
- Cardiac origin embolism should be suspected in young patients in whom atherosclerosis is unlikely.

**LABORATORY PROCEDURES**
- Blood test should include lipid profile, RPR, BUN, creatinine, CBC and platelet, PT, PTT, and INR.
- Hypercoagulability can contribute to cardioembolic strokes, so a hypercoagulable profile should be requested in young patients.
- Serial blood cultures should be obtained when infective endocarditis is suspected.

**IMAGING STUDIES**
- Chest x-ray film should be obtained to look for cardiomegaly.
- CT scan must be performed in all patients presenting with suspected stroke because it is very sensitive in detecting intracranial hemorrhage. It is also inexpensive, quick, and readily available. When CT shows strokes in multiple vascular distribution, then cardiac source of emboli must be suspected.
- MR angiography is the gold standard for an accurate assessment of both the extracranial and intracranial vasculature. However, it is an invasive procedure and should be reserved for use in patients in whom noninvasive testing has not shown a source of embolism and an arterial source is suspected.
- Ultrasound is safe, portable, and less expensive. It includes transcranial Doppler to look for intracranial disease and carotid duplex to assess for extracranial carotid and vertebral artery disease.
- ECG and cardiac monitoring should be performed to evaluate for arrhythmias.

**Management**

**GENERAL MEASURES**
- General treatment of stroke includes acute supportive care, management of contributory cardiac lesions, and secondary stroke prevention.

**SURGICAL MEASURES**
- Some cardiac lesions require surgical or radiologic interventions, such as valve replacement for infected prosthetic valve, resection of cardiac tumors (myxoma), occasionally closure of PFO or atrial septal defect, removal of mobile protruding aortic arch atheroma, and pacemaker placement for sick sinus syndrome.
SYMPTOMATIC TREATMENT

- Includes treatment of hyperglycemia, fever, and infection; deep vein thrombosis prophylaxis; aspiration precaution; adequate hydration and Na+ ion; judicious control of blood pressure with avoidance of excessive reduction in the acute setting and adequate control in the long run; avoidance of prolonged use of indwelling catheter to prevent urinary tract infection
- Amitriptyline or gabapentin for pain related to thalamic strokes; antidepressants for the cortical strokes with resultant depression; muscle relaxant with baclofen for residual spasticity; stool softener for constipation

ADJUNCT TREATMENT

- Physical, occupational, speech, and cognitive therapy may be needed.

ADMISSION/DISCHARGE CRITERIA

- In general, any patient presenting with acute ischemic stroke should be admitted to the hospital for evaluation of etiology and appropriate prevention measures; prevent ion and management of stroke complications; early initiation of physical, occupational, and speech therapy; evaluation for eligibility for inpatient rehabilitation; assistance with appropriate placement; and patient and caretaker education.

Medications

**DRUGS OF CHOICE**

- Recombinant tissue plasminogen activator (r-TPA) is indicated for acute ischemic strokes, including those with cardiac source, and must be given within 3 hours of the onset of symptoms. The dose is 0.9 mg/kg up to a maximum of 90 mg; 10% of the dose is given as an IV bolus over 1 minute and the rest as IV drip over 1 hour.
- Antiplatelet agents are indicated for stroke prevention in irregular nonstenotic valve sifaces and in patients who are not warfarin Coumadin candidates. Aspirin: clopidogrel (Plavix) (75 mg qd) or Aggrenox (combination aspirin 25 mg/extended release dipyridamole 200 mg one tablet bid).
- Antiaggregants (warfarin) are indicated for atrial fibrillation, especially when associated with other cardiac lesions or other stroke risk factors; intracardiac thrombi; myocardial aneurysm; prosthetic valves; noninfective endocarditis; and sometimes PFO.

**Contraindications**

- r-TPA: suspicion of subarachnoid hemorrhage; recent (within 3 months) intracerebral or intrasplstial surgery; recent head trauma; recent previous stroke; history of intracerebral hemorrhage; uncontrolled hypertension at time of treatment (SBP >185 mm Hg or DBP >110 mm Hg) seizure at the onset of stroke; active internal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis, including but not limited to current use of oral anticoagulants (e.g., warfarin sodium) or INR >1.7 or PT >15 seconds; administration of heparin within 48 hours preceding the onset of stroke and elevated aPTT at presentation; platelet count <100,000/mm³
- Aspirin/Aggrenox: mainly allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer
- Clopidogrel: mainly active systemic bleeding
- Warfarin: mainly active bleeding, bleeding tendency, noncompliance, and gait difficulty with increased falling risk

**Precautions**

- r-TPA: Noncompressible arterial or venous punctures must be avoided. Blood pressure must be monitored closely during administration of the medicine and treated if elevated. If serious bleeding is suspected, it must be stopped immediately. Watch for allergic reaction.
- Clopidogrel: Monitor for any UP symptoms at the beginning of treatment.
- Warfarin: Watch for compliance, bleeding events, and falling events.

Follow-Up

- Close monitoring of INR is important for treatment with warfarin. Therapeutic range is usually 2-3. Mechanical prosthetic valves require a higher INR. If follow-up shows noncompliance with the medication, bleeding events, or falling episodes, discontinuation of warfarin must be considered.

EXPECTED COURSE AND PROGNOSIS

- Most important predictor of recovery from brain embolism is whether or not ischemic brain is reperfused and how quickly. Most patients survive the initial insult. In 80% of cases, the first episode will be followed by another event, frequently with more severe damage. Appropriate prophylactic treatment significantly decreases the recurrence rate. However, patients will still be at increased risk for recurrent events despite appropriate measures. If recurrent events occur, the combination of platelet antiaggregants and warfarin is a reasonable alternative to either agent alone.

PATIENT EDUCATION

- American Stroke Association, National Center 7227 Greenville Avenue, Dallas TX, 75231. Phone: 1-888-478-7653, website: www.strokeassociation.org

SYNONYMS

N/A

ICD-9-CM: 436 Cerebrovascular accident

REFERENCES


Author(s) Roth al-Dahhak, MD; Yous ef Mohammad, MD, MSc
Carpal Tunnel Syndrome

**Basics**

**DESCRIPTION**
- Carpal tunnel syndrome is a compression injury of the median nerve as it traverses the carpal tunnel in the wrist, with resultant pain, numbness, and/or weakness in a median nerve distribution.

**EPIDEMIOLOGY**
- Most common nerve entrapment syndrome
- Lifetime individual risk of 10%
- Incidence of 200-500 per 100,000 individuals over a 1-year period
- As many as 50% may have an occupational etiology
- May be bilateral in >50% of patients

**ETIOLOGY**
- The etiology of carpal tunnel syndrome is multifactorial. As the median nerve enters the wrist, it traverses the carpal tunnel, a narrow anatomic pathway bounded by carpal bones on its floor and sides and the transverse carpal ligament as its roof. The nerve is accompanied by nine flexor tendons in this space; any activity or metabolic derangement that causes edema may increase pressure on the nerve or compress it.

**GENETICS**
- Patients with hereditary neuropathy with predisposition to pressure palsies (HNPP) are more susceptible to carpal tunnel.
- HNPP is due to a deletion on chromosome 17 in the region that codes for the PMP22 gene (a component of peripheral nerve myelin).

**RISK FACTORS**
- Metabolic disorders
  - Diabetes
  - Renal disease
  - Thyroid dysfunction
  - Amyloidosis
  - Monoclonal gammopathy
- Underlying peripheral neuropathy
- Occupational
  - Individuals with repetitive manual tasks, such as keyboarding, carpentry, knitting, or food handling
- Perimenopausal state
- Pregnancy
- Connective tissue disorders, e.g., rheumatoid arthritis
- Acromegaly
- Osteoarthritis
- Trauma

**PREGNANCY**
- Carpal tunnel syndrome may present during pregnancy, especially in the last trimester when peripheral edema may develop.

**ASSOCIATED CONDITIONS**
- Peripheral neuropathy
- Other entrapment syndromes

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Cervical radiculopathy
- Brachial plexopathy
- Proximal median nerve injury
- Motor neuron disease
- Arthritis
- Tendinitis
- Peripheral neuropathy

**SIGNS AND SYMPTOMS**
- Paresthesias of the hand and fingers; patient may not be able to localize to the median nerve distribution (first three digits and the lateral aspect of the fourth digit)
- Pain in the wrist, sometimes radiating to the shoulder and even the scapula
- Weakness is a late presentation; may involve thumb abduction and opposition
- Liners sign is elicited by gently tapping over the median nerve at the wrist. A positive finding includes reproduction of paresthesias in the fingertips or traveling through the hand. It should be noted that this is not diagnostic for carpal tunnel entrapment, as there is a high false-positive rate.
- Phalen’s sign is elicited by placing the wrists in flexion for 30-60 seconds. A positive finding is the reproduction or exacerbation of symptoms. Again the false-positive rate is high.

**LABORATORY PROCEDURES**
- Nerve conduction studies
  - Sensory nerve testing is the most sensitive — Demonstration of slowing across the carpal tunnel
  - May be accompanied by loss of amplitude or response
  - Motor conductions are also useful
  - Prolonged distal latency
- Electromyography
  - Usually normal in mild cases
  - Useful to determine extent of injury
  - Important to differentiate carpal tunnel from other entities such as cervical radiculopathy, peripheral neuropathy, and brachial plexopathy
- Blood work
  - Screening for predisposing conditions should be based on degree of clinical suspicion

**IMAGING STUDIES**
- A history of trauma (especially a Colles fracture) or fullness in the wrist or palm (ganglion, lipoma, schwannoma) is an indication for CT or MRI.

**SPECIAL TESTS**
- N/A

**Management**

**GENERAL MEASURES**
- Conservative therapy is successful for patients with mild-to-moderate symptoms and findings on clinical examination.
  - Immobilization ideally done with a custom-made, neutral position, rigid splint worn primarily at night or after activities that precipitate symptoms
  - Nonsteroidal antiinflammatory agents — If possible, avoidance of predisposing activities is beneficial
  - Consider ergonomic redesign of the workplace to avoid repetition injury (although data supporting this approach are not available)
  - 90% of mild-to-moderate cases should improve in 4-6 weeks
  - Therapy should continue for at least 2 months
  - If no response to above measures, consider steroid injections, particularly if pain is a significant feature
  - Training in steroid injections is essential, as complications can include infection, tendon rupture, and scarring of the nerve
Carpal Tunnel Syndrome

SURGICAL MEASURES

• Surgery is considered if
  — There is no response to conservative measures
  — Symptoms significantly limit the patient's activity
  — Findings on examination demonstrate significant axon loss (atrophy or denervation by EMG)
• Traditionally, surgery for carpal tunnel syndrome was performed through an open release technique (palmar incision).
• More recently, endoscopic techniques have been developed.
• There is no significant difference in the outcomes of the two types of surgeries; however, the endoscopic approach requires significant surgical experience to avoid possible complications.

SYMPTOMATIC TREATMENT

• Nonsteroidal antiinflammatory agents may provide symptomatic relief of pain and swelling.
• Occasionally, diuretics are useful to decrease edema around the carpal tunnel.

ADJUNCTIVE TREATMENT

N/A

ADMISSIONS/DISCHARGE CRITERIA

N/A

Medications

DRUG(S) OF CHOICE

• Symptoms may respond to nonsteroidal antiinflammatory medications.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

• For those patients treated conservatively, follow-up should be performed within 2 months. If symptoms persist or if there is evidence of disease progression, consider surgical treatment.

EXPECTED COURSE AND PROGNOSIS

• Most patients will do well with conservative therapy and avoidance of exacerbating activities.
• For patients with mild-to-moderate signs and symptoms, neurologic function should return to near normal after surgery.
• Patients with moderate-to-severe neurologic dysfunction can avoid progression of nerve injury with surgery and, at best, may demonstrate minimal improvement in nerve function.

PATIENT EDUCATION

• Involves avoidance of activities, behaviors, or postures that might exacerbate symptoms

Miscellaneous

SYNONYMS

N/A

ICD-9-CM: 354.0 Carpal tunnel syndrome

SEE ALSO: N/A

REFERENCES


Author(s) Miriam L. Freimer, MD
Cauda Equina Syndrome

**DESCRIPTION**

Cauda equina syndrome occurs with lesions of the "tail" of the spinal cord. Secondary to the foreshortening of the spinal cord, which ends in the conus medullaris at approximately the L2 vertebral level, the nerve roots from the Lumbar and sacral spinal cord must travel for a variable length within the spinal canal before they exit through their respective neural foramina. This produces a bundle of nerve roots descending within the spinal canal, resembling a horse's tail (cauda equina).

Compression of the lower spinal canal may variably injure these nerve roots while they remain in the canal. Lesions of the lower nerve roots produce sensory and motor dysfunction of the lower extremities, as well as sacral dysfunction. Asymmetric pain, asymmetric sensory loss or hyperesthesia, and asymmetric motor weakness will develop. The asymmetry results because the lesion rarely compresses nerve roots equally; that is, some nerve roots are involved more than others and one side may be more affected than the opposite. Patients may have bowel and bladder dysfunction as well as numbness and paresthesias of the sacral area. If the conus medullaris is involved, or any more proximal part of the spinal cord, signs and symptoms of myelopathy, or upper motor neuron dysfunction, may additionally be seen. Thus cauda eq uina primarily produces a lower extremity and sacral tower motor neuron dysfunction; but upper motor neuron signs and symptoms, such as hyperreflexia and spasticity are sometimes seen.

**EPIDEMIOLOGY**

Cauda equina syndrome is uncommon, being rarer than other lumbosacral compressive syndromes. The distribution is unaffected by race, sex, and age.

**ETIOLOGY**

Causes of cauda eq uina syndrome are any compressive lesion within the spinal canal, not just a single spinal neural foramina. Thus, a central disc herniation may cause cauda eq uina syndrome, but not a paracentral disc herniation, which compresses a neural foramina, resulting in a radiculopathy. Infectious processes that produce a mass effect, either through inflammation (bacterial, CMV) or granuloma (TB, sarcoid) may result in a cauda equina presentation. Any strutureal abnormality (disc, abscess, hematoma, metastasis) in the lower spinal canal will compress multiple nerve roots. Other, less easily identifiable causes, include carcinomatous meningitis, in which cancerous cells coat the nerve roots, may also cause a cauda equina syndrome.

Tethered cord syndrome may present as a cauda equina syndrome, by presenting subacutely in an adult rather than an infant or child.

**PREGNANCY**

Little is known regarding the relationship of cauda equina and pregnancy.

**ASSOCIATED CONDITIONS**

- Conus medullaris syndrome
- Tumors of the base of the spinal cord
- Multiple lumbosacral radiculopathies
- Tethered cord syndrome

**DIFFERENTIAL DIAGNOSIS**

- Spinal cord compression
  - Tumors of the lower spinal cord, especially ependymoma
  - Epidural abscess or hematoma
  - Central disc herniation
  - Metastasis
  - Spinal stenosis
- Infections of the CNS
  - Syphilis
  - Tuberculosis
  - Cryptococcus —Bacterial abscess —Cytomegalovirus (CMV) infection
  - HIV (with or without CMV)
- Sarcoidosis
- Carcinomatous meningitis
- Radiculopathies
- Acute inflammatory demyelinating polyradiculopathy (AIDP)

**SIGNS AND SYMPTOMS**

The symptoms of cauda equina syndrome may develop acutely, subacutely, or chronically, depending on the underlying etiology. Typically, there is a patchy disturbance, as various nerve roots within the spinal canal are involved. In addition, there may be significant asymmetry between the right and left extremities. Most of the symptoms are lower motor neuron signs, such as weakness and sensory loss. Some upper motor neuron signs may rarely be seen, if the conus medullaris is involved. Bowel incontinence and bladder retention indicate sacral nerve root involvement. Radicular pain may occur in the territory of affected nerve roots.

**LABORATORY PROCEDURES**

Blood work should be checked with a view to diagnosing the underlying abnormality. HIV, RPR, ACE level may all be warranted. PT/PTT and CBC with platelets should be performed if a lumbar puncture is under consideration.

**IMAGING STUDIES**

MRI of the Lumbosacral spine, with gadolinium, should be performed immediately to evaluate for a compressive lesion that requires emergent surgery. Inflammation and infiltration of the cauda equina may be seen as high signal and thickening of the nerve roots.

**SPECIAL TESTS**

If there is no contraindication, a lumbar puncture should be performed, checking glucose, protein, all cultures, including fungal, and cytology, if cancer is suspected. CAR should be checked if sarcoid or TB is suspected. An EMG/NCS may be useful to distinguish this lesion from a more peripheral nerve root lesion, such as radiculopathies or AIDP (Guillain-Barre syndrome).
Cauda Equina Syndrome

**Management**

**GENERAL MEASURES**

Treatment is aimed at the underlying cause. If the lesion is mechanical, then urgent surgery is required. If the lesion is infectious, then the appropriate antimicrobial therapy should be initiated. Sarcoïd requires immunosuppression, usually initially with steroids. Fungal and tuberculous CNS infections may also require steroids in addition to antimicrobial therapy. If cancer is the etiology, then radiation therapy provides the quickest, but not necessarily permanent, relief. Consultation with an oncologist should be undertaken.

**SURGICAL MEASURES**

If a compressive lesion is seen on MRI, neurosurgical consultation should be obtained immediately. This is imperative for epidural abscesses and hematomas. Disc disease and intrinsic cord tumors are urgent but do not require immediate intervention. Some compressive lesions may be better served by an initial course of steroids before surgery.

**SYMPTOMATIC TREATMENT**

Supportive care should include bowel and bladder management, if they are involved. Straight catheterization is performed every 4 to 6 hours as needed, if the bladder has greater than 200 cc postvoid residuals. Stool softeners and other bowel management (such as digital rectal stimulation, qd) are indicated to prevent significant constipation. Physical therapy should be initiated early to avoid sequelae from prolonged bed rest. If the patient is profoundly weak, then an egg-crate mattress and appropriate turning of the patient may prevent decubitus ulcers. The patient should be out of bed at least two times per day to prevent atelectasis of the lungs. DVT prophylaxis should be composed of either 5,000 units of heparin SC, or SCD compression hose, worn at all times.

**ADJUNCTIVE TREATMENT**

Radiation therapy: if a metastatic lesion is found to be the underlying etiology on MRI, then an urgent radiation therapy consult is required. Return of function is best seen if radiation begins immediately.

**ADMISSION/DISCHARGE CRITERIA**

Patients are generally admitted for acute evaluation and treatment. If significant symptoms persist after initial therapy, consider inpatient rehabilitation. Discharge depends on the stability of the patient's clinical exam, adequacy of treatment, and stabilization of the underlying cause.

**Follow-Up**

**PATIENT MONITORING**

Monitoring over the long-term depends entirely on the underlying cause. In patients with a compressive lesion from a disc, or tethered cord syndrome, no follow-up may be necessary. In patients with an underlying neoplasm, appropriate tumor management is indicated. In patients with a chronic infection, occasional reevaluations are necessary to ensure that no relapses occur.

**EXPECTED COURSE AND PROGNOSIS**

Recovery depends entirely on the underlying etiology and length of symptoms. Acute-onset lesions recover better than do chronic ones. Lesions due to a strultural defect, such as a herniated disc, do better than a diffuse, systemic process, such as cancer. Patients with sblte or partial deficits recover more function than patients with complete paralysis and neurogenic bladder.

**Patient Education**

N/A

**Medications**

**DRUG(S) OF CHOICE**

Steroids are often used to reduce initial inflammation. If the cauda equina syndrome has developed chronically and is due to a slowly compressive lesion, such as spinal stenosis, then steroids are of little benefit. Steroids, such as methylprednisolone 1 g/d for 5 days (or dexamethasone 4 mg q6h for 4-5 days), provide the most benefit for acute, rapidly progressive lesions, most often due to infectious or carcinomatous causes.

**Contraindications**

Hypersensitivity to specific corticosteroid—use alternative medication.

**Precautions**

Assess patient for peptic ulcers, hyperglycemia, steroid-induced behavioral changes, and hypokalemia during steroid therapy.

**ALTERNATIVE DRUGS**

N/A

**Miscellaneous**

**SYNONYMS**

None

**ICD-9-CM**

344.6 Cauda equina syndrome; 344.60 Without mention of neurogenic bladder; 344.61 With neurogenic bladder; 336.3 Myelopathy in other diseases classified elsewhere; 13.4 Tuberculosis of spinal cord; 115.9 Histoplasmosis, other; 136 Sarcoïdosis; 192.2 Malignant neoplasm of other and unspecified parts of the nervous system, spinal cord

**SEE ALSO**

SPINAL CORD TUMOR; RADICULOPATHY, LUMBOSACRAL

**REFERENCES**


Author(s): Holli Horak, MD
Cavernous Sinus Thrombosis

Basics

DESCRIPTION
• Cavernous sinus thrombosis (CST) is a rare disorder characterized by clot formation in the cavernous sinuses. Although typically due to hematogenous spread of infection, aseptic and chronic forms also exist.

EPIDEMIOLOGY
Incidence/Prevalence
• Only a few hundred cases have been reported in the literature. The incidence has declined dramatically since the advent of antibiotics.

Race
• No known difference

Age
• This disorder typically affects young adults.

Sex
• No known difference

ETIOLOGY
• The cavernous sinuses are paired, interconnected, venous structures located on either side of the sella turcica, superior to the sphenoid sinus and posterior to the optic chiasm. They drain veins of the face, orbits, sinuses, and brain via the superior ophthalmic, inferior ophthalmic, central retinal, superficial middle cerebral, and inferior cerebral veins, as well as the sphenoparietal sinus. The carotid artery and abducens nerve lie medially within the sinuses, whereas the oculomotor nerve, trochlear nerve, and ophthalmic and maxillary branches of the trigeminal nerve lie within the lateral wall of the sinuses.
• In the septic form of CST, infection in sinuses with venous drainage to the cavernous sinuses propagates through valveless veins over 5-10 days. Once the organisms are caught in the trabeculations of the sinuses, inflammation and secretion of coagulase may lead to clot formation and thrombosis.
• In the aseptic form, surgical or blunt trauma or hypercoagulable state leads to thrombosis of the cavernous sinus and often to bacterial superinfection.
• In the rare chronic form, slow thrombosis of the sinuses allows time for formation of venous collaterals.
• Coagulase-positive Staphylococcus aureus is the most common organism isolated. Other commonly encountered organisms include streptococcal species, pneumococcal species, Gram-negative bacilli, Rhizopus, Aspergillus, and Nuxor.

Genetics
N/A

RISK FACTORS
• Septic form: infection of the middle third of the face, paranasal sinuses, pharynx, maxilla, middle ear, or mastoid process
• Aseptic form: otolaryngologic surgery, trauma, subarachnoid hemorrhage, malignancy, pregnancy, oral contraceptive use, and other hypercoagulable states
• Chronic form: diabetes mellitus, toxic sinusitis

PREGNANCY
• Pregnancy is a risk factor for the aseptic form of CST.

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Contralateral spread of signs and symptoms within 48 hours is virtually pathognomonic for CST. In contrast to the most significant disorder in the differential diagnosis, postseptal orbital cellulitis, in CST there is a source of sepsis remote from the eye, systemic illness out of proportion to local signs, positive blood cultures, meningismus, ophthalmoplegia, visual impairment, papillary defect, funduscopic abnormality, and inflammatory CSF. Other disorders in the differential diagnosis include postseptal orbital cellulitis, periorbital cellulitis, sinusitis, orbital apex syndrome, superior orbital fissure syndrome, intraorbital abscess, orbit or optic nerve tumor, rhinocerebral mucormycosis, intracavernous carotid artery aneurysm, carotid-cavernous fistula, intraorbital pseudotumor, Tolosa-Hunt syndrome, and exophthalmic goiter.

SIGNS AND SYMPTOMS
• Categories: signs and symptoms of the primary infection, venous congestion, sepsis, retroorbital inflammation, and cranial nerve irritation
  — Fever
  — Ptsis
  — Chemosis of bulbar conjunctiva
  — External ophthalmoplegia
  — Proptosis and periorbital edema
  — Headache
  — Internal ophthalmoplegia
  — Meningismus
  — Decreased visual acuity
  — Altered mental status
  — Retinal edema and retinal vein dilation

LABORATORY PROCEDURES
• CST is primarily a clinical diagnosis. The presence of peripheral leukocytosis on CBC confirms an infectious etiology. Identification of the infectious agent with blood cultures is necessary as CSF Gram stain rarely demonstrates organisms.

IMAGING STUDIES
• MRI and contrast-enhanced CT of the head are the most sensitive and specific imaging studies. In addition to aiding in diagnosis, they evaluate for contraindications to anticoagulation. Angiography and venography are only indicated for suspected carotid-cavernous fistula or intracavernous aneurysm.

SPECIAL TESTS
• Lumbar puncture; CSF is typically inflammatory but aseptic.
• Funduscopic examination

Management

GENERAL MEASURES
• Treatment of CST involves eradicating the infection, halting progression of thrombosis, and reducing inflammation. Rapid diagnosis and instigation of treatment are essential.

SURGICAL MEASURES
• Surgical interventions are limited to drainage of refractory infections in the paranasal sinuses.

SYMPTOMATIC TREATMENT
• Routine pain control

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• Patients with diagnosed or suspected CST are admitted to an intensive care unit.
Cavernous Sinus Thrombosis

**Alternatives of Choice**

- **Anticoagulation**: intracerebral hemorrhage, subarachnoid hemorrhage, bleeding diathesis
- **Anticoagulation**: cortical venous hemorrhage, subarachnoid hemorrhage, bleeding diathesis

**References**

- Southwick F, Richardson E, Swartz M. Septic thrombosis of the dural venous sinuses. Medicine 1986;65:82-106.

Author(s): Richard E. Bees, MD, PhD

**Medications**

**Follow-Up**

- **Patient Monitoring**
  - Follow clinical course rather than normalization of imaging studies. Late sequelae include meningitis, encephalitis, brain abscess, pituitary infection, sphenoid, empyema, epidural abscess (consider if not responding to therapy), dural sinus thrombosis, cortical vein thrombosis and hemorrhagic infarction, hydrocephalus, and carotid stenosis or occlusion (leading to dysphasia or hemiparesis).

**Expected Course and Prognosis**

- Signs typically develop unilaterally 5-10 days after instigating infection elsewhere in the head. Bilateral spread occurs within 48 hours in most cases. In the absence of treatment, meningitis, intracranial spread, and death follow universally. With treatment, mortality is 30%. Greater than 50% have morbidity including blindness, visual impairment, diplopia, pituitary insufficiency, hemiparesis, seizure disorder, or vascular steal syndrome. Due to sequestration of bacteria within thrombus, relapses have been reported within 6 weeks and intracranial abscesses up to 8 months. Thus, patients should be followed for several months after antibiotics are stopped.

**Patient Education**

N/A

**Contraindications**

- Antibiotics: known sensitivity to the agent
- Anticoagulation: intracerebral hemorrhage, subarachnoid hemorrhage, bleeding diathesis

Precautions

- Anticoagulation: cortical venous hemorrhage, intracavernous carotid artery necrosis, intraorbital hemorrhages, epistaxis

**Alternatives Drugs**

- Vancomycin 1 g IV q12 plus meropenem 1 g IV q8
- Corticosteroids: anecdotal benefit only in the absence of pituitary dysfunction. A recent study demonstrates benefit in meningitis. Indicated for Addisonian crisis.
Central Pontine Myelinolysis

Basics

DESCRIPTION
Central pontine myelinolysis (CPM) is an acute demyelination of the central basis pontis. The characteristic presentation includes spastic tetraparesis, pseudobulbar paralysis, and decreased level of consciousness.

EPIDEMIOLOGY
The precise incidence is unknown. Autopsy data suggest a prevalence of approximately 0.25%. The peak incidence occurs between the ages of 30 and 50 years, although pediatric cases have been reported. A slight male predominance has been noted.

ETIOLOGY
• The pathogenesis of CPM remains unknown. CPM is most often associated with rapid correction of hyponatremia. One hypothesis suggests that the increase in sodium leads to endothelial injury and osmotic disruption of the blood-brain barrier, which causes edema and leakage of myelinotoxic factors. Mechanisms of controlling osmotic balance may not respond quickly enough, leading to cerebral edema that destroys the neighboring myelin sheaths and blood vessels.
• Others propose that osmotic imbalance may dehydrate the brain such that the myelin sheaths are stripped away from the axons, and oligodendrocytes are injured. Others have argued for an autoimmune etiology.
• Those with elderly medical illness may be more susceptible to CPM, because of decreased ability to generate the necessary osmoles to protect against the above processes. Alternatively, it may be that those with other medical conditions are more likely to be hospitalized, where iatrogenic fluctuations in osmolality can occur.
• The pons is particularly affected by demyelination. This selective vulnerability may be due to the proximity of oligodendrocytes to vascular gray matter, where they are susceptible to injury from edema and myelinotoxic substances. Another hypothesis proposes that the close apposition of gray to white matter allows gray matter to “steal” nutrients from oligodendrocytes, resulting in demyelination.

RISK FACTORS
• CPM is commonly associated with rapid correction of hyponatremia. Varying susceptibility to myelinolysis makes establishment of protective guidelines difficult. The general recommendation is that sodium correction rates should not exceed 12 mEq/L within the first 24 hours or 20 mEq/L within the first 48 hours. Others advocate more rapid rates of sodium delivery. CPM, however, can occur with modest levels of hyponatremia and rates of correction, indicating that more conservative guidelines may be needed. Some argue that a greater risk of CPM occurs with chronic hyponatremia and that rates of sodium replacement should depend on the chronicity of the deficit. They recommend a minimum rate of correction of 1 mmol/L/h for acute hyponatremia and a maximum rate of correction of 0.5 mmol/L/h for chronic hyponatremia.
• Hypokalemia is an additional risk factor for CPM, and should be addressed prior to treatment of hyponatremia.

PREGNANCY
CPM is associated with hyperemesis gravidarum and pregnancy.

ASSOCIATED CONDITIONS
• Almost all cases of CPM occur with severe comorbid medical conditions.
  — Alcoholism (39.4-78%). Alcohol blocks antidiuretic hormone (ADH). During alcohol withdrawal, ADH function may be overactive, resulting in hyponatremia.
  — Rapid correction of hyponatremia (21.5-61%).
  — Liver transplant patients (17.4%). Incidence of CPM among liver transplant patients is 0-29%. Onset is usually within the first 30 days after transplant. Liver transplant-associated CPM occurs more commonly in children and those with sepsis, metabolic disorders, hepatic encephalopathy, and hypoxia, and cyclosporine use.
  — Other liver disease, including cirrhosis (4.8%) and Wilson’s disease
  — Burns (2.5%). CPM occurs in 7% of burn patients.
  — Diabetes (2%).
  — AIDS (1.4%).
  — Pregnancy (0.5%) and hyperemesis gravidarum (1.4%).
  — Other electrolyte disturbances and abnormalities in osmolality (0.7%), including hyponatremia, hypokalemia, lithium toxicity, and correction of hypoglycemia.
  — Neoplasms (0.5%), particularly of lung or GI tract; Hodgkin’s disease.
  — Cerebral infarct (0.5%) and other CNS diseases.
  — Sibozophoria (0.5%).
  — Acute porphyria (0.5%).

• Pulmonary infections
• Eating disorders, malnutrition, folate deficiency
• Hypoxia
• Sepsis
• ADH deficiency, adrenal insufficiency, pitiuitary apoplexy
• Heat stroke
• Hemorrhagic pancreatitis
• Trauma
• Ischemic syndrome
• Ornithine-carbamoyltransferase deficiency
• Arginine hydrochloride deficiency
• Sjogren’s syndrome
• Extraventricular myelinolysis (EPM) occurs in 10% to 15% of patients with CPM. The demyelinating lesions are typically located in the cerebellum, lateral geniculate body/thalamus, putamen, cerebral cortex, and subcortical white matter.

Diagnosis

DIFFERENTIAL DIAGNOSIS
The differential diagnosis includes any acute neurologic process that localizes to the pons. Other demyelinating diseases, such as multiple sclerosis and acute disseminated encephalomyelitis, should be considered. Comorbid conditions such as Wernicke’s encephalopathy and hepatic encephalopathy may have symptoms that overlap with CPM.

SIGNS AND SYMPTOMS
Symptoms of CPM vary widely and may reflect damage to the pons and ascending and descending tracts of the brainstem. Presentation can range from no deficit to devastating neurologic injury. Pseudobulbar paralysis, spastic tetraparesis, and coma are characteristic of CPM. Pseudobulbar paralysis includes dysphagia, dysarthria, tongue weakness, and emotional lability, and occurs in approximately 40% of cases. Tetraparesis, paraparesis, or the locked-in syndrome occurs in 33% of patients. Alternative presentations include hemiparesis or weakness more pronounced in the upper extremities. Alterations in consciousness occur in 70% of cases, and can range from lethargy to coma. Ocular findings may include miosis or sixth nerve palsies. Patients may also present with seizures (25% of cases) hyporeflexia, hypotension, respiratory depression, and bowel or bladder dysfunction. In 25% of cases, the only manifestations of CPM are psychiatric such as pseudobulbar la ughing and crying, agitated delirium, akinetic mutism, or catatonia. Patients can also have cognitive deficits affecting speech, judgment, insight, attention, and memory. Ataxia and other cerebellar signs rarely occur in isolation and may be masked by weakness.
Central Pontine Myelinolysis

**LABORATORY PROCEDURES**

Electrolytes.

**IMAGING STUDIES**

- MRI is the study of choice. Characteristic images show a symmetric, non-space-occupying lesion located in the central pons. The lesion is hypointense on T1 and hyperintense on T2 images. The demyelinated area is more visible on T2 sequences. The shape of the affected area typically looks like a "bat's wing" on coronal views, appears triangular on axial views, and has an oval shape on sagittal views.
- The CT finding in CPM is usually a symmetric central pontine hypodense lesion, similar to that demonstrated on MRI. CT is not as sensitive as MRI.
- Findings on neuroimaging lag behind clinical symptoms. Hence, it is recommended to repeat imaging in suspicious cases in 10 to 14 days if early scans are unrevealing. A time lag also exists, however, between clinical improvement and the resolution of MRI changes, in that radiologic findings may persist for months or longer after neurologic recovery. Some propose that early CT and MRI changes are secondary to edema and will often resolve, while later changes are secondary to demyelination itself and are more likely to be permanent. The severity of clinical manifestations does not necessarily correlate with the radiographic evidence of disease.

**SPECIAL TESTS**

- Positron emission tomography (PET) studies have shown the demyelinated patches to have increased metabolic activity early and decreased metabolic activity as CPM progresses. PET, however, is not routinely used in the evaluation of CPM.
- Auditory evoked potentials may be abnormal, with prolongation of the latency period between waves I and V, secondary to demyelination of auditory pathways in the pons. This finding, however, is nonspecific and inconsistent.

**Pathology**

- Autopsy studies demonstrate a single, symmetric region of demyelination in the central basis pontis, grossly seen as a triangular region of soft, discolored tissue.
- Microscopic examination reveals demyelination with loss of oligodendrocytes, myelin-filled phagocytes, astrocytic gliosis, and fat decomposition. Evidence of inflammation is notably absent. Axons, nuclei, and blood vessels are relatively spared.

**Management**

**GENERAL MEASURES**

No consensus guidelines have been established for the treatment of CPM. It remains unclear whether early initiation of treatment improves prognosis.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

Rehabilitation programs including cognitive, speech, occupational, and physical therapy may be helpful.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

Initial treatment should take place in an ICU setting.

**Medications**

**DRUG(S) OF CHOICE**

There is no accepted treatment for CPM. Case reports of anecdotal successful treatment regimens have included:
- Varying regimens of corticosteroids, plasma exchange, and IVIG
- Thyrotropin-releasing hormone (TRH) (0.6 mg IV daily for 6 weeks)
- Methylphenidate, titrated to a final dose of 10 mg bid, for treatment of neuropsychiatric symptoms

**Contraindications**

N/A

**Precautions**

N/A

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

After stabilization of electrolyte abnormalities, patients should be monitored for swallowing dysfunction and progress in PT, OT, and speech therapy.

**EXPECTED COURSE AND PROGNOSIS**

- In cases of hyponatremia, symptoms of CPM typically manifest 2 to 6 days after correction of sodium levels. The course may range from death to nearly complete recovery. Symptoms typically worsen over the first week, then stabilize or improve. Improvement may be seen over the span of weeks to months, and even those with severe symptoms may survive. Recovery is possible.
- Electrophysiological studies, MRI, and CT are not particularly useful for establishing prognosis. Nodesthe a associated disease process, e.g., alcoholism or hyponatremia, help to predict outcome. Mortality depends in large part on effective prevention and treatment of complications such as pulmonary emboli and pneumonia. The majority of those who survive CPM have remaining neurologic deficits, such as ataxia and dysarthria. The cognitive effects of CPM may be most persistent.

**PATIENT EDUCATION**

N/A

**SYNONYMS**

Osmotic demyelination syndrome refers to pontine and extrapontine myelinolysis.

ICD-9-CM: 341.8 CNS demyelination NEC

**SEE ALSO:** N/A

**REFERENCES**


Author(s) Beth A. Leeman, MD
Cerebral Palsy

Basics

DESCRIPTION
Cerebral palsy is the term used to describe the neurologic disorder of motor dysfunction that occurs as a direct result of injury to the developing brain. The insult is nonprogressive and occurs before the age of 3 to 5 years and manifests as abnormalities of tone, posture, or motion. Although the insult is nonprogressive, the manifestations of motor dysfunction may subtly change with time, as the injured brain matures. However, by definition this condition does not involve true neurologic regression.

EPIDEMIOLOGY
Prevalence
The prevalence of cerebral palsy among children at school entry is about 2 per 1,000 live births.

ETIOLOGY
It is known that many conditions can injure the developing brain and lead to cerebral palsy. Yet, approximately one quarter of all cases have no definable cause.

Causes of Cerebral Palsy
• Prenatal
  — First trimester (44%): teratogens, genetic syndromes, brain malformations, chromosomal abnormalities
  — Second and third trimesters: intrauterine infections, fetal/placental dysfunction
• Labor and delivery (19%): Preeclampsia/ectampsia, complications of labor and delivery
• Perinatal (8%): Sepsis/CNS infections, asphyxia, prematurity
• Childhood (5%): Meningitis/encephalitis, traumatic brain injury, toxins
• No obvious cause (24%)

Note: Cerebral palsy occurring repeatedly in a family that is not due to a definable genetic syndrome or chromosomal abnormality should raise the concern that the diagnosis of cerebral palsy is inaccurate. In these cases, an underlying neurometabolic or neurodegenerative disorder should be sought.

RISK FACTORS
Prematurity is a risk factor for cerebral palsy. The risk of cerebral palsy rises steadily as birth weight declines. The risk is approximately 3.4 per 1,000 in infants 2,500 g and over, 13.9 per 1,000 in infants 1,501 to 2,500 g, and 90.4 per 1,000 in infants less than or equal to 1,500 grams. Infants of normal birth weight with a 5-minute Apgar score of 3 or less had a 5% risk of cerebral palsy. Similar scores at 10 minutes increased the risk to 17%, and scores of 3 or less at 20 minutes were associated with a 57% risk of cerebral palsy.

Diagnosis
Cerebral palsy is a clinical diagnosis. To make the diagnosis there has to be motor dysfunction that localizes to the brain as opposed to the peripheral nervous system. Motor dysfunction can manifest as failure to attain motor milestones at the appropriate age, or abnormalities in tone. Clinical examination should localize the lesion to the brain. Cases on physical examination that raise the suspicion of peripheral nervous system dysfunction include difficult-to-elicit or absent reflexes. Neurologic regression or loss of neurologic skills either in the area of motor dysfunction or in other areas of development makes the diagnosis of cerebral palsy suspect.

CLASSIFICATION OF CEREBRAL PALSY
Multiple classifications have been proposed for cerebral palsy.

Swedish Classification of Cerebral Palsy
Spastic: Quadriplegia, hemiplegia, diplegia
Dyskinetic: Choreoathetosis, dystonia
Ataxic
Mixed type
Spastic cerebral palsy: abnormalities of the pyramidal tract, increased tendon reflexes, increased muscle tone.
Dyskinetic: choreoathetosis or dystonia with variable tone and rigidity.
Ataxic cerebral palsy: truncal ataxia, limb dysmetria and tremor.

DIFFERENTIAL DIAGNOSIS
Differential diagnosis includes progressive brain diseases that initially manifest as delayed motor milestones. Aspects of the history and physical examination in a child with motor dysfunction that would steer the clinician away from the diagnosis of cerebral palsy toward a diagnosis of a progressive neurometabolic or neurodegenerative disorder would include:
• Regression of previously acquired skills
• Strong family history of similar conditions
• Family history of sudden infant death

PREGNANCY
See above.

ASSOCIATED CONDITIONS
Many children with cerebral palsy have at least one additional disability associated with damage to the CNS. The most common associated deficits are:
• Cognitive impairment
• Sensory deficits
• Communication disorders
• Seizures
• Feeding problems
• Behavioral and emotional problems

LABORATORY PROCEDURES
Laboratory testing in patients suspected of having cerebral palsy is undertaken to delineate extent of neurologic impairment and the presence of other associated deficits, as well as in selected cases a thorough evaluation for progressive disorders mimicking cerebral palsy. Testing that may be helpful includes:
• Hearing evaluation
• Eye examination including dilated eye examination
• Swallowing evaluation
• X-rays when scoliosis or dislocation of hips are suspected
• Serial developmental assessments
• EEG when spells suspicious of seizures are present

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• Communication disorders
• Seizures
• Feeding problems
• Behavioral and emotional problems

• Repetitive episodes of ulexplained vomiting, shock, or metabolic acidosis
• Unusual body odors
• Hypotonia with absent or diminished reflexes
• Abnormal movements
• Ataxia
• Pigmented retinopathy
Some of the mimickers of the various types of cerebral palsy are listed below.
• Spastic quadriplegia
  — Leukodystrophies occurring in infancy
    such as Krabbe's disease, congenital
    adrenoleukodystrophy, and Pelizaeus-
    Merzbacher disease
  — Other hereditary metabolic diseases
• Spastic diplegia
  — Arginase deficiency
  — Familial spastic paraparesis
  — Tethered cord syndrome
• Ataxic cerebral palsy
  — Vitamin E deficiency
  — Ataxia telangiectasia
  — Late infantile spherolipidoses
  — Late infantile ceroid lipofuscinoses
  — Abetalipoproteinemia
  — Hypobetalipoproteinemia
  — Spinocerebellar ataxias (SCAB)
• Dyskinetic cerebral palsy
  — Mitochondrial disorder
  — Fahr syndrome
  — Hallervorden-Spatz disease
  — Lesch-Nyhan disease
  — Segawa syndrome or dopa-responsive dystonia
  — Dystonia musculorum deformans
  — Glutaric aciduria
  — Rett syndrome

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Laboratory testing in patients suspected of having cerebral palsy is undertaken to delineate extent of neurologic impairment and the presence of other associated deficits, as well as in selected cases a thorough evaluation for progressive disorders mimicking cerebral palsy. Testing that may be helpful includes:
• Hearing evaluation
• Eye examination including dilated eye examination
• Swallowing evaluation
• X-rays when scoliosis or dislocation of hips are suspected
• Serial developmental assessments
• EEG when spells suspicious of seizures are present
IMAGING STUDIES
Imaging studies are helpful with regard to pattern recognition. Certain patterns are recognized as occurring in static disorders:
• Developmental abnormalities such as migrational disorders
• Patterns of previous insult such as periventricular leukomalacia, multicystic encephalomalacia, and porencephalic cysts. Certain imaging abnormalities are specific in pointing away from cerebral palsy to a neurodegenerative disorder such as white matter changes indicative of leukodystrophy. In a portion of children with cerebral palsy, the MRI of the brain reveals no radiographic abnormality. In general the MRI is a better tool for assessing brain parenchyma, whereas the CT is a better test for evaluation of the size of the ventricles.

SPECIAL TESTS
Evaluation for a neurometabolic or neurodegenerative disease should be undertaken in any child with motor dysfunction with neurologic regression.

Management

GENERAL MEASURES
Once the clinical diagnosis has been made, a comprehensive evaluation should be undertaken to define the extent of motor disability, and to determine the presence of associated conditions. Early and aggressive physical and occupational therapy is recommended, with enrollment in an early intervention program. Speech therapy should be instituted if speech is delayed as well. Treatment, by medications and surgical measures, is aimed at maximizing motor function, treatment of associated conditions, and monitoring and treatment of complications.

SURGICAL MEASURES
• Dorsal rhizotomy to decrease spasticity
• Tendon lengthening and transplant measures to decrease impact of contractures

SYMPTOMATIC TREATMENT
See Meduations, below.

ADJUNCTIVE TREATMENT
N/A

ADMISSION AND DISCHARGE CRITERIA
N/A

Medications

DRUG(S) OF CHOICE
There are no specific medications for cerebral palsy. Medications used for spasticity include baclofen (Lioresal) diazepam (Valium), or tizanidine (Zanaflex). Dosages depend on age and body weight.

Contraindications
Baclofen, diazepam, or tizanidine is contraindicated if there is a history of prior hypersensitivity to these or similar agents.

Precautions
Baclofen may in higher doses cause reversible muscular weakness or sedation. Diazepam may be habit forming, and cause sedation and respiratory compromise in higher doses. Tizanidine may cause fatigue or hypotension.

ALTERNATIVE DRUGS
Danazol is occasionally used for syndromes of muscular spasticity.

Follow-Up

PATIENT MONITORING
Patient monitoring should target the following:
• Efficacy and adequacy of therapies, e.g., physical therapy
• Monitoring of musculoskeletal system, e.g., bones/joints
• Adequacy of nutrition and growth
• Treatment of associated conditions such as seizures
• Adequacy of daily programs in the school or preschool systems
• Serial monitoring to determine that there is no true regression

EXPECTED COURSE AND PROGNOSIS
Although cerebral palsy is a static condition, the clinical symptoms can stbly change with time. Usually infants who are hypotonic with increased reflexes eventually become hypertonic within a few years. Ataxia is a common early sign of dyskinetic cerebral palsy. In patients with spasticity, the degree of delay in motor milestones, and the degree of associated deficits in intelligence, sensation, and emotional adjustment. The following are general guidelines:
• More than 50% of children with spastic diplegia learn to walk by the age of 3 years.
• Of children with quadriplegia, 25% may require total care, approximately 33% will learn to walk—usually after age 3 years.
• Few children who do not sit by age 4 years will learn to walk.

PATIENT EDUCATION
Educating parents of children with cerebral palsy, demonstrating how positioning can be an effective way of helping the child with mobility, encouraging the parent-child interaction, and muscle stretching should be part of the teaching given to parents. Counseling on the need to monitor for associated conditions and complications is also an important aspect of treatment.

Miscellaneous

SYNONYMS
Static encephalopathy manifested by motor dysfunction.
ICD-9-CM: 343.9 Cerebral palsy NOS

SEE ALSO: N/A

REFERENCES

|Author(s)| S. Anne Joseph, MD

Cerebral Palsy

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Cerebrovascular Disease, Arteriovenous Malformation

**Basics**

**DESCRIPTION**
Arteriovenous malformations (AVMs) are congenital masses of arteries and veins with no intermediate capillaries. They appear as well-circumscribed tangles of vessels fed directly by arteries. AVMs exert pressure on draining veins and prevent adequate extraction of nutrients and oxygen by adjacent tissues. Most are asymptomatic; but left untreated, AVMs can cause hemorrhage, hypertrophy, and/or mass effect, resulting in minimal symptoms, focal deficits, or catastrophic neurologic injury. AVMs can cause seizures by directly irritating surrounding brain.

**EPIDEMIOLOGY**
- Several autopsy studies reflect a 0.01% to 0.05% prevalence of sporadic AVMs. About 300,000 Americans are believed to have intracranial or intraspinal AVMs; 65% are supratentorial, and 15% are infratentorial.
- The natural history is not well known as most symptomatic lesions are treated and most asymptomatic lesions are undetected; however, it is estimated that 12% of patients harboring AVMs are symptomatic. Most patients present with hemorrhage.
- Best evidence suggests a 1.3% to 4%/year cumulative hemorrhage risk with 10% to 17.6% mortality and 53% to 81% significant neurological morbidity per hemorrhage. The risk of rehemorrhage in the first year after a hemorrhage increases to 6% to 6.9%. There is a 22% risk of hemorrhage-induced epilepsy. About 2%/o of hemorrhagic strokes in adults and up to 40% in children are attributed to AVMs. Very rare spontaneous obliteration has been reported.

**AGE**
Patients are generally 20 to 40 years of age; most are diagnosed before 30.

**Race/Sex**
Males and females of all races and ethnic groups are equally affected.

**ETIOLOGY**
Current evidence suggests that AVMs result from dysregulated angiogenesis producing persistent primitive arterovenous connections or redevelopment of such connections after initial closure. Trauma to developing vessels may also contribute. The lack of normal capillaries results in a high-flow, high-pressure arterovenous shunt. High flow produces vascular steal, and high pressure promotes growth of the AVM, formation of aneurysms, and rupture. Persistent high pressure also causes feeding arteries to swell and distort and draining veins to stenose. Vessels become progressively thinner and weaker. Multiple AVMs are very rare.

**Genetics**
Sporadic AVMs have no known genetic susceptibility. AVMs have been associated with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) and other rare neurologic syndromes (Wyburn-Mason syndrome, Sturge-Weber syndrome, von Hippel-Lindau disease).

**RISK FACTORS**
The risk of hemorrhage cannot be accurately predicted. Irregular growth of AVMs complicates this further. Several factors may increase the risk of hemorrhage: deep venous drainage, high feeding artery pressure, hypertension, prior hemorrhage, related aneurysms, smaller size, and venous stasis.

**PREGNANCY**
Current evidence indicates that pregnancy and method of delivery do not increase the risk of hemorrhage. Pregnancy-related hemodynamic changes have been postulated potentially to increase hemorrhage risk or to exacerbate symptoms. Treatment should be considered before pregnancy. During pregnancy, the risk of treatment should be carefully considered against the risk of hemorrhage.

**ASSOCIATED CONDITIONS**
Aneurysms may be present within, near, or far from the AVM (17-48%). These aneurysms behave like non-AVM-related aneurysms. As aneurysms are much more likely to hemorrhage, they should be sought in any patient with an AVM-related hemorrhage and may need to be treated before or at the same time as the AVM.

**IMAGING STUDIES**
- CT has low sensitivity but may demonstrate calcifications (25-30%).
- MRI is very sensitive and demonstrates a characteristic honeycomb tangle of flow voids. Large arteries, arterialized veins, and the relation of the AVM to intracranial structures can often be seen. Areas of hemorrhage, blood products of various ages, and local edema may be present.
- MRA and MRA can noninvasively create 3D representations of the AVM.
- Cerebral angiogram best demonstrates blood vessel architecture. Superselective angiogram is recommended to delineate the internal architecture of an AVM. Associated aneurysms should also be identified.
- MRI and cerebral angiography are recommended prior to surgery.

**SPECIAL TESTS**
The Wada test and functional imaging techniques can be useful in localizing eloquent areas prior to treatment.
Cerebrovascular Disease, Arteriovenous Malformation

**Management**

**GENERAL MEASURES**
Indications for treatment include prevention of hemorrhage, treatment of seizures, enhancement of local perfusion, and treatment of hemorrhage. Hemorrhage risk is unchanged as long as an AVM is present; early treatment to achieve angiographic obliteration while mitigating neurologic risk is usually recommended. Incomplete treatment is generally not recommended.

There are treatments: observation, surgery, radiosurgery, and endovascular therapy. Treatment planning considers the lowest risk of injury with the highest chance of lesion obliteration. Many centers treat AVMS with a combination of interventions.

**SURGICAL MEASURES**
- Surgery: surgical removal of the entire AVM while limiting brain injury is the treatment of choice. Spetzler and Martin devised a grading system of AVMS, based on size, location, and venous drainage, to estimate the risk of surgical intervention (grades 1 to 5). Low surgical risk lesions (grades 1 to 3) are treated with 94% to 100% efficacy and negligible morbidity. High surgical risk lesions (grades 4 to 5) can be treated with 17% to 22% morbidity.
- Radiosurgery: conventional radiotherapy is not considered effective, but stereotactic radiosurgery can treat high surgical risk lesions. Radiosurgical treatment through vessel wall injury takes years, during which the risk of hemorrhage remains unchanged. Angiographic cure occurs in 65% to 85% of lesions <3 cm in size at 3 years, but is significantly less for larger lesions. There is radiation exposure and a small risk of recurrence. Still, treatment-related risks are low, and outpatient treatment is employed.
- Adjunctive treatment: Embolization: carent techniques of plugging vessels intravascularly are generally inadequate as sole therapy (<10%), but embolization can reduce the flow or size of a lesion to facilitate surgery or radio surgery. Functional tests can also be performed by injecting barbiturates through the AVM. This technique is invasive but less so than surgery and carries modest treatment-related risks. Multiple procedures may be required.

**ADJUNCTIVE TREATMENT**
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**SYMPTOMATIC TREATMENT**
No medical management can completely mitigate AVM hemorrhage risk. Acute hemorrhage should be treated like any intracranial hemorrhage. Seizures can be treated with sedation. Focal neurologic deficits may be modified by surgery. Surgery should be strongly considered for low surgical risk lesions that are easily accessible. Small lesions that cannot be easily accessed may be treated with radiosurgery. A combined embolization and surgery approach may be recommended for moderate surgical risk lesions. High surgical risk and unresolvable lesions may be treated by radiosurgery with or without embolization. Some centers may attempt palliative partial embolization of very high risk lesions, but long-term results are poor.

**ADMISSION/DISCHARGE CRITERIA**
The decision to treat an AVM is based on age, neurologic status, hemorrhage risk factors, medical condition, and the architecture of the lesion. Carefully planned treatment with multiple preoperative visits for testing and counseling affords the best possible outcome. Due to the lifetime risk of hemorrhage, more aggressive treatment is warranted in younger patients.

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**ADMISSION/DISCHARGE CRITERIA**
The decision to treat an AVM is based on age, neurologic status, hemorrhage risk factors, medical condition, and the architecture of the lesion. Carefully planned treatment with multiple preoperative visits for testing and counseling affords the best possible outcome. Due to the lifetime risk of hemorrhage, more aggressive treatment is warranted in younger patients.

**SYMPTOMATIC TREATMENT**
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Cerebrovascular Disease, Intracerebral Hemorrhage

**Basics**

**DESCRIPTION**
Intracerebral hemorrhage (ICH) results from bleeding directly into the brain substance.

**EPIDEMIOLOGY**
Approximately 10% of all strokes in North America.

**Incidence/Prevalence**
Incidence in the general population is 12–29/100,000.

**Race**
African Americans have an approximate twofold increase in the risk for ICH with incidence rates up to 50/100,000. Asian populations also have higher rates of ICH.

**Age**
Incidence rates increase with age.

**Sex**
Males and females affected equally.

**ETIOLOGY**
Frequently associated with location of hemorrhage and patient age.

- **Hypertension**: implicated in over 50% of ICH. Most commonly located in the basal ganglia, thalamus, deep subcortical white matter, pons, or cerebellum. Lobar hypertensive ICH occurs more frequently.
- **Vascular malformations**: account for 4% to 8% of ICH and include arteriovenous malformations, cavernous malformations, and venous angiomas. Frequently located at the cerebral convexity or in the subcortical white matter. More common in younger patients.
- **Aneurysm**: accounts for 3% to 4% of ICH. Usually associated with subarachnoid hemorrhage (SAH), but rupture into the parenchyma may occur when located in the intrahemispheric or Sylvian fissures.
- **Cerebral amyloid angiopathy**: results from deposition of amyloid protein in leptomeningeal and cortical arteries. Common cause of lobar ICH in the elderly (>50% in patients over 75 years old). Bleeding diathesis: anticoagulant therapy implicated in 5% to 2% of all ICH, especially in patients treated with warfarin with the international normalized ratio (INR) >4.0. Symptomatic ICH rates with thrombolytic therapy are 1% with treatment for acute myocardial infarction and 6.4% for acute ischemic stroke (AIS). Also occurs in disseminated intravascular coagulopathy, thrombocytopenia, specific clotting factor deficiencies, polycythemia/hyperviscosity syndromes, leucemias (especially promyelocytic), von Willebrand disease, and sickle cell anemia.
- **Drug-related**: use of cocaine, amphetamines, and over-the-counter sympathomimetic agents found in cold remedies and diet pills, and heavy alcohol use.
- **Cerebral venous occlusive disease (CVOD)**: venous infarction resulting from venous occlusive disease may undergo hemorrhagic transformation. Associated with pregnancy and the postpartum period, contiguous air space infections, hypercoaguable disorders, and dehydration.
- **Hemorrhagic transformation of ischemic arterial infarct**: up to 50% of ischemic infarctions undergo some amount of hemorrhagic transformation within 1 to 3 weeks of the original event. Symptomatic transformation is much less frequent.
- **Arteritis/arteriopathies**: infectious vasculitis, multisystem vasculitis, isolated CNS angiitis, or moyamoya disease.
- **Other**: trauma, after carotid endarterectomy or other neurosurgical procedures, postmyelography.

**RISK FACTORS**
As above.

**PREGNANCY**
Increased risk of vascular malformation hemorrhage or aneurysmal rupture during pregnancy and labor. CVOD more frequent during pregnancy and the puerperium.

**ASSOCIATED CONDITIONS**
N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
Acute ischemic stroke, SAH, epidural hematoma, seizure, migraine.

**SIGNS AND SYMPTOMS**
Abrupt onset and rapid evolution of signs and symptoms over minutes. Over half of patients complain of headache, and almost half have nausea and vomiting. Focal neurologic symptoms reflect location of ICH. Decreased level of consciousness (LOC) found with large or rapidly expanding ICH and when structures regulating consciousness are involved (e.g., brainstem). Seizures occur in 10% to 15% of cases, especially in lobar ICH.

**LABORATORY PROCEDURES**
No specific blood work to diagnose ICH. The following studies should be obtained to help establish etiology or in preparation for further diagnostic testing:
- CBC and platelet count
- Coagulation studies (prothrombin time/INR, activated partial thromboplastin time)
- Electrolyte panel, including renal function studies
- Urine drug screen
- Blood typing/cross-matching, if delivery of blood products or surgical intervention is planned
- Other testing may include liver function tests, sedimentation rate, antinuclear antibodies, blood cultures, fibrinogen, fibrin split products, bleeding time, hemoglobin electrophoresis

**IMAGING STUDIES**
- CT: Noncontrasted CT should be performed immediately to provide rapid information about hemorrhage location and size, presence of mass effect, and extraventricular extension. No further imaging study required if ICH is found in a location typical for hypertensive hemorrhage in a patient with known hypertension.
- MRI: Generally not useful in acute imaging of ICH, but should be used acutely in suspected cases of CVOD. Useful in diagnostic workup of ICH to search for underlying neoplasm or vascular malformation. Timing of MRI controversial; acute hematoma can obscure underlying lesions. Typically delayed for 4 to 6 weeks but can be used sooner to identify other previous hemorrhagic lesions, as seen with amyloid angiopathy or multiple caver nous malformations.

**SPECIAL TESTS**
- Cerebral angiography: indicated when a primary vascular abnormality such as aneurysm, vascular malformation, or vasculitis is suspected, based on hemorrhage location or patient characteristics. Should be performed in young, nonhypertensive patients and in those with atypical location for hypertensive hemorrhage. If angiography negative in young patient with lobar hemorrhage, should be repeated in 1 to 2 months, as large hematomas may compress underlying vascular malformations in the acute phase.
Management

**GENERAL MEASURES**

- Rapid assessment of LOC, airway, and adequacy of ventilation. Patients with inability to protect the airway or with respiratory depression should be intubated immediately and mechanically ventilated.
- Increased intracranial pressure (ICP) may be treated with hyperventilation to a Pack of about 30 mm Hg. Medical and surgical management of increased ICP discussed below.
- Correction of any underlying coagulopathy.
- Seizures generally occur within 72 hours of the ictus. Prophylaxis is use of anticonvulsant agents reserved for patients with cortical involvement.
- Prophylaxis for deep venous thrombosis with pneumatic sequential compression devices.

**SURGICAL MEASURES**

- Supratentorial ICH: comatose patients with massive ICH and neurologically stable patients with small hematomas are not considered surgical candidates. For other cases, surgical evacuation remains controversial. Older randomized trials of surgery found no benefit for surgery, but the largest were performed in the pre-CT era and before development of modern neurosurgical techniques. Endoscopic evacuation, as compared to open craniotomy, is currently being explored. Cortical ICH is more often evacuated than are deeper, ganglionic hematomas. Timing of surgery is also controversial, with some authors arguing for early evacuation to prevent primary hematoma expansion and neurologic decompensation and also to prevent secondary brain injury from toxic blood products.
- Cerebellar ICH: surgical evacuation indicated for cerebellar hemispheric ICH >3 cm in diameter or for decreased LOC.
- Ventricular drainage: associated intraventricular hemorrhage may result in communicating or noncommunicating hydrocephalus. Ventriculostomy performed to drain CSF and to monitor ICP. Intraventricular instillation of thrombolytic agents to aid in dissolving of clot remains investigational.
- ICP monitoring: not proven to improve survival or outcome, but may be used to help direct therapy.

**SYMPTOMATIC TREATMENT**

Physical therapy, occupational therapy, and speech therapy are often helpful once the patient is stable.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

All patients admitted for acute evaluation and management. ICU admission often required. Depending on residual symptoms, patients may need inpatient rehabilitation.

**Follow-Up**

**PATIENT MONITORING**

Monitor vital signs and neurologic status closely. Worsened neurologic status may arise from increased intracranial pressure, hydrocephalus, or rebleeding.

**EXPECTED COURSE AND PROGNOSIS**

Outcome is poor with 6-month mortality rate of 43%. Only 12% of patients are left with minor or no disability. Predictors of poor outcome include hemorrhage volume >60 cc, Glasgow Coma Score less than 9 at presentation, brainstem ICH, and intraventricular extension.

**PATIENT EDUCATION**

Given poor outcome once ICH occurs, educational efforts should be directed at prevention through risk factor modification. Further information may be obtained by contacting the American Stroke Association at 1-888-4STROKE or visiting www.strokeassociation.org.

**Medications**

**DRUGS OF CHOICE**

No medical therapies have been shown to decrease mortality or improve recovery. Randomized studies of dexamethasone and glycerol for ICH were negative. Medical intervention is currently directed at conditions that result from ICH.

- Increased ICP
  - Mannitol 20% solution
    - Initial IV bolus 1 g/kg over 30 minutes and maintenance dose of 0.25-0.5 g/kg every 4 to 6 hours. Do not adjust to clinical status, ICP valves, and serum osmolality (300-310 mosm/L).
    - Intravenous barbiturate use limited by hypotension and not shown to improve outcome.

- Acute hypertension
  - Control of acute hypertension has never been proven to prevent recurrent bleeding or improve outcome, but recommendations to keep mean arterial pressure <130 mm Hg are preferred. Short-acting, easily titratable agents are preferred. Precipitous lowering of blood pressure should be avoided.
    - Labetalol: 10-20 mg IV bolus, then 20 mg IV boluses every 10 to 15 minutes or IV infusion 0.5-1.0 mg/min (maximum 300 mg/day).
    - Enalaprilat: 1.25 mg IV bolus over 5 minutes every 6 hours. For elderly or hypertensive patients, a starting dose of 0.625 mg is recommended. - Ntropur usside: 0.2-0.5 μg/kg/min IV, titrated to desired blood pressure.

**Contraindications**

- Sublingual nifedipine contraindicated in all stroke syndromes.
- Labetalol not recommended for patients with asthma, chronic obstructive pulmonary disease, congestive heart failure, heart block, hypotension, or severe bradycardia (due to beta-blockade properties).
- Ntropur usside not recommended in pregnancy.

**Precautions**

- Ntropur usside and other vasodilators should be used with care as they may increase ICP.

**ALTERNATIVE DRUGS**

N/A

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**ALTERNATIVE DRUGS**

N/A

**SYNONYMS**

Intraparenchymal hemorrhage (IPH)
Parenchymatous hemorrhage (PH)

**ICD-9-CM**: 431 Intracerebral hemorrhage; Code for etiology (e.g., 437.6 Nonpyogenic thrombosis of intracranial venous sinus, 747.81 Anomalies of cerebrovascular system including arteriovenous malformation of brain); 674.0 Intracerebral hemorrhage occurring during pregnancy, childbirth, or the puerperium; 671.5 Cerebral venous thrombosis as a complication in pregnancy and the puerperium

**SEE ALSO**: N/A

**REFERENCES**


Author(s): Susan L. Hickenbottom, MD
Cerebrovascular Disease, Intracranial Aneurysms, and Subarachnoid Hemorrhage

**Basics**

**DESCRIPTION**
Saccular aneurysms, the most common type of intracranial aneurysms, are focal protrusions arising from vessel wall weaknesses at major arterial bifurcations along the base of the brain. Their rupture results in hemorrhage into the subarachnoid spaces in which they reside, and is the second most common cause of hemorrhagic stroke.

**Epidemiology**
Incidence/Prevalence
The prevalence of unruptured aneurysms is controversial; however, most reports estimate their occurrence to be 1% to 6% in the general population. Incidence of aneurysmal subarachnoid hemorrhage (SAH) is approximately 10 to 15 per 100,000 people per year of which 80% to 90% are from ruptured saccular aneurysms.

**RISK FACTORS**
Hypertension, cigarette smoking, oral contraceptives, alcohol consumption, pregnancy, and cocaine use are all known risk factors for SAH and probably increase the risk of aneurysmal rupture. Other risk factors include trauma, atherosclerosis, and infection (bacterial endocarditis).

**Pregnancy**
Intracranial hemorrhage during pregnancy is rare (incidence: 0.01-0.05% of all pregnancies). However, over half are SAH and most of these are aneurysmal, representing an increased incidence of aneurysmal SAH in pregnant women relative to the general female population. While the increased blood volume and pressure during pregnancy and late gestation are believed to contribute, the exact pathophysiological and hormonal factors associated with the increased risk remain unknown. Mortality and morbidity of aneurysmal SAH during pregnancy is high, with a maternal mortality rate of 13% to 35% (accounting for about 1 in 25 maternal deaths during pregnancy) and a fetal mortality rate of 7% to 25%.

**ASSOCIATED CONDITIONS**
Aneurysms have been associated with a number of conditions including polycystic kidney disease (PKD), arteriovenous malformations (AVMs), moyamoya disease, fibromuscular dysplasia (FMD), and other hereditary connective tissue disorders.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
The differential diagnosis of aneurysmal SAH narrows considerably following the confirmation of blood in the subarachnoid spaces:
- Arteriovenous malformations
- Dural arteriovenous fistula
- Vasculopathy (amyloid angiopathy, systemic lupus erythematosus, polyarteritis nodosa)
- Carotid dissection
- Pituitary apoplexy
- Hemorrhage from a tumor
- Benign perimesencephalic hemorrhage

**Clinical Presentation**
The clinical presentation of aneurysmal SAH is usually characterized by the acute onset of severe headache that may initially be localized, but often generalizes quickly. Headache is the most common symptom in over 90% of cases and is classically described as "the worst headache of my life." Nausea and vomiting are frequent, and loss of consciousness may occur. Signs of meningeal irritation, including nuchal rigidity (especially to flexion) and photophobia, are often present within 4 to 8 hours after the onset of SAH. Focal neurologic signs and symptoms may also be present, depending on the size and location of the aneurysm, and the severity and location of the hemorrhage. Ocular hemorrhages may cause blurred vision and are frequently found on funduscopic examination, the most common of which are subhyaloid (preretinal) hemorrhages, seen in approximately 25% of patients.

**Laboratory Procedures**
- Lumbar puncture (LP) is the most sensitive test for SAH, and should be performed in cases where the head CT is negative but there remains a high clinical suspicion. Typical CSF findings in SAH are an elevated opening pressure, nonclotting bloody fluid that fails to clear with sequential tubes, xanthochromia of the supernatant, a RBC count of usually >100,000 cells/ml, elevated protein, and normal glucose.
- Serum electrolyte abnormalities are frequent, with hyponatremia found in about one third of patients.

**IMAGING STUDIES**
The sequence of evaluation for suspected aneurysmal SAH begins with a high-resolution noncontrast CT scan. A good-quality head CT will detect SAH in over 95% of patients who undergo the study within 24 hours of the hemorrhage. The scan will also demonstrate the extent and location of the hemorrhage, as well as the presence of hydrocephalus. MRI provides a noninvasive method of evaluating patients who present several weeks after acute symptoms, since subacute or remote hemorrhages can be differentiated by their signal characteristics long after CT findings have normalized. Cerebral digital subtraction angiography (DSA) is the "gold standard" for diagnostic evaluation of aneurysms, and should be performed in CT- or LP-confirmed nontraumatic SAH and in patients in whom the clinical suspicion remains high despite negative CT scan and/or inconclusive LP. Magnetic resonance angiography (MRA) and rapid spiral CT angiography (CTA) are both noninvasive methods to evaluate the cerebral circulation that are increasingly being used for both screening and diagnosis.

**Signs and Symptoms**

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**Cerebrovascular Disease, Intracranial Aneurysms, and Subarachnoid Hemorrhage**

**SPECIAL TESTS**
Transcranial Doppler ultrasonography (TCD) can be used to evaluate for the development of cerebral vasospasm, which is the leading cause of death and morbidity following successful treatment of the ruptured aneurysm.

**GENERAL MEASURES**
Early diagnosis and treatment is imperative for the best possible outcome. Treatment of intracranial aneurysms centers on efforts to exclude the aneurysm from the intracranial circulation while maintaining patency of the normal vasculature, restoring and maintaining normal cerebral blood flow.

**SURGICAL MEASURES**
- Microsurgery: clipping: Most cerebral aneurysms are now treated with clipping, where a craniotomy is performed and a clip is placed, occluding the aneurysmal neck. Following adequate placement, long-term data suggest that this treatment is curative.
- Endovascular Coiling: Intra-arterial microcatheters can be used to place detachable, thrombogenic platinum coils (GDC coils) into saccular aneurysms, promoting their exclusion from the normal vasculature and reducing the risk of hemorrhage. Recent data suggest this treatment is safe and effective in preventing short-term rebleeding for some aneurysms, but long-term recanalization rates and efficacy are not yet known.

**SYMPTOMATIC TREATMENT**
The natural history of aneurysmal SAH carries an extremely high risk of death and/or disability, and medical management alone does little to change this outcome.

**ADJUNCTIVE TREATMENT**
Following elimination of the aneurysm via surgery, the remainder of therapeutic intervention focuses on preventing cerebral vasospasm and treating associated hydrocephalus. Treatment of vasospasm consists of the combination of calcium channel blockers, hypertensive-hypervolemic therapy, and endovascular angioplasty. Treatment of hydrocephalus includes either temporary CSF drainage or placement of a permanent ventriculoperitoneal (VP) shunt.

**ADMISSION/DISCHARGE CRITERIA**
All patients suspected of harboring a ruptured cerebral aneurysm should be admitted and urgently evaluated by a neurosurgeon.

**Follow-Up**
**PATIENT MONITORING**
Survival from and successful treatment of a ruptured aneurysm does not provide cure of the disease. Patients who have had a previous SAH from an aneurysm are at increased risk for the development of new aneurysms. For this population, there is a 2% annual rate of new aneurysm development and the incidence of aneurysmal rupture is five times higher than the general aneurysmal population. Therefore, periodic follow up with imaging is recommended not only for the treated lesion, but also to evaluate development of new ones.

**EXPECTED COURSE AND PROGNOSIS**
Despite advances in recognition, diagnosis, and treatment, the natural history of ruptured saccular aneurysms remains poor, with approximately one third of patients left dead or severely disabled by the initial hemorrhage. Another third of those who reach treatment die or are severely disabled because of rehemorrhage or cerebral vasospasm, leaving only one in three patients as functional survivors following aneurysmal SAH. Furthermore, some reports suggest that as many as 66% of the functional survivors never return to the same quality of life before the SAH because of mild cognitive or other neurologic deficits.

**Medications**

**DRUG(S) OF CHOICE**
- Antihypertensive medications, to control blood pressure.
- Nimodipine, a calcium channel antagonist used to treat vasospasm, has been demonstrated in prospective, randomized, placebo-controlled clinical trials to improve the outcome after aneurysmal SAH, and should be routinely administered during the first 21 days following SAH.
- Anticonvulsant medications should be administered if seizures occur.
- Analgesics to treat headaches.

**Contraindications**
Known hypersensitivity to particular medication.

**Precautions**
None

**ALTERNATIVE DRUGS**
None

**PATIENT EDUCATION**
American Association of Neurological Surgery (AANS)/Congress of Neurological Surgery (CNS)
www.neurosurgery.org/health/patient/detail.asp?DisorderID = 87

**SYNONYMS**
None

**ICD-9-CM: 430.0 Aneurysm, ruptured**

**SEE ALSO:** N/A

**REFERENCES**

Author(s) Robert L. Dodd, MD, PhD; Stephen I. Ryu, MD; Gary K. Steinberg, MD, PhD

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Cerebrovascular Disease, Ischemic Infarcts

**DESCRIPTION**
Ischemic stroke is defined as an irreversible focal, and sometimes multifocal, brain damage caused by blood disruption to the affected area.

**EPIDEMIOLOGY**

<table>
<thead>
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<th>Incidence/Prevalence</th>
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<td>There are approximately 700,000 new strokes every year; 80% of these are ischemic in nature.</td>
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**Age**
It is more common in the elderly, though a significant portion occurs in individuals over 40 years of age.

**Sex**
It is more common in males.

**Race**
It is more common in African Americans and Hispanics.

**ETIOLOGY**
- Hypercoagulable state: includes deficiencies of protein C, 5, or antithrombin III, factor V mutation, factor II mutation; antiphospholipid antibody syndrome; sickle cell anemia; mucocutaneous carcinomas.
- Cardiac emboli: conditions that predispose to the formation of cardiac emboli include atrial fibrillation, mitral valve stenosis, sick sinus syndrome, prosthetic heart valve, infective endocarditis, marantic endocarditis, congestive heart failure, dilated cardiomyopathy, myxomas, intraatrial septal defect, patent foramen ovale, dilated atria, and atrial septal aneurysm.
- Large artery disease: the extracranial carotid, intracranial carotid, extracranial vertebral, intracranial vertebral, middle cerebral, basilar, anterior cerebral, and posterior cerebral are all large arteries. Disease in these vessels can lead to ischemic stroke. The most common is atherosclerosis. Other diseases include dissection, vasculitis, moyamoya, and fibromuscular dysplasia.
- Small vessel disease: the most common cause of small vessel disease is hypertension. Other etiologies include diabetes, vasculitis, and rare genetic conditions like mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and cerebral autosomal-dominant arteriopathy with subcortical infaracts and leukencephalopathy (CADASIL). The stroke caused by small vessel disease is small and frequently called a lacunar stroke.

**GENETICS**
- MELAS and CADASIL are rare genetic conditions that lead to ischemic stroke.

**ETIOLOGY**
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**PREGNANCY**
- Pregnancy increases the risk of ischemic stroke. Conditions peculiar to pregnancy that lead to stroke include paradoxical embolism from the legs or pelvic veins, cardiomyopathy of pregnancy, cervical arterial dissection during labor and delivery, hypercoagulable state, anoxic cerebral fluid embolism, and vasoconstrictive medications like ergotamines.

**ASSOCIATED CONDITIONS**
- Coronary artery disease and peripheral artery diseases.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Intracerebral hemorrhage
- Multiple sclerosis
- Migraine aura
- Seizures (Todd's paralysis)
- Intracranial subdural effusions
- Intracranial infections
- Metabolic disorders
- Somatic ion disorders
- Labyrinthine disorders

**SIGNS AND SYMPTOMS**
Stroke symptoms are usually sudden and abrupt. The clinical features depend on the brain area infarcted. Common symptoms include:
- Hemiparesis
- Hemisensory loss
- Visual field defects
- Ataxia and incoordination
- Aphasias
- Dysarthria
- Dysphagia
- Diplopia
- Vertigo

**LABORATORY PROCEDURES**
- All patients with ischemic stroke should have blood for fasting lipid profile, RPR, BUN, creatinine, CBC and platelets, PT, PTT, and INR.
- Hypercoagulable profile, including protein C, protein S, antithrombin III, factor V, factor II, lupus anticoagulant, antiphospholipid antibodies, and homocysteine should be requested in young patients.
- Serial blood cultures should be sent when infective endocarditis is suspected.

**IMAGING STUDIES**
- Chest x-ray to evaluate for cardiomegaly.
- CT scan may be performed in all patients presenting with suspected stroke because it is very sensitive in detecting intracranial hemorrhage, which can easily mimic ischemia. It is also cheap, quick, and readily available.
- MRI of the brain (especially diffusion weighted imaging and FLAIR) is more sensitive than CT scan in detecting early infarction, and infarcts in the cerebellum, brainstem, and inferior temporal lobes.
- MR Angiography is a noninvasive test, and is accurate for assessing the major extracranial and intracranial arteries, though it may overestimate the severity of the stenosis.
- Transesophageal echocardiogram (TEE) is indicated in most patients with ischemic stroke. If the TTE is negative and a cardiac source is still suspected, then transesophageal echocardiogram (TEE) must be performed. TEE is also indicated in all young patients. TEE is more accurate than TTE in showing atrial and ventricular thrombi, vegetation, and left atrial enlargement, detecting shunts, and evaluating the proximal aorta.
- Angiography: the gold standard for an accurate assessment of both the extra- and intracranial vasculature. However, it is an invasive procedure and should be reserved for patients in whom noninvasive testing has not definitely shown the source of stroke, and to assess accurately the degree of stenosis.
- Ultrasound is safe, portable, and less expensive. It includes transcranial Doppler to look for intracranial disease and carotid duplex to assess for extracranial carotid and vertebral artery disease.

**SPECIAL TESTS**
ECG and cardiac monitoring to evaluate for arrhythmias.

**GENERAL MEASURES**
General treatment of stroke includes acute supportive care, management of coexisting medical illnesses and secondary stroke prevention.

**SURGICAL MEASURES**
- Carotid endarterectomy (CEA) is indicated for significant (>50%) symptomatic carotid artery stenosis. For those patients who are considered high risk for surgery, carotid angioplasty with stent placement is performed in a few medical centers. Intracranial large artery (basilar, vertebral, middle cerebral, and internal carotid) angioplasty with or without stent placement is occasionally performed in a few academic centers for those patients who fail maximal medical therapy.
- Intracranial thrombolysis for acute ischemic stroke, only within 6 hours from the onset of symptoms, is being provided in few experienced centers.
Cerebrovascular Disease, Ischemic Infarcts

SYMPTOMATIC TREATMENT

• Includes treatment of hyperglycemia, fever, and infection; deep vein thrombosis prophylaxis; aspiration precaution; adequate hydration and r/n t; judicious control of blood pressure with avoidance of excessive reduction in the acte sett ing and adequate control in the long run and av olance of prolonged use of indwelling catheter to prevent urinary tract infection.

• Amitriptyline or gabapentin for pain management of stroke complications; early ischemic stroke should be admitted to the neurology unit for evaluation of etiology and appropriate preventive measures; prevent ion and management of stroke complications; early initiation of physical, occupational, and speech therapy; evaluation for eligibility for inpatient rehabilitation; assistance with appropriate placement; and patient and caregiver education.

ADJUNCTIVE TREATMENT

Physical, occupational, speech, and cognitive therapy may be needed.

ADMISSION/DISCHARGE CRITERIA

In general any patient presenting with acute ischemic stroke should be admitted to the hospital for the evaluation of etiology and appropriate prevention measures; prevent ion and management of stroke complications; early initiation of physical, occupational, and speech therapy; evaluation for eligibility for inpatient rehabilitation; assistance with appropriate placement; and patient and caregiver education.

Medications

DRUGS OF CHOICE

• Recombinant tissue plasminogen activator (rt-PA) is the only FDA-approved medication for acute ischemic stroke and must be given within 3 hours from the onset of symptoms. The dose is 0.9 mg/kg up to a maximum of 90 mg; 10% of the dose is given as an IV bolus over 1 minute and the rest as an IV drip over 1 hour.

• Antiplatelet agents: indicated for stroke prevention in small vessel disease, intracranial large artery disease, mild (<50%) extracranial carotid artery disease, extracranial vertebral artery disease, aortic arch disease without mobile plaque, irregular nonstenotic valve surfaces, and in patients who are not Coumadin candidates.
  — Aspirin: 50-325 mg qd
  — Plavix: 75 mg qd
  — Aggrenox (combination aspirin 25 mg/extended release dipyridamole 200 mg one tablet bid)

• Anticoagulants
  — Warfarin (Coumadin): indicated in hypercoagulable states; cardiac sources like atrial fibrillation, intracardiac thrombi, etc.; and intracranial large artery stenosis.

Contraindications

• rtPA: suspicion of subarachnoid hemorrhage; recent (within 3 months) intracerebral or intraparenchymal hemorrhage; recent head trauma; recent previous stroke; history of intracerebral hemorrhage; uncontrolled hypertension at time of treatment (SBP >185 mm Hg or DBP >110 mm Hg) seizure at the onset of stroke; active internal bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis including but not limited to coagulate of oral anticoagulants (e.g., warfarin sodium), or an international normalized ratio (INR) >1.7, or a prothrombin time (PT) >15 seconds; administration of heparin in the preceding 48 hours and an elevated activated partial thromboplastin time (aPTT) at presentation: platelet count <100,000/mm³.

• Aspirin/Aggrenox: mainly known allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer.

• Clopidogrel: mainly systemic bleeding.

• Warfarin: mainly active bleeding, bleeding tendency, noncompliance, and gait difficulty with increased falling risk.

Precautions

• rtPA: Noncompressible arterial or venous punctures must be avoided. Blood pressure must be monitored closely during administration of the medicine and treated if elevated. If serious bleeding is suspected, then it must be stopped immediately. Watch for allergic reaction.

• Clopidogrel: monitor for any TTP symptoms at the beginning of treatment.

• Warfarin: watch for compliance, bleeding events, and falling events.

ALTERNATIVE DRUGS

N/A

EXPECTED COURSE AND PROGNOSIS

Appropriate preventive secondary measures significantly decrease the risk of recurrent stroke. However, despite these measures patients continue to be at increased risk. If recurrent events occur, reevaluation for the etiology and modification of the management is important.

PATIENT EDUCATION/ORGANIZATIONS


Follow-Up

PATIENT MONITORING

• Frequent follow-up visits are important to assess patients for recurrent events, compliance with treatment and recommendations, and adverse reactions from the treatment medications.

• Close monitoring of INR is crucial for treatment with Coumadin.

REFERENCES


Author(s): Yousef Mohammad, MD, MSc
Cerebrovascular Disease, Transient Ischemic Attack

Basics

DESCRIPTION
Transient ischemic attack (TIA) is defined as a transient focal, and sometimes multifocal, brain ischemia from disrupted blood supply that completely resolves within 24 hours.

EPIDEMIOLOGY
Incidense/Prevalence
The annual incidence of TIA in the United States is estimated to vary from 1 in 200,000 to 1 in 500,000. However, the accurate incidence is probably much higher because many of these attacks are not reported by the patients.

Age
It is more common in the elderly, as is stroke.

Sex
It is more common in males, as is stroke.

Race
It is probably more common in African Americans and Hispanics, given the increased incidence of stroke in these populations.

ETIOLOGY
It is the same as ischemic stroke. This includes the following:
- Cardiac emboli: conditions that predispose to the formation of cardiac emboli include atrial fibrillation, mitral valve stenosis, sick sinus syndrome, prosthetic heart valve, infective endocarditis, marantic endocarditis, congestive heart failure, dilated cardiomyopathy, myxomas, intraatrial septal defect, patent foramen ovale, and dilated atria.
- Large artery disease: the extracranial internal carotid, intracranial internal carotid, extracranial vertebral, intracranial vertebral, middle cerebral basilar, anterior cerebral, and posterior cerebral are all large arteries in the cerebrovascular circulation. Disease in these vessels can lead to TIA. The most common is atherosclerosis. Other diseases include dissection, vasculitis, moyamoya, and fibromuscular dysplasia.
- Small vessel disease: an uncommon cause of TIA.

Genetics
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), factor II, and factor V mutations are all genetic conditions that can present with TIA.

RISK FACTORS
Risk factors include hypertension, diabetes mellitus, hyperlipidemia, tobacco, sedentary life, obesity, family history of stroke, and history of coronary or peripheral vascular disease.

PREGNANCY
It is likely that there is an increased incidence of TIA in pregnancy, as there is an increased incidence of ischemic stroke in pregnancy.

ASSOCIATED CONDITIONS
Ischemic stroke, coronary artery disease, and peripheral artery disease.

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Ischemic stroke
- Migraine aura
- Multiple sclerosis
- Seizures (Todd's paralysis)
- Labyrinthine disorders
- Syncope
- Metabolic disorders
- Intracerebral hemorrhage
- Subdural hematoma
- Malignant ion disorders

SIGNS AND SYMPTOMS
By definition a TIA must resolve within 24 hours; otherwise it is considered a stroke. However, it usually resolves within 1 hour. As in ischemic stroke, the symptoms are typically sudden and abrupt. The clinical features depend on the brain area affected. Common symptoms include:
- Hemiparesis
- Hemisensory loss
- Visual field defects
- Ataxia and incoordination
- Aphasia
- Dysarthria
- Dysphagia
- Diplopia
- Vertigo

LABORATORY PROCEDURES
- All patients with TIA should have blood drawn for fasting lipid profile, RPR, BUN, creatinine, CBC and platelets, PT, PTT, and INR.
- Hypercoagulable profile, including protein C, protein S, antithrombin III, factor V mutation, factor II mutation, lupus anticoagulant, antiphospholipid antibodies, and homocysteine should be requested in young patients.
- Serial blood cultures should be done when infective endocarditis is suspected.

IMAGING STUDIES
- Chest x-ray to evaluate for cardiomegaly.
- CT scan must be performed in all patients with suspected TIA because it is very sensitive in detecting intracerebral hemorrhage or subdural hematoma, which can mimic TIA. Also, it can be performed quickly and is cheap and readily available.
- MRI of brain is more sensitive than CT scan in detecting small or early infarction. The infarction is sometimes shown despite the resolution of the symptoms within 24 hours, a fact that urged the stroke community to work on redefining TIA, which is currently in process.
- MR angiography is a noninvasive test, and is accurate for assessing the major extracranial and intracranial arteries, though it may overestimate the degree of stenosis.
- Transesophageal echocardiogram (TEE) is indicated in most patients with TIA. If the TTE is negative and a cardiac source is still suspected, the transesophageal echocardiogram (TEE) must be performed. TEE is also indicated in almost all young patients.
- TEE is more accurate than TTE in showing atrial and ventricular thrombi, vegetations, and left atrial enlargement, detecting shunt, and evaluating the proximal aorta.
- Angiography is the gold standard for an accurate assessment of both the extra- and intracranial vasculature. However, it is an invasive procedure and should be reserved for patients in whom noninvasive testing has not definitely shown the source of TIA, and to assess precisely the degree of stenosis.
- Ultrasound is a safe, portable, and less expensive. It includes transcranial Doppler to look for intracranial disease and carotid duplex to assess for extracranial carotid disease.

SPECIAL TESTS
ECG and cardiac monitoring to evaluate for arrhythmias.
Cerebrovascular Disease, Transient Ischemic Attack

Management

**GENERAL MEASURES**
Management of coexisting medical illnesses and secondary stroke prevention.

**SURGICAL MEASURES**
- Carotid endarterectomy (CEA) is indicated for significant (>50%) symptomatic carotid artery stenosis. For those patients who are considered high risk for surgery, carotid angioplasty with stent placement is performed in a few medical centers. Intracranial large artery (basilar, vertebral, middle cerebral, and internal carotid) angioplasty with or without stent placement is occasionally performed in a few academic centers for those patients who fail maximal medical therapy.
- Some cardiac lesions require surgical or radiologic interventions.

**SYMPTOMATIC TREATMENT**
This includes prophylaxis for deep vein thrombosis and judicious control of blood pressure with avoidance of excessive reduction in the acute setting and adequate control in the long run.

**ADJUNCTIVE TREATMENT**
None needed since symptoms resolve completely within 24 hours.

**ADMISSION/DISCHARGE CRITERIA**
In general any patient presenting with TIA, within 1 week from the onset of symptoms should be admitted to the hospital for the evaluation of etiology and appropriate stroke prevention measures.

**Medications**

**DRUG(S) OF CHOICE**
- Antiplatelet agents: indicated for stroke prevention in small vessel disease, intracranial large artery disease, mild (<50%) extracranial carotid artery disease, extracranial vertebral artery disease, aortic arch disease without mobile plaque, irregular nonstenotic valve surfaces, and in patients who are not coumadin candidates.
  - Aspirin: 50-325 mg qd
  - Plavix: 75 mg qd
  - Aggrenox: combination aspirin 25 mg/extended release dipyridamole 200 mg one tablet bid
- Anticoagulants
  - Warfarin (Coumadin): indicated in hypercoagulable states, cardiac sources like atrial fibrillation, intracardiac thrombi, and intracranial large artery stenosis.

**Contraindications**
- Aspirin/Aggrenox: mainly known allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer.
- Clopidogrel: mainly active systemic bleeding.
- Warfarin: mainly active bleeding, bleeding tendency, noncompliance, and gait difficulty with increased falling risk.

**Precautions**
- Clopidogrel: monitor for any TTP symptoms at the beginning of treatment.
- Warfarin: watch for compliance, bleeding events, and falling events.

**ALTERNATIVE DRUGS**
None

**Follow-Up**

**PATIENT MONITORING**
- Frequent follow-up visits are important to assess patients for recurrent ischemic events, compliance with treatment and recommendations, and adverse reactions from the treatment medications.
- Close monitoring of INR is crucial for the patients maintained on coumadin.

**EXPECTED COURSE AND PROGNOSIS**
- TIA is a precursor for a stroke or vascular death. The risk of stroke or death in untreated patients, after a TIA, is about 10% a year. The risk of stroke is highest within the first few weeks and month after the TIA. Appropriate secondary preventive measures significantly decrease the risk of stroke.

**Patient Education**

**Miscellaneous**

**SYNONYMS**
None

| ICD-9-CM | 435.9 Transcerebral ischemia NOS |

**SEE ALSO:** CEREBROVASCULAR DISEASE, ISCHEMIC INFARCT

**REFERENCES**
- Adams HP, Kassell NF, Mazuz H. The patient with transient ischemic attacks—is this the time for a new therapeutic approach? Stroke 1984;15:371-375.

Authors: Yousef Mohammad, MD, MSc; Umesh Sharma, MD
Cerebrovascular Disease, Venous Thrombosis

**Basics**

**DESCRIPTION**
Thrombosis of the cerebral veins and sinuses is an uncommon but important cause of stroke whose diagnosis is often missed or delayed.

**EPIDEMIOLOGY**

- **Incidence/Prevalence**: Unknown in the general population. The incidence in the peripartum period in India is 4.5 cases per 1,000 obstetric admissions compared to less than 1 in 3,000 in Western countries.
- **Age**: Can occur in any age group.
- **Sex**: It is more common in females.

**ETIOLOGY**
- Infections of the head and neck
- Pregnancy and puerperium
- Severe dehydration
- Hypercoagulable state
- Disseminated intravascular coagulation
- Sickle cell disease
- Polycythemia rubra vera
- Paroxysmal nocturnal hemoglobinuria
- Oral contraceptive pills
- r-asparaginase
- Nephrotic syndrome
- Liver disease
- Head trauma
- Intracranial operations
- Systemic lupus erythematosus
- Behcet's disease
- Sarcoidosis
- Wegener's granulomatosis
- Cancer
- Idiopathic

**PREGNANCY**
Pregnancy and the peripartum period are times of significantly higher risk for the development of cerebral venous thrombosis (CVT). Almost 50% of adult cases occur in this group.

**ASSOCIATED CONDITIONS**
Venous thrombosis of the pelvic and lower extremities veins.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Pseudotumor cerebri
- Arterial stroke
- Hemorrhagic stroke
- Migraine
- Preeclampsia
- Eclampsia
- Encephalitis
- Meningitis

**SIGNS AND SYMPTOMS**
CVT is associated with a wide range of signs and symptoms, depending on the specific cerebral venous structures involved. Common symptoms include:
- Headache
- Nausea
- Vomiting
- Focal neurologic deficit (weakness, sensory loss, visual changes, and aphasia)
- Focal or generalized seizures
- Altered conscious level
- Coma
- Papilledema
- Chemosis
- Proposis
- Painful ophthalmoplegia

**LABORATORY PROCEDURES**
All patients should have blood tests for CBC and platelet count, PT, PTT, and INR, renal and liver panels, hypercoagulable profile (including protein C, protein S, antithrombin III, factor V Leiden mutation, factor II, lupus anticoagulant, antiphospholipid antibodies and homocysteine), sedimentation rate, rheumatoid factor, and antinuclear antibodies. Blood cultures if infection is suspected.

**IMAGING STUDIES**
- CT scan of the brain might show hemorrhagic or ischemic changes. In some of the patients, contrast study demonstrates the empty delta sign, which is consistent with sagittal sinus thrombosis.
- MR imaging and MR venogram (MRV) help to define the anatomy of the cerebral venous system and have a better sensitivity to detect CVT.
- Conventional cerebral angiography is the gold standard to fully evaluate the venous anatomy and the clot burden.

**SPECIAL TESTS**
Lumbar puncture should be performed if meningitis is a consideration but should be deferred if the patient has mass effect on brain CT or MRI.
EEG should be obtained in patients with recurrent seizures or in coma.

**Management**

**GENERAL MEASURES**
General measures include acute supportive care and management of coexisting illnesses and underlying cause if established.

**SURGICAL MEASURES**
N/A

**SYMPTOMATIC TREATMENT**
Includes aggressive treatment of seizures and metabolic derangements, adequate hydration and nutrition, aspiration precautions, DVT prophylaxis, elevation of the head of the bed by 15 to 30 degrees; other measures to reduce intracranial pressure as dictated by the clinical situation. Use of antibiotics if infection is suspected. Discontinuation of oral contraceptive pills.

**ADJUNCTIVE TREATMENT**
Physical, occupational, speech, and cognitive therapy may be needed. Prenatal or postpartum care when appropriate for women who present with this condition.

**ADMISSION/DISCHARGE CRITERIA**
Any patient who presents with CVT should be admitted for treatment, evaluation, and management of the cause; early initiation of physical, occupational, and speech therapy; evaluation of eligibility for inpatient rehabilitation; assistance with appropriate placement; and patient and caregiver education.

**SPECIAL TESTS**
- Lumbar puncture should be performed if meningitis is a consideration but should be deferred if the patient has mass effect on brain CT or MRI. EEG should be obtained in patients with recurrent seizures or in coma.
  - Seen in cavernous sinus thrombosis.
**Medications**

**DRUGS OF CHOICE**

- Anticoagulants: though there was a history of controversy regarding its role, there is a strong evidence that anticoagulation can prevent further thrombus formation and larger venous infarction. Most authors recommend its use in the absence of radiologic evidence of significant hemorrhage. It should be used with extreme caution in patients with evidence of intracerebral hemorrhage because of the risk of further intracerebral bleeding.

After the use of heparin in the acute stage, oral anticoagulation with Coumadin is used for 3 to 6 months. Patients with an underlying hypercoagulable state might require prolonged period of coumadin intake.

- Thrombolytics: Limited data Local infusion of thrombolytics into the dural sinus thrombosis is reported to be effective and safe in small series. This should be reserved for rapidly declining patients despite anticoagulation.

**Contraindications**

Anticoagulants: significant intracerebral hemorrhage or significant active systemic bleeding.

**Precautions**

Warfarin: watch for compliance, bleeding events, and falling events.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

Frequent follow-up visits are important to assess patients for recurrence, control of the underlying etiology, compliance with treatment and recommendations, and adverse reactions from the medications.

Close monitoring of the INR is crucial for the patients who are maintained on warfarin.

**EXPECTED COURSE AND PROGNOSIS**

Mortality from CVT is estimated to be 6% to 30%. Poor outcome is expected in patients with involvement of the deep cerebral veins, coma, large intracerebral hemorrhage, and if sepsis is the underlying cause.

**PATIENT EDUCATION**


**Miscellaneous**

**SYNONYMS**

Venous thrombosis of the brain
Cerebral vein thrombosis

**ICD-9-CM:** 453.9 Venous thrombosis NOS

**SEE ALSO:** N/A

**REFERENCES**

- Benamer HT, Bone I. Cerebral venous thrombosis; anticoagulants or thrombolytic therapy? J Neurol Neurosurg Psychiatry 2000;69:427-430.

Author(s): Yousef Mohammad, MD, MSc, Bakri Elsheikh, MBBS, MRCP (UK)
DESCRIPTION

The evaluation of suspected cerebrovascular disease in the young patient should be undertaken in patients between the ages of 15 and 44 who present with the clinical presentation of ischemic stroke. While this age range is somewhat arbitrary, the consideration of ischemic stroke in the young patient suggests a specific diagnostic strategy, which includes the evaluation of those causes of stroke seen in the older population as well as additional etiologies found in young persons.

EPIDEMIOLOGY

Incidence/Prevalence

The incidence is 3 to 5 per 100,000 in the 15- to 44-year-old age group.

Race

Higher incidence of up to 20 per 100,000 has been reported in the African-American population.

Sex

Overall, males and females are affected equally; however, females have a higher incidence during the childbearing years. The relative risk for ischemic stroke is 0.7 during pregnancy and increases to 9.7 for the postpartum period.

ETIOLOGY

While some causes of ischemic stroke in the young are similar to causes of stroke in the elderly, the list of potential etiologies is longer and more consideration needs to be given to unusual causes of stroke. The specific etiology of stroke in the young remains unclear (cryptogenic) in up to 40% of patients even after extensive evaluation.

- Large artery atherosclerosis
  - Accelerated atherosclerosis may be associated with hyperlipidemia, elevated serum lipoprotein (a), or homocysteine levels
- Nonatherosclerotic large artery disease
  - Arterial dissection
  - Fibromuscular dysplasia
  - Angiitis associated with atherosclerotic disease: polyarteritis nodosa, Wegener's granulomatosis, systemic lupus erythematosus, giant cell arteritis, Takayasu's disease, or primary angiitis of the central nervous system
  - Moyamoya disease
  - Other infectious/immune vasculopathies: bacterial meningitis, syphilis, herpes zoster, fungal, tuberculosis, coccidioidomycosis, sarcoid

- Small vessel atherosclerosis
- Cardioembolism
  - Bacterial endocarditis
  - Atrial fibrillation
  - Intracardiac shunt (patent foramen ovale) with associated deep venous thrombosis
  - Left atrial thrombus or spontaneous echo contrast, intrapulmonary septic aneurysm
- Acute myocardial infarction
  - Prosthetic valve
  - Mitral stenosis
- Hypercoaguable states
  - Antiphospholipid antibody syndrome
  - Sickle cell disease
  - Thrombotic thrombocytopenic purpura
  - Disseminated intravascular coagulation
  - Polyarteritis vera, essential thrombocytosis, and other hypercoagulable states
- Other causes
  - Systemic infection/inflammation: cytomegalovirus, chlamydia, herpes simplex virus
  - Substance abuse: cocaine, amphetamines
  - Migraine headache
  - Pregnancy- and puerperium-related causes
  - Oral contraception

Genetics

Multiple genetic factors increase the risk of ischemic stroke, including those associated with hyperlipidemia, early-onset diabetes, and severe hypertension. Several hereditary disorders are specifically related to stroke in the young: sickle cell disease; neurofibromatosis (Moyamoya-like syndrome); cerebral autosomal-dominant arteriopathy with subcortical infaracts and leukoencephalopathy (CADASIL); mitochrondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS); epidermolysis bullosa dysplasia; Snderson's syndrome.

Risk Factors

- Atherosclerotic: family history of early cerebrovascular or cardiovascular disease, cigarette smoking, hypertension, hyperlipidemia, diabetes mellitus, elevated serum homocysteine levels, radiation therapy to neck
- Dissection: trauma, chiropractic manipulation
- Cardiogenic: intravenous drug use, valve replacement
- Hematologic: inherited or acquired hypercoaguable state, deep venous thrombosis, pregnancy

PREGNANCY

Pregnancy and the puerperium are associated with increased risk of stroke and suggest a specific differential diagnosis, depending on the time of presentation.

- Third trimester: cardiogenic embolus, venous infarction secondary to cerebral venous occlusive disease (CVOD), eclampsia
- Labor/delivery: amniotic, air or fat embolus
- Postpartum: same as labor/delivery, also cardiogenic embolus, CVOD, postpartum eclampsia, trophoblastic disease, or arterial occlusions.

ASSOCIATED CONDITIONS

As above.

DIAGNOSIS

Differential Diagnosis

As with ischemic stroke in the general population, may include intracerebral hemorrhage, subarachnoid hemorrhage, generalized/focal seizure with Todd's phenomenon, complicated migraine, conversion disorder.

SIGNS AND SYMPTOMS

Identical in clinical presentation to ischemic stroke in the general population, with focal neurologic signs and symptoms relating to the affected anatomy.

LABORATORY PROCEDURES

- Initial blood work: CBC with platelets, chemistry profile, sedimentation rate, fasting glucose, prothrombin time, partial thromboplastin time, lipid profile, fluorescent treponemal antibody, anticardiolipin antibodies, toxidology screen, pregnancy screen, serum homocysteine, and lipoprotein (a) levels. If infection is suspected, blood cultures and CSF analysis are warranted. African-American patients should have hemoglobin electrophoresis.
- Additional blood work: if etiology is elusive, evaluation should be expanded to include antithrombin III, protein C antigen and activity, protein S antigen and activity, D-dimer, fibrin split products, fibrinogen, other antiphospholipid antibodies, factor V Leiden mutation, prothrombin 20210 G–>A mutation, Russell viper venom time, and HIV screen.
Cerebrovascular Disease, Young Patient Evaluation for Ischemic Stroke

IMAGING STUDIES

- Brain imaging: noncontrast CT is performed initially to rule out acute hemorrhage. Otherwise, MRI with diffusion-weighted imaging is preferable.
- Vascular imaging: initial investigation should include noninvasive imaging with carotid and/or transcranial Doppler ultrasound. Magnetic resonance angiography can also be used. If the clinical suspicion of intracranial disease is high, or initial evaluation is inconclusive, cerebral angiography is warranted. Magnetic resonance venography should be used when CVOD is suspected.

SPECIAL TESTS

- Electrocardiogram
- Transesophageal echocardiogram (TEE) if infection is suspected or routine evaluation does not provide an etiology. Transesophageal with bubble contrast rather than transthoracic echocardiogram is preferred to increase the sensitivity and specificity for detecting an atrial septal defect, septal aneurysm, vegetation, or left atrial "smoke."

Management

GENERAL MEASURES

General management is identical to that of the general ischemic stroke patient.

SURGICAL MEASURES

Identical to those for the general ischemic stroke patient, e.g., carotid endarterectomy when appropriate.

SYMPTOMATIC TREATMENT

- Speech therapy
- Physical therapy

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Patients should be admitted for evaluation and treatment using the same criteria for the general ischemic stroke patient.

Follow-Up

PATIENT MONITORING

Acute ischemic stroke patients require frequent monitoring of vital signs and neurologic status and may require admission to an intensive care setting.

EXPECTED COURSE AND PROGNOSIS

Course and prognosis, including recurrence rates, vary widely depending on the underlying etiology of the stroke.

PATIENT EDUCATION

The importance of aggressive management of the modifiable stroke risk factors should be stressed, as well as the need for medical compliance. Patients and their families should begin the self-education process by contacting the American Stroke Association at 1-888-4STROKE or visiting www.strokeassociation.org.

Medications

DRUG(S) OF CHOICE

Overall, medications and indications/contraindications for the young stroke patient are identical to those used for the general stroke patient. However, many of the conditions associated with stroke in the young patient are reported to be more effectively treated with long-term anticoagulation with warfarin. These conditions include arterial dissection, hereditary and acquired hypercoagulable disorders, patent foramen ovale, and other atrial abnormalities discovered on TEE. Levels of evidence and resulting recommendations for anticoagulation for these conditions vary according to the condition.

ALTERNATIVE DRUGS

N/A

Miscellaneous

SYNONYMS

- Stroke in the young
- Young stroke

ICD-9-CM:
- 433.0 Occlusion and stenosis of precerebral arteries (with or without cerebral infarction);
- 434.0 Occlusion of cerebral arteries with or without cerebral infarction;
- 435.0 Transient cerebral ischemia;
- 436.0–437.9 Other and ill-defined cerebrovascular disease;
- 674.0 Cerebrovascular disorders occurring during pregnancy, childbirth, or the puerperium;
- 671.5 Cerebral venous thrombosis as a complication in pregnancy and the puerperium

SEE ALSO: THE OTHER CEREBROVASCULAR DISEASE TOPICS

REFERENCES


Author(s): Susan L. Hickenbottom, MD; Jeffrey S. Kitcher, MD
Cervical Stenosis/Spondylosis/Spondylotic Myelopathy

Basics

DESCRIPTION
Cervical spondylosis refers to intervertebral disc degeneration, disc space narrowing, and spur formation associated with age-related changes of the cervical spine. Cervical stenosis is the narrowing of the cervical spinal canal. Cervical spondylotic myelopathy (CSM) refers to the clinical presentation resulting from the degenerative processes leading to neural canal compromise and subsequent myelopathy. CSM is the most common cause of spinal cord dysfunction in adults over the age of 55.

EPIDEMIOLOGY
Incidence/Prevalence
Degenerative changes of cervical spine have been observed in up to 957 of asymptomatic individuals over 65 years old. Up to 20% of individuals with evidence of spondylosis are thought to progress to myelopathy.

Sex
There is no known racial or ethnic predilection.

Age
The disease process is associated with natural aging, and individuals over 65 years old have a higher rate of spondylosis, and therefore a higher rate of CSM.

Race
There is no known racial or ethnic predilection.

ETIOLOGY
The pathophysiologic hallmark is cord dysfunction brought on by a combination of mechanical compression and degenerative instability. With aging, the intervertebral disc degenerates and collapses, leading to spur formation. This process tends to begin at C5-6 and C6-7. There is a relative decrease in spinal motion at these levels with a concomitant increase in spinal motion at C3-4 and C4-5. At these higher levels, the resultant degeneration and motion leads to instability with antero- or retroolisthesis (subluxation of vertebral bodies of the normal cervical alignment). Therefore, at C5-6 and C6-7 the cord tends to be compressed from spur formation, and at C3-4 and C4-5 from listhesis. Anterior cord compression from degenerated discs and spurs is often accompanied by posterior compromise from ligamentum flavum hypertrophy. In addition to the static compressive forces, the cord is subject to further injury from repetitive dynamic injury during normal neck movements. These static and dynamic compressive forces on the cord lead to spinal cord injury and the clinical myelopathic syndrome.

Genetics
The disease is sporadic with no known genetic factors involved.

RISK FACTORS
Male sex, older age (>55), repetitive neck trauma, congenital narrowing of cervical canal (less than 12-mm diameter).

PREGNANCY
There is no additional risk with pregnancy.

Diagnosis
DIFFERENTIAL DIAGNOSIS
Alternative diagnoses should be considered in patients without risk factors (young, female, no history or cervical stenosis) or if there is findings on the exam that are inconsistent with CSM (e.g., cranial nerve palsy). However, many of the following present with similar clinical findings:

- Tumor
- Amyotrophic lateral sclerosis
- Syringomyelia
- Multiple sclerosis
- Transverse myelitis
- Herniated disc
- Ossified posterior longitudinal ligament
- Spinal arteriovenous malformation
- Subacute combined degeneration
- Neurosyphilis
- Rheumatoid arthritis with subluxation

SIGNS AND SYMPTOMS
- Initial symptoms may be subtle. Loss of hand dexterity, painless weakness of the upper extremities, and ambulatory difficulty may be present. There is often a history of progressive difficulty with the hands. Pain may or may not be a significant complaint. If pain is present, it is usually neck pain with or without some radicular component down the arm. Loss of fine motor control in the hands, such as difficulty with writing, buttoning, or painting, is a usual complaint. Walking difficulty is usually present but may initially be subtle.
- The exam usually shows bilateral (or initially unilateral) weakness of the hands and arms with varying degrees of lower extremity weakness. Long tract signs resembling an anterior cord syndrome may be present. Initially the strength may not be affected, but spastic quadripareis is seen as patients experience clinical progression. Disturbances of bowel and bladder are rarely caused by CSM, although these symptoms are common in the elderly. Hyperreflexia in all four extremities and pathologic reflexes such as bilateral Hoffmann’s, clonus, and even Babinski’s may be present.

LABORATORY PROCEDURES
No specific laboratory tests have been identified.

IMAGING STUDIES
MRI is the most useful diagnostic tool in evaluating cord compression, canal diameter, and most of the other causes of myelopathy. Plain x-ray films may demonstrate disc degeneration, loss of vertebral height, subluxation, and loss of lordotic curvature. CT with myelography is recommended in cases where MRI is contraindicated or unavailable.

SPECIAL TESTS
Electrophysiologic studies may be useful in confirming dysfunction at the root or cord level. A majority of patients with CSM have abnormal findings on EMG and nerve conduction velocity (NCV) testing. These studies also offer a useful method to follow the progression of CSM in the absence of obvious changes on MRI or the neurologic examination.

Management
GENERAL MEASURES
- Immobilization with a rigid neck brace: there is no well-recognized nonsurgical therapy for CSM other than this.
- Cervical traction under the supervision of a physician and physical therapist for severe pain (radiculopathy). This may have associated risks in patients with narrow cervical canal, and should be used with caution in patients with myelopathy.
- Ultrasound with electronic stimulation for severe neck/shoulder pain.
Cervical Stenosis/Spondylosis/Spondylotic Myelopathy

- Discriminate use of anti-inflammatory medication and analgesics.
- Avoidance of excessive neck motion and trauma

SURGICAL MEASURES
- Because patients with CSM may deteriorate, surgery to alleviate compression and instability has been the primary treatment of this condition. Laminctomy alone has been used extensively and is excellent at spinal cord decompression, but it does not address the dynamic forces in CSM. Its use is limited to lordotic spines, and there is associated risk of postoperative instability and late deterioration.
- Anteror discectomies and corpectomies combined with fusion and fixation can be performed on kyphotic spines and address the compressive and dynamic forces leading to CSM. However, they can be associated with high morbidity and complications, especially when deployed over a long segment (three or more vertebral. Levels). Laminoplasty had been performed in different fashions to decompress the cord and minimize postoperative instability. Recent studies of laminectomy with fusion appear to have promising results and low morbidity in straight or lordotic cervical spines. A lordotic spine can be treated with a decompressive laminectomy alone in a patient with advanced age (>75 years).

SYMPTOMATIC TREATMENT
Refer to general measures.

ADJUNCTIVE TREATMENT
Body mechanics emphasizing optimal posture (easier with rigid collar) with avoidance of neck twisting and excessive flexion and extension are recommended. Rest, isotonic exercise, and application of ice or heat for symptomatic relief can be prescribed.

ADMISSION/DISCHARGE CRITERIA
Patients with new neurologic deficit, progressive myelopathy, new gait or bowel/bladder disturbance, or uncontrollable pain should be admitted for serial evaluations. Significant neck trauma in a patient with known CSM also warrants an evaluation.

Medications

DRUG(S) OF CHOICE
- NSAIDs: must be used with caution in patients over 65 years of age and in patients with history of gastrointestinal problems or renal insufficiency.

- Oral steroids: very short course (a few days) only, and must consider the additional risk imposed by steroid use in patients with diabetes mellitus or uncontrolled patients, or those with history of infection. This seems to be effective only in the treatment of radiculopathic pain. Steroids may exacerbate NSAIDs’ gastrointestinal side effects and should not be routinely used in conjunction with other antinflammatory medications.
- Muscle relaxants: no benefit seen for use longer than 3 weeks.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
- Frequent evaluation of patients with overt myelopathy is recommended due to its probability of deterioration. All patients should undergo complete radiologic evaluation. In the most severe cases, MRI will reveal evidence of cord injury. After serial examinations depicting a stable neurologic status, the frequency of clinical monitoring may be gradually decreased. All patients with CSM should undergo a neurosurgical evaluation for consideration of surgical intervention.
- Patients who opt for nonsurgical therapy should be followed by periodic MRIs to evaluate the extent of spinal cord deformation and spinal alignment. Patients with clear CSM who do not undergo surgery should wear a cervical collar at all times to minimize further injury associated with normal motion.

EXPECTED COURSE AND PROGNOSIS
The natural history of CSM is difficult to elucidate, because early in its presentation combined patients with cervical stenosis, cervical spondylosis, and CSM. Up to 75% of patients with myelopathy show episodic deterioration; 20% are thought to show steady deterioration. Spontaneous, rapid progression is seen in only 5% of patients. Useful indicators of poor prognosis are duration of symptoms, severity of myelopathy, presence of high-intensity cord lesion on MRI, and multilevel compression. These patients should be strongly considered for surgery.

PATIENT EDUCATION
The Congress of Neurological Surgeons has ample educational material on this subject on the Web at Neurosurgery-On-Call (www.neurosurgery.org). The Cervical Spine Research Society provides useful educational material as well as in depth research on the pathophysiology and management of CSM (www.csrs.org).

Miscellaneous

SYNONYMS
Refer to basic descriptions.

ICD-9-CM: Stenosis: 724.00 Spinal—unspecified region; 723.0 Cervical. Disc: 722.71 Cervical—with myelopathy; 722.70 Replacement—with myelopathy (unspecified site); 722.0 Cervical—without myelopathy

SEE ALSO: N/A

REFERENCES

Author(s): Amir Vokshoor, MD; Gary L. Rea, MD, PhD

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Cervical Trauma

**Basics**

**DESCRIPTION**
Cervical trauma constitutes the broad spectrum of soft tissue, bony, and spinal cord injury (SCI) involving the cervical spine. Cervical trauma includes:

- Musculotendinous injuries: strain/sprain
- Bony injuries: flexion-extension/vertical compression/distraction flexion/distraction extension/lateral flexion injuries
- Spinal cord injury without radiologic abnormality (SCIWORA)
- Transient cervical cord injury—central cord syndrome

**EPIDEMIOLOGY**
Incidence/Prevalence
Incidence of SCI is 10,000 cases per year in the United States. Cervical spine injuries constitute 50% of all SCI, i.e., the incidence of cervical SCI is 5,000 cases per year. Midcervical spine—levels C4 to C6—are the most commonly involved levels.

Age
Young adults (less than age 40) are most commonly affected.

Sex
Males (80%) are more commonly affected than females.

**ETIOLOGY**
- Motor vehicular injuries are the most common cause.
- Sports injuries, e.g., horseback riding, gymnastics, diving injuries
- Falls
- Penetrating spinal injuries—missile (gunshot) or nonmissile (stabbing) injuries constitute 12% of all traumatic SCIs.
- Industrial and domestic injuries

**GENETICS**
See Risk Factors.

**RISK FACTORS**
Patients with osteoporosis or ankylosing spondylitis are at high risk of spinal fractures even with minor trauma. Patients with preexisting spinal stenosis (congenital or acquired) are at increased risk of neurologic deficits with minor trauma. Children younger than 10 years of age are at risk of SCIWORA, although recent use of high-field MRI has shown soft tissue injury in many cases previously thought to be SCIWORA.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Polytrauma with head injuries.
- Missed lesions are common: (a) intoxicated or comatose patients; (b) multilevel noncontiguous spinal injuries; (c) upper cervical injuries (e.g., odontoid fractures) where neurologic deficits are frequently absent.

**SIGNS AND SYMPTOMS**
- Pain: neck pain, radicular arm pain, occipital headache
- Neurologic deficits due to SCI, which can be complete or incomplete
- Complete injury: no motor or sensory function below the level of injury
- Incomplete injury: partial preservation of motor or sensory function below the level of injury
  - Central cord syndrome: upper extremity more than lower extremity weakness, with sacral sparing
  - Anterior cord syndrome: motor paralysis, hypesthesia, loss of pain and temperature, preservation of posterior columns (position, proprioception, and vibration)
  - Brown-Saunders syndrome: ipsilateral loss of motor function and posterior column sensation, contralateral loss of pain and temperature sensation
- Mixed syndromes: combination of the above syndromes
- Spinal shock may be seen immediately after injury. Total loss of neurologic function (sensory, motor, reflexes) plus hypotension without tachycardia.
- Persisting hypotension and bradycardia after cervical SCI indicate a poor prognosis.
- High cervical spine injuries (at or above C4) often present with respiratory insufficiency due to phrenic nerve involvement.
- Neurologic status is often assessed by Frankel grading or the American Spinal Injury Association (ASIA) scale.
- Frankel grading:
  - Type A—no motor or sensory function below the injury level
  - Type B—sensory preservation without motor function
  - Type C—motor function useless
  - Type D—motor function useful
  - Type E—normal motor and sensory function

- ASIA scale:
  - Total motor score (normal = 100). Strength is graded from 0 to 5 in (a) five upper extremity muscles (biceps, brachioradialis, extensors, wrist extensors, finger flexors, finger extensors of middle phalanx, finger abductors of the little finger), and (b) five lower extremity muscle groups (hip flexors, knee extensors, ankle dorsiflexors and plantar flexors, long toe extensors) bilaterally.
  - Total sensory score (normal = 224). Sensation (pain + light touch) is graded from 0 to 2 (0 = absent, 1 = impaired, 2 = normal) by testing 28 dermatomes (C2 to S5) bilaterally.
  - The ASIA score more accurately predicts neurologic recovery than Frankel grading.
- Ascending neurologic deficits can occur a few days after injury, likely due to vascular compromise.
- Autonomic dysreflexia may result in headache, sweating, nasal congestion, etc.

**LABORATORY PROCEDURES**
N/A

**IMAGING STUDIES**
- Plain radiographs may show an increase in prevertebral soft tissue (normal soft tissue less than 5 mm at C2 to C4, and up to 15 mm at C4 to C7). Dynamic radiographs (flexion and extension) can identify instability due to ligamentous injuries. Open-moth view and swimmer’s view are important to evaluate odontoid fractures and the cervicothoracic junction, respectively.
- CT often detects fractures not evident on plain radiographs or MRI. It can delineate the fracture geometry and the extent of spinal canal encroachment. CT with coronal and sagittal reconstructions is recommended to rule out cervical spine injuries in all unconscious trauma patients. It is useful in the evaluation of penetrating spinal injuries due to gunshot wounds (the metallic bullet fragments prevent evaluation by MRI).
- MRI is the imaging modality of choice for direct SCI and cord compression. It can detect soft tissue and ligamentous injuries as well as traumatic disc lesions. Because it can differentiate cord edema from cord contusion, it can provide prognostic information. Dynamic MRI may demonstrate instability due to ligamentous injuries (e.g., atlantoaxial dislocations).

**SPECIAL TESTS**
Neuromuscular testing—somatosensory evoked potential recording (SSEP)—can be of prognostic value after SCI.
Management

GENERAL MEASURES
As in all trauma cases, assessment of patient’s airway, breathing, and circulation are the initial priority. All comatose and polytrauma patients should be considered to have a cervical spine injury until ruled out by radiologic evaluation, and kept in cervical immobilization (backboard, hard cervical collar). In-line emergency intubation or tracheostomy should be performed if the patient presents with respiratory distress. Cervical SCI is often complicated by hypotension and bradycardia due to sympathetic insufficiency. Maintenance of normotension and normal blood pressure is essential to avoid worsening of SCI. Soft tissue injuries can be managed with rest, cervical collar, physical therapy, analgesics, and muscle relaxants.

SURGICAL MEASURES
Surgery is clearly indicated in the presence of spinal cord compression, spinal instability, neurologic deficits (especially incomplete SCI), and certain cases of penetrating SCI. The goals of surgery include (a) correction of deformity and restoration of normal spinal alignment, (b) decompression of spinal cord and nerve roots, and (c) rigid internal fixation for early mobilization and rehabilitation with minimal orthotic supports. Though the timing of surgery is controversial, early surgery may afford greater neurologic recovery. Halo fixation may be an alternative to surgical stabilization, especially in upper cervical spine injuries and high-risk surgical patients, or as an adjunct to surgery where the strength of the internal stabilization is questionable in the early healing period.

SYMPTOMATIC TREATMENT
Pain control by nonsteroidal anti-inflammatory drugs, narcotics, and/or muscle relaxants is often required.

ADJUNCTIVE TREATMENT
Cervical traction may reduce dislocations, restore normal alignment, and stabilize the spine. In the presence of respiratory insufficiency, ventilatory support by endotracheal intubation or tracheostomy is mandatory. Patients with permanent respiratory insufficiency can be treated by phrenic nerve pacemaker implantation or domiciliary mechanical ventilatory support. Patients with SCI benefit from comprehensive multidisciplinary rehabilitation. This is best achieved in a SCI unit. Patients with SCI require appropriate bladder, bowel, and skin care. Psychological counseling and support are essential to make necessary mental adjustments to the residual disability.

ADMISSION/DISCHARGE CRITERIA
Admission should be considered in all patients with severe neck pain, neurodeficits, and severe trauma with suspected spinal instability. It is imperative to rule out unequivocally any cervical spine injury before discharge.

MEDICATIONS

DRUG(S) OF CHOICE
Methylprednisolone has been shown to be of some benefit in improving neurologic outcome when given within 8 hours after SCI. It is given as an intravenous bolus of 30 mg/kg followed by 5.4 mg/kg/h for 23 hours when begun within 3 hours (or for 48 hours when begun 3 to 8 hours) after SCI.

CONTRAINDICATIONS
Known history of gastrointestinal bleeding.

PRECAUTIONS
History of peptic ulcer/immunosuppression.

ALTERNATIVE DRUGS
There is evidence suggesting that antioxidants (e.g., trilazad mesylate, ganglioside) may be of some benefit in improving neurologic outcome after SCI in human studies.

Follow-Up

PATIENT MONITORING
Follow-up neurologic assessment with the ASIA scale provides objective evidence of neurologic improvement. Radiologic assessment is required for evaluation of fusion progression and to rule out delayed spinal deformity, instability, or a posttraumatic syrinx. Delayed neurologic deterioration should prompt an MRI of the cervical spine to rule out a posttraumatic syrinx—a treatable cause of delayed neurologic deterioration (e.g., by syringosubarachnoid or syringoperitonealshunting).

EXPECTED COURSE AND PROGNOSIS
Neck pain usually resolves, or decreases significantly, in the initial weeks to months postinjury. Patients with complete SCI usually remain complete except for one or two cervical root level recovery. Incomplete cord injuries (especially Brown-Souza or central cord syndromes) may show significant recovery, especially with surgical decompression of the cord. Patients with penetrating wounds usually experience limited recovery, unless the spinal canal has not been violated (e.g., ricochet gunshot injury).

PATIENT EDUCATION
Patients with SCI and their families require education and psychological support to facilitate rehabilitation and for reintegration into the social environment.

• National Spinal Cord Injury Association
  8701 Georgia Avenue-Suite 500
  Silver Spring, MD 20910
  1-800-962-9629
  www.spinalcord.org
• Paralyzed Veterans of America
  801 18th Street NW
  Washington, DC 20006
  1-800-424-8200
  www.pva.org

Miscellaneous

SYNONYMS
Cervical spine injuries
Cervical spinal cord injuries
ICD-9-CM: 805.00 Cervical fracture; 847.0 Cervical strain
SEE ALSO: NA

REFERENCES

Author(s): Raja S. V. Balabhadrá, MD; Russell J. Andrews, MD
DESCRIPTION

Chiari malformations consist of four congenital hindbrain malformations, probably mechanistically unrelated to each other. These malformations can involve only the menenchymal elements of the posterior fossa (bone, dura, muscle, and skin) or include the cerebellum and brainstem. Patients with Chiari malformation can exhibit symptoms of headache, fatigue, cerebellar or brainstem dysfunction, and sometimes hydrocephalus and syringomyelia depending on the type. The vast majority of Chiari malformations are types I or II, and only a small subset of cases represent the other Chiari types.

- Chiari type I: abnormal development of the posterior fossa resulting in ectopic descent of the cerebellar tonsils and medial inferior cerebellar lobes into the upper cervical spinal canal. The basis for diagnosis is dependent on evaluation of the posterior fossa and identification of the foramen magnum. Chiari I malformations are the cause of approximately 70% of all syringomyelia.
- Chiari type II: an anomaly of the hindbrain, possibly a failure of pontine flexure during embryogenesis, resulting in elongation of the fourth ventricle. Type II has type I features, along with displacement of the inferior vermis, and caudal displacement of the pons and medulla. These patients also have an elongated fourth ventricle and often an associated lumbar meningocele.
- Chiari type III: the suggested mechanism for type III is defective closure of the roof plate resulting in displacement of the entire cerebellum and medulla into an infratentorial meningoencephalocele. This is usually incompatible with life.
- Chiari type IV: complete cerebellar hypoplasia is referred to as type IV Chiari, also known as Dandy-Walker malformation. This type consists of a cystic expansion of the fourth ventricle in the posterior fossa, due to a developmental failure of the 4th ventricle roof.

RISK FACTORS

Myelomeningocele has been associated with folic acid deficiency during early pregnancy. Chiari type II is commonly associated with myelomeningocele.

PREGNANCY

Patients with headache associated with Chiari malformations may experience more headache during the active stage of labor. Otherwise, there are no major issues related to pregnancy and Chiari malformations.

ASSOCIATED CONDITIONS

- Chiari type I is associated with syringomyelia.
- Chiari type II is associated with myelomeningocele.
- Chiari type IV is associated with hydrocephalus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

A variety of chronic conditions affecting the cerebellum, brainstem, and foramen magnum region may mimic the findings of Chiari malformations. Cerebellar degenerations or mass lesions may cause slowly progressive ataxia with gait disorder. Brainstem gliomas and other brainstem tumors may present with nystagmus, vertigo, ataxia, and headache. Mass lesions at the foramen magnum may cause downbeat nystagmus with or without weakness, spasticity, and headache.

SIGNS AND SYMPTOMS

- Chiari type I: the most common initial presenting symptoms are headaches, gradual dysphasia, cervical pain, vertigo, weakness, paresthesias and ataxia. Symptoms of Chiari type I are divided into early and late symptoms. Early symptoms consist of headache, fatigue, vertigo, intermittent nausea, dyspha gia, and tinnitus. Headache may occur with exercise or coughing. Late symptoms are generally associated with syringomyelia, and consist of a dissociated sensory examination with acape-like distribution of hypesthesia over the shoulders and upper back. In addition, patients can become myelopathic, with prominent upper extremity dysfunction. Signs may include ataxia, spastic quadriparesis, syringomyelic signs, and downbeating nystagmus. Lower cranial nerve palsies are often seen (absent gag, tongue wasting, etc.).
- Chiari type II: patients are usually diagnosed in early childhood along with the diagnosis of myelomeningocele. Symptoms of Chiari type II can be mild or severe, and can include head lag, apnea, respiratory distress, stridor, and dysphagia. Patients may develop progressive hydrocephalus.
- Chiari type III: these malformations are usually incompatible with life.
- Chiari type IV: patients with Dandy-Walker syndrome can present with headaches and symptoms of raised intracranial pressure due to hydrocephalus. Chiari type I patients present in late childhood to early adulthood and commonly have multiple and variable clinical manifestations. This often results in delay or incorrect diagnosis until imaging is obtained. The systems involved include, but are not limited to, the lower brainstem, lower cranial nerves, and the otologic, cerebellar, sensory, and motor systems. Chiari type II patients present as neonates and infants. When symptomatic, these patients most often have an associated myelomeningocele and exhibit signs of neurogenic dysphagia, stridor, apneic spells and opisthotonia. Chiari III patients present as neonates on the basis of their meningocele/ocele. Chiari IV patients often present with symptoms of hydrocephalus. Most patients with this type of Chiari malformation have normal development and normal intelligence.

No specific laboratory studies are helpful in the diagnosis and treatment of the Chiari malformations.

IMAGING STUDIES

- Chiari type I: MRI is used to diagnose Chiari type I. The hallmark imaging finding is pointed cerebellar tonsils that lie greater than 5 mm below the foramen magnum.
- Chiari type II: MRI is the imaging study of choice and will show displacement of the inferior vermis and caudal displacement of the pons and medulla causing descent of the cerebellar tonsils below the foramen magnum. These patients also have an elongated fourth ventricle and may have other abnormalities of the hindbrain and brainstem including beaked tectum, absence of the septum pellucidum, poorly myelinated cerebellar folia, hydrocephalus, heterotopias, hypoplasia of falx, microgyria, and degeneration of lower cranial nerve nuclei.
- Chiari III: MRI imaging shows a high cervical or occipitocervical meningocele with cerebellar herniation.
- Chiari IV: MRI imaging classically shows hypoplasia or absence of the cerebellar vermis, extension of the fourth ventricle into the posterior fossa, and cerebellar hypoplasia.

EPIDEMIOLOGY

- Chiari I: average age at presentation is 41 years, with a slight female predilection.
- Chiari II: most common serious malformation of the posterior fossa, with a frequency of approximately 1 case per 1,000 population in the United States.
- Chiari III and IV: very rare.

ETIOLOGY

Chiari malformations are congenital anomalies of the hindbrain and associated tissues.
Management

GENERAL MEASURES
N/A

SURGICAL MEASURES
Surgery is the only treatment for symptomatic Chiari type I malformations. Surgical therapy is usually reserved for progressive and debilitating symptoms. The surgery involves a craniectomy to remove the suboccipital bone and foramen magnum along with an upper cervical laminectomy of C1, C2, and sometimes C3. The decompression is further augmented by a duraplasty, which is patched using a dural substitute. If there is an associated syrinx, serial MRIs are used to assess the progression of syringomyelia. In most cases, an adequate posterior fossa decompression will halt the progression of syringomyelia. If the syrinx persists and becomes more symptomatic, a syringosubarachnoid shunt may be placed.

For Chiari type II, correction of associated malformations is performed first, with the closure of a myelomeningocele and ventriculoperitoneal shunting if hydrocephalus is present. Surgical therapy for type II Chiari malformations is reserved for patients with critical warning signs of neurogenic dysphagia, stridor, and apnea. The operative results for posterior fossa decompression in type II Chiari malformation are poor, partly due to inherent uncorrectable brainstem and cerebellar abnormalities.

Chiari IV patients who develop hydrocephalus must be treated with conventional ventricular shunting procedures. Often, there is little communication of the lateral ventricular system with the Dandy Walker cyst. In these patients, it may be necessary to place a shunt to decompress the posterior fossa cyst as well.

SYMPTOMATIC TREATMENT
Headache may be treated in a similar fashion to migraine. Beta-blockers, tricyclic antidepressants, or nonsteroidal anti-inflammatory medications may be useful in therapy for headache related to Chiari I malformations.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
Patients usually require admission for surgery, often on the day of surgery. Discharge depends on postoperative status and course in hospital.

Follow-Up

PATIENT MONITORING
Patients with Chiari type I and associated syringomyelia must be monitored on a yearly basis for progression of the syrinx. For Chiari type II patients, close follow-up by a pediatric neurologist is critical in identifying progressive symptoms and the need for operative or reoperative therapy.

EXPECTED COURSE AND PROGNOSIS
Surgical management may stabilize progressive symptoms of Chiari I malformation, and improve headache symptoms. Patients may continue to have neurologic symptoms of gait disorders and dysphagia depending on the extent of prior injury.

PATIENT EDUCATION
Patients should be made aware of the congenital nature of these abnormalities, the usual symptoms, the potential for progression, and the options for treatment. They should inform their doctor about any progression of symptoms.

Medications

DRUG(S) OF CHOICE
N/A

ALTERNATIVE DRUGS
N/A

Miscellaneous

SYNONYMS
Arnold-Chiari malformation
ICD-9-CM: 348.4 Chiari type 1; 741.0 Chiari type 2; 742.0 Chiari type 3; 742.2 Chiari type 4

SEE ALSO: SYRINGOMYELIA

REFERENCES

Author(s) R. Mark Li, MD
Chorea

**Basics**

**DESCRIPTION**
Chorea is a hyperkinetic movement disturbance typically characterized by rapid, non-stereotyped, semipurposel movements that flow from one body part to another. Clinical manifestations exist along a wide spectrum.

**EPIDEMIOLOGY**
Incidence and prevalence is variable, depending on etiology.

**ETIOLOGY**
- The etiologies of chorea number well over 100.
- A classification of potential etiologies of chorea:
  - As a distinct neurologic entity, e.g., benign hereditary chorea, senile chorea
  - As a feature of an inherited neurologic disease, e.g., Huntington's disease (HD)
  - As a sign/symptom of underlying neurologic disease, systemic disease, or insult to the nervous system
- See Associated Conditions, below, for further description of these etiologies.

**RISK FACTORS**
- Family history of chorea, progressive neurologic condition, or other movement disorder.
- Some medications or drug use; see Associated Conditions, below.

**PREGNANCY**
Chorea can occur during pregnancy, i.e., chorea gravidarum (CG), and typically resolves following delivery. However, the occurrence of CG may be the initial manifestation of systemic lupus erythematosus, HD, and the antiphospholipid antibody syndrome.

**ASSOCIATED CONDITIONS**
Distinct Neurologic Entities
- Benign hereditary chorea: characterized by the onset of chorea in childhood, which is nonprogressive through adult life, with no impairment of cognition; demonstrates autosomal-dominant inheritance. HD should be excluded if any suspicion exists.
- Senile chorea: chorea appearing in late life with heightened, psychiatric disturbance, or a family history of chorea and no other identifiable cause. HD should be excluded if any suspicion exists.

**Inherited Neurologic Disorders**
- Autosomal dominant
  - HD: a neurodegenerative disease characterized by onset of chorea in mid-adulthood, followed by dementia and psychiatric disturbances. The genetic basis is an expansion of unstable stretch of CAG trinucleotide repeats in the Huntington gene on chromosome 4p. See chapter on Huntington's Disease.
  - Dentatorubropallidoluysian atrophy (DRPLA): a rare neurodegenerative disease most prevalent in Japan. Like HD, it is also a trinucleotide repeat disorder; an expansion of unstable CAG trinucleotide repeats occurs in the "atrophin" gene on chromosome 12p to give rise to a variable phenotype that has been categorized into three types: (a) an ataxo-choreoathetoid type, (b) a pseudo-Huntington type, and (c) a myoclonic-epileptic type.
- Autosomal recessive
  - Wilson's disease (WD): the underlying defect is impaired biliary excretion of copper due to a defect in the WD gene.
  - W-placeholder on chromosome 13q, which encodes a copper transporting adenosine triphosphatase (ATPase). The resulting copper toxicity results in the deposition of copper initially in the liver and then the CNS. Neurologic manifestations are varied, often resulting in a movement disorder.
  - Tremor is the most common, though chorea, dystonia, tics, myoclonus, parkinsonism, and ataxia are not infrequent.
  - Neurologic syndromes associated with acanthocytes: there are three such syndromes, the latter of which is X-linked recessive — Bassen-Kornzweig syndrome: Abetalipoproteinemia, very low cholesterol (<1.5 mmol/L) and triglycerides (<0.1 mmol/L). Clinically, these patients present with a progressive spinocerebellar syndrome, pigmentary retinopathy, and areflexia. Involuntary movements are typically not part of the clinical picture, although severe position sense loss can result in pseudoathetosis. There is absent apolipoprotein B with resultant fat malabsorption, including the fat-soluble vitamins; it is the absence of vitamin E that is responsible for the clinical features and are reversible with vitamin E supplementation.
  - Chorea-acanthocytosis: normal lipoprotein study in association with acanthocytosis.
  - Clinical features consist of chorea, orofacial dyskinesias with tongue and lip biting, motor tics, peripheral neuropathy, amyotrophy, and vocalizations.

**Other Causes of Chorea**
- Medications:
  - Dopamine receptor blockers — antipsychotics, antiemetics
- Levodopa
- Anticonvulsants — valproic acid
- Stimulants — amphetamines
- Lithium
- Oral contraceptives
- Metabolic disturbances
  - Abnormalities in glucose, sodium, calcium, or magnesium
- Hematologic disturbances
  - Polycythemia vera
- Structural lesions
  - Vascular — infarction, hemorrhage, subdural hematoma
  - Neoplastic — or metastatic lesions
  - Congenital — cerebellar palsy
- Endocrine disturbances
  - Hyperthyroidism
  - Hypoparathyroidism
  - Hyperparathyroidism
- Immunologic conditions
  - Systemic lupus erythematosus (SE)
  - Sydenham's chorea
  - Antiphospholipid antibody syndrome (APAS)
  - Multiple sclerosis
- In infants and children:
  - Kernicterus
  - Lesch-Nyhan syndrome
  - Post-pump chorea following cardiac bypass surgery for congenital heart disease

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
Other Hyperkinetic Movement Disorders
- Tics — rapid, nonrhythmic movements or sounds that are suppressible for a short time
- Myoclonus — random, irregular movements caused by rapid muscle contractions
- Dystonia — characterized by sustained muscle contractions, resulting in twisting, repetitive, and patterned movements, or abnormal postures
- Tremor — regular, rhythmic movement
Chorea

SIGNS AND SYMPTOMS
The clinical manifestations of chorea exist along a wide spectrum. In its mildest expression, the patient may simply appear to be fidgety or restless; in its most extreme fashion, chorea can exist as large amplitude flinging movements of the proximal extremities, i.e., ballistic movements. Chorea may be present with other neurologic findings, in particular athetosis, which can be thought of as a slow form of chorea and consists of slow writhing movements. Dystonia may occur also.

LABORATORY PROCEDURES
• Serum and urine for drug/medication screen
• Serum glucose, sodium, calcium, phosphate, magnesium
• CBC and smear for acanthocytes
• Lipid profile (including lipoproteins)
• Endocrine studies: thyroid function studies; PTH level
• For suspected WD: serum total and free copper; ceruloplasmin level; 24-hour urine collection for copper
• For suspected SE: ANA, anti-DNA antibodies, anti-Smith antibodies
• For suspected sotid E: anti-La, anti-JO, anti-Scl-70, anti-Sm, anti-U1-RNP, anti-Ro/SS-A, anti-La/SS-B, anti-PM/Scl, anti-SS-A/Ro, anticardiolipin antibody

IMAGING STUDIES
Brain MRI: caudate atrophy in HD; focal stratal lesions; multiple sclerosis

SPECIAL TESTS
• Genetic testing for suspected HD and DRPLA; both are CAG repeat expansion disorders
• Silt-lamp examination for Kayser-Fleischer rings
• CSF exam and evoked potentials for suspected multiple sclerosis

DRUG(S) OF CHOICE
Dopamine-Receptor Antagonists—Antipsychotic Medications
• Mechanism: the high-potency antipsychotic medications have strong affinity for blockade of the D2 dopamine receptor; these include haloperidol, piphenazine, perphenazine, trifluoperazine, and pimozide.
• Dose: initially with a small nightly dose (0.5-2 mg) titrate as needed for symptom control.
• Adverse effects: extrapyramidal side effects—akathisia.
• Precautions: an ECG should be obtained prior to the use of pimozide; pimozide slows cardiac conduction and can result in arrhythmias (heart block, torsades de pointes ventricular tachycardia).

ALTERNATIVE DRUGS
Tetraabenazine
Tetraabenazine is not approved by the FDA; available only as an investigational drug in the U.S.
• Mechanism: reversible depletion of presynaptic monoamines and postsynaptic dopamine receptor antagonist.
• Dose: 12.5-200 mg/d
• Only rarely associated with acute dystonic reaction; tardive dyskinesia has not been seen.

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
N/A

EXPECTED COURSE AND PROGNOSIS
• Dependent on etiology:
  — BHC and senile chorea—benign course, life span is not threatened
  — Inherited neurologic disorders—typically a more malignant disease course with shortened life span
  — Chorea secondary to medications may be transient or persistent
  — Chorea can recur in Sydenham’s chorea, SE, and APAS

PATIENT MONITORING
N/A

PATIENT EDUCATION
www.wemove.org: A comprehensive resource for movement disorder information.

SYNONYMS
Huntington’s chorea/Huntington’s disease
Sydenham’s chorea/rheumatic chorea/St. Vitus’ dance
ICD-9-CM: 333.5 Chorea/choreoathetosis; 392.9 Sydenham’s chorea; 333.4 Huntington’s disease/hereditary/chronic

SEE ALSO: HUNTINGTON’S DISEASE, WILSON’S DISEASE, SYSTEMIC LUPUS ERYTHEMATOSUS, SYDENHAM CHOREA, ANTIPHOSPHOLIPID ANTIBODY SYNDROME

REFERENCES

Author(s): Paul G. Wasielewski, MD
Chronic Inflammatory Demyelinating Polyneuropathy

Basics

DESCRIPTION
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired disorder of the peripheral nervous system with a chronic, subacute, or relapsing course.

EPIDEMIOLOGY
Incidence/Prevalence
CIDP has a prevalence of 1—2 per 100,000.

Age
Maximum occurrence is in 70- to 79-year-olds. The mean age of onset of 48. CIDP may occur in children.

Sex
The male/female ratio is 1.3:1.

ETIOLOGY
CIDP is an autoimmune demyelinating low-grade inflammatory polyneuropathy, but its triggers are unknown. Unlike its acute cousin, Guillain-Barre syndrome (GBS, acute inflammatory demyelinating polyneuropathy), it generally does not follow a flu-like illness or vaccination. While the primary pathologic change in CIDP is that of segmental and paranodal demyelination, loss of axons may also occur. Repeated bouts of denarylation and remyelination may lead to the formation of concentric whorls of Schwann cells and fibroblasts surrounding fibers, resulting in structures known as "onion bulbs." CIDP patients may have autoantibodies to protein zero (P0), a peripheral myelin protein.

RISK FACTORS
None known.

PREGNANCY
CIDP may have onset or worsen during pregnancy or postpartum.

ASSOCIATED CONDITIONS
CIDP has been associated with benign monoclonal gammopathy. Monoclonal immunoglobulin M (IgM) K subtype, associated with an autoantibody directed to myelin-associated glycoprotein (anti-MAG), has more prominent distal motor fiber demyelination (very prolonged distal motor latencies on nerve conduction studies) and inappropriate separation and widening of the spaces between myelin spaces (widened myelin lamellae) with abnormal deposition of the monoclonal protein in these widened spaces. There are sporadic reports of CIDP-like polyneuropathies associated with malignancy with and without gammopathy. Overall, uncommon associations with CIDP are Charcot-Marie-Tooth disease, lymphoma, melanoma, carcinoma, diabetes mellitus, collagen vascular disease, thyrotoxicosis, chronic hepatitis, inflammatory bowel disease, HIV infection, hepatic transplantation, glomerulonephritis, alopecia universalis, and the medication procainamide.

Diagnosis

DIFFERENTIAL DIAGNOSIS
In examining patients with prominent upper limb weakness, the clinician should consider motor neuron disease, multifocal motor neuropathy, hand wasting from a high cervical myelopathy, cervical radiculopathy, paraneoplastic motor and sensory polyneuropathy, plexopathy from infiltrative tumor or radiation, and others. Some polyneuropathies that do not fulfill CIDP criteria may be milder versions of CIDP, while others are axonal polyneuropathies with a remyelinating demyelinating change. In diabetes, for example, there may be segmental demyelination especially at sites of entrapment, but sensory loss is more prominent than the motor weakness of CIDP. Hereditary neuropathy with sensitivity to pressure palsy (HNPP) is an autosomal-dominant inherited deletion of the peripheral nerve myelin protein gene. HNPP is a generalized polyneuropathy with focal demyelination at sites of entrapment and it may sometimes resemble CIDP in patients without a family history. CIDP progresses to peak disability by at least 8 weeks compared to 4 weeks in GBS.

SIGNS AND SYMPTOMS
CIDP presents with motor weakness and incoordination especially of the hands, impaired walking, and foot drop. There may be muscle cramps and fasciculations. Sensory symptoms may include loss of sensation (numbness), paresthesias (tingling, prickling, "pins and needles," "asleep" sensations), and sometimes pain. Tremor may be prominent during recovery from an exacerbation. Cranial nerves, respiration, and autonomic function are usually not involved. In long-standing untreated CIDP there may be intrinsic hand or foot wasting, but usually there is an absence of wasting in the setting of prominent weakness. Weakness is usually symmetrical and may be proximal and distal, and especially involves intrinsic hand muscles, and foot and toe dorsiflexors. Some patients may be quadriparetic. Deep tendon reflexes are frequently absent or reduced. Sensory loss may be minimal or there may be stocking and glove distribution loss to pinprick, thermal appreciation, light touch, vibration perception, and joint position sense. In many patients, however, the sensory loss to light touch, vibration, and position is more prominent, reflecting the greater involvement of large myelinated sensory fibers. Additional features are gait ataxia and rombergism or a flopping gait reflecting bilateral foot drop. The peripheral nerves are sometimes palpably enlarged, reflecting nerve hypertrophy from repeated cycles of demyelination with remyelination.

LABORATORY PROCEDURES
On nerve conduction studies features of demyelination include prolonged distal latencies, motor and sensory conduction velocity slowing, temporal dispersion of compound muscle action potentials (CMAPs) and conduction block in motor nerve territories. Sensory nerve action potentials are reduced or absent. Needle EMG of weak muscles may identify abnormal recruitment of motor unit potentials, but infrequent fibrillations. Some patients with CIDP have axonal damage with reduced distal CMAP amplitudes and fibrillations.

CSF prote in in is usually elevated without pleocytosis. If present, pleocytosis may suggest associated HIV infection. Serum protein electrophoresis, immunoelectrophoresis, and immunofixation may identify a monoclonal spike. Patients with IgMK monoclonal gammopathy may have elevated anti-MAG antibodies. Nerve biopsy is not routinely required to make the diagnosis. IgA deficiency, associated with anaphylaxis after IVIG, should be excluded. Inquiring about a history of TB or a TB skin test is important if prednisone is to be offered (see below).

IMAGING STUDIES
Nerve root hypertrophy and enhancement may occur on spinal MRI studies. Rarely, brain MRI has identified concurrent CNS demyelination.

SPECIAL TESTS
Surat nerve or deep and superficial peroneal nerve biopsies are reserved for "atypical" instances of CIDP, for example patients who do not fulfill its strict electrodiagnostic criteria or have normal CSF protein. Biopsies may identify myelinated fiber loss, axonal degeneration, regenerative clusters, segmental and paranodal demyelination, remyelination, and sometimes infiltrates of inflammatory cells. It is important that nerves are harvested, processed, and interpreted by specialized laboratories with expertise in peripheral nerve pathology.
**Management**

**GENERAL MEASURES**
Patients with CIDP may be unable to work, may need the input of an occupational therapist to help prevent falls at their homes and to provide other types of assistance with activities of daily living.

**SYMPTOMATIC TREATMENT**
Pain may be treated with simple analgesics; more severe pain may be treated with tricyclic antidepressants and anticonvulsants such as gabapentin, carbamazepine, or phenytoin. Patients with foot drop should be prescribed a custom-fitted ankle-foot orthosis.

**ADMISSION/DISCHARGE CRITERIA**
Quadriparetic and rapidly deteriorating patients can require hospitalization for investigation and therapy. Most management, however, is carried out in an outpatient setting.

**Follow-Up**

**PATIENT MONITORING**
Patients require follow-up by primary care physicians to monitor steroid or azathioprine side effects and by their neurologist to monitor the need for and dose of therapy. Periodic electrophysiologic monitoring may add to the precision of clinical monitoring.

**EXPECTED COURSE AND PROGNOSIS**
Patients may experience long-term remissions after a prolonged course of prednisone, or may require ongoing WIG to maintain their functional status. There may be relatively rapid downhill relapses in CIDP that require urgent therapy.

**PATIENT EDUCATION**
Excellent educational and support services are offered through the Peripheral Nerve Association patient group: www.neuropathy.org.

**ALTERNATIVE DRUGS**
Azathioprine, with careful monthly monitoring of blood counts and hepatic function, is equally effective compared to prednisone and may be used in some patients with steroid side effects or inadequate response to the above therapies.

**Medications**

**DRUG(S) OF CHOICE**
Level 1 evidence supports the use of high-dose chronic prednisone in CIDP starting at 80 mg daily or 120 mg alternating with 7.5 mg. High doses are required for the first 1 to 3 months followed by very slow tapering, depending on the clinical response. Patients should receive osteoporosis prophylaxis (e.g., etidronate and calcium). Complications can include hypertension, diabetes, susceptibility to infection, peptic ulceration, weight gain, edema, osteoporosis, and hip necrosis. All are relative contraindications/precautions. Intra venous gamma globulin may be used in lieu of or together with prednisone. The dose is 0.4 g/kg/d for 5 days monthly, although higher doses over fewer numbers of days or more frequent treatment courses can be given in stable patients. This is expensive therapy. Anaphylaxis is a contraindication. Headaches, chills, and nausea are benign side effects, though aseptic meningitis, hyperviscosity, susceptibility to thrombosis, and transmission of viral infections have been reported rarely. Patients may require ongoing treatments over years. Plasma exchange is of benefit in CIDP but less commonly used now because of the difficulties obtaining venous access and less common availability of appropriate facilities.

**Contraindications**
See above.

**Precautions**
See above.

**REFERENCES**

**Author(s):** Douglas W. Zochodne, MD

**SYNONYMS**
Chronic relapsing polyneuropathy
Chronic inflammatory radiculoplexus neuropathy
Chronic inflammatory demyelinating radiculoneuropathy
Chronic Guillain-Barra syndrome (this term is discouraged)

ICD-9-CM: 357.8 Inflammatory and toxic neuropathy—other

**SEE ALSO**
N/A
Conversion Disorder

**Basics**

**DESCRIPTION**

Conversion disorder is a somatoform disorder defined as a condition characterized by symptoms or deficits affecting voluntary motor or sensory function in which there is a loss or alteration in physical functioning. These symptoms are suggestive of a physical disorder but are in fact the expression of an underlying psychological conflict. By definition, the symptoms are not voluntarily produced.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

- The incidence of conversion symptoms varies widely depending on the population being studied; it is common on a general medical service where prevalence is estimated at 20% to 25%. It is estimated that conversion symptoms account for 5% to 14% of all psychiatric consultations for hospitalized medical or surgical patients.
- Conversion symptoms are more common in rural areas, and lower socioeconomic groups (less psychologically sophisticated populations). These symptoms are also more common in military personnel exposed to combat situations.
- **Sex**
  - Conversion symptoms are more frequently diagnosed in women, although some authorities suggest that the disorder is probably gender-equal.
- **Age**
  - Conversion symptoms may present at any age, although onset is rare before age 5 or after age 35. Typically conversion symptoms are first seen in adolescence or early adulthood.

**ETIOLOGY**

Conversion symptoms are caused by the conversion of psychological stress or conflict into somatic symptoms. There is still disagreement about whether the conversion phenomenon reflects primarily:

- An intrapsychic conflict. The patient may experience conflict over an unconscious, unacceptable, sexual, aggressive, or dependency wish. The somatic symptom maintains the unacceptable wish of awareness and often resolves the conflict by "punishing or not rewarding" the wish (primary gain).
- An interpersonal communication motivated by obtaining gratification from the environment. In this model, patients who have great dependency needs use their conversion symptoms to obtain attention and to influence their environment (secondary gain). The patient's disability and "helplessness" can become powerful tools in controlling friends, family, or physicians.
- Recently some studies have indicated that there may be cerebral dysfunction in patients with conversion disorder. According to this hypothesis, conversion may reflect certain neurophysiologic vulnerabilities in these patients.

**Genetics**

No information is available.

**PREGNANCY**

No association described.

**ASSOCIATED CONDITIONS**

- Conversion is probably multidetermined and represents a common pathway for a variety of etiologic factors. High rates of concomitant psychopathology have been found in patients with conversion symptoms. Depression and antisocial personality disorder are the most commonly reported. Patients with dissociative disorders have relatively high rates of conversion symptoms. Hysterical personality features are found in less than half of patients with conversion symptoms.
- A number of studies have found that patients with conversion symptoms also have high rates of medical and neurologic illness. Physical trauma, temporal lobe abnormalities, and multiple sclerosis may predispose to the development of conversion symptoms. Long-term follow-up studies up to 10 years past diagnosis of conversion disorder found a 25% to 62% incidence of false positives. It is extremely important to keep an open mind regarding the possibility of an organic etiology when making a diagnosis of conversion disorder and to seek appropriate consultations in order to rule out organic etiology.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

The list of differential diagnoses may cover a good portion of a neurologic textbook. Diagnoses that may be more problematic to exclude are:

- Multiple sclerosis
- Myasthenia gravis
- Periodic paralysis
- Polymyositis
- Guillain-Barre syndrome
- Transient ischemic attack

- Stroke
- Mercury toxicity

The DSM-IV diagnostic criteria for conversion disorder are:

1. One or more symptoms or deficits affecting voluntary motor or sensory function that suggest a neurologic or other general medical condition.
2. Psychological factors are judged to be related with the symptom or deficit in the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors.
3. The symptom or deficit is not intentionally produced or faked (as in factitious disorder or malingering).
4. The symptom or deficit cannot, after appropriate investigation, be fully explained by a general medical condition, or by the direct effects of a substance, or as a culturally sanctioned behavior or experience.
5. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.
6. The symptom or deficit is not limited to pain or sexual dysfunction, does not occur exclusively during the course of somatization disorder, and is not better accounted for by another mental disorder.

The diagnosis of a conversion symptom can be made only when the symptom in question cannot be adequately explained on the basis of a medical condition. What complicates the diagnosis is the fact that conversion symptoms and physical illness frequently coexist. The history is most helpful in diagnosing conversion reactions. It should include information about the patient's family, work, other possible stressors, as well as the possibility of secondary gain.

**SIGNS AND SYMPTOMS**

- Weakness, paralysis, sensory disturbances, pseudoseizures, blindness, deafness, and aphonia are the most frequent complaints.
- Patients often show a puzzling lack of concern about their deficits. This characteristic lack of concern has been termed "La belle indifference." Neurologic abnormalities usually suggest an anatomic distribution on physical exam.

**LABORATORY PROCEDURES**

Laboratory testing should be considered to rate the patient's organic etiology. There are no specific tests to diagnose or rule out conversion disorder. Laboratory studies that are inconsistent with the presenting symptom(s) may help with diagnosis of conversion disorder.
Management

GENERAL MEASURES

- Many conversion symptoms are fleeting and half to almost all symptoms remit by the time of hospital discharge. Prompt resolution is important since a number of studies have shown that there is a direct relationship between duration of conversion symptoms and chronic disability.
- In acute cases the initial aim is to remove the symptom. Direct confrontation of the patient regarding the psychological nature of the symptom is not recommended. A simple approach of reassurance, relaxation, and suggestion is indicated. Patients are reassured that their symptoms will disappear and are encouraged to discuss any stressful events or feelings that most likely have been on their mind.
- Nalidixic acid to the conversion symptoms should be suggested.
- Most patients respond to a course of brief supportive psychotherapy. The focus is on developing a working alliance in an environment of mutual trust, respect, and acceptance. The aim of this treatment is to help patients explore various areas of conflict or stress and to help them develop better coping mechanisms. The focus generally shifts from the conversion symptoms to the psychological makeup of the individual. Behavioral therapy, focusing on the development of adaptive behaviors at the expense of maladaptive conversion reactions, is also helpful.

Hypnosis

Hypnotherapy has been found beneficial, especially in patients with acute symptoms. While patients are under hypnosis, it is suggested to them that their symptoms will gradually improve posthypnotically. Patients are also encouraged to discuss areas of conflict or stress.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

N/A

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Admission should be considered to rule out a serious medical condition or when the severity of the conversion disorder prevents patients from caring for themselves.

MEDICATIONS

DRUGS OF CHOICE

- Medication has not been found to be effective for conversion disorder with the exception of nonpharmacological treatment. In narcoanalysis, the patient is given amobarbital IV to the point of drowsiness. The patient, who is in a relaxed state, is encouraged to discuss recent stresses or conflicts.
- Amobarbital IV is given at a rate no faster than 1 mg/min. Infusion is continued until drowsiness, slurring of speech, or sustained lateral nystagmus occur. It is very uncommon to need to use 500 mg or more of Amytal.

Contraindications

- Any condition in which pharmacologic respiratory depression would be likely to cause respiratory failure.
- A history of porphyria.

Precautions

Narcoanalysis must be administered with close monitoring for respiratory depression.

ALTERNATIVE DRUGS

None

Follow-Up

PATIENT MONITORING

Following discharge, patients should be referred to a psychiatrist for individual treatment (brief psychotherapy or hypnotherapy).

EXPECTED COURSE AND PROGNOSIS

- Good prognostic indicators include:
  - Acute symptoms (less than 30 days)
  - Fewer symptoms
  - Absence of psychiatric comorbid conditions
  - An identifiable stressor
  - Good premorbid health
  - Good intelligence
- Chronic conversion symptoms (over 1 year) have a much poorer prognosis and may require long-term psychotherapy.
- Even though individual conversion symptoms are generally self-limited and remit quickly, a study found that symptoms resolve within 1 year in 2% to 25% of patients.
- Aphonia, blindness, and paralysis are associated with a better prognosis than pseudoseizures and conversion tremor.

PATIENT EDUCATION

Patients should be educated about the possibility of recurrent symptoms under stress.

Miscellaneous

SYNONYMS

Conversion hysteria

ICD-9-CM: 300.11 Conversion disorder

SEE ALSO: N/A

REFERENCES

**Creutzfeldt-Jakob Disease**

**Basics**

**DESCRIPTION**
The triad of rapidly progressive dementia, myoclonus, and a characteristic EEG define classical Creutzfeldt-Jakob disease (CJD). It occurs in sporadic and familial/community clusters. CJD is the most common of the prion diseases, or transmissible spongiform encephalopathies (TSEs). The histologic hallmarks in the brain are neuronal loss (by apoptosis), gliosis, and vacuolization of gray matter (microscopic spongiform change) without significant inflammation.

**EPIDEMIOLOGY**

**Incidence**
About 1 per million per year.

**Age**
Peak incidence in sixth decade. Rare in children.

**Sex**
No sex preference.

**Special Populations**
Bitches and farmers have been reported to have an increased incidence. Variant CJD (vCJD) is a special cross-species transmitted form of CJD associated with the epidemic of bovine spongiform encephalopathy (BSE), largely confined to Great Britain. Clusters of cases are usually associated with the inherited form.

**ETIOLOGY**
- Sporadic: caused by a change in struture or conformation in the protease resistant protein (PrP-C going to PrP-SC), creating a prevalence for PrP-SC to form an amyloid (beta pleated sheet) protein. This protein is then deposited in the CNS, and is the presumed toxic agent. In sporadic CJD, the event that triggers the first PrP-C molecules to change struture is unknown, but it is then apparently autocatalytic. Alternatively, there may be a primary somatic cell mutation leading to a PrP with increased predilection to form PrP-SC. PrP is a membrane-bound glycoprotein whose exact function is unknown. About 85% of cases are sporadic.
- Inherited: several mutations in PrP cause it to be more amyloidogenic. The disease is usually inherited as an autosomal-dominant disease with incomplete penetrance. The gene is located on the short arm of chromosome 20q6. Mutations may be associated with specific clinical symptoms or variants, but these findings are not absolute. About 10% of cases are inherited.

- Transmitted: disease can be induced by introducing PrP-SC directly to the bloodstream (thus transmissible) or CSF. This forms the basis for the general term transmissible spongiform encephalopathy (TSE). The incubation time for this process to become clinically evident in humans is usually several years. Less than 5% of cases are documented as transmitted.

**RISK FACTORS**
Consuming tissue known to be contaminated with an agent of an animal TSE is a risk. This is the presumed cause of BSE. The TSE Kuru was shown to be associated with ritual cannibalism. Latrogenic disease from cornea or dura mater transplant, invasive EEG leads, contaminated neurosurgical equipment, and through giving contaminated growth hormone extracts are known risks. Receiving a blood transfusion from a patient with CJD is a theoretical risk, which has led to changes in blood collection and distribution policies.

**PREGNANCY**
No known risk. **ASSOCIATED CONDITIONS**
- Variants
  - Heidenhain—cortical blindness, occipital lobe involvement
  - Brownell-Oppenheimer—cerebellar predominant
  - Stern-Garci a—basal ganglia and thalamic predominat in
  - Panencephalic—white matter involvement; more common in Japan
- Gerstmann-Strausler syndrome (GSS) is a variant of inherited CJD with prominent cerebellar signs. Pathologic changes predominate in the cerebellum.
- Familial fatal insomnia (FFI) is an inherited form of CJD in which insomnia, autonomic, and behavioral abnormalities predominate. Pathologic changes are most prominent in the thalamus and basal ganglia.
- Variant CJD (vCJD) is a rare form of the disease, seen predominantly in young adults in Great Britain, associated with the BSE epidemic in that country.
- Kuru is the form of the disease associated with ritual cannibalism in New Guinea. Cerebellar signs predominate. Amyloid plaques in the cerebellum (“Kuru plaques”) are characteristic.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
Several weeks or months into the disease, the rapid progression of the dementia and appearance of myoclonus make the diagnosis certain. Early CJD may resemble any adult dementing illness—degenerative, infectious, metabolic, or reversible in etiology. Most can be ruled out by appropriate laboratory and radiologic testing.

- Alzheimer disease
- Parkinson disease
- Amyotrophic lateral sclerosis
- Frontotemporal dementia
- Vascular dementia
- CNS vasculitis
- AIDS dementia
- Progressive multifocal leukoencephalopathy
- Progressive supranuclear palsy
- Tertiary syphilis
- Subacute sclerosing panencephalitis
- Infectious encephalitis
- Toxic encephalopathy—bismuth, bromides, lithium
- Adult-onset leukodystrophies
- Brain tumor, particularly frontal or diffuse

**SIGNS AND SYMPTOMS**
- Early
  - Asthenia, insomnia, mild anorexia, fatigue
  - Rapidly progressive dementia
  - Cerebellar signs—ataxia, incoordination
  - Extrapyramidal signs—rigidity, choreoathetoid movements
  - Behavioral problems
  - Myoclonus, with startle and persisting during sleep
  - Visual difficulties—blurring or decreased acuity
  - Late
  - Akineti c mutism
  - Occasional signs
  - Fasciculations, muscle atrophy, focal cortical signs

**LABORATORY PROCEDURES**
No standard laboratory test assists in the diagnosis, although the lack of abnormalities may help to rule out other conditions. CSF analysis of the 14-3-3 protein and neuron-specific enolase are gaining popularity, and elevated levels correlate with disease, although the tests may be positive in other degenerative brain disorders. The diagnostic surgical biopsy is still the gold standard, but small biopsies away from areas of clinical involvement may yield equivocal or negative results. Autopsy confirmation may be necessary, or requested by the family.
Creutzfeldt-Jakob Disease

IMAGING STUDIES
- Nonspecific cerebral atrophy may be seen on CT late in the disease.
- MRI may show high signal intensities in the basal ganglia or other gray matter in T2-weighted images.
- SPECT scan shows an irregular decrease in metabolic activity predominantly in gray matter.

SPECIAL TESTS
EEG will show characteristic periodic high-voltage sharply contoured discharges, particularly as the disease progresses. It may be normal early in the disease.

Management

GENERAL MEASURES
- Support, particularly of family.
- Counsel family on noninfectious nature of disease.
- Hospice care

SURGICAL MEASURES
Diagnostic biopsy is reserved for unusual cases, or where antemortem confirmation is required.

SYMPTOMATIC TREATMENT
See medications, below.

ADJUNCTIVE TREATMENT
None

ADMISSION/DISCHARGE CRITERIA
Rarely a cause for admission to hospital, except for complicating comorbidities. Consider hospice admission later in disease when patient cannot be cared for at home.

Follow-Up

PATIENT MONITORING
Prior to definitive diagnosis, careful workup to exclude all treatable causes of disease is necessary.

EXPECTED COURSE AND PROGNOSIS
The median survival is 4 to 8 months, with almost all patients dead within 2 years.

PATIENT EDUCATION
The primary education is for the family, preparing them for the devastating course of the disease. Careful counseling on the nature of transmissible as opposed to infectious disease is necessary, to allow proper home or hospice care. Health care workers performing EEGs or invasive testing should be informed of the diagnosis. Funeral directors should be notified of the diagnosis. Autopsy should be requested to confirm the diagnosis in all cases.

Medications

DRUGS OF CHOICE
There is no known treatment to reverse the disease in humans. Phenothiazine derivatives, quinacrine, and chlorpromazine have been shown to inhibit the production of prion proteins in cell culture; they are unproven to date in humans. Clinical trials are in process.

ALTERNATIVE DRUGS
Myoclonus may be treated with clonazepam (0.5-1 mg tid) if necessary. Consider antidepressant therapy or antianxiety therapy as needed.

Follow-Up

Miscellaneous

SYNONYMS
Jakob-Creutzfeldt disease
ICD-9-CM: 046.1 Creutzfeldt-Jakob disease; 294.10 CJD with dementia; 294.11 CJD with behavioral disturbance

SEE ALSO: N/A

REFERENCES

Author(s) Brian W. Little, MD, PhD
### DECOMPRESSION SICKNESS

**DESCRIPTION**
Decompression sickness (DCS) develops when nitrogen gas, in solution at an elevated concentration within the bloodstream and tissues at depth, forms bubbles after rapid lowering of ambient pressure, with subsequent ischemia, inflammation, and mechanical disruption of the nervous system.

**EPIDEMIOLOGY**

#### Incidence/Prevalence
Estimated incidence of DCS is 1 case per 5,000 to 10,000 dives for recreational scuba divers; 1 case per 500 to 1,000 dives for commercial divers.

#### Race
No studies have demonstrated any ethnic predominance.

#### Age
Adults of all ages are at risk for DCS; risk is increased in older patients. The peak incidence of DCS is in the fourth and fifth decades.

#### Sex
Reported more often in men than women (due to the substantially lower number of women engaged in diving). Women may be at increased risk for DCS.

**ETIOLOGY**
Exposure to elevated ambient pressure causes partial pressures of the gases in the breathing mixture to increase proportionately and reach a new equilibrium within the tissues. Although oxygen is actively metabolized within tissues, nitrogen is an inert gas that will become dissolved in tissues and body fluids until saturation, proportional to the ambient pressure. The diver will be at risk for DCS only if there is a sudden reduction of the ambient pressure. If the ambient pressure is decreased slowly (i.e., careful stow ascent to the surface), the nitrogen can be passively transferred down concentration gradients from tissues into the bloodstream and then to the lungs, where off-gassing can occur. In cases where ambient pressure is reduced rapidly, the potential for bubble formation will depend on the depth of the dive, length of time at depth, and the rate of ascent. If the ambient pressure is released too quickly, nitrogen dissolved in tissues will need to reach a new equilibrium, such that excess gas that cannot remain in solution will form bubbles. In type II neurologic DCS, the brain, spinal cord, cranial and peripheral nerves, and/or neural vasculature are affected by bubble formation. If the concentration of bubbles reaches a certain threshold, nervous system structures may be damaged by mechanical disruption, tissue compression, vascular stenosis or obstruction, and activation of inflammatory pathways (e.g., leukocyte cytokines, complement). Cerebral DCS (30-40% of cases) most often involves the arterial circulation, while spinal cord DCS (50-60% of cases) more typically involves obstruction of venous drainage from the cord.

**Genetics**
Genetic factors have not been identified.

**PREGNANCY**

Pregnancy may increase the risk for developing DCS. If DCS were to occur in a pregnant diver, the fetus would be at risk for significant damage from bubble formation. In general, it is recommended that pregnant women refrain from diving.

**ASSOCIATED CONDITIONS**
Air gas embolism (AGE): DCS and AGE can occur together and the combined syndrome is referred to as decompression illness.

### Diagnosis

**DIFFERENTIAL DIAGNOSIS**
An alternative diagnosis to DCS should be considered if severe symptoms begin more than 6 hours after return to atmospheric pressure without altitude exposure, if any symptom develops more than 24 hours after surfacing, or if a diver fails to improve despite prompt recompression treatment.

- Contaminated breathing gas (carbon monoxide)
- Near drowning and hypoxic brain injury
- Ingestion of toxic seafood— ciguatera, puffer fish, paralytic shellfish
- Envenomation—sea snake, cone shell
- Migraine
- Guillain-Barre syndrome
- Porphyria
- Multiple sclerosis
- Transverse myelitis
- Spinal cord compression
- Middle ear or sinus barotrauma with cranial nerve compression
- Inner ear barotrauma
- Oxygen toxicity with seizure
- Unrelated seizure
- Ischemic or hemorrhagic stroke
- Subarachnoid hemorrhage

**SIGNS AND SYMPTOMS**
Greater than 50% of patients with neurologic DCS have onset of symptoms within 1 hour of returning to atmospheric pressure. Within 6 hours, more than 90% of patients will have become symptomatic. The thoracic spinal cord is the most commonly affected region of the nervous system. The most frequent symptoms are numbness and paresthesias of the trunk that often begin in a band-like pattern and then progressively worsen, ascending weakness of the lower extremities that may progress to paralysis, and bowel and bladder dysfunction. Less often, patients develop cervical cord involvement with quadriplegia or paraplegia. General cerebral symptoms can manifest as headache, confusion, fatigue, lethargy, change in personality, or poor concentration. Focal symptoms and signs are numerous and may include hemiparesis, hemisensory loss, ataxia, loss of vision or Hemianopsia, dysphasia, and gait disturbance. When DCS involves the inner ear, patients usually complain of vertigo, sensorineural hearing loss, nausea, emesis, and tinnitus. On neurologic examination, the most common findings are weakness (legs more often than arms) sensory deficits, gait disturbance, ataxia, visual dysfunction, and alterations of consciousness.

**LABORATORY PROCEDURES**
N/A

**IMAGING STUDIES**
CT scans are relatively insensitive to the structural changes induced by DCS. MRI T2-weighted images may show high-signal abnormalities within the brain or spinal cord. Regions of injury are often swollen and edematous, but usually do not enhance with administration of contrast. MRI of the brain correlates with the clinical symptoms in approximately 55% of neurologic DCS patients, while imaging of the spinal cord correlates in one third of patients.

**SPECIAL TESTS**
- EEG and evoked potentials may be helpful to determine the extent of injury and follow recovery from neurologic DCS. However, these tests are not sensitive enough to recommend routine EEG, especially in the acute setting. Neuropsychological testing may be helpful to screen for subtle cognitive and motor deficits that may not be detectable on the bedside neurologic examination.
- Audiography and electronystagmography are sensitive tests that may be helpful in cases of vestibular DCS.
Decompression Sickness

Management

GENERAL MEASURES
- Initial management of DCS occurs in the field, most often at some form of dive site (e.g., lake, dive boat, ocean beach). The patient should be assessed for adequacy of the airway, ventilation, pulse, and blood pressure. Cardiopulmonary resuscitation should be initiated in appropriate patients. In all cases, 100% oxygen should be started immediately. The patient should be placed in the supine position and prepared for transport to a medical facility with a recompression chamber.
- During transport the patient should be monitored carefully for further deterioration (e.g., shock). If the patient is unconscious or apneic, intubation and mechanical ventilation should be initiated. Proper ventilation with 100% oxygen should continue. Intravenous fluids should be started, since dehydration is common in DCS. In patients suspected of spinal cord DCS, the bladder should be catheterized and the urine output monitored.

SURGICAL MEASURES
There are no beneficial surgical procedures for DCS.

SYMPTOMATIC TREATMENT
- The definitive treatment for DCS is recompression therapy, using algorithms established by the United States Navy (USN). The treatment algorithm used most often for patients with neurologic DCS is USN Table 6. The patient is recompressed to 60 Fs W, breathing 100% oxygen, for a total of 60 minutes. Three brief periods of air breathing (5 minutes each) are interposed during this initial recompression to reduce the risk of oxygen toxicity. The patient is then recompressed to 30 Fs W for two additional periods each of breathing pure oxygen (60 minute sessions) and air (15 minute sessions). The total treatment takes 4 x hours. For patients with incomplete resolution of symptoms and signs, the treatment may be extended to as long as 12 hours. More complex treatment algorithms can be used for severely ill patients.
- Recompression therapy reduces the bubble volume in tissues and body fluids by allowing easier reabsorption and dissipation of the bubbles.

ADJUNCTIVE TREATMENT
- Aggressive hydration with isotonic fluids may accelerate off-gassing of nitrogen and is recommended for all patients. Because neurologic injury can be exacerbated by hyperglycemia, intravenous solutions should not contain glucose. Blood glucose levels should be monitored and kept at or below 200 mg/dL. See form of prophylaxis against deep vein thrombosis is recommended for patients with spinal or severe cerebral DCS, in which there may be a risk for venous thrombosis and pulmonary embolism. Fevers should be treated aggressively, since hyperthermia may aggravate neurologic injury.
- Rehabilitation and physical therapy are helpful in DCS patients with residual neurologic deficits. Function may slowly improve for several months to years after the effects of recompression therapy have plateaued.

ADMISSION/DISCHARGE CRITERIA
Patients are generally admitted for acute evaluation and recompression therapy as outlined above. Patients with significant residual neurologic deficits following treatment should be considered for inpatient or aggressive outpatient rehabilitation.

Medications

DRUG(S) OF CHOICE
There are no medications specific for DCS. Other than recompression therapy, oxygen is the only specific therapeutic intervention that expedites and enhances recovery. Aspirin and corticosteroids are often used; however, there is no conclusive evidence for benefit.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Follow-up of neurologic status is required.

EXPECTED COURSE AND PROGNOSIS
Prognosis for complete recovery following neurologic DCS is good for military and commercial divers, with relief of all symptoms reported in 95% and 70% of patients, respectively, after prompt recompression therapy. For recreational divers, the prognosis is more guarded. Recent data indicate that residual symptoms exist after treatment in 75% of recreational divers with severe DCS and 46% of those with mild to moderate cases of DCS. The poorer outcomes in recreational divers are likely related to delays in the initiation of recompression therapy and less frequent utilization of surface oxygen at the dive site.

PATIENT EDUCATION/ORGANIZATIONS
The Divers Alert Network (DAN), at Duke University Medical Center in Durham, North Carolina, maintains a database of information related to diving injuries, including the location of recompression facilities around the world. They are able to provide instant referral for potentially injured divers to the nearest facility that can properly manage DCS. DAN also has a 24-hour hotline for consultation on suspected dive injuries: 919-684-8111.
## Dementia, General

### Basics

**DESCRIPTION**
Dementia is progressive impairment of memory and cognition that interferes with a patient's work and social relationships. Level of consciousness and attention are preserved in dementia. It is important to recognize that although Alzheimer's disease is the most common form of dementia, there are many other types that can be diagnosed premortem by careful clinical evaluation. Frequently, prominent presenting symptoms such as personality changes, or associated neurologic complaints such as gait change, or clinical course such as rate of progression can direct the differential diagnosis.

**EPIDEMIOLOGY**

#### Incidence/Prevalence
Alzheimer's disease affects 5% to 10% of elderly Caucasian Americans. Similar prevalence in blacks, Hispanics, and Americans of Japanese descent when corrected for age and level of education. Prevalence increases exponentially with age. Prevalence doubles with every 5-year increase in age. It is estimated in people age 90 to 95 years old, the prevalence is possibly as high as 30% to 40%. It is unknown if the prevalence continues to increase after age 95. Prevalence is estimated at 0.6% in patients 65 years old and continues to increase after age 95. Incidence is 30% to 40% to 95 years old, the prevalence is possibly as high.

**ASSOCIATED CONDITIONS**

- **Inflamation/infection**: chronic meningitis (tuberculosis, cryptococcus)  
- **Syphilis**  
- **Post-herpetic simple encephalitis**  
- **Focal ceberosis/abscess**  
- **HIV dementia and opportunistic infections**  
- **Progressive multifocal leukoencephalopathy**  
- **Creutzfeldt-Jakob disease**  
- **Lyme encephalopathy**  
- **Sarcoidosis**  
- **Subacute sclerosing panencephalitis**  
- **Whipple's disease of the brain**  
- **Neoplastic: tumor—benign; tumor—malignant, primary or metastatic; paraneoplastic limbic encephalitis**  
- **HIV dementia and opportunistic infections**  
- **Personality changes**  
- **Language and naming difficulties**  
- **Difficultly using everyday objects**  
- **Disorientation**  
- **Poor judgment**  
- **Poor logic**  
- **Hallucinations or delusions**  
- **Wandering**  
- **Abnormalities on a detailed neurologic exam can suggest a specific cause, such as asymmetric reflexes in vascular dementia or extracranial movement abnormalities in progressive supranuclear palsy.**

**LABORATORY PROCEDURES**

- **Initial evaluation should include CBC, liver function tests, sodium, ca, icum, thyroid stimulating hormone, RPR, vitamin B12 level.**  
- **In appropriate cirumstances, consider HIV testing or Lyme serology.**  
- **Atypical presentations of dementia may require one of the following: ceruloplasmin and copper levels (Wilson's disease), plasma levels of very long chain fatty acids (adreno- leukodystrophy), WBC arylsulfatase A (metachromatic leukodystrophy), vitamin E and B1 levels, porphyrins, blood gas, hemoglobin Aic, tumor markers (anti-Hu/Yo/Ro) ANA, vasculitis workup, or in arly heavy metals, thyroid antibodies, toxicity screen.**

### Diagnosis

#### DIFFERENTIAL DIAGNOSIS

- **Normal aging**  
- **Mild cognitive impairment (excessive, predominant memory loss with preservation of daily function)**  
- **Psychiatric disorders (mood is affected predominantly)**  
- **Toxic/confusional states or encephalopathy (level of attention and/or impaired consciousness present)**

#### SIGNS AND SYMPTOMS

Once it has been established that the patient meets the criteria for dementia, the history of present illness should be directed toward soliciting presenting symptoms and associated medical conditions that suggest a specific diagnosis. These include the symptoms noted below, as well as speed of progression, mode of onset, associated focal neurologic deficits, presence or absence of headache, and incontinence. A thorough review of the patient's medications, assessment of patients vascular and HIV risk factors, alcohol use, and fam i ly history of deme-  

#### ASSOCIATED CONDITIONS

Some dementias have a associated neurologic symptoms (e.g., parkinsonian symptoms, cerebellar degeneration, motor neuron disease, etc.), or medical conditions. These depend on the specific diagnosis.
Dementia, General

IMAGING STUDIES
- CAT scan of head without contrast; consider brain MRI especially in dementias not typical of Alzheimer's disease or suspected vascular dementia.
- PET/SPECT can be useful in diagnosing Alzheimer's disease.
- Tumor screen if limbic encephalitis is considered.

SPECIAL TESTS
- EEG and cerebral arteriography are appropriate in certain circumstances. Examples include Creutzfeldt-Jakob disease and CNS vasculitis, respectively.
- Bedside neuropsychologic testing
  - Standardized testing including the Mini-Mental Status Exam and the Clinical Dementia Rating Scale. These provide objective, reproducible scores for future comparison.
  - Tests of memory, orientation, attention, calculation, reading, writing, naming, drawing, abstraction, praxis.
  - Observation of comportment, judgment, and insight.
- Formal neuropsychological testing: can be used to aid in diagnosis, assess severity, dissect out spurious depression, and provide formal documentation of impairment for disability applications and legal purposes.
- The following biomarkers are available but not yet generally accepted for clinical diagnosis:
  - Genetic tests such as serum apoE-4, and documentation of impairment for disability
  - CSF analysis for the A beta form of the amyloid precursor protein and tau.

Diagnostic Procedures
- Lumbar puncture should be considered in the following circumstances:
  - Age <60
  - Rapid progression
  - Immunocompromised patient
  - Cancer
  - Reactive syphilis or Lyme serology
  - Unusual clinical presentation
  - CNS infection —Systemic infection
  - Connective tissue diseases
  - CNS vasculitis
  - For 14-3-3 (Creutzfeldt-Jakob protein) testing
- Brain biopsy should be considered in unusual cases as follows:
  - Focal, relevant lesions of undetermined cause, after extensive evaluation
  - CNS vasculitis—Subacute sclerosing panencephalitis
  - Progressive multifocal leukoencephalopathy where lymphoma cannot be conclusively ruled out by neuroimaging or spinal fluid analysis
  - Degenerative neurologic illnesses such as Kufs' disease, Alexander's disease.
  - Muscle biopsy in suspected mitochondrial disorders

Management

GENERAL MEASURES
- Treat any reversible causes of dementia.
- Evaluate for spurious ed illnesses or depression and treat them.
- Establish an etiologic diagnosis and institute therapy for specific cause.
- Determine if specific pharmacologic intervention inappropriate, such as centrally acting acetylcholinesterase inhibitors in Alzheimer's disease.
- Identify and address symptoms that brought the patient to medical attention, e.g., patient's and/or caregivers' primary concerns.
- Suggest to patients that they may want to consider designating a family member who will help with future legal and financial decisions.
- Assess patients' personal security (for instance, in regard to wandering, judgment, and monitoring their own medications) as well as possible threats to public safety (driving).

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
Depends on the specific diagnosis. Risperidone has been shown to reduce psychotic symptoms and aggression in demented patients. Selective serotonin reuptake inhibitors (SSRIs) may be useful in depressed patients with dementia.

ADJUNCTIVE TREATMENT
- Activity: low levels of exercise may aid in behavioral management in agitated, demented patients.
- Diet: anorexia may complicate dementia or be a side effect of its treatment, so weight should be monitored and it may be appropriate to eliminate dietary information.

ADMISSION/DISCHARGE CRITERIA
Usually managed as an outpatient, may require admission for evaluation of rapid decline, advanced workup (biopsy), or caregiver's inability to care for the patient at home.

Medications

DRUGS OF CHOICE
Depends on the specific cause of dementia. Refer to the chapters on specific causes of dementia for information on their treatment. Gingko biloba has been found to improve cognition and is well tolerated in studies where multiple causes of dementia were included; the largest effect is seen in Alzheimer's patients.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Depends on the specific cause of dementia.

EXPECTED COURSE AND PROGNOSIS
Generally, relentless decline, although with periods of stability; fluctuations in severity and speed of progression vary depending on type.

PATIENT EDUCATION
- Discussion of patient's diagnosis and prognosis.
- Explain necessity of changing routines and expectations in response to the disease.
- Educate family about stages of disease and changes in patient's daily function.
- Educate about risk of stress, enlisting the help of friends and family and need for occasional respite. The NIH's Web site has information on experimental research trials in various aspects and causes of dementia: www.ninds.nih.gov/nindsnotes2000.htm#Jad.

Miscellaneous

SYNONYMS
None. Consider specific diagnosis.

ICD-9-CM: 294.8 Dementia; 294.1 Dementia in conditions classified elsewhere; 3310 Alzheimer's disease; 046.1 Jakob-Creutzfeldt disease; 290.4 Dementia—arteriosclerotic (simple type) (uncomplicated); 331.3 Communicating hydrocephalus; 331.1 Pick's disease
SEE ALSO: ALZHEIMER'S DISEASE

REFERENCES
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Dementia, Alzheimer's Disease

DESCRIPTION
Alzheimer's disease (AD) is the most common form of degenerative dementia. It is characterized pathologically by neurofibrillary tangles, neuritic plaques, and neuronal loss starting first in the entorhinal cortex, hippocampus, and the temporal and parietal association cortex before affecting frontal association cortex.

EPIDEMIOLOGY
Incidence/Prevalence
Age-specific incidence of 0.5%, 2%, and 5% at ages 70, 80, and 90, respectively. Age-specific prevalence of 3% at ages 65 to 74, 18% at ages 75 to 84, and 30% to 47% at ages 85 and over.

Age
Typically >60 but some genetic cases as young as the late thirties.

Sex
Female/male ratio of 2:1.

Race
Higher rates reported in African Americans and Hispanics, but effect wanes when controlling for education level. Rural Chinese and Nigerians have lower prevalence rates.

ETOLOGY
• Genetic and sporadic forms
• Amyloid hypothesis: either overproduction or decreased metabolism of amyloid beta peptide lead to a toxic state causing degeneration of neuronal processes, neuritic plaque formation, and eventually neuronal loss and clinical dementia.
• Tau hypothesis: abnormally phosphorylated tau proteins (tauopathy) accumulate in neurons as neurofibrillary tangles and ultimately cause neuronal death.
• Other suggested etiologies: disorder of immune function, oxidative stress, excitatory amino acid toxicity, and primary mitochondrial abnormality.
• There is little evidence for aluminum intoxication, viral infections, or prion diseases as causes of AD.

Genetics
• Autosomal dominant with age-dependent penetrance: 40% to 50%.
• 2% have known mutations on chromosomes 21, 14, or 1 with onset late 30s to early 50s.
• Trisomy 21 (Down syndrome) individuals develop AD pathology after age 35 and clinical AD symptoms by age 50.
• Chromosome 19 carries the apolipoprotein E gene, a cholesterol transport and AD susceptibility gene. The ε4 allele is a risk factor for AD, while the ε2 allele appears to be protective.

RISK FACTORS
• Definite risk factors: increasing age, being female, increased apolipoprotein E ε4 allele load, and family history of AD, dementia, or Down syndrome.
• Possible risk factors: history of significant head trauma with loss of consciousness, myocardial infarction, coronary artery disease, and cerebral white matter disease.
• Protective factors: higher educational achievement, increased apolipoprotein E ε2 allele load, use of estrogen in postmenopausal women, use of cholesterol-lowering statin medications, rheumatoid arthritis, and taking nonsteroidal antiinflammatory drugs for longer than 2 years.

PREGNANCY
Narelat ionship known.

ASSOCIATED CONDITIONS
NA

DIAGNOSIS
ACUTE/confusional states and delirium
Vascular dementia
Frontotemporal degenerations (i.e., Pick's disease)
Dementia with Lewy bodies
Parkinson plus syndromes
Huntington's disease
Traumatic dementias
Neuroplastic and paraneoplastic dementias
Hydrocephalic dementias
NMS vasculitis
Toxic dementias
Uremia
Hepatic encephalopathy
B12, folate, or niacin deficiencies
Thyroid, parathyroid, or adrenal conditions
Hypoxic encephalopathy
Infectious dementias
Multiple sclerosis
Depression

SIGNS AND SYMPTOMS
• Course: insidious onset, gradually progressive over years.
• Elemental neurologic examination: normal until very late.
• Mild-stage AD: disorientation to date, mild anoma, low verbal fluency, impaired delayed recall, difficulties copying 3-D figures (cube), trouble with illness paying and complicated financial transactions, diminished insight, irritability, and apathy.
• Moderate-stage AD: disorientation (time and place), fluent aphasia, difficulties with comprehension, impaired delayed recall, impaired recognition memory, getting lost in familiar areas, difficulties in copying 2-D figures, impaired calculations, concrete abstractions, poor judgment, trouble with instrumental activities of daily living (cooking, shopping, and handwriting) and increased behavioral symptoms (aggression, restlessness, psychosis, sleep disturbance, and dysphoria).
• Severe-stage AD: unable to use language effectively, may become mute, memory only for the moment, unable to find one's way around one's home, need assistance with basic ADLs (bathing, dressing, and toileting) due to increasing apraxia, urinary and fecal incontinence, and often trouble some behavioral symptoms.

LABORATORY PROCEDURES
• Lab tests are used to rule out other dementias.
• Apolipoprotein E genotyping is seldom useful.
• Genetic markers for known chromosome mutations are only useful to consider in patients in their early 50s or younger with a significant family history of dementia.
• Biomarkers for AD including reduced beta amyloid peptide and elevated tau protein in CSF and increased neural thread proteins in urine and CSF need to be more sensitive before they are recommended for routine use.

IMAGING STUDIES
• CT or MRI scans show atrophy in AD and can rule out other conditions.
• MRI volumetric measurement of hippocampus and entorhinal cortex atrophy is 95% sensitive but only 40% specific for AD.
• Functional imaging using single photon emission computed tomography (SPECT) and positron emission tomography (PET) may be useful for early diagnosis and typically shows bilateral temporal and parietal hypoperfusion and hypometabolism respectively. These patterns on SPECT and PET predict the risk of progression to AD in mild cognitive impairment (MCI) subjects in 83% and 9410, respectively.
• Functional MRI (fMRI) shows increased activation during memory tasks in individuals at high risk for AD.
• Functional imaging techniques are not currently recommended at this time.

SPECIAL TESTS
• Mental status examination or neuropsychological testing profiles a patient's cognitive functioning and should be done in every suspected AD case. It is the most sensitive tool we have for early diagnosis.
• The earliest changes on mental status examination include difficulties with memory, language, visuospatial skills, orientation, and problem-solving abilities.
Dementia, Alzheimer's Disease

**Management**

**GENERAL MEASURES**
- AD patients underreport symptoms of coincidental illness, infection, dehydration, and pain that cause increased disability if not discovered and treated.
- Minimize adverse drug effects and drug interactions. Avoid anticholinergic and benzodiazepine medications.
- Provide adequate supervision for medication compliance, proper oral intakes, and accident prevention.
- Minimize sensory deprivation by social stimulation, vision, and hearing care.
- Watch for overstimulation that may cause agitation.
- In early stages, limit driving to local areas during daytime and good weather. Caregivers should ride with patients monthly to ensure they are driving safely with good judgment.

**SURGICAL MEASURES**
None available.

**SYMPTOMATIC TREATMENT**
- Cholinesterase inhibitors are the only approved drugs for AD treatment in the U.S., providing, in mild to moderate disease, efficacy for cognitive and functional impairments compared to placebo. Most also show behavioral symptom improvement. Typically, these medications stabilize symptoms for 1 year but continue to offer advantages over no treatment for another 5 years.
- Vitamin E and selegiline showed disease-modifying benefits in one study.

**ADJUNCTIVE TREATMENT**
- The behavioral abnormalities seen with AD are treated with symptom-specific agents including antidepressants, antipsychotics, and mood stabilizers.
- Antiinflammatory drugs, estrogen in women, and statin (lipid-lowering) medications may reduce the risk or delay the onset of AD.

**ADMISSION/DISCHARGE CRITERIA**
- Patients are occasionally admitted for wandering or aggressive behaviors.
- Provide a sitter to ensure patient safety when delirium or a cute confusional states occur.
- Low-dose antipsychotics are the most effective and tolerated agents for acute agitation.

**Medications**

**DRUGS OF CHOICE**

**Cognitive Therapy**
- Cholinesterase inhibitors (strive for highest recommended dose): donepezil 5 mg/d for 6 weeks then 10 mg/d; or galantamine 4 mg bid for 4 weeks then 8 mg bid for 4 weeks then 12 mg bid; or rivastigmine 1.5 mg bid for 4 weeks then 3 mg bid for 4 weeks then 4.5 mg bid for 4 weeks then 6 mg bid
- Antioxidants: Vitamin E 1000 IU bid
- Behavioral Therapy
  - Depression or anxiety: selective serotonin reuptake inhibitors (SSRIs)
  - Psychosis: quetiapine 25 mg qhs to 75 mg bid or risperdone 0.25 mg qd to 1.0 mg bid or olanzapine 2.5 to 10 mg qd
  - Sleep disturbance: trazodone 50 to 150 mg qhs
  - Restless behaviors: citopram 20 to 40 mg qd or divalproex sodium 125 to 500 mg bid
- Aggression: SSRIs or antipsychotics or mood stabilizers (divalproex sodium, carbamazepine)

**Contraindications**
- SSRIs: avoid monoamine oxidase inhibitors.
- Divalproex sodium: avoid in patients with hepatic dysfunction.
- Carbamazepine: avoid monoamine oxidase inhibitors and in patients with previous bone marrow depression.

**Precautions**
- Cholinesterase inhibitors: avoid medications with anticholinergic effects including: antihistamines, certain psychotropics.
- SSRIs: may cause hyponatremia and SIADH.
- Atypical antipsychotics: may lower seizure threshold; watch for orthostatic hypotension.
- Divalproex sodium: may cause hepatotoxicity, thrombocytopenia, teratogenicity, pancreatitis, and hyperammonemia; liver tests and platelet counts should be monitored.
- Carbamazepine: may cause aplastic anemia, hepatotoxicity; CBC and liver tests should be monitored.

**ALTERNATIVE DRUGS**

**Cognitive Therapy**
- Antioxidants: selegiline 10 mg qd
- Behavioral Therapy
  - Depression: venlafaxine, bupropion, nefazodone, nor triptyline, or mirtazapine
  - Anxiety: bupropion e, propranolol, or lorazepam
  - Psychosis: haloperidol or clozapine
  - Sleep disturbances: zolpidem
  - Restless behaviors: other SSRIs
  - Aggression: propranolol or bupropion e

**Follow-Up**

**PATIENT MONITORING**
- Every 6 months measure cognitive status and ask about behavioral and functional abilities.
- Mini-Mental Status Examination (MMSE), the most commonly used evaluation tool, will decline 3 points per year on the average in untreated mild to moderate patients.

**EXPECTED COURSE AND PROGNOSIS**
Gradually progressive cognitive and functional declines leading to death.

**PATIENT EDUCATION**
Provide information about the disease, local Alzheimer's Association (www.alz.org), support groups, family counseling, social services, daily care services, in-home health care assistance, assisted living, long-term care facilities, legal services, advanced directives, and financial planning.

**Miscellaneous**

**SYNONYMS**
Senile or presenile dementia
Dementia of the Alzheimer's type

**ICD-9-CM:** 331.0 Alzheimer's disease; 290.0 Senile dementia; 290.1 Presenile dementia

**SEE ALSO:** DEMENTIA, GENERAL

**REFERENCES**

Author(s): Douglas W. Scharre, MD
Dermatomyositis

**Description**

An idiopathic inflammatory myopathy characterized by proximal muscle weakness and a characteristic rash. Dermatomyositis (DM) is epidemiologically, histologically, and immunologically distinct from the other idiopathic inflammatory myopathies, polymyositis (PM), and inclusion body myositis.

**Epidemiology**

*Incidence/Prevalence*

Uncommon, with an annual incidence of less than 1:100,000.

*Age*

Unique in that it can present at any age from infancy to adult. Juvenile form presents most commonly at ages 5 to 15.

*Sex*

Affects both males and females, with female preponderance.

*Race*

No known racial predominance.

**Etiology**

Based on histologic and immunologic studies of muscle biopsy, DM appears to result from a humorally mediated microangiopathy. The inciting event for this autoimmune phenomenon is not known. Deposits of IgM, IgG (less common), C3, C9, and the C5b-9 membrane attack complex (MAC) have been demonstrated in the perifascicular microvasculature and at the dermal-epidermal junction. The immunologic destruction of the microvasculature causes ischemic damage to perifascicular muscle fibers and recruitment of CD4+ T cells, B cells, and macrophages. This secondary perimysial and perivasculare infiltration by inflammatory cells then leads to further muscle damage.

**Genetics**

At this time, no genetic predisposition has been conclusively determined, although some investigators have proposed an association with certain human leukocyte antigen (HLA) haplotypes.

**Risk Factors**

None are known for idiopathic DM. Secondary DM is associated with the several overlap connective tissue diseases (see Associated Conditions, below).

**Pregnancy**

There is no known relationship to pregnancy.

**Associated Conditions**

**Autoimmune Diseases**

Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, Sjogren's syndrome.

**Neoplasia**

Ovarian, lung, pancreatic, and colorectal (seen particularly in adults over 40 and peak incidence within 5 years of DM diagnosis).

**Diagnosis**

**Differential Diagnosis**

Polymyositis

Inclusion body myositis

Connective tissue disease (sarciodosis, SLE, mixed connective tissue disease).

Infectious myositis (viral, bacterial, helminthic, protozoan, fungal).

Toxic myopathy (illicit drugs and medications).

Eosinophilic myopathies.

Endocrinopathies (hypothyroidism, hypercalcemia).

**Signs and Symptoms**

Classic DM presents with subacute (over weeks) proximal weakness and characteristic heliotrope (purple) rash over the eyes. Weakness predominantly involves the neck flexors, hip flexors/extensors, and shoulder girdle. Dysphagia is reported in up to one third of patients, but respiratory muscle involvement is rare. Sensation is unaltered and muscle stretch reflexes are maintained until severe involvement occurs. In addition to the heliotrope rash, sun-sensitive erythema, scaling, and telangiectasias may be found over the malar region and over the chest (V-sign), shoulders (shawl sign), knees, and elbows. Gottron's papules (red, scaly lesions) may be found over the joints of the dorsal hand; dilated capillaries may be seen in the nailfold bed. Cutaneous calcifications can be found over pressure points, especially in children with severe, long-standing disease.

Less common manifestations include:

- Arthropathy: joint contractures, arthralgias
- Cardiac involvement with cardiomegaly, dyspnea, arrhythmias
- Pulmonary: aspiration pneumonia in patients with significant pharyngeal and upper esophageal weakness, interstitial lung disease (5-10%)
- Necrotizing vasculitis: skin, muscle, gastrointestinal tract, retina, and kidney especially in childhood DM

**Laboratory Procedures**

Serum creatine kinase (CK) is the most sensitive and specific marker for muscle destruction and necrosis. CK is elevated in nearly 90% of patients at some point in disease progression and may be as high as 50 times normal; however, a random CK may be normal in approximately 30% of DM and persistently normal in 10%. Antinuclear antibodies (ANAs) may be found in 24% to 60% of DM but are more common when DM is associated with the overlap connective tissue diseases. The same is true for the ESR, which is usually normal or only mildly elevated in idiopathic DM. Certain myositis-specific antibodies may be found, including anti-Jo-1 and anti-Mi-2. Anti-Jo-1 is found in approximately 20% of the cases of PM and DM, and may predict a subset of patients destined to have interstitial lung disease and/or arthritic complications. CBC, chemistry panel, PSA, urinalysis, and stool for occult blood may also be checked for underlying malignancy. Referral for breast and pelvic examination for women and testicular and prostate for men may also be needed in malignancy workup.

**Imaging Studies**

MR of affected muscles may show edema and inflammation, although this is not used routinely in evaluation. Chest radiography and mammography are useful in malignancy workup.

**Special Tests**

- EMG is a good screening test for inflammatory myopathy and reveals increased insertional activity with polyphasic, short duration, and low-amplitude motor unit potentials and complex repetitive discharges. Also, positive sharp waves, fibrillations, and early recruitment are found.
- Muscle biopsy is the best test for pathologic confirmation of the disease and should be performed in the vast majority of cases. The typical pathology is that of perifascicular muscle fiber atrophy and decreased capillary density. Perimysial and perivasculare inflammation with B cells and T-helper cells are present. Microvascular deposits of immunoglobulin and MAC, relatively specific to DM, are also found.
Management

**GENERAL MEASURES**

Medical therapy is primarily immunomodulation with corticosteroids or IVIG. High-dose oral prednisone (1.5 to 2 mg/kg/d) or IV methylprednisolone (1 g/d) is the initial treatment. In severe cases, however, some centers also consider IVIG for young patients to spare the steroid side effects. Steroids are slowly transitioned to alternate-day dosing over 2 to 4 weeks and maintained until strength returns to normal, plateau or shows no response after 3 to 6 months. Adjuvant medications are considered if there is little or no response to steroids, disease relapse upon tapering, or if side effects are intolerable.

**SURGICAL MEASURES**

Biopsy may be required for diagnosis. Surgical excision may be necessary for digital calcinosis.

**SYMPTOMATIC TREATMENT**

Cardiac disease and hypertension secondary to steroid therapy require treatment. Arthritis can be managed with NSAIDs. An exacerbation of weakness during steroid taper requires immediate increase to double current dose (max 100 mg) daily for 2 to 3 weeks, followed by another taper.

**ADJUNCTIVE TREATMENT**

Physical, occupational, and speech therapy may be needed, depending on the affected muscle groups. Referral to dermatology for the rash and to ophthalmology may be necessary.

**ADMISSION/DISCHARGE CRITERIA**

Patients are admitted for severe weakness and/or respiratory compromise. Certain institutions may require admission for IV methylprednisolone or IVIG.

### Medications

#### DRUG(S) OF CHOICE

- Prednisone: 1.5-2.0 mg/kg/d (maximum dose 100 mg PO qAM for 2 to 4 weeks) then switched over to 2 to 4 weeks to qod regimen. Treat until maximum response or for 3 to 6 months and then slowly taper.
- A pulse of high-dose intravenous corticosteroids may be needed for severe presentations or exacerbations.
- Methylprednisolone (fulminant disease): 1 g IV qd x 3 to 6 doses followed by 1.5 mg/kg PO for 3 to 4 weeks
- IVIG: 2.0 g/kg over 2 days per month for 3 months. May need periodic booster infusions.

#### Contraindications

Immunosuppression should be avoided or minimized if an infection is identified. Prior history of hypersensitivity or allergic reaction to any of the above drugs may preclude their use.

**Precautions**

Corticosteroid therapy is associated with hypertension, gastric ulcers, hyperglycemia, cataracts, glaucoma, sodium retention, hypokalemia, osteopenia, and aseptic necrosis. Prophylaxis with 112 antagonists, calcium carbonate 1,200 to 1,500 mg qd, calcitriol 0.25 µg qd, bisphosphonate, and hormone replacement in postmenopausal women is recommended. A tuberculin skin test should be performed to screen for tuberculosis exposure before starting chronic corticosteroid treatment. Isoniazid may be necessary for those with positive PPD or history of tuberculosis. Bactrim should be given tiw for those on chronic oral prednisone (over 2 to 3 months). For IVIG, blood pressure, heart rate, and BUN/Cr should be monitored during and after infusion. Azathioprine and methotrexate require monthly liver enzyme and CBC, as leukopenia, anemia, and hepatotoxicity are dangerous side effects. All of these drugs should be prescribed only by individuals experienced with their potential toxicity.

#### ALTERNATIVE DRUGS

- The next best drugs:
  - Azathioprine—1.5-2.0 mg/kg/d PO, or
  - Methotrexate—7.5-15.0 mg PO once a week
- Other immunosuppressive drugs may be useful in steroid failures: cyclosporine, mycophenolate mofetil, tacrolimus, cyclophosphamide, and chlorambucil.

### Follow-Up

**PATIENT MONITORING**

Patients are followed to monitor progression of symptoms, efficacy of therapy, and drug side effects.

**EXPECTED COURSE AND PROGNOSIS**

Partial response (improved strength) to corticosteroids is reported to be 58% to 100% and complete response of 30% to 66% within 6 months. Poor prognostic features include coexisting malignancy, cardiac involvement, lung involvement, and older age. Some patients may require 10 to 30 mg of prednisone qod for 2 or more years to achieve remission.

**PATIENT EDUCATION**


### Miscellaneous

**SYNONYMS**

Idiopathic inflammatory myopathy

ICD-9-CM: 729.1 Myositis

**SEE ALSO:** POLYMYOSITIS, INCLUSION BODY MYOSITIS

**REFERENCES**


Author(s): Ted Woodruff, MD

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**Dermatomyositis**
Developmental Delay

Basics

DESCRIPTION
Developmental delay is a common problem presenting to pediatricians and family physicians. Children with delayed development are usually identified in the preschool years. This review focuses on conditions that have symptoms affecting cognition or language development. Motor delays may be found as part of a global developmental dysfunction or be recognized as a form of cerebral palsy. Although the term mental retardation is little used by the Lay public and educators, it is currently synonymous with global developmental delay in the medical literature. Developmental delay is nonspecific, seldom provides an accurate diagnostic description of a child's disability, and should have restricted formal use as a present ing symptom or in situations where assessment and investigations have failed to yield a definitive diagnosis.

EPIDEMIOLOGY
Incidence/Prevalence
Mental retardation has an incidence of 2% to 3%, with the prevalence of mild retardation being inversely related to family socioeconomic status. Mild retardation affects 85% to 89%. An organic cause can be found in 55% to 75% of children with severe retardation who represent the smaller remaining proportion. Sex
Twice as many males as females are affected.

ETIOLOGY
It is recognized that some children have delayed milestones or exhibit variations from normal. The norms and standard deviations from normal are well documented but, particularly in language development, are variable and broad (for example, lack of speech development in the hearing child may be acceptable to 2 to 3 years of age depending on a variety of factors if receptive language is age appropriate). Disorders of cognition, language, and social development may have many different causes, the common factor being nonprogressive pathology affecting the CNS, including fetal environmental syndromes (in utero infection or toxic exposure), disorders of chromosomal or molecular genetics (Down syndrome and fragile X syndrome), and major brain dysgenesis or malformation. More severely affected children are usually identified in the first year of life. Prenatal factors (including genetic conditions, neurometabolic disorders, neurocutaneous syndromes, and nonchromosomal dysmorphic syndromes) account for 65% to 70% of cases. Prenatal problems (prematurity, birth asphyxia, or injury) cause 10%, with postnatal brain injury (meningitis/encephalitis or trauma) being somewhat less than 10%.

RISK FACTORS
N/A

PREGNANCY
As a significant percentage of conditions with delayed development are prenatal in origin, the pregnancy history is critical to obtain information related to toxin exposures (fetal alcohol syndrome), teratogens (anticonvulsant and other medical treatment), infections (cytomegalovirus), and maternal trauma.

ASSOCIATED CONDITIONS
• Children with developmental delay may present with other disorders affecting brain growth and development. Motor delays may represent the initial symptoms of cerebral palsy (a nonprogressive disorder of movement and posture).
• Language disorders indicate that communication skills are significantly behind cognitive development; stbypes are mixed receptive and expressive disorders, expressive disorders, and conditions in which higher order language processing is affected.
• Autistic spectrum disorders including "classical" autism, pervasive developmental disorders, and Asperger syndrome are characterized by impaired social interactions and communication.
• Other common associated conditions are vision and hearing problems as well as attention deficit and hyperactivity disorders.

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Developmental delay/mental retardation must be distinguished from primary speech and language disorders and autistic spectrum conditions. Children with isolated motor delays require evaluation for neuromuscular disorders (muscular dystrophy, congenital myopathies).
• Broad categories of etiologic diagnosis include malformations of brain development, prenatal infections, or exposure and neurogenetic disorders.
• A careful history is necessary to distinguish delayed development from disorders in which there is a loss of acquired skills and developmental regression (the neurodegenerative disorders of childhood).

SIGNS AND SYMPTOMS
• Development may be globally delayed with involvement of gross and fine motor skills, speech and language acquisition, social or daily adaptive skills. Motor delay is usually noted early in the first year or two of life as a child fails to meet sitting and walking milestones; early identification of delay generally implies a more severe disorder of brain development.
• As the etiology of developmental delay/mental retardation is related to various environmental and genetic processes, the clinical and laboratory investigations must be based on a careful history, and neurologic and developmental examination of the child.
• The pregnancy history may reveal risk factors for poor fetal growth and development. The prenatal, labor, and delivery records should be obtained whenever possible. The results of fetal ultrasound and newborn growth measurements, particularly head circumference, are invaluable in assessing a child who has failed to thrive or has micro- or macrocephaly.
• The comprehensive evaluation of the child's current level of functioning should include physical motor, cognitive, communication (speech and language), and social and play development. It is useful to ask parents to bring photographs or videocassettes that will demonstrate previous developmental skills.
• Family history must be reviewed in detail; it is essential to complete a three-generation pedigree.
• Physical examination is focused on detection of dysmorphic features, major and minor anomalies and organomegaly. Findings on neuromotor examination should clearly localize to the CNS, and rule out myopathy or dystrophic disorders.

LABORATORY PROCEDURES
There is no consensus on the choice of laboratory investigations for developmental delay. The decision to perform diagnostic imaging and laboratory procedures is based on the comprehensive historical and physical examination described above (and should include ophthalmology and audiology assessments). A stepwise approach to minimize unnecessary investigations, should begin with a clinical and neuroimaging workup followed by thoughtful and careful choice of metabolic and cytogenetic/molecular genetic studies. The following are considered screening investigations:
• Cytogenic/molecular genetic
  — Karyotype (standard)
  — Fragile X
• Metabolic screening
  — Serum amino acids, Lactate, ammonia, and very-long-chain fatty acids
  — Urine amino acids, organic acids, oligosaccharides, and mucopolysaccharides

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Developmental Delay

**Imaging Studies**
Screening imaging evaluation includes:
- MRI
- CT
- Skeletal survey

**Special Tests**
Children with developmental delay also need neuropsychological evaluation. Program recommendations and current level functioning are provided by educational, speech, physical, and occupational therapy assessment.

**Management**

**General Measures**
As there are many diverse origins for developmental disorders, management is based on thorough assessment and program planning; for example, the child with an isolated speech delay requires audiology evaluation, communication testing, and focused speech and language treatment programming.

**Symptomatic Treatment**
- General treatment and rehabilitation measures are necessary following assessment recommendations, with educational programming provided in structured classroom environment for the older child.
- The multidisciplinary team approach is considered the most comprehensive assessment and treatment model. Management is usually best arranged and supervised at a special children's treatment center.

**Surgical Measures**
N/A

**Adjuvant Treatments**
Parents who have children with developmental disorders may be assisted in caring for their child through the provision of a variety of nonmedical services, for example, behavioral counseling and respite care.

**Admission/Discharge Criteria**
N/A

**Medications**

**Drug(s) of Choice**
There are no specific pharmacologic treatments for children with developmental delay, although if situations arise when behavioral management methods fail, then psychotropic medication options can be cautiously considered.

**Alternative Drugs**
Many alternative treatments for developmental disorders are available: multivitamins, craniosacral therapy, and pattering treatment. There are no evidence-based studies to support the use of alternative treatment methods.

**Follow-Up**

**Patient Monitoring**
- After a comprehensive diagnostic evaluation and arrangements made for developmental and rehabilitation treatment carried out by an appropriate members of the multidisciplinary team, medical follow-up can focus on general monitoring of expected progress in providing anticipatory counseling. Such issues as the need for formal genetic counseling (in defined disorders) and assessment for requirement for medication intervention with behavioral problems may need to be addressed.
- In cases in which no specific diagnosis is made, a thoughtful tailored reinvestigation should be conducted every 2 to 3 years.

**Expected Course and Prognosis**
N/A

**Patient Education**
Parents of children who have a defined developmental diagnosis should be referred to the appropriate family association and provided with a list of Internet resources.

**Miscellaneous**

**Synonyms**
- Developmental delay
- Mental retardation
- Developmental disability

ICD-9-CM: 319 Unspecified mental retardation; 315 Specific delays in development; 343 Cerebral palsy

**References**

Author(s): Daune L. MacGregor, MD

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Diffuse Lewy Body Disease

**DESCRIPTION**
Diffuse Lewy Body Disease (DLBD) shares a classic pathological feature with idiopathic Parkinson’s disease (IPD), the eosinophilic, cytoplasmic intraneuronal inclusion bodies (precipitates) known as Lewy bodies, but with additional brain regions affected. These two diseases may be difficult to differentiate in the early stages of disease. Neurodegeneration and Lewy body formation are seen in the substantia nigra, locus ceruleus, the nucleus basalis of Meynert, dorsal motor nucleus of the vagus, and cortical regions, including limbic, neocortex, hippocampus and amygdala. There may be coexistent senile plaques.

**Epidemiology**
The incidence, prevalence and other population features (Age, Race) of DLBD are unknown. It has been suggested that this disease is the most common form of dementia with extrapyramidal features and represents the second most common form of dementia after Alzheimer's disease.

**ETIOLOGY**
DLBD is thought to be a disorder on a continuum between PD and Alzheimer’s disease.

**RISK FACTORS**
None known

**Pregnancy**
N/A

**Associated Conditions**
N/A

**Diagnosis**

**Differential Diagnosis**
Includes both disorders of extrapyramidal type and dementing illnesses. • Essential or Familial tremor
- Parkinson’s disease (IPD)
- Drug-induced parkinsonism (e.g. anti-psychotics, anti-emetics, and other dopamine blocking agents)
- Multiple System Atrophy (MSA)
- Progressive Supranuclear Palsy (PSP)
- Vascular parkinsonism
- Post-traumatic parkinsonism
- Wilson’s disease
- Frontotemporal dementia with parkinsonism
- Alzheimer’s with extrapyramidal features (probably a DLBD variant)
- Creutzfeldt-Jakob disease

**Signs and Symptoms**
The clinical symptoms of diffuse Lewy body disease have not been fully characterized. There is extensive clinical overlap with primary dementing disorders and IPD, as well as with other parkinsonian disorders. A combination of parkinsonian manifestations (bradykinesia, tremor, mask faces, gait disorder, rigidity) and early dementia suggest the possible diagnosis of DLBD. Symptoms more characteristic of DLBD include dramatic fluctuations in motor function and mentation that do not coincide with their medication dosing schedule. Patients may have syncope-like spells. Visual hallucinations (sometimes prior to the administration of dopaminergic medication) are common in DLBD.

**Laboratory Procedures**
There are no specific blood tests to diagnose DLBD, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism: serum vitamin B12 level, thyroid function tests, serum ceruloplasmin, 24 hour urine copper excretion.

**Imaging Studies**
There is no evidence to suggest that structural imaging studies (CT, MRI) can assist in the diagnosis of DLBD. PET or SPECT scanning are not specific for DLBD, although some studies have suggested hypometabolism in parietal and occipital regions of DLBD patients in contrast to parietal and temporal hypometabolism in Alzheimer’s patients. MRI imaging may reveal evidence of other causes of parkinsonism and/or dementia such as vascular insults, mass lesions, communicating hydrocephalus, calcium or iron deposition in the striatum, atrophy in the posterior fossa suggestive of multiple system atrophies, and cortical atrophy patterns suggestive of other dementing illnesses.

**Special Tests**
A therapeutic trial of Sinemet, a combination of carbidopa and levodopa, at doses of up to 600–800 mg of levodopa equivalents in 24 hours, is sometimes considered diagnostic of true idiopathic PD when the patient responds with dramatic symptomatic improvement. Patients with DLBD usually have only partial results with anti-parkinsonian agents.

**Management**

**General Measures**
The management of DLBD is complicated by cognitive decline, behavioral changes, and frequent delusions and hallucinations. Management of the parkinsonian symptoms in DLBD is best managed by single agent therapy using carbidopa/levodopa formulations. Cholinesterase inhibitors for the cognitive decline and atypical anti-psychotics for the symptoms of psychosis are useful tools for the management of these difficult cases.

**Surgical Measures**
Not presently an option for DLBD.

**Symptomatic Treatment**
See section below under Medications for a complete discussion of pharmacological therapy of DLBD.

**Adjunctive Treatment**
See section below under Medications for a complete discussion of pharmacological therapy of DLBD.

**Admission/Discharge Criteria**
DLBD is usually managed in an outpatient setting. Rarely, concomitant illnesses (e.g., pneumonia, UTI) can lead to an acute exacerbation of parkinsonian or cognitive symptoms, requiring hospitalization for dysphagia, airway management; confusion and issues of decreased mobility. Psychosis frequently precipitates hospitalization and/or institutionalization.
**Medications**

**DRUGS OF CHOICE**

The parkinsonian manifestations of DLBD may be managed with anti-parkinsonian agents as outlined on the chapter on idiopathic Parkinson's disease (IPD). While such medications may be helpful, they are complicated by side effects in this disorder, particularly confusion and visual hallucinations. Low doses of combination carbidopa/levodopa medications are best tolerated, with relatively increased toxicity from dopamine agonists and anticholinergic preparations in this patient population.

**Carbidopa/levodopa or C/L**: (brand name Sinemet, multiple generic formulations) is the prototype drug and provides the standard of care for people with idiopathic PD. While its use is controversial as a first line agent due to predictable development of motor fluctuations after prolonged exposure to levodopa, it is nevertheless the most efficacious and biologically effective medication available. Doses vary, but patients are usually initiated with 25/100 mg TID and titrating gradually to a total daily dose of dopamine of 300-800 mg. (Note: the 25 mg refers to Carbidopa, and the 100 mg refers to L-Dopa). The complications of levodopa therapy are common to all the dopaminergic agents and include confusion, hallucinations, gastrointestinal distress including nausea and vomiting, orthostatic hypotension, and others. The long-term motor complications associated with levodopa usage include dyskinesias (involuntary abnormal movements) dystonias (abnormal involuntary posturing), on/off symptoms in which medication quits working abruptly, and complicated combinations of all of the above.

**Cholinesterase inhibitors**: are an emerging class of medications for the treatment of dementia. Originally targeted to treat the symptoms of Alzheimer's dementia, the therapeutic benefit of these agents on the cognitive and behavioral features seen in DLBD are being increasingly documented. Except for donepezil, these agents typically need to be taken with food and titrated slowly to their target doses in order to avoid GI side effects. Tacrine: (Cognex, 80-160 mg/day) was the first cholinesterase inhibitor released. It has largely been replaced by newer agents secondary to frequent dosing requirements, poor GI tolerability and potential hepatotoxicity.

**Donepezil**: (Aricept, 5-10 mg/day) is given once daily and occasionally causes GI upset. It can cause bradycardia when used concomitantly with beta-blockers.

**Rivastigmine**: (Exelon, 6-12 mg/day) is given twice daily. It must be given with food in order to avoid nausea and/or vomiting.

**Galantamine**: (Reminyl, 16-24 mg/day) is also given twice daily and should be administered with food. Atypical antipsychotics are used to treat the symptoms of drug-induced hallucinations in PD as well as the spontaneous hallucinations and behavioral disturbances associated with DLBD. These medications are normally given in dosages representing a fraction of that used for patients with schizophrenia.

**Clonazepam**: (Clozaril, 12.5-25 mg/day) is the prototypic atypical antipsychotic. Its use is complicated by the rare, but life-threatening potential side effect of agranulocytosis. Weekly CBC is required during the first 6 months of therapy followed by every two weeks testing thereafter.

**Clozapine**: (Seroquel, 25-100 mg/day) is another atypical antipsychotic currently on the market that, like clozapine, shows no dose-dependent extrapyramidal side effects.

**ALTERNATIVE DRUGS**

**N/A**

**Follow-Up**

**PATIENT MONITORING**

- Some patients with DLBD have a relatively rapid course and will require monitoring every 2-3 months. Psychiatric consultation may assist in the management of DLBD patients.
- By its very nature, DLBD requires steadily increasing doses of medications, for the treatment of dopaminergic deficiency, the side effects of (exogenous) dopaminergic therapy, and especially for expected course and prognosis.

**EXPECTED COURSE AND PROGNOSIS**

DLBD is a progressive, neurodegenerative disorder. DLBD is typically more relentless than Parkinson's disease in its progression, some authors suggesting significant disability—emotionally, cognitively, and physically—by 7-10 years after onset of symptoms.

**PATIENT EDUCATION**

Support groups for parkinsonian disorders are available locally in many areas of the country. There are several large national organizations that provide educational materials to patients and their families. Regular daily exercise has been proven beneficial in alleviating many symptoms of immobility in DLBD, especially when coupled with careful titration and use of proper medications.

**REFERENCES**


Author(s) Lawrence W. Elmer, MD, PhD

**Miscellaneous**

**SYNONYMS**

- Parkinson's with dementia (PDD)
- Dementia with Lewy bodies (DLB)
- Alzheimer's with extrapyramidal features (AD with PD)

ICD-9-CM: 294.10 Dementia conditions classified elsewhere

SEE ALSO: MULTIPLE SYSTEM ATROPHY, PROGRESSIVE SUPRANUCLEAR PALSY

**PROGRESSIVE SUPRANUCLEAR PALSY**

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SEE ALSO: MULTIPLE SYSTEM ATROPHY, PROGRESSIVE SUPRANUCLEAR PALSY

**REFERENCES**


Author(s) Lawrence W. Elmer, MD, PhD
Distal Myopathies

DESCRIPTION
Myopathic disorders usually produce a pattern of weakness predominantly in proximal muscle groups of the arms and legs. However, occasionally patients with myopathies can present with predominantly distal weakness. Several distinct clinical entities were united under an umbrella of distal myopathy syndrome. They include Welander (late adult type I), Markesbery-Udd (late adult type II), Nonaka or familial inclusion body myopathy (IBM) (early adult onset type I), Miyoshi or limb-girdle muscular dystrophy (early adult onset type II), Laing (early adult onset type III), and myofibrillar (Desmin) myopathy with onset varying from childhood to the seventh decade.

EPIDEMIOLOGY
Distal myopathies are rare. Given clinical and genetic heterogeneity of distal myopathies, no specific data on prevalence and incidence are available. Some myopathies were discovered among specific ethnic groups, however. For example, myopathy of Welander type was noted in a large cohort of Scandinavian patients; Markesbery-Udd myopathy was described in English, French, English, and Finnish families; Nonaka and Miyoshi were first reported in the Japanese literature, although a lot of non-Japanese cases were described as well.

ETIOLOGY
Distal myopathies are genetically heterogeneous disorders. Pattern of Inheritance
• Welander, Markesbery-Udd and Laing myopathies demonstrate an autosomal-dominant pattern of inheritance. Nonaka and Miyoshi are inherited in an autosomal-recessive fashion or can be sporadic.
• The pattern of inheritance of desmin myopathy varies from autosomal dominant and sporadic (more common) to autosomal recessive to X-linked.

Gene Localization
Gene localization was determined for Welander (2p13) Markesbery-Udd (2p31), Nonaka (9p1-ql), Miyoshi (2p12-14, 10, and others) Laing (14), desmin (11q21-23-autosomal dominant or sporadic; 2q35—autosomal recessive; 12—X-linked).

Gene Proteins
Several gene proteins were identified. MM (dysferlin) for Miyoshi (located at 2p12-14); HIBM (IBM2) for familial or hereditary IBM; MPD1 for Laing; and TMD for Markesbery-Udd myopathy.

RISK FACTORS
N/A

PREGNANCY
Morbidity during pregnancy might be related to cardiac manifestations (cardiomyopathy and conduction defects) in cases of desmin myopathy. Patients with other forms seem not to be at increased risk for complications during pregnancy.

ASSOCIATED CONDITIONS
Cardiac complications were encountered in numerous patients with desmin myopathy and manifested as conduction defects, syncopal episodes, and cardiomyopathy with associated heart failure. Similar features were described in some cases of Markesbery-Udd and Nonaka myopathies.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
Muscle Disorders
• Facioscapulohumeral dystrophy
• Scapuloperoneal myopathy
• Emery-Dreifuss muscular dystrophy (humeroperoneal)
• Myotonic dystrophy
• Oculopharyngeal dystrophy
• Inflammatory myopathies (inclusion body myositis, polymyositis)
• Metabolic myopathies (debrancher and acid-maltase deficiency)
• Congenital myopathies (nemaline, central core, centronuclear)
Peripheral Nerve Disorders
• Charcot-Marie-Tooth disease
• Acquired neuropathies
Motor Neuron Disorders
• Spinal muscular atrophy (distal adult form)
• Progressive muscular atrophy (distal forms)
• Amyotrophic lateral sclerosis

Disorders Of Neuromuscular Transmission
• Myasthenia gravis (distal form)
• Congenital myasthenic syndrome (slow channel, acetylcholinesterase deficiency)

ASSOCIATED CONDITIONS
Cardiac involvement is common, and sometimes including respiratory musculature. Cardiac involvement is common, and on occasion can precede development of skeletal muscle weakness.

SUGN AND SYMPTOMS
Initial site of weakness and the age of onset vary depending on a type of distal myopathy.
• Welander: weakness begins in the distal upper extremities, usually finger and wrist extensors. Later, distal lower limbs become affected. Involvement of proximal muscles is rare, even as the disease progresses. Muscle stretch reflexes and sensory examination are normal as a rule. The onset of first symptoms is after 40 years of age.
• Markesbery-Udd: weakness starts in the anterior compartment of the distal lower extremities (ankle dorsiflexors) and toe extensors. (Patients present with foot drop and steppage gait.) Can progress to generalized weakness.
• Miyoshi: symptoms develop between the ages of 15 and 25. Initial symptoms are in the distal lower extremity posterior compartment. (Patients cannot walk on their toes or climb stairs.)
• Laing: weakness begins in the anterior compartment of the legs and neck flexors, followed by distal finger extensor involvement. Patients develop weakness between 4 and 25 years of age.
• Desmin: it is unclear if desmin myopathy is a distinct entity. Most patients develop weakness between 25 and 45 years of age, although there are reports of onset in infancy and later in life. It can start in either hands or legs, and usually progresses to proximal muscles, sometimes including respiratory musculature. Cardiac involvement is common, and on occasion can precede development of skeletal muscle weakness.
LABORATORY PROCEDURES

Three tests might be helpful in establishing a diagnosis of distal myopathy:

1. Creatine enzymes (CK). It is normal, slightly, or moderately (3–5 x normal) elevated in all conditions, except Miyoshi myopathy, in which it is increased up to 150 x normal.


3. Muscle biopsy. Myopathic dystrophic features, such as fiber size variability, increased amount of central nuclei, fiber splitting present uniformly. A distinctive but not pathognomonic histologic finding; vacuoles are seen in specimens from patients with Markesbery-Udd and Nonaka myopathies. They might be also present in Welander and desmin myopathy cases. The vacuoles are lined with granular material that is basophilic on staining with hematoxylin and eosin and purple-red with Gomori trichrome stain, or so-called rimmed vacuoles. The vacuoles exhibit acid phosphatase activity. On electron microscopy, in addition to autophagic vacuoles, some patients with Nonaka/familial IBM and Welander have nuclear or cytoplasmic 15–18 nm filamentous inclusions.

IMAGING STUDIES

Neuroimaging is not helpful for making a diagnosis.

SPECIAL TESTS

Although localizations for all distal myopathies and gene proteins for some of them are known, no commercially available genetic tests have been introduced so far.

SYMPTOMATIC TREATMENT

Prophylaxis of contractures includes physical therapy. Occupational therapy is helpful to maximize function as weakness progresses.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Patients with distal myopathies are followed in an outpatient setting. Admissions might be required for treatment of a associated conditions or corrective surgeries (see above).

Management

GENERAL MEASURES

• Lower limb weakness usually requires the use of mobility aids, such as braces, a cane, or a walker within a decade of the diagnosis. A wheelchair is often needed for mobility several years afterward.

• Associated cardiac problems, such as conduction defect and heart failures are to be managed by a cardiologist and might require implantation of pacemaker.

SURGICAL MEASURES

Surgical correction of contractures is possible.

SYNONYMS

Dis tal muscular dystrophies

ICD-9-CM: 359.1 Hereditary progressive muscular dystrophy

SEE ALSO: N/A

REFERENCES


Author(s): Yelena Lindenbaum, MD
Down Syndrome

Basics

DESCRIPTION

Down syndrome (DS) is a genetic disorder involving an extra copy of a region (partial translocation trisomy) or the entire chromosome 21. Classic features observed in DS are phenotypically mapped to the 21q22 band of chromosome 21 (Chr21), known as the critical region. These include:

- Mental retardation (MR)
- Bilateral palpebral (“simian”) crease
- Short digits/extremities
- Bilateral palmar (“simian”) crease
- Chromosome 21 (Chr21), known as the critical region. These include:
  - Mental retardation (MR)
  - Bilateral palpebral (“simian”) crease
  - Short digits/extremities
  - Bilateral palmar (“simian”) crease
- Median epicantal fold
- Midfacial hypoplasia
- Oblique palpebral fissures
- Low/flat nasal bridge
- Protruding tongue
- Congenital heart disease

EPIDEMOLOGY

Incidence/Prevalence

- Incidence: about 1 in 600-1,000 live births
- About 50% of spontaneous abortuses are trisomies (primarily chromosomes: X, 13, 18, or 21). Trisomy 21 has the greatest gestational survival rate (approximately 26%).
- DS is the most common genetically identified type of MR (4-12% of the MR population).

ETIOLOGY

The cause is unknown. Three types of chromosomal abnormalities are observed:

- Aneuploidy
  - Due to meiotic nondisjunction
  - 95% of DS cases
  - Frequency increases with increasing maternal age
  - Nonfamilial
  - Chromosomal Rearrangements
  - Due to unbalanced Robertsonian translocation (partial trisomy 21) between portions of Chr21 and usually Chr14 (11q:21)
  - 4% of DS cases
  - Sporadic in about two thirds of cases; familial in one third
  - Results in trisomy 21
  - Frequency increases with increasing maternal age
  - Mosaicism
  - Typically occurs during embryogenesis or early cell division results in two cell lines: normal and trisomic in about 1 to 2% of DS cases.

RISK FACTORS

- The incidence of trisomy 21 offspring due to maternal nondisjunction correlates with maternal age:
  - **MATERNAL AGE**
  - **INCIDENCE**
  - <30 years old: <1/1,000 births
  - 45 years old: 1/54 births

- Oo third of translocation DS cases are familial involving a balanced carrier parent. The theoretical risk of affected offspring from a balanced carrier parent is (mosaicism 21 is lethal):
  - **OFFSPRING**
  - **THEORETICAL RISK**
  - Female carrier: 20%
  - Balanced carrier: 40%
  - Mosaic: 40%
  - Male carrier:
    - DS: 59%
    - Balanced carrier: 50%
    - Mosaic: 50%

PREGNANCY

- About 31% of females are ovulatory; 39% ovulate regularly.
- Approximately 50% are fertile.
- Infertility may exist in males.

ASSOCIATED CONDITIONS

- Additional physical stigmata:
  - Low-set ears
  - Hypotonia
  - Infantile spasms
  - Brushfield spots (light “speckles” around iris)
  - Congenital medical comorbidities:
    - Cardiac (e.g., atrioventricular defect, tetralogy of Fallot, patent ductus arteriosus, ventricular or atrial septal defects) 40% to 50%
    - Mitral valve prolapse, aortic regurgitation
    - Gastrointestinal (duodenal stenosis, tracheoesophageal fistula): 12°/n
  - Unstable atlantoaxial joint: 12% to 20%
  - Anomalies resulting in sleep apnea
  - Endocrinopathies:
    - Diabetes mellitus/Hypothyroidism: congenital and acquired type, thyroid antibodies
    - Immunologic/hematologic abnormalities: Recurrent infections, Aberrant delayed hypersensitivity reaction: 59%, Viral hepatitis, Leukemia, 1% of children, Anemia
  - Dermatologic (e.g., eczema, psoriasis)
  - Ophthalmologic: 77%; Cataracts: congenital, 3%; acquired, 30% to 60%
  - Dental (e.g., gingivitis)
  - Obesity
  - Hearing deficits: 1590 to 50%
  - Seizures
  - Alzheimer’s disease (AD): neuropathology: in almost all over 40 years old
  - Dementia: about 30% of adults over 40 or 50 years old
  - Psychiatric

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- See chapter on Mental Retardation.

SIGNS AND SYMPTOMS

- MR (mild to severe)
- Low-normal intelligence in about 10% of cases
- Aberrant/delayed growth pattern
- Common physical exam findings:
  - Physical stigmata and comorbid features
    - Mild bradyarrhythmia and hypotension — Heart murmur (congenital or acquired)
    - Microbrachycephaly
    - Gynecomastia
    - Hearing/visual deficits
    - Factory deficits
    - Pyramidal signs secondary to subluxated upper cervical joints

LABORATORY PROCEDURES

- Cytogenetic studies of:
  - All patients to rule out familial partial translocation type
  - Parents: if translocation type revealed
  - Relatives: if carrier parent identified
  - Several tissue samples may be needed for detecting mosaicism.

IMAGING STUDIES

- X-rays of cervical spine (as early as in 2 year olds)
- Consider
  - MRI or CT: if suspect coexisting CNS disease (e.g., seizures, dementia, focal deficits)
  - Gastrointestinal studies: for suspected congenital anomalies

SPECIAL TESTS

- Neuropsychological assessment: typically verbal/nonverbal skills
- Consider:
  - EEG (suspected seizures)
  - Evoked potentials (for neurosensory deficits)
  - Audiometry/ophthalmologic
  - Electrocardiogram
  - Echocardiogram: some recommend in all newborns by the age of 2 months
**Down Syndrome**

**Management**

**GENERAL MEASURES**
- Multidisciplinary approach
- Verbal skills are often inadequate to express symptoms; thorough examination and diagnostic testing are necessary.
- Assess for congenital anomalies and secondary complications.
- Routine vaccinations and consider hepatitis and flu vaccinations.

**SURGICAL MEASURES**
Sometimes required for:
- Congenital anomalies
- Tubes for middle ear effusion
- Subluxated cervical joints

**SYMPTOMATIC TREATMENT**
- Failure to thrive in infants:
  - Consider congenital anomalies
  - Consider surgical correction
- Heart failure:
  - Infants/children: consider congenital heart disease
  - Adults: congenital anomalies or acquired valvular insufficiency
  - Pulmonary hypertension: secondary to pulmonary hypoplasia
- ECG, CXR, ECHO, cardiology consultation
- Dermatologic disorders (e.g., psoriasis, eczema):
  - Topical agents, dermatologic consult
- Bacterial skin infections:
  - Good hygiene, sitz baths, topical antibiotics
- Otis media: close management/monitoring
  - Decongestants
  - Antibiotics
  - Frequently chronic/recurrent:
    - Long-term antibiotic treatment often beneficial
  - Often associated with hearing loss
  - Affecting language/social development
  - May be prevented by placement of tubes for drainage of effusion
- Hypothyroidism:
  - Thyroid replacement therapy
- Seizures:
  - Work up and treat accordingly
- Psychopathology or functional/cognitive decline:
  - Rule out underlying medical/neurologic disease
  - Monitor cognitive/adaptive functioning.
  - If underlying treatable disorder is not revealed, then:
    - Diagnostic workup for AD
    - Obtain psychiatric consultation
    - Address psychosocial/competency issues
    - Depressive symptoms
    - Suspect early AD in adults
    - Conduct serial cognitive screenings before and during treatment

**ADJUNCTIVE TREATMENT**
- Ophthalmologist
- Audiologist/speech therapist
- Consider:
  - Cardiology consult
  - Genetics consultant/counselor for translocation DS subtype
  - ENT specialist for recurrent upper respiratory infections or otitis

**ADMISSION/DISCHARGE CRITERIA**
- Severe congenital anomalies requiring inpatient treatment or surgery

**MEDICATIONS**

**DRUG(S) OF CHOICE**
Nasal decongestants

**Contraindications**
N/A

**PRECAUTIONS**
N/A

**ALTERNATIVE DRUGS**
N/A

**Follow-Up**

**PATIENT MONITORING**
- Thorough annual physical/neurologic examinations monitoring for:
  - Congenital anomalies and secondary or acquired complications
  - Nutritional status, weight, and height
  - In children: signs/symptoms of leukemia (consider annual CBC with differential)
  - Infections
  - Hearing deficits throughout life span (in adults may be premature age-related loss)
  - Consider annual ENT evaluation
  - Geriatric disorders (40 years or older), which can occur prematurely in DS
  - Conduct ECHO by 2 months of age, annual cardiac assessments
  - Fasting glucose and thyroid function test at least every 2 years throughout life span
- Consider annual:
  - Thyroid panel in adults 35 years and older
  - Fasting glucose in adults

**EXPECTED COURSE AND PROGNOSIS**
- Shortened life span. Many survive beyond 50 years old with a few surviving into seventies or eighties.
- Leukemia accounts for low survival in about 1/4 of children with DS.
- Bronchopneumonia is a common cause of death in adults.
- Age-related conditions/disorders occur prematurely in adults (e.g., skin wrinkling, graying of the hair, immunologic aberrations) and neurodegenerative disorders (e.g., macular degeneration and AD) reported to be more prevalent.

**PATIENT EDUCATION**
National Down Syndrome Society:
800-221-4602, www.ndss.org

**Miscellaneous**

**SYNONYMS**
Trisomy 21 (pertains specifically to nondisjunction type of DS)
ICD-9-CM: 758.0 Down syndrome

**SEE ALSO:** N/A

**REFERENCES**

Author(s): Karen L. Br ugge, MD
Dysmyelinating Disorders

**Basics**

**DESCRIPTION**

Dysmyelination of the CNS refers to the production of an abnormal and unstable myelin sheath, often associated with hypomyelination. Frequently of metabolic origin, many dysmyelinating disorders are represented in the sphingolipidoses (see Sphingolipidoses). Four novel disorders are presented: adrenoleukodystrophy (ALD), Pelizaeus-Merzbacher disease (PMD), Canavan disease, and Alexander disease.

**EPIEDEMIOLGY**

**Incidence/Prevalence**

ALD: incidence is not known. Estimates range from 1 in 20,000 to 1.1 in 100,000 births.

**Race**

ALD is panethnic. Canavan disease affects all ethnic groups but is especially prevalent among Ashkenazi Jews and Saudi Arabians.

**Age**

See Signs and Symptoms, below.

**Sex**

Because of X-linked inheritance, patients with ALD and PMD are male.

**ETIOLOGY**

Genetics

ALD and PMD are X-linked. Canavan disease is autosomal recessive. Alexander disease is presumed to be autosomal recessive despite infrequency of involved siblings. Genes for ALD, PMD, and Canavan have been identified. Prenatal diagnosis is available for ALD, PMD, and Canavan disease.

**RISK FACTORS**

N/A

**PREGNANCY**

N/A

**ASSOCIATED CONDITIONS**

N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

The dysmyelinating diseases presented in this chapter must be differentiated from other inherited metabolic neurodegenerative disorders. Additionally, disorders of dysmyelination, which are characterized by the production of an abnormal and unstable myelin sheath, should be distinguished from disorders of demyelination, which are characterized by destruction of apparently normal myelin. Examples of demyelinating disorders in childhood are multiple sclerosis, Devic disease (neuromyelitis optica), acute disseminated encephalomyelitis (ADEM), acute necrotizing encephalomyelitis, and central pontine myelinolysis. Other causes of progressive dementia to consider include encephalitis, chronic infections such as subacute sclerosing panencephalitis (SSPE), exposure to neurotoxins and drugs of abuse, side effects of medications, collagen vascular diseases, and CNS complications of other diseases such as sickle cell anemia and end-stage renal disease.

**SIGNS AND SYMPTOMS**

- **ALD:** Peroxisomal disorder that can cause damage to the CNS and adrenal cortex. Patients present with a history of normal early development with onset of neurologic/behavioral symptoms, commonly hyperactivity, and school failure, between 4 and 8 years of age. Subsequent onset of adrenal insufficiency is seen in 90% of patients. The course is characterized by progressive dementia, visual loss with optic atrophy, pyramidal tract dysfunction, dysphagia, deafness, and seizures. A second phenotype, which is characterized by progressive paraparesis and sphincter disturbance due to spinal cord disease (adrenomyeloneuropathy), is seen in young men.

- **PMD:** Infantile onset variant is the classic form. A prominent, irregular nystagmus and head tremor or head rolling are noted at birth or during the first few months of life. Progressive dementia, ataxia, spasticity, and choreocathetic movements ensue. The connatal variant is present at birth and is much more rapidly progressive.

- **Canavan disease:** Onset of symptoms by 3 months of age. Megalencephaly is common but not invariable (also seen in Tay-Sachs disease and Alexander disease). Lack of psychomotor development, progressive spasticity, optic atrophy, seizures, and dysphagia.

- **Alexander disease:** Patients with the infantile form present between 6 months and 2 years of age with megalencephaly and/or hydrocephalus (the large head is usually due to an enlarged brain but some do develop hydrocephalus due to obstruction at the aqueduct of Sylvius) psychomotor retardation, spasticity, and seizures. A juvenile-onset form and an adult-onset form characterized by progressive bulbar weakness, spasticity, ataxia, and cognitive deterioration are described.

**LABORATORY PROCEDURES**

See Special Tests, below.

**IMAGING STUDIES**

- **MRI in patients with ALD shows characteristic symmetric periventricular white matter lesions in the posterior parietal and occipital lobes.**
- **The MRI in patients with Alexander disease is significant for marked demyelination with frontal predominance.**

**SPECIAL TESTS**

- **ALD: abnormally high levels of very long chain fatty acids in plasma and fibroblasts. Mutation is found in the gene for Aft, which encodes for a transport protein in the peroxisomal membrane.**
- **PMD: tigroid appearance of the white matter on myelin stains because of islands of spared myelin against a nonmyelinated background. Mutation in the gene encoding proteolipid protein.**
- **Canavan disease: deficient aspartoacylase activity in skin fibroblasts. Detection of mutation in the gene encoding aspartoacylase.**
- **Alexander disease: Rosenthal fibers, protein inclusions formed in astrocytic footplates, are the characteristic histologic finding.**
**Dysmyelinating Disorders**

### Management

**GENERAL MEASURES**

Patients with ALD who demonstrate early cerebral involvement by MRI, neuropsychological testing, and/or neurologic exam should be considered candidates for bone marrow transplant. Matched unrelated human umbilical cord blood transplantation may be an option when a suitable bone marrow donor is not available.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

Patients with ALD will usually require treatment for adrenal insufficiency.

**ADJUNCTIVE TREATMENT**

Physical therapy may improve quality of life.

**ADMISSION/DISCHARGE CRITERIA**

Patients are usually admitted for evaluation and treatment of complications of their disease.

### Medications

**DRUG(S) OF CHOICE**

No specific medication treatment is available to slow or stop the progression of these diseases.

**ALTERNATIVE DRUGS**

N/A

### Follow-Up

**PATIENT MONITORING**

Patient follow-up is guided by the predicted course and potential complications of the disease.

**EXPECTED COURSE AND PROGNOSIS**

- ALD: rapid deterioration to a vegetative state once neurologic symptoms become evident.
- PMD: by school age boys are mute and confined to a wheelchair. Patients die of an intercurrent illness in late adolescence or early adulthood.
- Canavan disease: death may occur within the first decade, although survival into the second and third decade is not uncommon.
- Alexander disease: most die in a vegetative state in infancy or during the preschool years. A few children survive to the second decade.

**PATIENT EDUCATION**

- United Leukodystrophy Foundation, 2304 Highland Dr., Sycamore, IL 60178. Phone: 800-728-5483. [www.ulf.org](http://www.ulf.org)
- Canavan Foundation, 600 West 111th Street H8A, New York, NY 10025. Phone: 212-316-6488. [www.canavanfoundation.org](http://www.canavanfoundation.org)

### Miscellaneous

**SYNONYMS**

N/A

**ICD-9-CM:** 330.0 Leukodystrophy

**SEE ALSO:** N/A

**REFERENCES**


Author(s): Eveline C. Traeger, MD
Dystonia

Basics

DESCRIPTION
Dystonia is an involuntary movement characterized by sustained muscle contractions, which may cause twisting, repetitive and patterned movements, or abnormal postures.

EPIDEMIOLOGY
Incidence/Prevalence

Focal dystonia: 24 per million/year
Focal dystonia: 30 per 100,000

Race

Generalized dystonia: 3.4 per 100,000
Focal dystonia: 30 per 100,000

AGE

Dystonia can occur at any age.

ETIOLOGY

Dystonia can represent a specific disease or be a symptom of an underlying nervous system disorder or insult. Most patients with dystonia have primary dystonia, i.e., idiopathic. Primary dystonias are characterized by a lack of both neurologic findings other than dystonia and distinct neuropathology. Primary dystonia may occur sporadically or be inherited. The inherited primary dystonias follow autosomal-dominant inheritance patterns; three gene loci are currently known (DYT1 on chromosome 9q, DYT2 on 8p, and DYT7 on 18p. These all demonstrate low penetrance (30-40%) and variable expression. Only with DYT1 is the gene product known (torsiNA, an ATP-binding protein). The genetic mutation consists of a 3 base pair (GAG) deletion. This mutation, most prevalent among the Ashkenazi Jews, results in early-onset limb dystonia with subsequent generalization. Other inherited primary dystonias include dopa-responsive dystonia (DRD), rapid-onset dystonia-parkinsonism, and myoclonic dystonia. Since these conditions are characterized by additional neurologic findings, they are classified among the dystonia-plus syndromes, which include both sporadic and inherited conditions. DRD is caused by mutations within the gene for GTP cyclohydrolase 1 on chromosome 14 (DYT5 on 14q). This is the rate-limiting enzyme in the formation of tetrahydrobiopterin, a cofactor of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. These patients respond dramatically to low doses of levodopa. A similar but milder common phenotype has been seen with mutations in the tyrosine hydroxylase (TH) gene, resulting in TH deficiency. This autosomal-recessive disorder also responds to levodopa. Less commonly, presentations of dystonia are due to insults to the CNS, i.e., secondary dystonia, or the dystonia may be part of an inherited neurodegenerative disease or an inherited disorder of metabolism. Examples of secondary dystonia are numerous and varied; see Associated Conditions, below. The clinical and family history and presence of other neurologic findings set these conditions, as well as the dystonia-plus syndromes, apart from the primary dystonias.

RISK FACTORS

- Family history of dystonia or other neurologic disease
- Exposure to antipsychotic medications
- Perinatal stress
- Toxin exposure

PREGNANCY

No known relationship of dystonia and pregnancy.

ASSOCIATED CONDITIONS

- Dystonia-plus syndromes
  - Sporadic
  - Parkinson's disease
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Cortical-basal ganglionic degeneration
  - Inherited
  - Dopa-responsive dystonia
  - Rapid-onset dystonia-parkinsonism
  - Myoclonic dystonia
- Secondary causes of dystonia
  - Medications
  - Dopamine receptor antagonists: antipsychotics, antiepileptics
  - Anticonvulsants
  - Levodopa, dopamine agonists
  - CNS infections
  - Perinatal CNS insult; kernicterus
  - Toxins
  - Manganese
  - Carbon monoxide
  - Carbon disulfide
  - Cyanide
  - Methanol
  - Head injury
  - Stroke
  - Multiple sclerosis
  - Brainstem or spinal cord lesions
  - Brain tumor
  - Brain surgery, i.e., thalamotomy
  - Arteriovenous malformation
- Inherited neurodegenerative diseases
  - X-linked recessive
    - "Lbag" or X-linked dystonia-parkinsonism of the Philippines
    - Autosomal dominant
    - Huntington's disease
    - Spinocebellar ataxias
- Dentatorubropallidoluysian atrophy (DRPLA)
  - Autosomal recessive
  - Wilson's disease
  - Hallervorden-Spatz disease
  - Neuroacanthocytosis
  - Ataxia telangiectasia
  - Maternal (mitochondrial) inheritance
  - Leber's hereditary optic neuropathy
- Inherited disorders of metabolism
  - Lipid storage disorders
  - Mitochondrial leukodystrophy
  - Niemann-Pick disease, type C
  - Gangliosidoses
  - Amino acid disorders

DIFFERENTIAL DIAGNOSIS

Other hyperkinetic movement disorders may simulate dystonia:

- Chorea—brief movements that occur continuously and randomly among different body parts
- Tics—brief, intermittent movements or sounds; range from jerks (clonic tics) to sustained contractions (tonic or dystonic tics)
- Paroxysmal dystonia—sudden onset of dystonic movements lasting minutes to hours
- Pseudodystonia
  - Atlantoaxial subluxation
  - Syringomyelia
  - Arnold-Chiari malformation
  - Trochlear nerve palsy
  - Posterior fossa mass
  - Soft tissue neck mass
- Psychogenic

SIGNS AND SYMPTOMS

Dystonia can occur in a wide variety of clinical presentations, e.g., inversion of a foot, excessive blinking, head tilting or turning, a change in speech or handwriting. Dystonia is usually exacerbated by voluntary activity, i.e., action dystonia. This can be a task-specific action dystonia, such as writer's cramp, when only the act of writing results in dystonia. Sometimes activity in one body part results in dystonia in another body part, i.e., overflow dystonia. Eventually, dystonic movements are seen at rest but usually disappear with sleep. Stress and fatigue may result in worsening of the dystonia, while sensory tricks, such as touching the chin in cervical dystonia (the geste antagoniste phenomenon) can relieve it. Dystonia may fluctuate, being minimal in the morning and worsening throughout the day. This diurnal dystonia is a characteristic feature of dopa-responsive dystonia. Dystonic movements may also occur suddenly, lasting for short periods; this is paroxysmal dystonia, which may be inherited as an autosomal-dominant trait or be secondary to medications or underlying neurologic disease.
Dystonia can be classified by distribution:
- Focal dystonia: affects a single body part; examples include cervical dystonia (torticollis); blepharospasm; writer’s cramp.
- Segmental dystonia: affects one or more contiguous body parts; example is cranio cervical dystonia, e.g., blepharospasm and torticollis. Mufti ocular dystonia: involves two or more noncontiguous body parts, for example, foot dystonia and torticollis.
- Generalized dystonia: segmental dystonia affecting one or both legs, the trunk, and one other body part.
- Hemidystonia: affects one half of the body; usually associated with lesion in the contralateral basal ganglia (especially the putamen). Clinical features of the more common dystonias:
  - Cervical dystonia: This is the most common focal dystonia, characterized by turning, tilling, flexion, or extension of the head and neck. Shoulder elevation and scoliosis are common.
  - Cranial dystonia: blepharospasm. A focal dystonia characterized by involuntary contraction of the orbicipularis oculi muscles. It usually begins as an increased frequency of blinking and progresses to clonic contractions of the eyelids, which may become more forceful and sustained. It may impair activities dependent on vision, such as driving and reading. It is often associated with dystonic contractions of other facial/cervical muscles.
  - Limb dystonia: In adults, this manifests as a task-specific action dystonia, occurring with writing, typing, sporting activities, or playing a musical instrument. In children, limb dystonia most commonly presents as inversion of a foot while walking or running.
  - Laryngeal dystonia (spasmodic dysphonia): This manifests either excessive closing (adductor type) or prolonged opening of the vocal cords (abductor type). The former is more common and is characterized by an effortful and strained voice. The latter is characterized by a whispering voice.

Clinical features suggestive of a secondary dystonia:
- Abnormal neurologic findings other than dystonia
- Hemidystonia
- Onset at rest
- Rapid progression
- Initial involvement of legs in adults
- Initial involvement of cranial structures in children
- Speech involved early

**LABORATORY PROCEDURES**

Only needed if there is a suspicion of secondary dystonia
- Serum free copper and ceruloplasmin

**IMAGING STUDIES**

Only needed if there is a suspicion of secondary dystonia due to a strabulum vision
- MRI or CT

**SPECIAL TESTS**

Only needed if there is a suspicion of secondary dystonia
- Urinalysis for 24-hour copper and amino acids
- CSF—lactate, pyruvate
- Slit-lamp examination—Kayser-Fleischer ring
- Skin biopsy—fibroblasts for lysosomal enzymes
- Genetic testing

**MANAGEMENT**

**GENERAL MEASURES**

The majority of patients with idiopathic dystonia are treated with botulinum toxin injections and medications. A trial of carbidopa/levodopa (25/100 mg PO tid) should be considered in children and young adults with limb-onset dystonia for the possibility of DRD. If a secondary dystonia is identified, treatment for that condition is indicated. Surgical therapy is only rarely performed for intractable generalized dystonia.

**SURGICAL MEASURES**

Bilateral pallidotomy

**SYMPTOMATIC TREATMENT**

N/A

**ADJUNCTIVE TREATMENT**

- Physical/Occupational therapy
- Biofeedback
- Braces that mimic the geste antagonist/clue

**ADMISSION/DISCHARGE CRITERIA**

Admission is needed only when dystonia is so severe as to cause my oglobinuria, neuromuscular blocking agents are then required with subsequent mechanical ventilation.

**SPECIAL TESTS**

- Bl epharospasm: 10-15 U per eye
- Cervical dystonia: 100-300 U
- Writer’s cramp: 25-100 U

**MEDICATIONS**

**DRUG(S) OF CHOICE**

- Botulinum toxin—type A
  - Blepharospasm: 10-15 U per eye
  - Cervical dystonia: 100-300 U
  - Writer’s cramp: 25-100 U
- Anticholinergics
  - Trichhexynilidyl: initial dose—1 mg; titrate slowly to 6-12 mg qd in divided doses
- Benzodiazepines
  - Clonazepam: initial dose—0.5 mg; titrate slowly to 1-12 mg qd in divided doses

**CONTRAINDICATIONS**

- Allergies to above medications
- Botulinum toxin contraindicated in:
  - Myasthenia gravis
  - Eaton-Lambert myasthenic syndrome

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**FOLLOW-UP**

**PATIENT MONITORING**

Patients should be seen 3 to 4 weeks after the first injection of botulinum toxin to assess for efficacy and complications. Injections should be given no more often than every 3 months to reduce development of antibodies to the toxin.

**EXPECTED COURSE AND PROGNOSIS**

Dystonia typically starts focally and can remain focal or progress to segmental or generalized. Childhood-onset dystonia is more likely to become generalized, while adult-onset dystonia tends to remain focal or segmental. Dystonia is a lifelong disorder; however, spontaneous remissions can occur occasionally in idiopathic dystonia.

**PATIENT EDUCATION**

The WEMOVE organization: www.wemove.org.
Dystonic Reactions

Basics

DESCRIPTION
Dystonia: involuntary muscular contraction leading to sustained postures that may be associated with writhing/twisting (athetoid) movements. A dystonic reaction (DR) implies that the dystonic activity observed is acute and has an identifiable cause, often medication. Movements associated with DR are often repetitive and appear paroxysmal.

ETIOLOGY

Incidence/Prevalence
DR is commonly seen in psychiatric practice affecting 2% to 12% of patients taking neuroleptics. DR may also occur with other drugs and substances.

Age
Children and young adults are much more vulnerable to this adverse effect of neuroleptics; the elderly rarely develop acute DR to neuroleptics. Predictors of DR for patients receiving neuroleptics, in order of importance: younger patients, male gender, dose, and potency of agent.

Sex
DR from neuroleptic exposure in the context of psychiatric disease favors males (2:1).

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Sex
DR from neuroleptic exposure in the context of psychiatric disease favors males (2:1).

DIFFERENTIAL DIAGNOSIS
Secondary dystonias may begin suddenly, often after some event, such as trauma, and are seen in association with other disorders, such as parkinsonism. Primary dystonias often begin insidiously and are more likely to be related to specific actions (e.g., writer’s cramp). Acute dystonia may occur in the context of Parkinson’s disease as dystonic cramps, often affecting feet in the morning, reflecting low dopamine levels. The signs of DR are dramatic, often frightening, and may be mistaken for seizure activity. However, unlike seizure, the acute DR is not associated with altered consciousness or postictal confusion. Simple partial seizures that are not associated with loss of consciousness may still pose a problem of differentiation. Paroxysmal dyskinesia, a poorly understood movement disorder associated with sudden involuntary movements, may be associated with dystonia. This group of disorders includes paroxysmal dystonic choreoathetosis, paroxysmal exertion-induced dyskinesia, transient paroxysmal dystonia, or torticollis of infancy.

INCIDENCE/PREVALENCE
DR is commonly seen in psychiatric practice affecting 2% to 12% of patients taking neuroleptics. DR may also occur with other drugs and substances.

ASSOCIATED CONDITIONS
Endocrinopathies: hyperthyroidism, hypoparathyroidism, hyperglycemia

LABORATORY PROCEDURES
Investigation should be appropriate for the setting. If a patient has a DR immediately after receiving a neuroleptic agent, no investigation may be indicated. Where the offending agent is not known but strongly suspected, a drug screen is indicated. If the tonic posture (opisthotonus) or other findings suggest a non-drug-related cause (as in the setting of renal dialysis), a search for metabolic or infectious etiologies should be initiated. In the setting of an acute inpatient movement disorder, especially in a young patient, testing may include ceruloplasmin, serum copper, slit-lamp examination (to rule out Wilson’s disease, a treatable entity), creatine kinase, myoglobin, glucose, lactate, pyruvate, uric acid, creatine, liver function studies, erythrocyte sedimentation rate, antinuclear antibody screen (see Dystonia; Torticollis).

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IMAGING STUDIES
• If history and physical examination suggest the possibility of a focal underlying process, such as stroke, MRI of the appropriate anatomic area is indicated. However, for DR that is obviously drug induced, imaging is not required.
• If seizure remains a question on a clinical basis, electroencephalography is indicated.

SPECIAL TESTS
N/A
Dystonic Reactions

Management

GENERAL MEASURES
Treatment of an acute dystonic reaction includes dose adjustment or discontinuation of the offending agent, administration of medication to abort this reaction, and reassurance of the patient as these reactions are often frightening and painful.

SURGICAL MEASURES
• DR, due to neuroleptic agents, is self-limited and does not require ongoing treatment once the offending agent is removed and DR resolves.
• Late-occurring dystonia, tardive dystonia, in the setting of chronic neuroleptic drug exposure, may respond to chemodenervation with botulinum toxin.

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
Admission for observation should be considered for severe DRs for observation and monitoring because of the tendency for waxing and waning and the need for repeated administration of anticholinergic agents.

Follow-Up

PATIENT MONITORING
Patients who have experienced acute dystonic reactions are at higher risk for future reactions when taking neuroleptic medications. The use of prophylaxis with medications such as anticholinergics, antihistamines, or amantadine may be considered if long-term neuroleptic use is required and should be decided on an individual basis.

EXPECTED COURSE AND PROGNOSIS
Most DRs resolve rapidly with treatment as above. Failure to respond to several doses of parenteral anticholinergic medication should prompt additional evaluation.

PATIENT EDUCATION
Patients should be educated about the risk of recurrence of DR with neuroleptic medication.

Medications

DRUG(S) OF CHOICE
Many DRs are frightening, dramatic, may be painful and require parenteral treatment.
• Mild reaction:
  — Diphenhydramine 50 mg PO tid for several days or
  — Benztropine 1-4 mg PO qd/bid (maximum dose 6 mg/d)
• Moderate to severe reactions:
  — Diphenhydramine 50 mg IV, followed by several days of oral treatment
  — Midazolam 2 mg IV
  — Benztropine 1 mg IV q15-20 mins up to 3 doses
  — Biperiden 2 mg IM/IV q 30 min (maximum doses 4 in 24 hours)
• Injectable medications are usually effective within 20 minutes. The effect may occasionally wear off with recrudescence of the dystonic reaction, necessitating a second injection.

Contraindications
• Known hypersensitivity to any of these medications.
• Diphenhydramine should not be used in neonates or nursing mothers.
• Benztropine is contraindicated in patients under 3 year of age.

Precautions
• Antihistamines (diphenhydramine) medications should be used with caution in patients with asthma, increased intracranial glaucoma, cardiovascular disease, hyperthyroidism, benign prostatic hypertrophy, and bladder neck obstruction.
• Acute dystonia related to Parkinson’s disease: the acute dystonic cramp associated with Parkinson’s disease may respond to adjustment medication if related to “off” time or part of a peak dose phenomenon.

ALTERNATIVE DRUGS
Other agents, such as lorazepam, biperiden, and benztropine, may be effective. Consider hospitalization for observation as DR may recur and laryngeal/pharyngeal involvement is possible.

Miscellaneous

SYNONYMS
N/A

ICD-9-CM: 333.7 Dystonia due to drugs; 781.0 Dystonic Movements; 847.0 Dystonia due to trauma

SEE ALSO: PARKINSON’S DISEASE, WILSON’S DISEASE, TORTICOLLIS

REFERENCES
• Tolosa E, Atom J, Marti MJ. Drug-induced dyskinesias in Jankovic J, Tolosa E. Parkinson’s disease and movement disorders, 2nd ed. 1993; Baltimore: Williams & Wilkins, 375-397

Author(s) Peter J. Barb our, MD
Encephalitis

Basics

DESCRIPTION
• Encephalitis is an inflammation of the parenchyma of the brain. CNS function may be affected by direct invasion of the offending organism, vasculitis, hydrocephalus, or demyelination.

ETIOLOGY
• Males and females are equally affected.

Incidence/Prevalence
• There are approximately 20,000 cases of encephalitis each year in the United States. Herpes simplex virus (HSV) is the most common cause of sporadic focal encephalitis in the United States.

Race
• There is no evidence of any ethnic predominance.

Age
• The disease occurs in all ages.

Sex
• Males and females are equally affected.

EPIDEMIOLOGY

• Encephalitis is an inflammation of the brain.

DESCRIPTION

Encephalitis
• HSV-1 encephalitis may occur from the primary infection or with reactivation of latent infection in the trigeminal ganglion with spread to the temporal lobe cortex and limbic structures. HSV-1 caues the majority of cases of HSV encephalitis in adults; in newborns most cases are caused by HSV-2.

• Postinfectious encephalitis may occur after influenza, measles, or varicella, or after immunizations. It is generally thought to be an acute inflammatory, demyelinating disease.

Genetics
• There is no known genetic predisposition for encephalitis.

RISK FACTORS
• Cases of encephalitis are generally sporadic, although outbreaks may occur, particularly with the arthropod-borne viruses. Genera lly, mosquito-borne encephalitis occurs from early summer to early fall, whereas tick-borne encephalitis occurs from spring to early fall. Patients who are immunocompromised, including those with HIV and AIDS, are at increased risk for certain causes of encephalitis, including Acanthamoeba, varicella-zoster virus, CMV, EBV, HHV-6, adenovirus enterovirus us and Toxoplasma gondii.

PREGNANCY
• Little is known regarding encephalitis in pregnancy. Neonatal HSV-2 infection is acquired during delivery by exposure of the fetus to maternal genital secretions. The risk of transmission is much higher during maternal primary infection compared to reactivation.

ASSOCIATED CONDITIONS
N/A

IMAGING STUDIES

• MRI scans of the brain may be helpful in suggesting the likely etiologic organism of encephalitis. For example, in HSV-1 encephalitis high-signal-intensity lesions on T2-weighted images may be localized to the medial and inferior temporal lobes of the brain, whereas Eastern Equine encephalitis generally localizes to the basal ganglia and thalamus. The cranial MRI may be normal early in the course of encephalitis.

SPECIAL TESTS

• Although brain biopsy is the gold standard for diagnosis, it is rarely done. Instead, CSF obtained by lumbar puncture is the most important and accurate diagnostic tool. Opening pressure, Gram stain, CSF culture, protein, glucose, and cell count and differential, and polymerase chain reaction (PCR) for HSV should all be done. Opening pressure typically is mildly to moderately elevated. CSF is generally clear, with up to several hundred white cells/mm³, mostly mononuclear cells, although polymorphonuclear cells may predominate early in the illness. Protein levels are generally normal to mildly elevated, and CSF glucose is generally normal. A hemorrhagic CSF may be seen with HSV encephalitis. PCR assay for HSV DNA may be falsely negative if collected during the first 48 hours of symptoms. The sensitivity of this test is very high if collected during the first 10 days of symptoms and then drops if collected further into the course of the illness.

SIGNS AND SYMPTOMS
• The onset of symptoms is rapid, with fever, nausea and vomiting, headache, and nuchal rigidity all being common. Alterations of consciousness, ranging from confusion and abnormal behavior to coma may be seen, as well as focal or generalized neurologic signs. These may include motor weakness, reflex asymmetry, aphasia, cranial nerve palsies, ataxia, seizures, or cortical blindness. For HSV encephalitis, clinical manifestations may progress over 2-3 weeks.

LABORATORY PROCEDURES
• Baseline blood work should include CBC and differential, blood cultures, serum electrolytes and glucose, liver function tests, and an HIV test. Serum may be sent for specific antiviral IgG antibodies, and determination of the cause of some cases of encephalitis may rely on the demonstration of a fourfold or greater increase in the viral antibody titer between acute and convalescent sera samples for the arthropod-borne viruses, HHV-6, and coxsackieviruses, echoviruses, and enteroviruses 70 and 71.

DIFFERENTIAL DIAGNOSIS

Infectious Etiologies
• Viral meningitis
• Acute bacterial meningitis
• Brain abscess
• Fungal meningitis
• Mycobacterial meningitis
• Primary HIV infection

Noninfectious Etiologies
• Benign or malignant brain tumor
• Cerebrovascular accident
• Sarcoidosis
• Systemic lupus erythematous
• Wegener’s granulomatosis
• CNS vasculitis
• Arachnoiditis
• Migraine
• Drugs, including nonsteroidal antiinflammatory drugs, trimethoprim/ sulfamethoxazole, and OK3
Encephalitis

EEG usually is abnormal and shows diffuse bilateral background slowing, sometimes with epileptiform activity. When HSV-1 is the cause of the encephalitis, periodic complexes with sharp-and-slow waves at regular intervals of 2-3 seconds or focal slowing originating from the temporal lobes may be seen.

Management

GENERAL MEASURES

• A thorough search for epidemiologic, physical, or historical (e.g., travel, seasonal, zoonotic, or entomologic exposures) clues is imperative. No specific therapy other than supportive care is available for most cases. Empiric therapy for the few treatable organisms may be reasonable. Patients should be covered for HSV with acyclovir. If Lyme disease, Rocky Mountain spotted fever, or ehrlichiosis are suspected, doxycycline should be used. Use of amphotericin B should be limited to patients with exposure to lakes or other bodies of fresh water or immunocompromised hosts, unless amebic encephalitis is clinically suspected.

SURGICAL MEASURES

• There are no surgical measures for encephalitis.

SYMPTOMATIC TREATMENT

• If the patient has increased intracranial pressure, hyperventilation, dexamethasone, and hyperosmolar agents are indicated. Seizures are not uncommon in encephalitis and should be managed with standard anticonvulsant therapy. The usual ICU care for comatose patients includes aggressive pulmonary toilet, hydration and natrium, and deep venous thrombosis prophylaxis.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

• Patients are admitted for supportive care and evaluation of the etiology of the infection.

Medications

DRUG(S) OF CHOICE

• Herpes encephalitis: Acyclovir 10 mg/kg IV q8h or foscarnet 60 mg/kg IV q8h for 10-14 days
• Varicella-zoster virus: Acyclovir 10 mg/kg IV q8h for 10-14 days
• Cytomegalovirus: Ganciclovir 5 mg/kg IV q12h for 14 days
• Rocky Mountain spotted fever, ehrlichiosis, Lyme disease: Doxycycline 100 mg IV q12h for 7-10 days; in children under age 8, substitute chloramphenicol 50 mg/kg/day IV divided q6h
• Leptospirosis: Penicillin G 4 million units IV q4h for 7-10 days

Contraindications

• Known hypersensitivity to individual agents

Precautions

• Foscarnet, ganciclovir, acyclovir, and penicillin may all require dose adjustment for renal insufficiency.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

• Once hemodynamically and neurologically stable, close monitoring is not indicated.

EXPECTED COURSE AND PROGNOSIS

• The course and prognosis of the disease is highly variable depending upon the pathogen. The clinical course may range from mild with no sequelae to a rapidly deteriorating course with death or severe neurologic deficits or death. The fatality rate is the highest for Eastern Equine encephalitis with reported rates of 50%-75%.

PATIENT EDUCATION

• National Encephalitis Foundation Inc., 332 North 9th Street, San Jose, CA 95112-3347. Phone: 408-298-260.

SYNONYMS

• Encephalomyelitis

ICD-9-CM: 323 Encephalitis, myelitis, encephalomyelitis; 320.0-320.9 Bacterial meningoencephalitis; 323.0 Encephalitis due to viral diseases; 323.1 Encephalitis due to rickettsial diseases; 323.2 Encephalitis due to protozoal diseases; 323.4 Encephalitis due to infections classified elsewhere; 323.5 Encephalitis following vaccination; 323.6 Postinfectious encephalitis; 323.9 Encephalitis of unspecified cause

SEE ALSO: N/A

REFERENCES


Author(s): Thomas C. Keeling, MD; Susan L. Koletar, MD

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Encephalopathy, Hepatic

Basics

DESCRIPTION
- Hepatic encephalopathy is classified into acute and chronic varieties according to its associated liver abnormality. Acute hepatic failure is characterized by an encephalopathy and coagulopathy within 6 months of the onset of liver disease. A state of fulminating hepatic failure that develops within 8 weeks of the onset of the hepatic dysfunction. Chronic liver disease evolves over a longer time and is associated with a fluctuating course of cerebral dysfunction, although some patients accumulate progressive motor and cognitive deficits.

EPIDEMIOLOGY

Incidence
- Acute hepatic failure affects >2,000 Americans per year. All are encephalopathic, and the mortality is about 80%.
- Conservatively, 1 in 3,000 of the American population is susceptible to chronic hepatic encephalopathy, based on the prevalence of cirrhosis.

Age
- The age range is wide, but most cases with chronic hepatic encephalopathy are middle-aged adults.

Sex
N/A

Race
N/A

ETOLOGY
- Many cases of acute liver are due to acute viral hepatitis or drug-induced liver injury (especially acetaminophen overdose). Less common causes include ischemia of the liver and toxins (e.g., mushroom poisoning or Wilson's disease).
- Chronic liver disease has a more varied association with encephalopathy, and the incidence is not well defined. Most cases are related to alcoholic cirrhosis. GI bleeding is a common precipitant of the encephalopathy in such patients, as this presents an increased load of nitrogen to the hepatic and then systemic circulation. Electrolyte disturbances, drugs (especially sedative drugs), infection, and sepsis are other precipitants.
- The specific cause of the brain dysfunction is not known, but exposure of the brain, via the systemic circulation, to nitrogenous substances (including ammonia and increased aromatic amino acids, which can act as false neurotransmitters) are probable causes. Increased y-aminobutyric acid (GAM), manganese, and opioids in the brain are also proposed to cause brain dysfunction. The cerebral edema that often accompanies acute hepatic encephalopathy is related to osmotic-induced astracytic swelling (probably related to ammonia), as well as brain hyperemia.

RISK FACTORS
- The risk for chronic hepatic encephalopathy is increased after portal-systemic shunting procedures used to treat portal hypertension, especially bleeding esophageal varices, including transjugular intrahepatic portal-systemic shunting (TIPS).

PREGNANCY
- Acute fatty liver of pregnancy occurs late in pregnancy. It is associated with jaundice and a small liver. Often, the fetus is male with a deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase.

ASSOCIATED CONDITIONS
- Hypoglycemia, hyponatremia, pulmonary infections, sepsis, coagulopathy (with bleeding complications, including subdural hematoma) are common accompaniments.
- Hepatorenal syndrome occurs in some cirrhotic patients and consists of worsening azotemia with sodium retention, oliguria, and hypotension. It is probably related to altered renal hemodynamics. The hepatopulmonary syndrome comprises hypoxemia-related right-to-left intrapulmonary shunts associated with increased endothelin-1 and pulmonary nitric oxide.
- Acquired (non-Wilsonian) hepatoencephalopathy associated with cognitive changes, extrapyramidal findings, ataxia, and myelopathy with widespread CNS damage may complicate protracted or repeated bouts of portal-systemic encephalopathy.

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Intoxication with alcohol and drugs
- Infections, e.g., sepsis, meningitis
- Subdural hematomas, especially if bilateral, may be associated with fluctuating level of consciousness without organic lateralized features
- Alcohol withdrawal syndromes
- Other metabolic disorders, including hypoglycemia

SIGNS AND SYMPTOMS
- Acute hepatic failure is characterized by an initial delirium, often with delusions and hyperkinesis. Chronic hepatic encephalopathy shows greater fluctuation, with relapses and remissions over a long period of time, although acute decompensation is also possible. Even at their best, patients with chronic portal-caval shunting show decreased psychomotor speed and deficits in visual perception, orientation, and constructive ability. Disorders of attention underlie these deficits. Some patients develop extra-pyramidal movement disorders, including chorea or athetosis. Asterisks or flapping tremor is a transient loss of tone of muscles, causing the body that is sustained against gravity to slump. This can include the distended arms and wrists, the head on the neck, or the whole body while standing upright.
- There are no stages of hepatic encephalopathy (Table 1).

Table 1 Stages of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>STAGE</th>
<th>MENTAL STATUS</th>
<th>ASTERIXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Euphoria-or depression, mild confusion, slurred speech, disturbed sleep</td>
<td>+/—</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy, confusion</td>
<td>+</td>
</tr>
<tr>
<td>III</td>
<td>Stupor: sleeps but rousable, confused and incoherent</td>
<td></td>
</tr>
</tbody>
</table>

LABORATORY PROCEDURES
- EEG shows typical triphasic waves in adult patients who are moderately encephalopathic, succeeded by diffuse delta (frequencies <4 Hz) and suppression in coma.
- Naladac, liver abnormalities on commonly available biochemical testing, but elevated serum ammonia is highly suggestive.
- Respiratory alkalosis is characteristic.
- Elevated glutamine in the CSF is characteristic, but lumbar puncture often is contraindicated.

IMAGING STUDIES
- CT scanning is helpful in gauging the degree of cerebral edema (cortical sulci less visible, increased visibility of white matter, and basal cisterns obliterated) in acute hepatic encephalopathy. With chronic hepatic encephalopathy there is increased T1 signal in the globus pallidus.

SPECIAL TESTS
- In young patients, Wilson's disease is worth excluding. The diagnosis is made by finding any of the following combinations:
  - Serum ceruloplasmin <20 mg/dL and Kayser-Fleischer rings
  - Serum ceruloplasmin <20 mg/dL and a copper concentration >250 μg/g dry weight on a Liver biopsy sample
  - Compatible clinical picture and urinary excretion <100 μg copper/day in the urine
Management

GENERAL MEASURES
- Decrease ammonia production in the gut. Evacate the bowel with laxatives and lactulose (also helps to convert ammonia to ammonium, which is less well absorbed) and enemas. Use neomycin to kill colonic bacteria.
- Give 2000 ml of glucose IV to prevent and correct for hypoglycemia.
- Restrict dietary protein and give carbohydrate supplements to exceed 1.6 00 cal/day.
- Check for and correct coagulopathy.
- Survey for and treat infections.

SURGICAL MEASURES
- Liver transplantation is appropriate for certain patients with acute hepatic failure (Table 2). Surgery should be done promptly, before the patient develops severe cerebral edema.

Table 2 Criteria for Consideration of Liver Transplantation in Acute Liver Failure

<table>
<thead>
<tr>
<th>Acetaminophen toxicity</th>
<th>pH &lt;7.3 (regardless of coma grade) or prothrombin time &gt;100 sec and serum creatinine &gt;3.4 mg/dL (300 µmol/L) in patients with grade III or IV encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other causes</td>
<td>Prothrombin time &gt;100 sec (regardless of coma grade) and any three of the following: Age &lt;10 yr or &gt;40 yr. Liver failure caused by non-A, non-B hepatitis, halothane-induced hepatitis, or idiosyncratic drug reactions. Duration of jaundice before the onset of encephalopathy &gt;7 days. Prothrombin time &gt;50 sec. Serum bilirubin &gt;17.5 mg/dl (300 µmol/L).</td>
</tr>
</tbody>
</table>

DRUG(S) OF CHOICE
- Induction therapy: Actily, lactulose syrup 30-60 mL is given every hour until diarrhea occurs. Neomycin 0.5-1.0 g every 6 hours is given orally.

ADMISSION/DISCHARGE CRITERIA
- Patients with impaired consciousness require hospital admission, as do patients with acute hepatic failure or disease, in anticipation of encephalopathy. Patients with upper GI bleeding require emergent therapy for the bleeding and careful monitoring for encephalopathy.
- Discharging patients is an individual matter, with due consideration to medical status and support measures being in place.

AlTERNATIVE DRUGS
- Alternative antibiotics such as metronidazole may be worthwhile.

Follow-Up

PATIENT MONITORING
- Actively, patients need to be checked at least daily for clinical level of consciousness. Serial or continuous EEG monitoring offers a sensitive and objective assessment. The Mini-Mental State Examination is commonly used to track attention and concentration, but the Confusion Assessment Method and the Delirium Symptom Interview are alternatives. After discharge, follow-up with a family physician helps to ensure compliance with the treatment regimen.

EXPECTED COURSE AND PROGNOSIS
- Mortality and morbidity are high in patients with all types of hepatic coma. Survivors may be left with neurologic impairment. Severity of encephalopathy, small liver size and epileptiform activity on EEG are unfavorable prognostic features.

PATIENT EDUCATION
- Regular follow-ups, checks for compliance with diet, prompt recognition and treatment of gastrointestinal bleeding and infections, and care with medications are important measures.

SYMPTOMATIC TREATMENT
- Patients with impaired consciousness should be cared for in an intensive care setting with the usual supportive measures.
- Mannitol has limited effectiveness in controlling cerebral edema.
- Consider mild hypothermia as a means of preventing brain hyperemia and increased intracranial pressure.
- Patients with bleeding complications may require transfusions of platelets or fresh frozen plasma.

ADJUNCTIVE TREATMENTS
- Branched-chain amino acid infusions, flumazenil (a benzodiazepine receptor Mocker), hemoperfusion, and extracorporeal liver assist techniques are unproven, but the latter two occasionally can "bridge" the patient who is to undergo liver transplantation.
- Maintenance therapy: Chronic encephalopathy, especially in patients with portal-systemic shunting, can be controlled by regular oral administration of lactulose and reducing dietary protein. Contraindications
  - Avoid sedating drugs, especially benzodiazepines and barbiturates, and any measure that produces a systemic alkalosis, which increases ammonia production from ammonium ion.
- Precautions
  - Avoid hypocalcemia, which increases ammonia production. Vigorous paracentesis may produce electrolyte imbalance and precipitate or aggravate encephalopathy. Prevention of constipation is important. Any patient who is to undergo surgery should be monitored closely and the anesthesiologist informed well in advance of the surgery.

SYNONYMS
- Portal-systemic encephalopathy
- Hepatic coma

ICD-9-M: 572.2 Hepatic coma/hepatic encephalopathy

SEE ALSO: N/A

REFERENCES

Author(s) G. Bryan Young, MD
Encephalopathy, Hypertensive

Basics

DESCRIPTION
• Hypertensive encephalopathy (HE) is a complication of malignant or accelerated hypertension and consists of focal and generalized central neurologic features. It is a medical emergency.

EPIDEMIOLOGY
Incidence
• HE is uncommon, but the exact incidence is unknown. Its incidence has lessened since effective antihypertensive therapy has been more available and more widely utilized.
Age
• HE can occur at any age, even young children. Manifestations are similar for different ages.
Sex
N/A
Race
• Given that hypertension is more prevalent in patients of African origin, HE is likely more common in this population. The racial difference is likely increased where there are discrepancies in medical care.

ETIOLOGY
• HE mainly occurs in the context of sudden elevations in blood pressure. This is common in acute or chronic renal failure, especially with volume overload or with the use of erythropoietin. The sudden withdrawal of some antihypertensives, especially clonidine, a centrally acting a-agonist, may precipitate HE. Other causes include the ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors, sudden BP elevation in patients with pheochromocytoma, and lower gastrointestinal or urinary tract stimulation in paraplegic patients (autonomic hyperreflexia).
• In HE, the normal autoregulation of blood flow through capillaries is overwhelmed, allowing for engorgement of the capillary beds by high-pressure blood flow. This leads to vasogenic edema, fibrinoid necrosis of the walls of small vessels, and focal or multifocal ischemia, possibly due to vasospasm or occlusion of vascular beds by increased interstitial pressure.

RISK FACTORS
• Renal artery stenosis, renal failure, coarctation of the aorta, pregnancy (especially with a previous history of toxemia)

Description

PREGNANCY
• Eclampsia is HE in the context of pregnancy-induced hypertension. Its manifestations are identical to those of HE. The HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome may occur as a complex associated with eclampsia. Intracerebral hemorrhages, often in the posterior cerebrum and commonly fatal, are frequent complications of the HELLP syndrome.

ASSOCIATED CONDITIONS
• HE occurs most commonly in patients with chronic renal failure, pregnancy (toxemia or eclampsia), and immunosuppression or interferon therapy.

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Occipital blindness and seizures occur as complications of cancer chemotherapy, transplantation, transfusion, or HIV-1 infection.
• Focal deficits in hypertensive patients require the exclusion of intracerebral hemorrhage or infarction.
• Occipital blindness, in particular, requires the exclusion of infarction in the posterior cerebral artery distribution.
• HE may mimic amphetamine or cocaine overdose, encephalitis, or cortical venous thrombosis.

SIGNS AND SYMPTOMS
• Clinical features include headache, visual disturbance (especially field defects, blurred vision, and cortical blindness), confusion, focal neurologic signs, and focal, multifocal, or generalized seizures.
• Hypertensive changes are found in the fundus, including papilledema. Papilledema is not always present and is commonly absent in the reversible posterior leukoencephalopathy syndrome.
• Many patients show end-organ damage, including renal dysfunction with proteinuria and cardiac left ventricular hypertrophy and strain if the hypertension has been present for a prolonged period of time.

LABORATORY PROCEDURES
NA

Management

GENERAL MEASURES
• With the clinical picture and exclusion of other processes (mainly by imaging), it should be possible to make a definitive diagnosis of HE. The main therapy is to lower the BP and to stop the ongoing process. Close observation in an intensive care environment, with monitoring of BP, neurologic status, and airway protection, is indicated.
• The cause of the hypertensive crisis should be sought and removed or treated directly, if possible.

SURGICAL MEASURES
• In severe, refractory hypertension or hypertensive crisis, bilateral nephrectomy is sometimes performed. This is a last resort measure because all renal functions (including renal erythropoietin production and vitamin D metabolic activity) will be lost, unless a transplant is performed.

SYMPTOMATIC TREATMENT
• Acute epileptic seizures should be treated. If coma is protracted, EEG monitoring is helpful in detecting and treating nonconvulsive seizures. Antiepileptic drug therapy for ongoing seizures usually begins with lorazepam or diazepam, followed by IV phenytoin (PHT) or fosphenytoin (15–20mg/kg IV of PHT or PHT equivalent). For refractory cases, endotracheal intubation, assisted ventilation, and anesthesia with midazolam, propofol, isoflurane, or pentobarbital may be necessary.

IMAGING STUDIES
• MRI studies commonly show occipital-parietal lobe edema bilaterally that classically involves the white matter. However, the adjacent cortex may also be involved in the reversible posterior leukoencephalopathy or occipitoparietalencephalopathy syndrome.
• Altered blood-brain barrier permeability can be demonstrated using gadolinium (or equivalent large molecule markers with other scanning modalities, such as CT) scans.
• Imaging is helpful in excluding some of the conditions mentioned in the Differential Diagnosis.

SPECIAL TESTS
N/A
Encephalopathy, Hypertensive

ADJUNCTIVE TREATMENTS

- Angiotensin-converting enzyme (ACE) inhibitors are slow in action but appear to have a beneficial effect in blocking vascular permeability in the brain, related to angiotensin II. Furosemide helps to maintain sodium diuresis in the face of declining blood pressure. In renal failure, extra fluid can be removed using hemodialysis or peritoneal dialysis.

ADMISSION/DISCHARGE CRITERIA

- All patients with malignant hypertension and HE should be admitted and preferably managed in an ICU setting. Discharge can be considered when BP is controlled and renal function is stable in the absence of significant permanent neurologic sequelae.

Medications

DRUG(S) OF CHOICE

- Induction therapy
  — Blood pressure is lowered effectively by sodium nitroprusside 0.25-8.0 µg/kg/minute IV, although other rapidly acting, IV-administered antihypertensives, such as labetalol, may be helpful.
  — Eclampsia is best treated with magnesium sulfate 4-5 g IV, followed by an infusion of 1 g/hoe/d for 24 h oes. Alternatively, 10 g is given IM, followed by 5 g IM every 4 hours for 24 hoes. Patients should be monitored for magnesium toxicity by checking for loss of deep tendon reflexes and with serum magnesium concentration determination.

- Maintenance therapy
  — There are six classes of maintenance anti-hypertensive therapy: diuretics, antiadrenergic drugs, vasodilators, calcium channel blockers, ACE inhibitors, and angiotensin receptor antagonists. The appropriate class and specific drug should be selected based on the underlying cause of the hypertension, severity of the hypertension, age of the patient, use of other medications, and goals of therapy. Guidelines were developed by the World Health Organization in 1999.

Contraindications

- Labetalol should not be used in patients with heart failure, asthma, bradycardia, or heart block. Avoid diazoxide in patients with aortic dissection or myocardial infarction (cardiac stroke volume may increase with diazoxide.)

Precautions

- Care should be taken that the DBP does not fall below 95 mm Hg during the acute treatment phase, because this may compromise cerebral or myocardial perfusion.

ALTERNATIVE DRUGS

- Diazoxide 50-100 mg can be given as an IV bolus. The same dose can be repeated in 5-10 minutes, up to 600-mg total daily dose.

Follow-Up

PATIENT MONITORING

- Patients require regular follow-up for BP checks and neurologic review.

EXPECTED COURSE AND PROGNOSIS

- Neurologic prognosis usually is excellent. Most patients recover without neurologic deficits, but small infarcts may produce focal signs and symptoms (uncommon in younger individuals). Most with acute symptomatic seizures do not require long-term antiepileptic drug therapy.

PATIENT EDUCATION

- The importance of regular medical checkups and compliance with medications should be stressed. Weekly blood pressure monitoring in the home by the patient, cohabitant, or visiting nurse is ideal.

Miscellaneous

SYNONYMS

- Reversible posterior leukoencephalopathy
- Occipitoparietal encephalopathy syndrome

ICD-9-CM: 401.0 Hypertensive encephalopathy; 401.0 Malignant hypertension; 642 Hypertension complicating a pregnancy, childbirth, or puerperium

SEE ALSO: NA

REFERENCES


Author(s) G. Bryan Young, MD

175
Encephalopathy, Hypoxemic

**Basics**

**DESCRIPTION**

- Hypoxic-ischemic encephalopathy (HIE) occurs in the setting of cardiovascular arrest. With the advent of cardiopulmonary resuscitation (CPR), large numbers of patients in whom circulation is reestablished are left with injury to the brain. An important duty of physicians in this setting is to establish the prognosis for recovery in a given individual. With cessation of circulation and respiration, an immediate cascade of energy depletion occurs. Lactate elevates, adenosine monophosphate rises, potassium leaks out of cells, and eventually calcium-mediated injury releases enzymes that cause breakdown of cellular fatty acids. Within minutes, neurons sustain irreversible damage that varies with different neuronal populations. Thus, a variety of patterns of neurologic injury occur in the setting of HIE.

**EPIDEMIOLOGY**

- In an observational cohort study in New York City, of 3,243 consecutive out-of-hospital cardiac arrests in a 6-month period, 1.4% survived. Of the in-hospital arrests, about 30% survive the CPR, and 10% survive to discharge. In one cohort of 1,832 patients with CPR, 1,472 died initially, 23 did not awaken after CPR, and of 124 who awoke after CPR, 61 were normal, 28 had moderate disability, and 36 were severely disabled. HIE occurs predominantly in populations at risk for cardiovascular arrest; therefore, it is seen commonly in elderly patients, usually those with cardiac or respiratory diseases.

**Race**

- HIE occurs in all races.

**Sex**

- HIE occurs with equal frequency in male and female populations.

**ETIOLOGY**

- HIE is due to any lack of oxygen and blood flow to the brain for more than a few minutes, as opposed to focal perfusion problems seen in stroke, and different from toxic exposures (such as carbon monoxide) or hypoglycemia.

**RISK FACTORS**

- Ischemic heart disease
- Hypertension
- Hyperlipidemia
- Smoking
- Known ventricular dysrhythmias

**PREGNANCY**

N/A

**ASSOCIATED CONDITIONS**

- See Risk Factors

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Diagnosis usually is obvious and based on the clinical scenario. Differential includes other encephalopathies. In settings such as after open heart surgery, there may be other etiologies of an encephalopathy, such as sepsis, multifocal embolism, and medication effects.

**SIGNS AND SYMPTOMS**

- With resumption of circulation, resumption of brain activity occurs at varied rates. The extent of neurologic recovery ranges from complete cerebral inactivity to rapid resumption of normal consciousness in seconds. Various neurologic syndromes are seen between these two extremes. Amnestic syndrome: a discrete memory disorder may occur, with reduced recall of events before the arrest (retrograde amnesia) and a more profound impairment in acquiring new memories (anterograde amnesia). Due to injury to bilateral hippocampi. Cortical blindness: inability to see despite intact anterior visual pathways. Papillary light reflexes remain normal. In some cases, patients deny blindness (Anton’s syndrome). Due to border zone infarction in distal posterior cerebral arteries. Action myoclonus: sudden, rapid, arrhythmic movement of the limbs, face, or trunk may occur; often after severe global ischemic injury. If the patient is aware enough, myoclonic jerks may occur with attempted movement. Due to widespread ischemic change. Bibrachial paresis (man in the barrel syndrome): occasionally patients show bilateral arm paralysis with relative sparing of leg and face function. Due to injury in the arm areas of the cortex tying in watershed regions between the anterior and middle cerebral arteries. Hypoxic-ischemic leukencephalopathy: a rare syndrome in which, after apparent recovery, within a few weeks patients show progressive intellectual change, involuntary movements, incoordination, and ultimately a vegetative state and death. Due to widespread white matter demyelination and necrosis. Parkinsonian syndrome: patients may develop parkinsonian signs of bradykinesia, rigidity, and gait disorders. Due to injury of basal ganglia. Choreaathetosis: writhing or jerking movements of the limbs or trunk. Due to basal ganglia involvement. Vegetative states: patients in whom no conscious interactions occur after months of survival. SleepWake cycles may occur, but patients do not interact with their environment. Due to severe injury to multiple cortical areas.

**Clinical examination is the key element in assessment of HIE. The neurologic examination is directed primarily toward assessment of the level of responsiveness, pupillary responses, corneal responses, oculocephalic responses (doll’s eyes, cold calories) respiratory pattern, and patter ns of motor response (hemiplegic, decorticate, or decerebrate posturing, flaccid).**

**LABORATORY PROCEDURES**

- There are no specific laboratory findings in HIE. Initial respiratory acidosis and lactic acidosis reverse rapidly with resumption of effective respiratory and circulatory support.

**Pathologic Findings**

- Omalogy there is ischemic neurons, loss of neurons, and occasionally generalized edema. Areas most affected include cerebellar Purkinje cells, hippocampal cells, and certain cortical neuronal populations (layers 3 and 5).

**IMAGING STUDIES**

- CT or MRI show little or no change initially after HIE. Later in the course of disease, either atrophy or white matter demyelination may be seen.

**SPECIAL TESTS**

- Cortical somatosensory evoked responses may be useful in prognosis of HIE. Bilateral loss of cortical peaks (N20 peaks) is consistent with a 100% chance of mortality. In patients with vegetative states, PET scanning may show reduced cerebral metabolic rates. EEG may be used to judge the level of coma. Patterns on EEG, such as burst suppression, a very low voltage pattern, alpha coma, or electrocerebral inactivity, all have a poor prognosis.

**Management**

**GENERAL MEASURES**

- Resumption of circulation and respiration is the key in caring for hypoxic-ischemic encephalopathy. Prevention of recurrent ventricular fibrillation or ventricular tachycardia, or restoration of metabolic status may be necessary. Appropriate intravenous fluid administration and fluid per standard ICU care are necessary. Reducing the risk of nosocomial infections, preventing venous thromboembolism, and avoiding stress peptic ulceration are important. Rapid treatment of fever, hypotension, hypoxemia, and metabolic disturbances aids in preventing secondary neurological damage.
**Encephalopathy, Hypoxemic**

**SURGICAL MEASURES**
N/A

**SYMPTOMATIC TREATMENT**
- If patients are agitated, appropriate sedative medications may be helpful as long as respiration is carefully monitored.

**ADJUNCTIVE TREATMENT**
N/A

**ADMISSION/DISCHARGE CRITERIA**
- Most patients with a cardiac arrest or other cause of acute hypoxemic encephalopathy will require admission to the hospital. Discharge depends on the extent of injury and speed of recovery. Patients with significant hypoxic encephalopathy may require inpatient rehabilitation to achieve an optimal functional status.

**Medications**

**DRUG(S) OF CHOICE**
- Despite multiple studies of various clinical agents, no specific treatments have been shown to be useful in improving the outcome after HIE.

**ALTERNATIVE DRUGS**
N/A

**Follow-Up**

**PATIENT MONITORING**

- Patients with significant HIE should be followed for signs of late deterioration. Usual follow-up is via the attending service or cardiology service.

**EXPECTED COURSE AND PROGNOSIS**

- Clinical outcome from HIE correlates closely with level of responsiveness of the patient. Patients who can be aroused during the first 12 hours after arrest usually do better, although mortality is still about 25%. Patients who are still decorticate, decerebrate, or flaccid and unresponsive at 24 hours have a 7% chance of survival. Absent pupillary response to light or corneal reflex for >6 hours after arrest indicates an extremely poor chance for survival. Any progression of neurologic signs in the first 48 hours denotes a poor prognosis. Other indicators of poor prognosis include the following at day 3 after arrest: abnormal brain stem responses, absent verbal response, absent withdrawal to pain, and age >70 years. Of out-of-hospital arrests, duration of CPR >15 minutes is related to a poor prognosis. Burst suppression or an isoelectric EEG in the first week has a 100% mortality in some series.

**PATIENT EDUCATION**

- Close communication with the patient’s family is key to caring for patients with in HIE. Providing information about the patient’s level of response, results of testing, and prognosis for recovery are key to allowing families to make important decisions regarding care.

**Miscellaneous**

**SYNONYMS**
- Anoxia
- Anoxic brain damage
- Anoxic encephalopathy
- Anoxic ischemic encephalopathy
- Hypoxia

ICD-9-CM: 348.1 Anoxic brain damage

**SEE ALSO:** N/A

**REFERENCES**


Author(s): Alexander D. Rae-Grant, MD
Encephalopathy, Metabolic and Toxic

DESCRIPTION

• Metabolic encephalopathy most commonly is a disorder in which the patient exhibits global neurologic dysfunction, such as confusion, lethargy, or coma, as a result of disruption of a biochemical process or introduction of a toxin. It is also possible for patients to exhibit a focal neurologic deficit due to exacerbation of a previous underlying lesion (e.g., glucose dysregulation causes worsening hemiparesis in a patient with previous recovery from stroke). Many medical conditions can result in encephalopathy, and key to effective therapy is diagnosis of the underlying cause. Encephalopathy may have a single etiology or may be due to multiple metabolic derangements. In multifactorial encephalopathy, the observed cumulative effect often is greater than the individual insults would predict. Patients with preexisting neurologic disease generally have a heightened susceptibility to metabolic or toxic derangements. Some of the potential causes of metabolic and toxic encephalopathy are reviewed in Differential Diagnosis. Several other specific encephalopathies related to disease state are covered in other chapters within this text, including renal dysfunction, hepatic dysfunction, and sepsis.

• The underlying medical problem often is obvious to the clinician. However, some cases of encephalopathy are not readily apparent in origin and require swift diagnosis and treatment to prevent irreversible neuropathic changes.

EPIDEMIOLOGY

• The precise frequency of metabolic encephalopathy is known, but neurologists are commonly consulted in such cases. It occurs frequently in elderly populations, particularly in patients with multiple medical problems or polypharmacy.

ETIOLOGY

• See Differential Diagnosis

RISK FACTORS

• Various medications, advanced age, prior neurologic disease, dementia, various medical diseases

PREGNANCY

• Nausea and vomiting

ASSOCIATED CONDITIONS

• See specific conditions

Diagnosis

DIFFERENTIAL DIAGNOSIS

• The following list reviews a variety of causes of metabolic and toxic encephalopathy. For the specifics of each of these disorders, consultation of subspecialty texts is recommended.

— Glucose misregulation, e.g., hypoglycemia, nonketotic hyperosmolar state, hyperglycemia, diabetic ketoacidosis
— Electrolytes/fluid imbalance, e.g., osmolality/sodium derangements, potassium disorders, magnesium disorders, phosphate disorders
— Endocrine dysfunction, e.g., cortisol abnormalities, thyroid dysfunction, adrenal dysfunction
— Toxic exposures, e.g., iatrogenic, accidental, intoxication, environmental exposure, drug withdrawal
— Pulmonary disease, e.g., pneumonia, pulmonary embolism
— Nutritional deficiency, e.g., vitamin B12, folate, niacin, thiamin (Wernicke's syndrome)
— Psychiatric abnormalities, e.g., bipolar disorder, schizophrenia
— Renal dysfunction
— Sepsis/septic states
— Hepatic dysfunction
— Primary neurologic disease

SIGNS AND SYMPTOMS

• Patients with metabolic or toxic encephalopathy show various stages of altered mental status: confusion, inattention, lethargy, stupor, or coma. They may be delirious, with signs of agitation, hallucination, increased motor activity, and sympathetic overactivity. Brainstem function usually is intact in such patients. Patients who are encephalopathic often show a gradual progression from their normal function to encephalopathy in a variety of degrees from confusion to coma. The patient's mental status may show fluctuation. Early in the development of encephalopathy, the patient may experience minor changes in personality, including mood elevation/depression, mood swings, and inappropriate affect. The patient may proceed to display confusion, inattention, hallucination, delirium, and memory dysfunction. Motor dysfunction is common, including psychomotor retardation, hyperactivity, asthenia, myoclonus, and tremor.

— Extracranial eye movements usually are normal in encephalopathic patients. Patients may exhibit roving conjugate eye movements. Abnormalities of brainstem reflex (loss of doll's eye response, loss of cold water caloric) can occur in severe metabolic encephalopathies but should suggest other disorders, such as brainstem infarction.
— Hypersympathetic function is often observed in metabolic and toxic encephalopathies, with tachycardia, hypertension, diaphoresis, hyperreflexia, and clonus exhibited on examination.
— Abnormalities in breathing patterns are encountered with metabolic and toxic dysfunctions. These include, but are not limited to, apnea, sustained hyperventilation, and Cheyne-Stokes respiration (crescendo-decrescendo breathing with intervening periods of apnea).

LABORATORY PROCEDURES

• Chemistry laboratory examinations: basic metabolic profile and liver function testing, including electrolytes, glucose, calcium, and magnesium; include ammonia level
• Hematologic evaluation: should include CBC, platelets, differential, and peripheral smear • Arterial blood gas: assists in establishing the acid/base status as well as oxygenation and ventilation
• Urine or serum toxicology: depending on the patient's history, ethanol, drugs of abuse, expanded toxicology, or specific drugs (or metabolites) should be investigated
• Cultures of blood, urine, sputum, or wounds
• ECG: The clinician should look for baseline rhythm, as well as any signs of foci implying an ischemic event.
• Additional specific tests if ingestion is suspected. Check with local poison control.

IMAGING STUDIES

• Head CT: In patients with metabolic encephalopathy, head CT usually is normal. If clinical examination shows focal signs not explained by previous historical details, then contrast may be needed to assess for focal lesions. Caution must be used with contrast, because it may worsen the underlying condition and metabolic encephalopathy.
• MRI: If the patient has focal deficits, MRI can provide more substantive information on brain parenchyma. MRI also allows better visualization of the brainstem when the clinical examination suggests involvement.
Encephalopathy, Metabolic and Toxic

SPECIAL TESTS
- Lumbar puncture: include evaluation of glucose, protein, cell counts, lactic acid, and culture. The opening pressure should be noted to evaluate increased intracranial pressures. Other specific tests should be performed as guided by the patient's history and examination (e.g., Lyme disease, syphilis). Before the patient undergoes a lumbar puncture, a head CT should be obtained to rule out possible sources for herniation, such as large focal mass lesions.
- EEG: useful in ruling out seizure activity (e.g., nonconvulsive status epilepticus). It also is helpful to look for signs of generalized dysfunction. Although the EEG rarely yields the specific cause of encephalopathy, it is useful for categorization and prognostication. Once the etiology has been determined and the treatment initiated, EEG can be a useful tool to determine improvement over time.
- Brainstem auditory evoked responses (BAER): can assist the neurologist in localization of brainstem abnormalities.

GENERAL MEASURES
- Once the underlying cause of the metabolic or toxic encephalopathy has been determined, the treatment should be directed toward it. Thus, the treatment will be variable depending on cause. In general, avoid, if at all possible, sedating agents while the workup is in progress so as not to confound the clinical examination. If agitation prevents adequate medical or surgical care of the patient, short-acting sedative/anxiolytic agents, such as midazolam, propofol, or fentanyl, are more desirable than agents with prolonged effects.
- If the patient's mental status is so depressed as to prevent adequate protection of the airway, intubation and mechanical ventilation should be used.

SURGICAL MEASURES
- No specific surgical measures are needed.

SYMPTOMATIC TREATMENT
- Specific treatments for septic, renal, and hepatic encephalopathies are discussed elsewhere. In patients with exposure to toxins, antidotes may be available (contact the local poison control center), or the patient may benefit from hemodialysis.

ADJUNCTIVE TREATMENT
- Depends on the underlying cause of encephalopathy

ADMISSION/DISCHARGE CRITERIA
- Close monitoring of the neurologic examination is essential in patients with encephalopathy. As the patient becomes more lethargic, obtundation and airway protection may become a crucial consideration. Thus, if a patient is having a progressive decline in mental status, admission to a neurology or medicine critical care unit is highly recommended.

FOLLOW-UP
- Patients often exhibit a hypersympathetic state; thus, monitoring of heart rate and BP should be done frequently. The nursing staff should be trained to perform a thorough neurologic evaluation if they are not commonly asked to make this evaluation.

EXPECTED COURSE AND PROGNOSIS
- Although metabolic encephalopathy is one of the most frequently encountered entities in critically ill patients, it is most often not necessarily fatal. If the underlying metabolic or toxic origin can be ascertained and treated, the patient has potential for complete recovery. The cause of death in patients who are critically ill and die from an encephalopathy is often neurologic.

PATIENT EDUCATION
- N/A

REFERENCES

Author(s): Teresa L. Smith, MD; Bradford Worrall, MD, MSc
Encephalopathy, Progressive Pediatric

**Basics**

**DESCRIPTION**
- Encephalopathy is a generalized cerebral dysfunction that may be static or progressive in nature. Progressive encephalopathies in childhood affect the gray matter (poliodystrophies), white matter (leukodystrophies), or both.

**ETIOLOGY**
- Lysosomal storage disorders are seen as often as 1 in 7,000. Total incidence of neurodegenerative disorders approaches 1 in 1,000.

**Genetics**
- Storage Disorders
  - Lipidoses: Excess lipid forms due to specific lysosomal enzyme deficiencies and is stored in the gray matter nuclei.
  - Hexosaminidase A deficiency (Tay-Sachs disease), hexosaminidase B deficiency (Sandhoff's disease)
  - Sphingomyelinase deficiency
  - Trihexosidase deficiency (Fabry's disease)
  - Glucocerebrosidase deficiency
  - Gaucher's disease
  - Trihexosidase deficiency (Fabry's disease)
  - Neuronal ceroid lipofuscinoses (NCL).
  - Various forms (Batten disease, Jansky-Bielschowsky, Kufs, etc.).
- Mucopolysaccaridoses: Hunter disease (MPS II; Gaucher's disease)
- Pelizaeus-Merzbacher leuкоdystrophy: (autosomal recessive)
- Sanfilippo disease (MPS III), Morquio (MPS IV; accumulation of various substances.
- Metachromatic leuкоdystrophy: (autosomal recessive) deficiency of arylsulfatase results in storage of sulfate in myelin — Krabbe disease or glioblast cell leuкоdystrophy: (autosomal recessive) deficiency of Q-galactocerebrosidase.
- X-linked adrenergic leuкоdystrophy: increased plasma very-long-chain fatty acids — Alexander disease: leuкоencephalopathy with megalencephaly, unknown etiology.
- Metabolic encephalopathies: predominantly autosomal recessive defects
  - Aminoacidopathies
  - Organic acidemias
  - Urea cycle defects

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Static encephalopathies caused by nonprogressive neurologic insult
- Mental retardation of genetic etiology
- Seizure disorders and migraine variants
- Acute encephalopathies (deltirum)

**RISK FACTORS**
- Genetic predisposition
- Measles, rubella, HIV, and other viral infections/vaccination

**PREGNANCY**
- Transmission of infectious agents can occur.

**ASSOCIATED CONDITIONS**
- Seizures
- Visual changes/ophthalmoplegia
- Ataxia
- Hypoponita/spasticity
- Myoclonus
- Dysmorphic features
- Micro/macrophagia
- Peripheral neuropathies
- Cutaneous or visceral manifestations

**LABORATORY PROCEDURES**

**Blood**
- Electrolyte panel to check for acidosis
- Serum amino acid levels
- Lactate, Pyruvate
- Ammonia Levels
- Lysosomal enzyme assays in white cells
• Very-long-chain fatty acids
• Serum ceruloplasmin levels
• Ultrastructure of lymphocytes reveal membrane-bound inclusions of lysosomal storage, curvilinear, fingerprint, or granular patterns in coroid lipofuscinoses, and abnormal mitochondria in mitochondrial disorders

**Urinary**

• Urine organic acids
• Excretion of dextran and heparan sulfate
• N-acetylaspartic acid
• CSF
• Glucose, Protein
• Lactate
• Viral polymerase chain reaction (PLR) and viral antibody levels

**IMAGING STUDIES**

• MRI usually is necessary:
  —Poliodystrophies: MRI may show cortical atrophy, widening of sulci and fissures, increased extraaxial fluid and atrophy, and altered signal intensities in deep gray matter.
  —Leukodystrophies: MRI may show altered signal intensities in white matter (unifocal, multifocal, cortical).***

**SPECIAL TESTS**

• EEG may demonstrate pathognomonic epileptiform discharges and patterns in various neurodegenerative disorders. West syndrome (an epileptic encephalopathy): hypersynchronia. Lennox-Gastaut syndrome: slow spike-and-wave pattern. Periodic spike and/or slow wave complexes are seen in SSPE and OD.
• Ophthalmologic examination may reveal retinal cherry-red spot (e.g., Tay-Sachs disease), Niemann-Pick disease, retinal degeneration, ophthalmomolgia (e.g., KSS), and optic atrophy (e.g., Krabbe disease).
• Nerve conduction studies may show peripheral nerve involvement.
• Evoked potentials demonstrate abnormalities depending on the etiology.
• Biopsy of tissue (skin, conjunctiva) will reveal abnormal intracellular inclusions and accumulation of abnormal materials in the various storage diseases. Muscle biopsy will reveal ragged red fibers in mitochondrial disorders.
• Genetic testing, including mitochondrial DNA analysis, is available for the majority of the disorders. Prenatal diagnosis is potentially available for all of the disorders with known genetic defect.
• Neuropsychological testing should be performed to assess the progression of deficits in the various cognitive domains.

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**Management**

**GENERAL MEASURES**

• Gene modulation: experimental.
• Enzyme replacement and bone marrow transplantation have been attempted, particularly in the leukodystrophies.
• Vitamin supplementation with coenzyme Q, folate, thiamin, and vitamin C has been tried, particularly in mitochondrial encephalopathies. Sodinol nite and vitamin E have been suggested in Batten disease.
• Dietary modification in cases of defects in glucose metabolism, aminoacidopathies, organic acidemias, and other inborn errors of metabolism is directed toward the specific defect. Glycerol and citrate has been tried in adrenoleukodystrophy.
• Lactic acidosis is managed with oral sodium bicarbonate or sodium citrate.
• Wilson's disease is treated with the copper chelating agent penicillamine.
• HIV encephalopathy is treated with antiretroviral drugs.
• HIV encephalopathy antiretroviral drugs.
• The other viral encephalopathies have no proven therapy, but immunomodulation with agents such as interferon, cimetidine, and isoxsuprine have been used.

**SURGICAL TREATMENT**

• Diagnostic biopsies and other supportive measures, such as CSF shunt procedures and tendon release procedures for spasticity.

**SYMPTOMATIC TREATMENT**

• Seizures are treated with anticonvulsants. Valproic acid usually is the first line of antiepileptic drug therapy. Other anticonvulsants, such as lamotrigine, topiramate, and felbamate, are used for difficult-to-control seizures.
• Spasticity can be treated with muscle relaxants, such as baclofen and tizanidine.

**ADJUNCTIVE TREATMENT**

• Rehabilitation with physical, occupational, and speech therapy.

**ADMISSION/DISCHARGE CRITERIA**

• Treatment of intractable seizures.
• Progressive deterioration of mental status.
• Acute respiratory distress.
• Infections.
• Discharge to home or facility usually requires extensive nursing facilities.

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**Follow-Up**

**PATIENT MONITORING**

• Serial neuroimaging, cognitive testing, visual examinations, and blood levels can be used to monitor these patients.

**EXPECTED COURSE AND PROGNOSIS**

• The progressive course of these disorders may be protracted over several years or rapidly deteriorate in a matter of months in the more aggressive types. The infantile forms of most of the neurodegenerative diseases are notoriously relentless with a rapid downhill course. There is usually a progression of worsening of neurologic deficits, intractable seizures, stupor, and coma. Death often occurs as a result of respiratory compromise.

**PATIENT EDUCATION**

• Most of the individual diseases have support groups and organizations that help disperse knowledge. Examples include:
  —Batten Disease Support and Research Association
  —National Gaucher Foundation
  —United Leukodystrophy Foundation
  —National Organization for Rare Disorders
  —International Rett Syndrome Association

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**Miscellaneous**

**SYNONYMS**

• Neuromuscular disorder
• Childhood dementia

ICD-9-CM: 330.0 Childhood cerebral degenerations, leukopoliocencephalopat
330.1 Cerebral lipidoses

**REFERENCES**


Author(s): Akita Venkataraman, MD; Steven G. Pavlakis, MD
### Encephalopathy, Renal

#### Basics

**DESCRIPTION**
- Renal encephalopathy is the occurrence of CNS dysfunction associated with either renal failure itself or the dialysis process. Renal patients may have other diseases causing encephalopathy.
- Acute uremic encephalopathy is suggested by development of daily to hotly flux, touting signs, including lethargy, confusion, irritability, hyperventilation, ataxia, myoclonus, and/or seizure. It appears to correlate with the rapidity with which renal failure ensues, rather than any single laboratory abnormality.
- Dialysis dysequilibrium syndrome (DOS) consists of headache, muscle cramps, disorientation, asterixis, somnolence, and possibly severe symptoms including frank psychosis, stupor, or generalized seizures that occur during or after dialysis.
- Progressive dialysis encephalopathy (POE) or dialysis dementia is related to the use of aluminum as both a phosphate-binding agent and as a constituent of water used in the dialysis procedure. Its initial presentation is effortful speech with word-finding difficulties (in 93% of patients). Behavioral changes include depression, paranoia, apathy, and somnolence. Myoclonus begins in the upper extremities and then becomes multifocal. Other manifestations may include parkinsonism, ataxia, and seizures.

**ETIOLOGY**
- Acute uremic syndrome: Several compounds, such as urea itself, purines, guanidine, and phenols, may have toxic effects on the nervous system. Possible methods of action include disturbed energy balance, altered sodium transport, increased blood-brain barrier permeability, increased exposure to aluminum, increased brain calcium, and decreased brain magnesium. These imbalances may alter neuronal transmission.
- Dysequilibrium syndrome: There is an increase in water content in the brain parenchyma as a result of changes in osmolarity during dialysis. As the solutes are greater in the brain than in the plasma, the net flow of water into the brain occurs over a lag time created by diffusion of osmotically active particles from the brain into the extracellular spaces.
- Progressive dialysis encephalopathy: The exact mechanism of PDE remains unclear despite the implication of aluminum. Neurofibrillary degeneration similar to Alzheimer's disease (AD) may occur in PDE. The aluminum deposits in PDE are intracytoplasmic rather than intraneuronal as seen in AD, giving support to the theory that th is may be aluminum-mediated neurotoxicity.

**RISK FACTORS**
- Patients are more likely to suffer dysequilibrium syndrome soon after initiation of dialysis. Aluminum in the dialysate is a risk factor for PDE.

**PREGNANCY**
- N/A

**ASSOCIATED CONDITIONS**
- Uremic neuropathy
- Restless leg syndrome

#### Diagnosis

**DIFFERENTIAL DIAGNOSIS**

**Acute Uremic Syndrome**
- Hypertensive encephalopathy
- Septic encephalopathy
- Diabetic ketoacidosis
- Thrombocytopenia purpura/hemolytic uremic syndrome
- Anoxia
- Circulatory failure
- Toxin exposure (methanol, salicylates, paraldehyde, formaldehyde, ethylene glycol)

**Dysequilibrium Syndrome**
- Depression
- Hypotension induced hypoxic ischemic encephalopathy
- Air embolism
- Subdural hematoma
- Hypermotremia or hyponotremia
- Wernicke's encephalopathy
- Hypoglycemia

**Progressive Dialysis Encephalopathy**
- Subdural hematoma
- Wernicke's encephalopathy
- Hypercalcemia/hyperparathyroidism
- Depressive psychosis
- Alzheimer's dementia
- Creutzfeldt-Jakob disease
- Multifocal ischemic disease

**SIGNs AND SYMPTOMS**

<table>
<thead>
<tr>
<th>Acute Uremic Syndrome</th>
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<tbody>
<tr>
<td>Lethargy followed by inattention and confusion</td>
</tr>
<tr>
<td>Delirium and hallucinations</td>
</tr>
<tr>
<td>Motor manifestations such as myoclonus, carpopedal spasm, and asterixis</td>
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<tr>
<td>Sleep disturbance</td>
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<tr>
<td>Catatonia (rare)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dysequilibrium Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>General: headache (diffuse, throbbing, or similar to preexisting migraines), nausea, vomiting</td>
</tr>
<tr>
<td>Mental status: irritability, agitation, disorientation, drowsiness</td>
</tr>
<tr>
<td>Ocular findings: exophtalmos, increased intraocular pressure, papilledema</td>
</tr>
<tr>
<td>Other: seizure, coma, psychosis, death</td>
</tr>
</tbody>
</table>

**Progressive Dialysis Encephalopathy**
- Speech disturbance: decrease fluency, word-finding difficulty, word substitution, dysarthria, stammering
- Motor abnormalities: myoclonus (upper extremities affected first), athetoid movements, asterixis, gait disturbance
- Behavioral changes: apathy, depression, paranoia, somnolence, directional disorientation

**LABORATORY PROCEDURES**
- General chemistry panel: This will enable the clinician to look at electrolyte abnormalities, blood urea nitrogen, and serum creatinine.
- Arterial blood gas: The patient's acid-base status can be evaluated along with any signs of hypoxia and hypercapnia.
- Urinalysis with microscopic examination: The information obtained can assist with determining the cause of renal failure.
- Drugs of abuse screen and toxin screen.
- Serum aluminum level may be of assistance in the patient suspected of having PDE.
- Other rule-out investigations include blood cultures and CSF examination (see below).

**IMAGING STUDIES**
- In isolated renal encephalopathies, brain imaging often is unrevealing. Given the possibilities within the differential diagnosis, a head CT can point to another source for the physical examination changes (intracranial hemorrhage, stroke, subdural hematoma, subarachnoid hemorrhage). Imaging studies do not show specific changes in renal encephalopathy syndromes.

**SPECIAL TESTS**
- EEG shows a diffuse or focal slowing of background rhythms and spindles, a bitemporal or bitemporal-hemispheric burst of high-voltage slow wave. Generalized epileptiform activity is seen in one third of patients with acute uremic syndrome but rarely seen in adults. In PDE, the most common reported finding is a frontally predominant rhythmic delta. Triphasic waves also are seen in these encephalopathies, although they are more common in hepatic encephalopathy.
Encephalopathy, Renal

Management

GENERAL MEASURES

Acute Uremic Encephalopathy
- Identify the cause of the acute renal failure. Once the acut e cause has been established, treat if reversible (e.g., obstructive uropathy or use of medi cation such as meperidine, acyclovir, magnesium, chronic NSAID).
- Dialysis if the patient has been exposed to a nephrotoxin or has acidosis, electrolyte imbalance, or fluid overload.
- Establish good urine flow by spoor of hemodynamic parameters.
- Maintain adequate natrium to prevent further protein catabolism.
- Treat seizures if they occur. Dilantin is an acceptable choice because it is does not have active metabolites, but free levels must be monitored due to the decreased protein binding of dilantin in uremia. Dilantin should be dosed at q8h in this patient population.

Dysequilibrium Syndrome
- Avoid rapid osmotic shifts from the plasma to the brain.
- Increase the osmolality of the dialysate by adding urea, sodium, mannitol, or glycerol.
- Decrease the flow rate during dialysis.
- Avoid hypotonic solutions.
- Consider using hemofiltration rather than hemodialysis.

Progressive Dialysis Encephalopathy
- Undertake preventative strategies.
- Monitor aluminum concentrations in dialysates.
- Avoid aluminum-containing antacids.
- Consider treatment with deferoxamine to chelate aluminum.
- Consider renal transplantation.

SURGICAL MEASURES
- If the cause of the patient’s acute illness can be treated with dialysis, the clinician must establish a vascular access.

SYMPTOMATIC TREATMENT
- Dialysis or other measures as prev iously discussed above.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
- If a patient is showing signs of encephalopathy that are not reduced by the regular dialysis session, hospital admission is warranted for workup of alternative causes of encephalopathy and to monitor potential progression of the patient’s clinical state.

Meditations

DRUG(S) OF CHOICE

Dilantin: Although not typically needed, if the patient is having recurrent seizures then loading with dilantin is a reasonable action. Dilantin dosage should be adjusted for the patient’s level of liver dysfunction and administered in three doses 8 hours apart. Typical loading dose for seizures is 15-18 mg/kg. May use fosphenytoin to avoid superficial phlebitis. In adults, initial dose is 100 mg PO tid, monitor free levels to achieve a therapeutic dose.

Thiamine: Because thiamine is significantly water soluble, thiamin replacement should be given to patients undergoing dialysis. Wernicke’s encephalopathy, although infrequent, has been observed in both children and adults on chronic dialysis.

Deferoxamine: This chelating agent is used in patients who are suspected of having elevated aluminum levels producing a dialysis dementia syndrome. The weekly dose is 4-6 g, with 1-2 g given IV during the last 2 hrs of dialysis.

Precautions
- Be aware of various side effects of dilantin or other seizure medications used.

Contraindications
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
- Although PDE has been described with a wide range of aluminum concentrations (15->1,000 µg/L) following aluminum levels may still be useful to the clinician.

EXPECTED COURSE AND PROGNOSIS
- The outcome for patients with renal encephalopathies can be excellent, provided there are few other comorbid conditions (such as GI bleed or sepsis). Mortality from acute renal failure without intervening illness is only 10%. Most patients recover from their encephalopathy after dialysis. Issues such as hypotension during dialysis can create additional problems, including ischemic stroke, which may preclude a complete recovery. Reversal of PDE has been reported after renal transplant.

PATIENT EDUCATION
- Diet suggestions and recipes can be found at the following website: www.rockwellmed.com/links.htm
- More information can be obtained from a search of the FDA’s website: www.fda.gov/default.htm

Miscellaneous

SYNONYMS
- Uremic encephalopathy or acte uremic encephalopathy
- Dialysis dysequilibrium syndrome
- Dialysis encephalopathy
ICD-9-CM: 348.3 Unspecified encephalopathy; E879.1 Kidney dialysis as a cause of abnormal reaction of patient; 38.95 Venous catheterization for dialysis

SEE ALSO
N/A

REFERENCES

Author(s) Teresa Smith, MD;
Bradford Worrall, MD
Encephalopathy, Septic

### Basics

**DESCRIPTION**
- Septic encephalopathy refers to the alteration of brain function in the presence of microorganisms or their toxins in the blood. It is generally a diagnosis of exclusion, as a number of conditions may exist in a febrile patient to account for the encephalopathy.

**EPIDEMIOLOGY**
- The incidence of septic encephalopathy is not precisely known, but its occurrence probably is underestimated. It is a common reason for neurologic consultation in the ICU.

**ETIOLOGY**
- The etiology is multifactorial.
  - CNS infection: By definition, in order to make a diagnosis, one should rule out any CNS infection. This can generally be done with CSF evaluation. However, some patients with septic encephalopathy (especially those with a protracted course) have been found to have cerebral microabscesses at autopsy despite normal CSFlinte mortem. This has not been a consistent finding, and septic encephalopathy occurs in noninfectious causes of sepsis such as pancreatitis.
  - Metabolic dysfunction: In patients with multiorgan failure, secondary metabolic disarray may manifest as altered mental status. However, encephalopathy can be the first manifestation of sepsis prior to significant organ failure. One possible explanation is that hepatic dysfunction that occurs early in sepsis is difficult to recognize with available tests. Electrolyte disturbances are commonly detected in sepsis. Total parenteral nutrition is associated with hypophosphatemia and hyperosmolality. At autopsy, central pontine myelinolysis has been found in some patients. It is critical to recognize that the cumulative impact of metabolic disarray in sepsis may exceed the sum of the individual abnormalities.
- Alteration of the blood-brain barrier: Cytokines and other factors such as nitric oxide are released by cells during sepsis and increase the permeability of cerebral endothelial cells. Chemicals, both endogenous and exogenous, normally excluded from the brain may enter and influence brain function. Thus, drugs that normally have limited penetration of the CNS may have effects beyond what is expected during these circumscribed cases. In addition, disruption of the blood-brain barrier may interfere with the diffusion of oxygen despite adequate delivery due to accumulation of edema. The cytokines themselves may have a direct effect on the brain as well.
- Alteration of neurotransmitter function: Alterations of neurotransmission have clearly been demonstrated in metabolic encephalopathies. An increase in the ratio of aromatic to branched chain amino acids can be found in the serum of septic patients. This results from altered systemic metabolism and muscle breakdown. In addition, there may be abnormal levels of other endogenous peptides, including benzodiazepine-like abetalas and hormones that in the setting of abnormal blood-brain barrier function may result in the alteration of neurotransmitter function in sepsis.
- Iatrogenic: Sedative drugs are commonly used in the septic patient. Effects of these medications may be enhanced due to increased penetration of the CNS. Clearance of the drugs may be impaired secondary to altered metabolism associated with organ dysfunction.
- Dysfunction of vaso motor reactivity: During sepsis, there is a reduction in carbon dioxide-induced vaso motor reactivity that may result in cerebral hypoperfusion. This may be mediated by cytokines and nitric oxide. Thus, ischemia may occur even at BP levels above the lower limit of autoregulation.

**RISK FACTORS**
- Immunocompromised states increasing risk of infection and sepsis
- Strutural brain abnormalities increase susceptibility to all encephalopathies

**PREGNANCY**
- N/A

**ASSOCIATED CONDITIONS**
- N/A

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### Diagnosis

**DIFFERENTIAL DIAGNOSIS**
- Septic encephalopathy is a diagnosis of exclusion and entails a workup of alternative causes. The differential diagnosis of septic encephalopathy includes but is not limited to:
  - Systemic infection
    - Cortical venous thrombosis
    - Intracranial hemorrhage related to coagulopathy
  - Heat stroke —
  - Nonconvulsive status epilepticus
  - Postictal confusion
  - Endocarditis —
  - Deep vein thrombosis
  - Intoxication/withdrawal
  - Fat embolism
  - Drug fever —
  - Acetylsalicylic acid toxicity
  - Malignant neuroleptic syndrome —
  - Pulmonary, renal, or hepatic failure —
  - Adrenal failure —
  - Thyroid storm

**SIGNS AND SYMPTOMS**
- The clinical picture is similar to that of multifocal encephalopathy of other causes. Alteration of mental status is the fundamental neurologic abnormality. The level of consciousness ranges from clouding of consciousness to coma. Patients with only mild symptoms often show fluctuations in their clinical condition. Attention, memory, and concentration are impaired, as is written communication. Paratonic rigidity (increased resistance to movement of a limb throughout the entire range of motion) is characteristic. If the limb is moved very slowly, the rigidity resolves. Tremor, asterixis, and multifocal myoclonus also occur, although less frequently. Generally pupillary reflexes are intact. Seizures and focal findings may occur, especially in those with underlying structural disease that may be microscopic in nature. The presence of peripheral neuropathy is more common in patients with encephalopathy, and the severity of the neuropathy increases with the severity of the encephalopathy.
**Laboratory Procedures**

- **EEG** is considered a more sensitive indicator than physical examination. It is abnormal in the encephalopathic patient with bacteremia. Reduction in faster frequencies and a slowing of rhythms with increasing severity are the most common findings. Triphasic waves are common. A burst suppression pattern can be found in advanced cases; however, none of these findings are specific. The EEG is also prognostic. Mortality rises with the degree of EEG abnormality; however, the EEG is not an absolute predictor of poor outcome. Some patients with burst suppression have made full neurologic recoveries.

- **Somatosensory evoked potential (SSEP) response testing** has demonstrated slowing of the subcortical component of the dorsal column–medial lemniscal pathway that carries information from the periphery to the somatosensory cortex. However, there was no correlation between the subcortical sensory evoked potential and the severity of illness.

**Management**

**General Measures**
- There is no specific treatment for septic encephalopathy. Once secondary causes have been ruled out, the focus of treatment should be directed at the underlying cause.

**Surgeal Measures**
- No specific surgical measures are dictated.

**Symptomatic Treatment**
- There are observations that patients may improve with flumazenil, a γ-amino butyric acid-A antagonist, although the risk of potentiating seizures may limit its use. Infusions of amino acid solutions rich in branched chain amino acids have improved the mental status of patients with hepatic encephalopathy. Neither of these is an accepted treatment for septic encephalopathy but may be areas of future exploration.

**Adjunctive Treatment**
- Treatment should be directed at the underlying cause and comorbidities. Appropriate antibiotic regimens, as well as supportive care, are indicated and should be aggressively pursued, including respiratory care (mechanical ventilation if indicated), hemodialysis for patients with renal impairment, fluid and electrolyte management, and pressors for those with hemodynamic instability. If seizures are suspected, then antiepileptic medications should be initiated. Many patients require intensive care management.

**Admission/Discharge Criteria**
- Patients with sepsis typically are already admitted into the hospital. The need for critical care becomes important when the patient's encephalopathy significantly clouds his or her mental status such that he or she cannot protect the airway. By definition, encephalopathic patients require close observation and are unstable.

**Medications**

**Drugs of Choice**
- As with all patients with encephalopathy, sedation should be minimized and the particular agent chosen carefully. In general, the underlying condition and patient's comorbidities should dictate pharmacologic interventions.

**Alternative Drugs**
- N/A

**Follow-Up**

**Patient Monitoring**
- The patient's underlying condition will dictate the degree of follow-up. Intensive care may be indicated. Serial neurologic examinations by staff trained in such evaluation to detect changes should be performed.

**Expected Course and Prognosis**
- Encephalopathy is a common occurrence in sepsis. Whether it is an independent predictor of mortality is unclear, but mortality is higher with more severe degrees of encephalopathy.

**Patient Education**
- N/A

**References**


Author(s): Robert Cavaliere, MD; Teresa Smith, MD; Bradford Worrall, MD
Epilepsy, Absence Seizures

DESCRIPTION
- Absence seizures are generalized seizures characterized by paroxysmal loss of consciousness and brief discontinuation of activity followed by abrupt recovery with no recollection of the event.

ETIOLOGY
- Some studies showed two-fold preponderance in girls.

AGE
- Absence seizures are seen more often in childhood, but they also occur in about 10%-15% of adults with epilepsies, often combined with other generalized seizures.

SEX
- Absence seizures account for 2%-16% of seizures in all ages and are the seizure type most commonly undiagnosed.

Genetics
- There is increasing evidence that genetic factors are involved in the etiology of typical absence seizures. On the other hand, acquired disorders are more common in atypical absence seizures.

A family history of epilepsy is found in 15%-44% of patients with generalized absence seizures. Recent genetic studies have shown a mutation in the gene encoding for y-amino butyric acid (GABA) receptors.

RISK FACTORS
- History of febrile seizures

PREGNANCY
- About 25% of pregnant women have an increase in seizure frequency. Antiepileptic drug levels usually decline during pregnancy and should be monitored carefully.

ASSOCIATED CONDITIONS
N/A

DIFFERENTIAL DIAGNOSIS
- Accurate diagnosis starts with a careful history: description of the seizures, including the duration and frequency, presence or absence of an aura, and postictal events. Primary diagnostic considerations for staring spells include absence seizures, complex partial seizures, and daydreaming. In contrast to absence seizures, complex partial seizures are much less frequent, are often preceded by an aura followed by postictal confusion, and are rarely activated by photic stimulation or hyperventilation. Daydreaming usually is caused by boredom, is of variable duration, can be interrupted by stimulation, and is never associated with clonic components. Absence seizures may frequently be misdiagnosed as nonepileptic disturbances of behavior. In addition, clouding of consciousness with ocular and oromotor automatisms may occur in partial and other generalized epilepsies.

- Absence seizures comprise the primary seizure type in several epilepsy syndromes. The syndromic diagnosis is important to determine optimal treatment and prognosis.

- Childhood absence epilepsy (CAE): the most common syndrome with typical absence seizures

  - Juvenile absence epilepsy (JAE)

  - Juvenile myoclonic epilepsy (JME)

  - Myoclonic absence epilepsy (MAE)

- Eyelid myoclonus with absences
- Perioral myoclonus with absences
- Stimulus-sensitive absence epilepsies
- Idiopathic generalized epilepsy with phantom absences

- Atypical absence seizures occur in children with severe symptomatic or cryptogenic epilepsies and usually are associated with other types of seizures (atonic, tonic, and myoclonic).

- In CAE, absence seizures begin between ages 5 and 10 years. The seizures occur many times per day. About 30% of children with CAE later develop generalized tonic-clonic (GTC) seizures.

  - JAE begins between 10 and 15 years. JAE patients usually have less frequent absences than those with CAE but higher risk for developing GTC seizures.

  - JME usually begins in adolescence with initial manifestations of myoclonic seizures, which predominantly occur on awakenings from sleep. GTC seizures usually develop later.

  - MAE usually is accompanied by severe bilateral rhythmic clonic jerks, often associated with a tonic contraction.

- The neurologic examination usually is normal in patients with typical absence seizures.

- Atypical absence seizures usually occur in children with subnormal mental function and are characterized by a less abrupt clear onset and offset, which usually is progressive. Atypical absence seizures last longer and have a higher incidence of changes in postural tone.

LABORATORY PROCEDURES

- Video-EEG is the single most important diagnostic procedure. In CAE, the EEG has a normal background and is characterized by bursts of rhythmic, generalized, high-amplitude 3-Hz spike-and-wave discharges of 4-20 seconds' duration, typically exacerbated by hyperventilation. In JAE, discharges are similar but with faster frequency, mostly 4-5 Hz with frequent polyspikes. JME is characterized by the occurrence of generalized polyspike and slow-wave discharges of 3-6 Hz. Atypical absences usually occur in the context of abnormal background and an ictal EEG of slow <2.5-Hz spike-and-slow wave.

IMAGING STUDIES

- Patients usually have normal neuroimaging. Neuroimaging, preferably MRI, is indicated if the patient has atypical features of the seizures, developmental delay, or abnormal neurologic examination.

SPECIAL TESTS
- QEEG (quantitative electroencephalography) can be evaluated with long-term video-EEG monitoring to record and characterize their events.
Epilepsy, Absence Seizures

Management

GENERAL MEASURES
• Typical absence seizures often are easy to control with antiepileptic medications.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
• Contact sports, unsupervised swimming, driving, and other potentially dangerous activities should be restricted until seizures are well controlled. Bicycle helmets are mandatory.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• Patients who present with prolonged periods of stupor and impaired memory or cognitive functions could be suffering from absence status epilepticus. Inpatient EEG monitoring may be diagnostic by showing prolonged generalized bursts of spike-and-wave discharges. Intravenous or rectal benzodiazepines could be helpful for both treatment and diagnosis.

Drugs of Choice

• Ethosuximide: first drug of choice for isolated typical absences, with 70% rate of control. The initial dosage is 15 mg/kg/day, gradually increased to a daily maintenance dose of 20-30 mg/kg. Serious but rare side effects include aplastic anemia, Stevens-Johnson syndrome, and hepatic impairment. Common side effects include GI disturbances, anorexia, weight loss, drowsiness, photophobia, and headache.

• Valproic acid: second choice if ethosuximide fails to control absence attacks or the patient develops GTC seizures. Effective for 75% of patients with absence seizures, as well as generalized convulsive and myoclonic seizures. Initial dosage is 10-15 mg/kg/day. Maintenance dose in children is 30-60 mg/kg/day in three divided doses. Serious side effects include acute hepatic failure and acute pancreatitis. Common side effects include nausea, vomiting, dyspepsia, weight gain, polycystic ovaries, tremor, transient hair loss, and thrombocytopenia.

• Lamotrigine: may control absences and generalized seizures in 50%-60% of patients, but may worsen myoclonic jerks. Lamotrigine may have less cognitive side effects. It requires long titration prior to establishing therapeutic efficacy. It is used mainly as an adjunctive therapy and can be used as a monotherapy for children >12 years. For children ages 2-12 years taking valproic acid, lamotrigine could be added at 0.15 mg/kg/day and increased every 2 weeks by 0.15 mg/kg/day to a maximum of 5 mg/kg/day. In adults and children >12 years, lamotrigine can be added to valproic acid at a dose of 25 mg every other day and gradually increased to a maximum of 200 mg/day. Lamotrigine monotherapy can be given to patients >12 years at 25 mg daily and increased to a maximum of 100 mg/day. An allergic rash that could progress to Stevens-Johnson syndrome is the most common and probably most serious adverse effect. Other common side effects include headache, nausea, diplopia, dizziness, tremors, and ataxia. Side effects are more common with rapid titration or when combined with valproic acid.

Contraindications
• Valproic acid is contraindicated for children <2 years and for patients with hepatic disease.
• Vigabatrin, tiagabine, and carbamazepine are contraindicated for treatment of absence seizures, as they tend to exacerbate the seizures and could produce absence status epilepticus.

Precautions
• Neural tube defects occur in 1%-2% of offspring of women who took valproic acid during pregnancy.

ALTERNATIVE DRUGS
• Clonazepam or acetazolamide may be useful adjunctive drugs.

Follow-Up

Patient Monitoring
• Patients taking ethosuximide should have blood counts to monitor for aplastic anemia. Those taking valproic acid should be monitored for thrombocytopenia and hepatotoxicity. Therapeutic trough levels range from 40-100 mg/mL for ethosuximide and 50-100 mg/mL for valproic acid.

Expected Course and Prognosis
• Typical absence seizures generally have a favorable prognosis. CAE carries the best prognosis; up to 95% of children with CAE will have complete remission. JAE has a less favorable prognosis than CAE but is better if absence seizures are the only seizure type. JME is usually a lifelong epilepsy.
• Poor prognostic factors include history of associated GTC or myoclonic seizures or absence status p ositive family history of epilepsy, abnormal EEG background, or subnormal intelligence.

Patient Education
• Compliance with antiepileptics should be encouraged to avoid breakthrough seizures.
• Epilepsy Foundation of America. Phone: 1-800-EFA-1000; website: www.epilepsyfoundation.org

Miscellaneous

SYNONYMS
• Absence seizures (petit mat seizures)
• Childhood absence epilepsy (pyknolepsy)
• Juvenile absence epilepsy (nonpyknolepsy absence epilepsy)
• Juvenile myoclonic epilepsy (Janz disease)

ICD-9-CM: 345.0 Nonconvulsive generalized epilepsy SEE ALSO: N/A

REFERENCES

Author(s) Khaled Tame, MD
Epilepsy, Febrile Seizures

BASICS

DESCRIPTION

• Febrile seizures are defined as "an event in infancy or childhood, usually between 3 months and 5 years, associated with fever, but without evidence of intracranial infection or defined cause." Febrile seizures are distinct from epilepsy, which is characterized by recurrent nonfebrile seizures. The febrile illness must have a temperature >38.4°C either before or after the seizure.

• Febrile seizures are simple or complex. Simple febrile seizures occur as solitary events, are generalized, and last <15 minutes. Complex febrile seizures have one or more of the following features: locality, duration >15 minutes, or recurrence in <24 hrs. A complex febrile seizure or series of seizures that occur without recovery between events and last >30 minutes is termed febrile status epilepticus.

EPIDEMIOLOGY

Incidence/Prevalence

• The majority of febrile seizures are simple (65%). The most frequently described complex feature is focality, followed by recurrence and prolonged duration. Febrile status epilepticus accounts for only 5% of all febrile seizures, but accounts for 25% of all childhood status epilepticus and more than two thirds of status epilepticus in the second year of life.

Age

• Febrile seizures occur in 2%-5% of all children <5 years of age. They are most common between 6 months and 3 years, with peak incidence at 18 months. Onset after 7 years is uncommon.

Sex

• Boys are affected slightly more frequently than girls.

ETIOLOGY

Genetics

• No definitive gene or locus for febrile seizures has been identified. However, children with a positive family history of febrile seizures are more likely to experience febrile seizures and to have recurrences. Genetic studies favor a multifactorial or polygenic mode of inheritance, although autosomal dominant, incomplete penetrance modes of inheritance also may occur.

RISK FACTORS

• First- or second-degree relative with a history of febrile seizures
• Neonatal nursing stay >1 month
• Presence of developmental delay
• Attendance at day care
• Height of temperature

PREGNANCY

N/A

ASSOCIATED CONDITIONS

• Include upper respiratory infections, otitis media, roseola infantum, tonsillitis, and gastroenteritis. Herpesvirus-6 (roseola or exanthema subitum) is commonly associated with febrile seizures.

Diagnosis

DIFFERENTIAL DIAGNOSIS

• Febrile seizures are distinguished from epilepsy by the absence of previous febrile seizures, CNS infection, and other precipitating causes (e.g., trauma, electrolyte imbalance, toxins). Nonepileptic events that can mimic seizures (e.g., breath-holding spells) can be excluded by a careful history. Shaking rigor (shivering) in a febrile child is frequently misdiagnosed as febrile seizures.

SIGNS AND SYMPTOMS

• Febrile seizures often occur early in the course of a febrile illness. Tonic-clonic seizures are most common, but partial seizures can occur. A typical seizure involves a cry, loss of consciousness, and atomic posture. Breath-holding or circular cyanosis may be observed, along with vomiting and incontinence. Focality may be observed during the clonic phase. Postictal lethargy or sleep is common. The majority of events are brief (<15 minutes).

LABORATORY PROCEDURES

• The incidence of meningitis with febrile seizures is 2%-5%. Lumbar puncture should be performed in any child presenting with meningismus, bulging fontanelle, prolonged lethargy, recurrent seizures, or status epilepticus, or in infants <12-18 months (unreliable clinical signs of meningitis in this age group). In children >18 months without clinical suspicion for meningitis, a lumbar puncture is unnecessary. Lumbar puncture is still recommended in children with a first, complex febrile seizure.

• Routine laboratory studies (e.g., CBC, electrolytes) are indicated only as part of the evaluation of febrile illness.

IMAGING STUDIES

• Brain CT scans are of limited benefit in the setting of febrile seizures. Brain MRI scans are only indicated in the evaluation of complex febrile seizures.

SPECIAL TESTS

• EEGs are only likely to be abnormal in the older child and in children with a family history of febrile seizures, with complex febrile seizures, or with preexisting neurodevelopmental abnormalities.

Management

GENERAL MEASURES

• Because many febrile seizures are brief, symptomatic care usually is unnecessary. If seizures persist, are recurrent, or develope status epilepticus, treatment is mandatory. Because febrile seizures are a benign, self-limited condition that represents an age-dependent response to fever, long-term prophylactic treatment is unwarranted.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

• The primary goal of management is treatment of ongoing seizure activity. Treatment of the fever is unnecessary. If the patient is actively seizing upon arrival to the hospital, treatment should be initiated. IV diazepam or lorazepam is effective. Rectal diazepam or diazepam gel can be used if IV access is difficult. If the child continues to seize after an adequate dose of benzodiazepine, a status epilepticus treatment protocol should be initiated.

• For seizures that are prolonged or recurrent, parents can be instructed to administer rectal diazepam.

ADJUNCTIVE TREATMENT

• There is little evidence suggesting that antipyretic therapy has any benefit in febrile seizures. In one study, 50% of children with febrile seizures had previously received antipyretic medication before the febrile seizure. Children whose febrile seizure occurs at the onset of fever have the highest risk of recurrence and the most difficulty initiating therapy prior to the febrile seizure.

• Alternatively, diazepam given orally or rectally (0.5 mg/kg) at onset of a febrile illness reduces the recurrence risk by 50%. The reduction in seizure recurrence must be weighed against the sedative side effects of treatment.
**ADMISSION/DISCHARGE CRITERIA**
- A child presenting with a first-time febrile seizure warrants medical observation but rarely needs hospital admission. If the child is alert and active, and the etiology of fever is diagnosed and treated, the child can be discharged. Parents should be counseled that 16% of children experience another febrile seizure within 24 hours. Hospital admission is necessary with severe underlying febrile illness, recurrent seizures, prolonged febrile seizure or status epilepticus, and prolonged postictal state.

**DRUG(S) OF CHOICE**

**Symptomatic**
- Rectal diazepam or diazepam gel has been proven to be effective in treating prolonged febrile seizures. Five minutes of continuous seizure activity or repeated seizures within 30 minutes is the criterion for treatment. Dosing is based on age and weight: 0.5 mg/kg for 0–5 years of age, 0.3 mg/kg for 6–11 years, and 0.2 mg/kg for >12 years. Alternative drugs include sublingual or rectal lorazepam, which has not been as extensively studied.
- Prophylactic
  - Recent studies have failed to confirm the efficacy of phenobarbital and suggest the possibility of long-term cognitive and behavioral side effects; therefore, long-term phenobarbital therapy is rarely, if ever, warranted.
  - Daily treatment with valproic acid does not consistently reduce febrile seizure recurrence.

**Contraindications**
- Known hypersensitivity to medications
- Precautions: N/A

**ALTERNATIVE DRUGS**
- Chronic benzodiazepine use has not been well studied as a prophylactic treatment. Carbamazepine and phenytoin are ineffective in febrile seizure recurrence.

**Follow-Up**

**PATIENT MONITORING**
- Children with febrile seizures require only routine pediatric follow-up.

**EXPECTED COURSE AND PROGNOSIS**

**Febrile Seizure Recurrence**
- Approximately 33% of children with a first febrile seizure will have a recurrence, and 10% will have >3 febrile seizures. Several factors are associated with an increased risk of recurrence, including a family history of febrile seizures and an early age at onset of febrile seizure (before 18 months). The risk of recurrent febrile seizures is 50% when the first seizure occurs before 1 year and 20% when the first seizure occurs after 3 years. The risk appears to be related to the duration for which the child will be in the age group for febrile seizures. Other risk factors include the peak temperature and the duration of the fever before the seizures. Children with multiple risk factors are at higher risk for recurrence. For example, a child with >2 factors has a 30% recurrence risk compared to 60% for a child with >3 risk factors.
- The presence of a neurodevelopmental abnormality, complex febrile seizures, gender, and ethnicity do not carry an increased risk. If the initial febrile seizure is prolonged, a recurrent febrile seizure is also more likely to be prolonged.

**Development of Epilepsy**
- Epidemiologic studies have shown that 2%–10% of children with febrile seizures develop subsequent epilepsy. Conversely, 15% of children and adults with epilepsy have a history of prior febrile seizures. In general, the risk of epilepsy after a simple febrile seizure is <1%, similar to the risk in the general population.
- Several studies of adults with intractable temporal lobe epilepsy and mesial temporal sclerosis report that up to 40% had a history of prolonged febrile seizures. Population-based studies have failed to document this association, as have prospective studies on febrile seizure patients.

**Intelligence and Neurodevelopment**
- Longitudinal, population-based studies have shown no effect of febrile seizures on neurodevelopmental outcome.

**PATIENT EDUCATION**
- Counseling and reassurance are the most important mainstays of therapy. Instructions on how to respond to subsequent events are important, including the use of symptomatic treatment with benzodiazepines and when to utilize emergency services.
Epilepsy, Generalized

**DESCRIPTION**

- Epilepsy syndromes can be divided into two general groups: partial (focal) and generalized (primary). Generalized epilepsies originate from multiple (bilateral) areas of the brain simultaneously. Partial seizures originate from a single focus (although they often secondarily generalize or spread to both hemispheres). The speed of generalization of a focal seizure may be fast, so only close scrutiny of the EEG can determine if the seizure was primarily or secondarily generalized.

**Specific Epilepsy Syndromes**

- Benign familial neonatal convulsions (BFNC): onset in first week of life, lasting only 3-5 days; generalized usually less frequent than focal seizures
- West syndrome (infantile spasms): onset 1-24 months; idiopathic or symptomatic; infantile spasms, myoclonic seizures; EEG shows hypersynchrony pattern; accompanied by mental retardation
- Lennox-Gastaut syndrome (LGS): onset within first 14 years, usually within first 5 years; atonic, tonic, atypical absence seizures most common, also have generalized tonic-clonic (GTC), myoclonic, usually accompanied by psychomotor retardation that may precede or follow onset of seizures; may be idiopathic or symptomatic; ictal EEG shows slow (1.5-2.5 Hz) spike-and-wave discharges; lifelong; notoriously difficult to control
- Juvenile myoclonic epilepsy of infancy: myoclonic seizures between ages 4 months and 3 years.
- Childhood absence epilepsy: typical absence, with GTC seizures in 40% and rarely myoclonic seizures beginning between ages 3 and puberty; may have dozens of absence seizures per day; EEG shows typical 3-Hz spike-and-wave discharges; up to 80% have complete remission, usually in late adolescence; strong genetic component (75% monozygotic twin concordance)
- Myoclonic-astatic epilepsy (Doose syndrome): myoclonic, astatic, and less commonly absence seizures beginning in first 5 years of life
- Juvenile absence epilepsy: generally same as childhood variant, except onset after puberty; GTC seizures are more common (up to 80%); remission is uncommon

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

- Psychogenic spells
- Atypical presentations of movement disorders

**SIGNS AND SYMPTOMS**

- GTC seizures: loss of consciousness followed by tonic stiffening of the body, often accompanied by a loud cry due to respiratory musculature involvement. After a variable period of time, a clonic phase ensues, typified by synchronous muscular contractions. This phase may result in tongue biting or other physical injury. The contractions then slow in frequency until ceasing, often with characteristic slow labored breathing and sometimes loss of bladder control. Patients may have decreased level of consciousness for a variable period of time afterward. The tonic and clonic phases may reoccur in various orders and be accompanied by marked increases in pulse and BP.
- Absence: sudden onset of decreased level of awareness and behavioral arrest without warning, lasting <15 seconds. May be accompanied by automatisms (purposeless motor activity, e.g., lip smacking, picking at clothes) and usually no postictal symptoms. Atypical absences have unusual features, such as significant tonic features, postictal confusion, and atypical EEG findings.
- Atonic: sudden loss of postural tone. May be so slight as to result only in brief nodding of head.
- Myoclonic: very brief muscle contractions (<0.5 seconds), often appearing as twitching or tremors
- Infantile spasms: brief, may be flexor, extensor, or both; resultant gross movement often appears as if the baby is reaching out or posing.
- Special attention should be paid to other signs of neurologic or systemic disease, such as growth failure, mental and motor development, dysmorphic features, and cranial findings.

**LABORATORY PROCEDURES**

- EEG most helpful when diagnosis is uncertain. Abnormalities are often but not always seen between seizures (interictally). Video-EEG monitoring is the gold standard to capture seizures and should be strongly considered in any patient in whom seizure type is unclear or in whom the first antiepileptic drug (AED) is not effective.

**IMAGING STUDIES**

- MRI with gadolinium contrast is the study of choice.
Management

GENERAL MEASURES
- The main focus is educating the patient and family about epilepsy and treatment with AEDs.

SURGICAL MEASURES
- Other than the placement of vagal nerve stimulators, surgery is not indicated in primarily generalized seizures except in refractory cases, in which palliative callosotomy is used for atonic and GTC seizures.

SYMPTOMATIC TREATMENT
- AEDs are initiated as soon as possible. Second-line nonmedication therapies include ketogenic diet (effective in select group of patients, mechanism unknown) and vagal nerve stimulation.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
- It is important to keep in mind that seizure patients who usually are well controlled and have a breakthrough seizure may have a new underlying cause, such as infection or metabolic derangement.

Patent Monitoring

Follow-Up
- Follow-up with a neurologist is recommended to determine the future need for AED therapy, as well as to receive specialized counseling regarding the diagnosis of epilepsy.

EXPECTED COURSE AND PROGNOSIS
- After a single unprovoked seizure with a normal EEG and MRI, the chance of a second seizure is only 30%-40%. The prognosis for generalized epilepsies depends to a large extent on the particular epilepsy syndrome and presence or absence of definable causes.

PATIENT EDUCATION
- Activities should not generally be restricted, except driving or flying (which is often dictated by state laws). Patients should get adequate sleep and avoid alcohol and any known stimuli.
- Epilepsy Foundation of America. Website: www.efa.org

Miscellaneous

SYNONYMS
- Generalized epilepsy
- Grand mal seizures (antiquated)
- Epilepsy, major (motor)

ICD-9-CM: 345.9 Epilepsy, generalized; 345.1 Epilepsy, generalized, convulsive; 345.0 Epilepsy, generalized, nonconvulsive; 345.4 Epilepsy, secondarily generalized

SEE ALSO: N/A

REFERENCES
- Author(s): Mark R. Gibson, MD; Joseph Sirven, MD
Epilepsy, Infantile Spasms

DESCRIPTION

- The triad of infantile spasms (IS), a hypersarrhythmia EEG pattern, and mental retardation constitutes West syndrome.

EPIDEMIOLOGY

- 90% of patients with IS present in infancy. The incidence is estimated at 0.24-0.6 per 1,000. IS comprises 1.4%-3.9% of all childhood seizure types.

ETIOLOGY

- In the majority (60%) of patients with IS, a specific etiology can be identified. (symptomatic IS). A second group of infants (termed cryptogenic) is assumed to have underlying CNS dysfunction based on abnormal neurologic examination or developmental delay. Idiopathic cases are defined as having normal development, neurologic examination, neuroimaging studies, and unremarkable etiologic evaluations. Family studies support a genetic susceptibility to epilepsy that requires environmental stimuli to precipitate seizures.
- Symptomatic etiologies include:
  - Prenatal causes: cerebral dysgenesis, Sturge-Weber syndrome, Aicardi's syndrome, hydrocephalus, congenital infections, trauma; genetic etiologies include tuberous sclerosis, Down's syndrome, and incontinencia pigmenti.
  - Perinatal disorders: hypoxic-ischemic encephalopathy, CNS infections, trauma, stroke.
  - Postnatal disorders: metabolic disorders such as pyridoxine dependency, nonketotic hyperglycinemia, maple syrup urine disease, phenylketonuria, mitochondrial encephalopathies.

RISK FACTORS

- Any CNS injury to the early developing brain.

PREGNANCY

N/A

ASSOCIATED CONDITIONS

- Developmental delay and mental retardation; only 10% of patients are developmentally normal at the time of diagnosis. Patients may also manifest other seizure types, especially focal and tonic seizures.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- IS sometimes are misinterpreted as normal infant movements such as hiccuping, posturing, or lack of head control.
  - Myoclonus in infancy: Differential of myoclonus in infants includes movement disorders such as hyperekplexia (excess startle response), and benign and hereditary essential myoclonus. Benign neonatal sleep myoclonus begins in the first month of life. The movements occur only in sleep, cannot be stopped by gentle restraint, and are eliminated on arousal. Infants are typically neurodevelopmentally normal, and spells usually remit by 6 months of age.
  - Benign myoclonus of infancy: onset between 3 and 15 months of age with clusters of tonic or myoclonic jerks frequently involving the head and trunk. EEGs are normal, and there is no evolution into epilepsy. The course is self-limited, diminishing within 3 months of onset and ceasing before 2 years of age. The diagnosis is made retrospectively, once serial EEGs and neurologic development remain normal.
  - Shuddering attacks are uncommon paroxysmal events that may start in infancy, but they also may occur later in childhood. They consist of behavioral arrest but no loss of consciousness, tonic posturing, and flexion or extension of the head and neck. Ictal EEG is normal.
  - Spasmus nutans is a condition of asymmetric nystagmus, head nodding, and an anomalous head position in infants.

SIGNS AND SYMPTOMS

- IS presents as a cluster of spasms of brief, usually bilaterally symmetric contractions of the muscles of the trunk, neck, and extremities. Predominantly flexor, extensor, or mixed flexor-extensor. The events are stereotyped in an individual child and vary from a massive abrupt contraction of all flexor muscles to a brief sibtle head nod. Clusters tend to wax and wane. The number of spasms and clusters/day can be variable. Associated phenomena include nystagmus, eye deviation, autonomic features (flushing, pallor, pupillary dilation), or a cry at the conclusion of the spasm.
- Arrest of neurologic development or a loss of milestones often accompanies the onset of IS. Neurologic examination abnormalities are present in approximately 70% of patients.

LABORATORY PROCEDURES

- Focus on uncovering an etiology for IS, especially metabolic causes (4% of cases). Evaluation includes serum electrolytes, liver function tests, CBC, serum ammonia, lactate, pyruvate amino acid quantification, biotinidase assay, cholesterol profile to screen for peroxisomal disorders, and urine organic acid quantification; chromosome analysis if examination suggests a syndrome. CSF should be tested for lactate for mitochondrial disorders and glucose for nonketotic hyperglycinemia. Ophthalmologic examination is included to evaluate for Aicardi's syndrome, congenital infections, neurodegenerative diseases, and tuberosclerosis; Wood's lamp skin examination for tuberous sclerosis.

IMAGING STUDIES

- Head MRI is recommended to evaluate for CNS malformation, present in 2% of IS cases, stroke, hypoxic-ischemic encephalopathy, infection, or tuberous sclerosis. Abnormal neuroimaging studies are seen in 70%-80% of cases and are associated with a poor prognosis.

SPECIAL TESTS

- A prolonged EEG that includes sleep is recommended. Ictal video-EEG recording is optimal. The characteristic demonstration of IS, hypersarrhythmia, is a background interictal pattern of disorganized, high-voltage activity with bursts of normal occipital and generalized epileptic activity. Hemispheric asynchrony and focal ictal abnormalities are not uncommon. Early in IS, hypsarrhythmia may not be present or present only in deep sleep, so ictal EEGs may be necessary. The ictal EEG pattern typically consists of an initial slow wave followed by low-amplitude fast activity (14-16 Hz) or diffuse attenuation, referred to as an electro-decremental response.
- To evaluate if pyridoxine deficiency is the etiology of IS, pyridoxine 100 mg IV is administered during the EEG. If significant background improvement is noted, chronic pyridoxine treatment is initiated.
Epilepsy, Infantile Spasms

Management

**GENERAL MEASURES**
- Both adrenocorticotropic hormone (ACTH) and corticosteroids are efficacious in treating IS. Other options include newer antiepileptic drugs.

**SURGICAL MEASURES**
- Surgical resection of focal cortical regions is reserved for children with persistent IS despite appropriate treatment. Surgical resection of areas of hypometabolism on PET, often located posteriorly in the temporal and occipital lobes, has led to recovery.

**SYMPTOMATIC TREATMENT**
- Developmental assessments and early intervention programs

**ADJUNCTIVE TREATMENT**
- H₂-blockers such as ranitidine for steroid-induced gastritis
- Diuretic therapy for steroid-induced hypertension and irritability

**ADMISSION/DISCHARGE CRITERIA**
- Patients presenting with IS often are hospitalized for video-EEG monitoring to allow etiologic evaluation and initiate therapy.

Medications

**DRUG(S) OF CHOICE**
- **ACTH:** Intramuscular ACTH is the most frequently used treatment. Treatment success is based on resolution of both the spasms and the hypsarrhythmia, so a follow-up EEG is required and must include sleep. Relapse occurs in up to 47% of patients but often can be successfully treated by a second course of therapy. Proponents of the low-dose regimen (20-40 U/m²) recommend an increase in dose if spasms continue for 2 weeks. Proponents of the high-dose regimen, which tends to be preferred, recommend 150 U/m² of body surface area per day, followed by a rapid taper over 1-2 weeks if spasms are gone and the EEG is not hypsarrhythmic. This approach minimizes side effects but has a high relapse rate, so longer tapers are often used, with every-other-day dosing after the first weeks to minimize side effects.
- **Corticosteroids:** The most common alternative to ACTH therapy is corticosteroids. Oral steroids are easier to administer but have similar side effects. Prednisone is administered at 2 mg/kg/day in 2-4 divided doses for 4 weeks, followed by a taper.

Patients who fail to respond to ACTH can respond to steroids, and vice versa. Studies have suggested a lower responder rate and a higher relapse rate with steroid therapy compared to ACTH.
- **Vigabatrin:** For patients who do not respond to or cannot tolerate either ACTH or corticosteroids, vigabatrin has shown effectiveness, especially for children with tuberous sclerosis. Unlike ACTH, response to vigabatrin is dose dependent: increasing doses up to 150 mg/kg/day gradually decreases spasm frequency. Ideal duration of therapy is unknown but is commonly continued for 1 year after cessation of IS, or up to 3 years of age.
- **Antiepileptic drugs:** Other antiepileptic drugs, including high-dose valproate, topiramate, tiagabine, nitrazepam, and zonisamide, have been used in uncontrolled trials.

**Precautions**
- Side effects of steroids/ACTH include Gl irritation, hypertension, irritability, cushingoid weight gain, electrolyte imbalance, hypoglycemia, and acne. The patient should be monitored for BP, Hemocult in stool, serum electrolytes, and glucose in the urine. During the course of therapy, the immune system is suppressed so that routine immunizations are contraindicated.
- Vigabatrin is not approved for use in the United States, nor is it commercially available because of risk for retinal damage resulting in loss of peripheral vision. Regular ophthalmologic or visual evoked response examinations are used to screen for this problem.
- Risk of valproate-induced hepatotoxicity is highest in the IS age group.

**Contraindications**
- Known hypersensitivity to these drugs

**ALTERNATIVE TREATMENT**
- High-dose vitamin B₆ (pyridoxine) 300-500 mg/kg/day has been used in uncontrolled trials. For refractory IS, the ketogenic diet has been attempted.

Follow-Up

**PATIENT MONITORING**
- For patients treated with ACTH or steroids, routine monitoring of BP, urine glucose, and stool Hemocults are performed at home. Follow-up EEGs are important to assess response.

**EXPECTED COURSE OF PROGNOSIS**
- IS can spontaneously remit: 89% of patients have been reported to be spasm-free at 5 years. However, the risk of poor neurologic outcome is high: 80%-90% with mental retardation and >50% with epilepsy. Of infants with IS, 30%-40% progress to Lennox-Gastaut syndrome. Prognosis is directly related to etiology; symptomatic cases have significantly worse outcome. Early cessation of the spasms and normalization of the EEG may have good prognostic significance.

**PATIENT EDUCATION**
- Parents require extensive training in ACTH administration, managing side effects of therapy, and precautions regarding immunosuppression.

Miscellaneous

**SYNONYMS**
- West syndrome ICD-9-CM: 345.
- 60 Infantile spasms

SEE ALSO: EPILEPSY, LENNOX-GASTAUT SYNDROME

**REFERENCES**

Author(s): Juliann Paolicchi, MD
Epilepsy, Lennox-Gastaut Syndrome

**DESCRIPTION**

- Lennox-Gastaut syndrome (LGS) is characterized by multiple seizure types refractory to treatment with antiepileptic drugs (AEDs).

**EPIPHENOMOLOGY**

- **Incidence/Prevalence**
  - LGS accounts for 1%-4% of all childhood epilepsy; 10%-40% of epilepsies present in the first 5 years. Prevalence rates are 0.1-0.29 per 1,000. The annual incidence is estimated at 2 per 100,000 children. The prevalence and percentage of LGS are higher in patients with mental retardation (MR) 0.06 per 1,000 and 7%, respectively.

- **Race**
  - No racial differences have been identified.

- **Age**
  - Although LGS is defined as having onset in children 1-8 years, the mean age at onset is 26-28 months (range 1 day-14 years).

- **Sex**
  - Males are affected more than females.

- **Etiology**
  - The syndrome is divided into primary (idiopathic) or secondary (symptomatic). Secondary cases (65%-75% of patients with LGS) are associated with a host of injuries to the developing brain: genetic causes (tuberous sclerosis), cerebral dysgenesis, infectious, hypoxic-ischemic, or traumatic etiologies. No significant genetic factors have been identified except for genetic-associated etiologies.

- **Risk Factors**
  - 30%-40% of patients with infanile spasms develop LGS.

- **Pregnancy**
  - NIA

- **Associated Conditions**
  - At onset, 26%-60% of patients have MR. The subsequent proprotion of patients with MR increases because of cognitive deterioration that occurs with LGS. Behavioral problems and psychological diseases, ranging from hyperactivity to autism, are common.

**DIAGNOSIS**

- **Differential Diagnosis**
  - LGS can be difficult to distinguish from other childhood epilepsy syndromes of multiple seizure types and cognitive dysfunction.
  - Myoclonic atatic epilepsy (Doose syndrome) consists of myoclonic, atomic, and atypical absence seizures. Myoclonic atatic epilepsy is predominantly idiopathic, has a better prognosis, and does not develop from West syndrome. Patients with childhood myoclonic epilepsies, such as benign myoclonic epilepsy of infancy, severe myoclonic epilepsy of infancy, and progressive myoclonic epilepsy, tend to have myoclonic seizures as their predominant feature, rarer tonic seizures than LGS, faster EEG (>2.5 Hz) patterns, and more variable cognitive decline.

- **Signs and Symptoms**
  - The most frequent seizure types in LGS are tonic, tonic-clonic, myoclonic, atypical absences, and "head drop," which are a form of atomic, tonic, or myoclonic seizures. Tonic seizures are the most prevalent, occurring in 74%-90% of patients. They occur in both awake and sleep states, and can involve the head and trunk, including the arms, or the whole body. Apnea and facial flushing are commonly associated. Events tend to be brief, lasting only a few seconds to a minute. They can occur multiple times per day, sometimes up to hundreds of seizures per day.
  - Atypical absences are often sible with a gradual onset and offset and an incomplete loss of consciousness. They may be accompanied by myoclonic jerks or automatisms.
  - Atomic seizures, myoclonic seizures, and myoclonic-atomic seizures can produce sudden "drop attacks" that can be very injurious. Frequency ranges from 10%-56%. Generalized tonic-clonic seizures occur in 15% of patients; complex partial seizures occur in 5%.
  - Status epilepticus (54%-75% of patients) can develop from multiple seizure types and tends to be prolonged, resistant to treatment, and recurrent.

- **Laboratory Procedures**
  - The initial evaluation of patients with LGS requires an extensive metabolic and radiologic evaluation to determine the etiology.

- **Imaging Studies**
  - Brain MRI is indicated to determine neuroanatomic etiologies of the disorder, such as cerebral dysgenesis, stroke, and hypoxic-ischemic encephalopathy.

**SPECIAL STUDIES**

- The EEG pattern that characterizes LGS is the generalized spike-and-wave interictal pattern in an otherwise slow background. The slow spike-and-wave or sharp-and-slow-wave complexes occur as generalized bursts with frequencies between 1.5 and 2.5 Hz. The interictal background slowing may be transient or continuous. Continuous slowing is associated with a poor cognitive outcome. The ictal (seizure) EEG patterns depend on the seizure types.

**MANAGEMENT**

- **General Measures**
  - Because freedom from seizure is rarely achievable, the primary goal of treatment is maximizing seizure control and quality of life. Monotherapy is rarely effective. Patients can have periods of relative seizure control, which usually correspond to marked improvements in cognition, alertness, and developmental progress. Unfortunately, cognitive deterioration resists a long with the seizures.

- **Surgical Measures**
  - Two surgical procedures have been used in LGS, but neither has been investigated in case-control studies. In corpus callosotomy, fibers in the anterior corpus callosum are surgically resected. The goal of the procedure is palliation: only 8% of patients are seizure-free, but 61% have improvement in seizures. Drop attacks, atomic seizures, and secondarily generalized seizures are most responsive to this procedure. Benefits are not permanent; seizure frequency can resume over time.
  - The vagus nerve stimulator, used to treat medically intractable epilepsy, delivers electrical afferent input to the brainstem via the left vagus nerve. The device is approved for use in refractory partial seizures but also is used for refractory generalized seizures, including LGS. Seizure freedom is rarely achieved. In small studies, 7% of LGS patients experienced a 50% reduction in seizure frequency with up to 5-year follow-up.
  - Isolated cases in which resection of localized lesions improved seizure control have been reported.
**Epilepsy, Lennox-Gastaut Syndrome**

**SYMPTOMATIC TREATMENT**
- Intercurrent illness, stress, changes in AED regimen, and use of concomitant medications can trigger an increase in seizures. Many LGS patients have weekly or monthly periodicity in seizure frequency unrelated to other factors or AEDs, so a long-term approach is often advisable. Parents and caregivers should be instructed on therapy for seizure exacerbation, such as intermittent use of the benzodiazepines.
- Treatment of status epilepticus needs to be individualized. IV phenytoin and benzodiazepines are the mainstays of therapy.

**ADJUNCTIVE TREATMENT**
- See Medications

**ADMISSION/DISCHARGE CRITERIA**
- Because children with LGS have multiple daily seizures, admission to the hospital usually is reserved for exacerbations, respiratory compromise, or status epilepticus.

**DRUGS OF CHOICE**
- Broad-spectrum AEDs are the mainstay of treatment. Sedating side effects can exacerbate seizure frequency, and tolerance is common.
  - Valproate has broad-spectrum effectiveness against the seizure types of LGS. Sedative/cognitive side effects are minimal, except at higher concentrations. Dose-dependent side effects include ataxia, tremor, and platelet dysfunction. Idiosyncratic reactions include weight gain, alopecia, and, of most concern in children <2 years of age, hepatotoxicity, which can be fatal.
  - Newer AEDs tested for efficacy in double-blind, placebo-control trials include felbamate, lamotrigine, and topiramate. Felbamate is effective in LGS but is associated with dangerous idiosyncratic reactions: aplastic anemia and hepatotoxicity. Although the incidence of both of these reactions is low (1 in 4,000-8,000 and 1 in 18,000-25,000 treated patients, respectively), their severity has limited its use.
  - Topiramate is an effective adjunctive treatment for most LGS seizure types. Common adverse events are somnolence, anorexia, cognitive or behavioral problems, renal stones, and glaucoma.
  - Lamotrigine is an effective adjunctive treatment. The most concerning side effects are idiosyncratic skin reactions: rash in 10%-12% of patients treated for LGS, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Risk factors for development of lamotrigine-induced rash include younger age (children > adults), concomitant valproate treatment, a high starting dose, and rapid dose titration.
    - In the past, Long-acting benzodiazepines such as clonazepam and nitrazepam were used for treatment of LGS. Tolerance and sedative side effects tend to limit their long-term effectiveness.
    - Carbamazepine usually is avoided in LGS because it can exacerbate the slow spike-and-wave pattern causing increased seizures or obtundation, as can phenytoin. Father trials are needed to determine the effectiveness of levetiracetam and zonisamide.

**ALTERNATIVE DRUGS**
- The ketogenic diet is a treatment alternative for children with medically refractory epilepsy including LGS. The diet consists of a high proportion of fats compared to small amounts of carbohydrate and protein in a ratio of 3:1 or 4:1, which induces ketosis. Overall, one third of patients on the diet experience significant or complete seizure control. Side effects include an inability to tolerate the diet, sedation, GI disturbance, and social limitations. The long-term cardiovascular side effects of a high fat diet are under investigation.

**PATIENT MONITORING**
- LGS patients require neurologic care in specialized epilepsy centers to address their multiple neurolologic and medical needs.

**EXPECTED COURSE AND PROGNOSIS**
- Despite the many advances in epilepsy treatments, the outcome of patients with LGS remains poor. By adolescence, the combination of continued seizures, MR, and behavioral difficulties leads to profound social consequences. In a 10-year follow-up study, MR was found in 95% of patients in the primary group and 1% in the secondary group.
- Psychiatric problems can progress from mood instability and personality disturbances in the young child to acute psychotic episodes in older children and adolescents. The main characteristics of mental deterioration include apathy, memory disorders, perseveration, and impaired vision or speech. Poor prognostic factors include secondary or symptomatic LGS, particularly after West syndrome, early onset of seizures, higher frequency of seizures, and continuous slow spike-and-wave EEG background. Mortality rates of 3%-7% is related to intercurrent illness or accidents.

**PATIENT EDUCATION**
- Patient/caregiver education should address the many social, educational, and medical needs.
- The National Epilepsy Foundation provides information and support. Website: www.epa.org
- MRDD services can assist with nursing and respite care needs.

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**Medications**

**Follow-Up**

**REFERENCES**

Author(s): Juliann Paolicchi, MD

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**SYNONYMS**
- N/A

**ICD-9-CM:** 345.91 Epilepsy, unspecified—with mention of intractable epilepsy; 345.11 Generalized convulsive epilepsy—with mention of intractable epilepsy; 780.39 Intractable seizures

**SEE ALSO:** EPILEPSY, INFANTILE SPASMS
### Basics

#### DESCRIPTION
- Status epilepticus (SE) is a prolonged seizure or multiple seizures with out full recovery of consciousness between seizures. The amount of time allowed before beginning abortive therapy varies with the clinical situation and individual preference. In most cases, initial medications should be given after 5 minutes of continuous seizure activity or more than 2 seizures without full recovery. Prolonged seizure activity has been shown to cause irreversible neuronal damage in animals and is associated with significant morbidity and mortality in humans. SE is divided into generalized convulsive status epilepticus (GCSE), nonconvulsive status epilepticus (NCSE), and focal status epilepticus (BE).

#### EPIDEMIOLOGY
- **Incidence/Prevalence**
  - Approximately 60 per 100,000 per year.
  - Exact incidence and prevalence are unknown.
- **Race/Sex**
  - Affects sexes and races equally.
- **Genetics**
  - Predisposition to SE seems to have a heritable component, but the exact mechanism is unknown. SE appears to be polygenic, and an increased prevalence of specific genes is observed in affected families.

#### Risk Factors
- Previous episode of SE
- Low antiepileptic drug (AED) levels (poor compliance, drug interactions)
- Metabolic: hypoglycemia, hypernatremia, hyperkalemia, hypocalcemia, renal or hepatic insufficiency
- Medications: theophylline, sympathomimetic agents, penicillins, general anesthetics, antipsychotics agents, antidepressants, anticholinergics
- Medication withdrawal: AEDs, sedative-hypnotics
- Structural lesions: AEDs, sedative-hypnotics
- Trauma
- Hypoxia
- Toxic: Carbon monoxide, cocaine, amphetamines
- Infection: meningitis, encephalitis, brain abscess
- Autoimmune: CNS vasculitis
- General risk factors for seizures: emotional or physical stress, lack of sleep, menstrual cycle, stimulants, individual provoking factors (e.g., flashing lights)
- Roughly one third of SE cases represent the presentation of epilepsy, one third occur in known epileptics, and one third are symptomatic

#### EPILEPSY, STATUS EPILEPTICUS
- Status epilepticus (SE) is a prolonged seizure associated with significant morbidity and mortality in humans. SE is divided into generalized convulsive status epilepticus (GCSE), nonconvulsive status epilepticus (NCSE), and focal status epilepticus (BE).
- **Description**
  - GCSE: loss of consciousness followed by tonic contraction of various muscle groups, often accompanied by eye deviation and head turning. Usually followed by clonic phase with rhythmic muscle contractions. The contractions often become gradually less frequent and apparent in fewer muscles. Tone may be increased or decreased. Eventually, contractions may cease as the muscles are critically fatigued (and often damaged) with only occasional twitches observed clinically. More stable signs include hypertension, tachypnea, and pupillary dilation.
  - NCSE (complex partial status, absence status): impaired alertness and consciousness to a widely varying degree. Can range from mild inattention, word-finding difficulty, and poor memory to deep coma. Can be misinterpreted as drug intoxication, fatigue, or psychiatric illness. Patients may demonstrate automatisms (lip smacking, picking at clothes) or repetitive clonic contractions of a muscle group, such as the hand and finger flexors.
- **Laboratory Procedures**
  - Investigations of possible causes include urine and serum drug screens, serum AED levels, and electrolytes including calcium, glucose, LFTs, and creatinine. If meningitis or encephalitis is suspected, perform CSF studies. In general, provoking factors should be ruled out, even in known epilepsy patients. SE can cause multiple serum laboratory abnormalities, including metabolic acidosis (often marked but usually not requiring correction), elevated creatine kinase, and electrolyte abnormalities. Prolonged convulsive status may result in rhabdomyolysis and resultant renal failure. Serum prolactin usually is elevated with epileptic seizures and normal with psychogenic spells, but the sensitivity and specificity of this test are relatively low.
- **Imaging Studies**
  - CT without contrast is the study of choice if intracranial bleeding or tumor is a suspected source of seizures. MRI with gadolinium contrast is the preferred study after the patient is stabilized to determine the presence of any structural lesion that may predispose to seizures.
- **Special Tests**
  - EEG often is helpful if the diagnosis is uncertain but must be interpreted in the context of the patient's clinical presentation. Interictal EEG (performed between seizures) is helpful when ab normal (may demonstrate subclinical seizure activity or epileptogenic abnormalities) but a negative interictal EEG does not rule out seizures. Conversely, psychogenic spells often coexist with epileptic seizures, so an abnormal interictal EEG does not diagnose seizures.

#### Diagnosis

#### Differential Diagnosis
- Convulsive: basically limited to psychogenic seizures and unusual presentations of movement disorders (myoclonus, tremors, chorea). Psychogenic spells can be extremely difficult to distinguish from epileptic seizures, and there are many case reports of unnecessary intubation and medication-induced coma. Even experienced epilepsy specialists may need to use video-EEG monitoring. Movement disorders do not affect consciousness (although a number of disease states can cause both movement disorders and seizures, e.g., CJD, hypoxia). The hyperactive reflexes and sustained postures seen in stroke and hypoxia victims can resemble seizures, as can hypocalcemic tetany.

#### Associated Conditions
- Epilepsy; see Risk Factors

#### Imaging Studies
- MRI with gadolinium contrast is the preferred study after the patient is stabilized to determine the presence of any structural lesion that may predispose to seizures.

#### Special Tests
- EEG often is helpful if the diagnosis is uncertain but must be interpreted in the context of the patient's clinical presentation. Interictal EEG (performed between seizures) is helpful when abnormal (may demonstrate subclinical seizure activity or epileptogenic abnormalities) but a negative interictal EEG does not rule out seizures. Conversely, psychogenic spells often coexist with epileptic seizures, so an abnormal interictal EEG does not diagnose seizures.
Management

GENERAL MEASURES
• Always begin with the ABCs! Airway protection may become necessary, especially in convulsive status. Intubation should always precede the use of high-dose barbiturates or benzodiazepines. Laboratory tests should be drawn as soon as possible to determine the presence of correctable causes of status (metabolic disturbances, drug overdose).

SURGICAL MEASURES
• Only considered in extremely refractory cases of status with known resectable lesions

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• Patients with SE almost always should be admitted for observation (to the unit if respiratory or cardiovascular status is compromised). The exception would be chronic, intractable seizure patients with a known history of status in whom possible causes of breakthrough seizures are ruled out or corrected.

Medications

DRUG(S) OF CHOICE
• Thiamine 100 mg IV followed by glucose 50 g IV should be administered to any patient in status in whom nitrate ion deficiency and abnormal glucose are possible.

• Acse: Lorazepam (Ativan) is the usual drug of choice, administered at 0.1 mg/kg to a maximum dose of 8 mg at 2 mg/min. Alternatively, diazepam (Valium) 5-10 mg IV or 5 mg/kg/min to maximum 30 mg per 8 hrs. If seizures continue after 2 minutes, administer fosphenytoin (Cerebyx) 200 mg/kg (1.5 g for a 75-kg person) IV at maximum rate 150 mg/min in adults, 3 mg/kg/min in children.

• Note: Fosphenytoin is measured in “phenytoin equivalents.” If “mg” is written, it is universally and automatically converted to phenytoin equivalents by pharmacists. For example, if 1.5 g of fosphenytoin is ordered, the dose administered will be equivalent to 1.5 g of phenytoin.

• If IV access not available, diazepam can be given as a rectal gel and fosphenytoin can be given IM. Phenytoin should not be given IM in SE because of slow erratic absorption.

• If fosphenytoin is not available, phenytoin can be dosed at 20 mg/kg IV at maximum rate of 50 mg/min.

• If seizures continue, an additional 5 mg/kg IV dose of fosphenytoin is administered, followed by IV phenobarbital at a dose of 20 mg/kg at maximum rate of 150 mg/min. If these regimens fail (around 15 minutes of status), a neurologist and an EEG team should be urgently consulted. Anticipatory intubation will nearly always be necessary at this point. The next step is inducing electrical shutdown of the CNS (verified with EEG) with one of the following:
  • IV pentobarbital 5-15 mg/kg loading dose, followed by 5 mg/kg/hour titrate to EEG
  • IV midazolam 0.2 mg/kg load, then 0.1 to 0.4 mg/kg/hour titrate to EEG
  • IV propofol 2 mg/kg load, then 0.1-0.2 mg/kg/min (6-12 mg/kg/hour); titrate to EEG

• NCSE: Begin as for benzodiazepines and fosphenytoin. Fother treatment of nonconvulsive status is controversial. Most authorities consider nonconvulsive status urgent but nonemergent. Some epileptologists believe that some treatments may actually worsen NCSE. Consultation with a neurologist is recommended.

Contraindications
• Known allergies to specific AEDs

Precautions
• Benzodiazepines, barbiturates, and fosphenytoin, especially at higher doses, can cause respiratory and cardiovacular depression necessitating intubation. Phenytoin and fosphenytoin can cause arrhythmias (heart block and prolonged QT interval).

ALTERNATIVE DRUGS
• IV valproate (Depacon) may be helpful, especially in NCSE or as a third-line agent in refractory GCSE. Other anesthetic agents such as lidocaine have been used anecdotally to stop refractory SE.

Follow-Up

PATIENT MONITORING
• AEDs should be continued (preferably using the agent that aborted the initial seizure). If only benzodiazepine therapy was required, patient should be loaded with phenytoin or fosphenytoin PO/IM 15-20 mg/kg over 4 hours and then 5 mg/kg/day. Patient should be monitored closely for 24-48 hours while the search for provoking factors is completed. Routine neurology consultation is advisable. Repeat EEG is advisable in cases in which nonconvulsive status or subclinical seizures are suspected (failure of mental status to improve, prolonged focal weakness). Keep in mind that prolonged decreased awareness after GCSE may be due to NCSE instead of drug effect or postictal state.

EXPECTED COURSE AND PROGNOSIS
• Depends primarily on the presence or absence of a provoking factor. Overall mortality is 10-4-20%, with the highest mortality in elderly stroke victims. In general, having an episode of SE increases the risk for future seizures, as well as future SE. NCSE and FSE are generally more difficult to treat. Permanent neurologic and psychological deficits may be related to prolonged SE. Most of the mortality of SE is related to the underlying cause (bleed, tumor, infection), but prolonged seizure activity alone is estimated to cause 5% mortality.

PATIENT EDUCATION
• In general, factors that increase seizure risk will increase risk of status (mortality). Other physical stress, fatigue, sleep deprivation, poor medication compliance, drug-drug interactions, other medications.

Miscellaneous

SYNONYMS
• Status (rarely may be confused with status migrainosus)

ICD-9-CM: 345.3 Epilepsy, status (grand mat); 345.7 Epilepsy, status focal
SEE ALSO: N/A

REFERENCES


Author(s): Mark R. Gibson, MD; Joseph Siven, MD
### Fibromyalgia

#### DESCRIPTION
- Fibromyalgia is a musculoskeletal pain amplification syndrome that includes symptoms of pain, stiffness, and exhaustion; physical findings of specific areas of tenderness; and no evidence of any specific etiology for cause of symptoms. Many terms have been used for similar medical conditions over the years, including tender points with rheumatism, neurologic, fibrositis, psychogenic rheumatism, myofascial pain syndrome, whiplash injury, posttraumatic stress disorder, Gulf War syndrome, chemical sensitivity syndrome, chronic fatigue syndrome, and variant reflex dystrophy.

#### ETIOLOGY
- The typical onset is between ages 9 and 60 years; most commonly presenting between ages 40 and 60. In the pediatric population, early precursors of this condition may include "growing pains" or "early migraines."

- The specific cause of fibromyalgia is unknown; however, a number of inciting events are known to be associated with this condition. They include trauma (particularly head and or neck injury from motor vehicle accidents), recent infection, and stress. Families with multiple afflicted members are known to occur. Other disease associations within affected families include depression, obsessive-compulsive disorder, and anxiety disorder. Recently, a link has been found with a functional polymorphism in the serotonin transporter gene in affected individuals. Sleep disturbances also play an important role in the pathology. Fibromyalgia patients lack stage 4, non-REM (or slow-wave) sleep relative to controls. Intrusion of alpha waves on slow delta waves is seen on EEG patterns. Normally during stage 4 sleep, we should see delta waves only. Alpha waves are an indication of a lighter (more easily arousable) sleep. This same EEG pattern can be experimentally induced by sleep depriving healthy subjects. Serotonin may be the neurotransmitter that mediates slow-wave sleep. Tryptophan crosses the blood-brain barrier and is converted to serotonin. Inhibition of serotonin production is associated with a decrease in slow-wave sleep and an increase in somatic symptoms; therefore, theories have been put forth to suggest that fibromyalgia may result from an insufficient concentration of circulating tryptophan.

#### RISK FACTORS
- Risk factors include preceding trauma (whiplash injury), infection, and/or other inciting events all associated with fibromyalgia. Risk factors may also include anxiety disorder, depression, irritable bowel syndrome, restless legs syndrome, temporomandibular joint (TMJ) syndrome, and Premenstrual syndrome.

#### SIGNS AND SYMPTOMS
- In childhood, a common presentation is "growing pains" or "migraines." In young adulthood, "chronic fatigue" eventually may evolve to global pain. Patients will generally describe aches/pains and/or articular pains with possible joint tenderness, although no actual synovitis is detected. Subjective feeling of swelling usually involves the hands, usually worse in the morning and better by midday. Stiffness lasts approximately 1 hour after awakening. An associated sleep disorder characterized by a nonrestorative sleep is common. Barometric weather changes may exacerbate symptoms. Activity may exacerbate some individuals' symptoms, causing them to seek a more sedentary state.

- Physical examination is characterized by the presence of diffuse tender points (>11 of 18) in all four quadrants of the body. The amount of pressure applied is approximately 4 lb (8.8 kg) at each point. Typically patients will be tender at sites outside of the 18 tested points. On occasion, testing a tender point might elicit a sudden withdrawal-like response from the subject (jump sign). The term trigger point is sometimes used. Trigger points are soft-tissue regions that, either spontaneously or following direct pressure, cause radiating pain, paresthesias, and autonomic symptoms. The diagnosis of fibromyalgia is made once the above noted symptoms have been persistent for >3 months.

#### LABORATORY PROCEDURES
- Fibrositis is a clinical diagnosis and is confirmed by the presence of normal laboratory data helping to exclude other conditions. Although there are documented laboratory abnormalities in the majority of patients affected by fibromyalgia (threelfold elevation in CSF substance P elevation in CSF nerve growth factor, decrease in CSF angiotensin-converting enzyme level, decrease in 24-hour urine 5-HIAA level), these tests are not routinely obtained as part of the clinical screening profile. Laboratories helpful for elucidating other conditions include the presence of normal ESR, TSH, muscle enzyme levels, hemoglobin and hematocrit, rheumatoid factor (RF), and anti-nuclear antibody (ANA). ANA levels may be positive in 30% of affected individuals; however, they do not indicate an underlying autoimmune condition.

#### IMAGING STUDIES
- There are no specific imaging abnormalities.

#### SPECIAL TESTS
- There are no special laboratories needed for diagnostic purposes.
Fibromyalgia

Management

GENERAL MEASURES

- An explanation of the condition is the initial approach. Reassurance; job modification with avoidance of repetitive activities; physical therapy consisting of weight loss, abdominal support exercises, and posture training; and heat therapy consisting of ultrasound and hot packs may all play a role. Exercising to increase heart rate to >150 beats/min is usually more effective than flexibility maneuvers.
- Sleep induction therapy is an important component of treatment of fibromyalgia. Various medications used in this effort are listed in the Drug(s) of Choice section.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

- Use of analgesics, acupuncture, biofeedback, and other stress management and relaxation techniques in conjunction with the medications listed below often is beneficial.

ADJUNCTIVE TREATMENT

- Autonomic dysfunction therapy: TMJ syndrome is treated with orthodontic bracing/night brace. Irritable bowel syndrome uses agents that decrease GI motility or might benefit from the use of peppermint oil extract. Zinc, magnesium, or manganese supplements might help modulate some symptoms.

ADMISSION/DISCHARGE CRITERIA

- Admission is not required for this condition.

Medications

DRUG(S) OF CHOICE

- Medications include nonsteroidal antiinflammatory drugs and muscle relaxants. On occasion, injection of trigger points with lidocaine steroid is indicated.
- Tricyclic antidepressants at night time (e.g., doxepin [Sinequan] or nortriptyline 10 mg; increase by 10 mg every 3–4 weeks until the patient is able to sleep through the night). Use of selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine), usually in the morning, may often provide patients with an energy boost. They probably work by increasing 5-hydroxytryptamine levels in synaptic cleft.

Contraindications

- The medications above should not be prescribed for any patient with a known hypersensitivity to a particular drug. SSRIs should not be used in conjunction with monoamine oxidase inhibitor (MAOI) drugs, and because of its long half-life fluoxetine should be discontinued at least 5 weeks before starting an MAOI antidepressant.

Precautions

- Fluoxetine may be associated with insomnia, changes in weight and appetite, decrease in seizure threshold, and, rarely, activation of mania or hypomania in predisposed individuals.

ALTERNATIVE DRUGS

- Other adjuncts used to modulate pain include sleep aids such as antihistamines or benzodiazepines, and anticonvulsants (γ-aminobutyric acid inhibitors, e.g., gabapentin).

Follow-Up

PATIENT MONITORING

- For many patients, fibromyalgia is a chronic disease. Encouragement and regular follow-up are helpful to ensure compliance with a graded exercise program, identification of contributing stress and depression, and adjustment of symptomatic medications.

EXPECTED COURSE AND PROGNOSIS

- Generally, fibromyalgia has a fluctuating course. Treatment is aimed at empowering the patient to understand the illness and be an active participant in its treatment. Promotion of a positive outlook helps to minimize depression as a result of the chronic pain and helps to reduce disability seeking. On average, 2% of patients obtain complete relief, 60% obtain a 50% decrease in symptoms, and 2% obtain in little relief of symptoms.

PATIENT EDUCATION

- There is no definite diet plan for patients with fibromyalgia. A number of diets supported by anecdotal evidence only have been proposed. A normal healthy balanced diet is the best approach. Numerous fibromyalgia support chapters are presently active throughout the United States.

Miscellaneous

SYNONYMS

- Fibrositis ICD-9-CM: 729.1
- Fibromyalgia

SEE ALSO: N/A

REFERENCES


Author(s) Kev in V. Hackshaw, MD
Friedreich's Ataxia

**DESCRIPTION**

- Friedreich's ataxia (FRDA) is one of the most common forms of autosomal recessive ataxia. In FRDA, the spinocerebellar tracts, dorsal columns, pyramidal tracts, and, to a lesser extent, the cerebellum and medulla are involved.

**etiologic**

- Friedreich's ataxia occurs with a prevalence of approximately 1/50,000 in Caucasian populations.
- It is rare among sub-Saharan Africans and does not exist in the Far East. Particularly high frequency of FRDA was found in Cyprus and among the French-Canadian population.
- Both sexes are affected with the same frequency as expected given an autosomal recessive pattern of inheritance of the disease.
- Approximately 15% of patients reported with this condition became symptomatic after age 20 years. The only significant differences between these late-onset patients and more typical early-onset patients are a lower occurrence of skeletal deformities in the late-onset groups and normal visual evoked potentials, which were abnormal in 69% of individuals presenting with FRDA before age 20. The disease progresses slower in the late-onset group.

**Etiology**

- 98% of cases of FRDA are due to expansion of a GAA trinucleotide repeat intron 1 of the FRDA gene frataxin, whereas 2% are due to point mutations in the frataxin gene located on chromosome 9. Seventeen mutations had previously recognized. Larger GAA expansions were correlated with earlier age at onset and shorter times to loss of ambulation. The size of the GAA expansions was associated with the frequency of cardiomyopathy and loss of reflexes in the upper limbs. The GAA repeats were unstable during transmission. Thus, the clinical spectrum of Friedreich's ataxia is broader than previously recognized.

**risk factors**

N/A

**Diagnosis**

**Differential Diagnosis**

- Spinocerebellar degeneration
- Predominantly cerebellar
  - Late cortical cerebellar atrophy of Marie-Font-Alajouanine syndrome
  - Holmes familial cortical cerebellar atrophy
  - Alcohol
  - Drug-induced phenylalanine ([Dilantin])
  - Paraneoplastic
  - Cerebellar and brainstem ataxias
  - OPC
  - Dentatorubropallidoluysian atrophy
  - Machado-Joseph disease

**Signs and Symptoms**

- Usually begins with gait ataxia; difficulty in standing steadily and running are early symptoms; upper extremity ataxia and dysarthria appear later
- Peripheral neuropathy, mixed sensory and cerebellar ataxia
- Pes cavus, hammertoes, kyphoscoliosis
- Cardiomyopathy in 50% cases; diabetes mellitus in 10%
- Physical examination: decreased or absent deep tendon reflexes, up-going toes, loss of vibratory perception and position sense, positive Romberg, ataxia, dysarthria

**Laboratory Procedures**

- Nerve conduction studies: sensory nerve responses absent in lower extremities, slowed in upper extremities. Motor nerve conductions usually are normal or show a mild reduction.

**Pregnancy**

- Morbidity during pregnancy is related to symptomatic manifestations and complications of the disease.

**Associated Conditions**

- Cardiac manifestations are conspicuous in some cases. Approximately half of 22 fatal cases of Friedreich's ataxia died of heart failure, and nearly three fourths had evidence of cardiac dysfunction in life. Abnormalities of the echocardiogram in patients with FRDA were in the form of symmetric, concentric, hypertrophic, or hypokinetic-dilated cardiomyopathy.
- Diabetes was present in 23%. Muscular subaortic stenosis has been described in cases of Friedreich's ataxia.
- Scoliosis is a well-known complication of FRDA. It can cause secondary impairment of pulmonary function.
- Chorea as a rare manifestation of FRDA has been reported.
- Partial deafness and loss of visual acuity occur in a minority of patients with FRDA.

**symptomatic treatment**

- Loss of balance and coordination usually require using mobility aids, such as braces, a cane, or a walker, within a decade of the diagnosis. A wheelchair often is needed for mobility several years afterward. Progressive weakness in the lower limbs can compound the problems caused by loss of coordination.
- Regular stretching and exercise as a part of a longitudinal physical therapy program are very important to minimize contractures and maintain strength.
- Occupational therapy is needed to determine the appropriate devices and strategies to improve function in the activity of daily living.
- Mild scoliosis is sometimes treated with a brace fitted around the chest and abdomen.
- A speech-language pathologist or speech therapist teaches compensatory techniques for both speech and swallowing. A dietitian or nutritionist advises on meals and preparation techniques that make food easier to swallow and increase nutrient content.
- Cardiac problems and diabetes are to be managed by a cardiologist and an endocrinologist, respectively.

** Adjunctive Treatment N/A**

**Admission/Discharge Criteria**

- FRDA, like almost all chronic conditions, is managed primarily on an outpatient basis. Admission might be required for treatment of associated conditions or corrective surgeries (see above).
Friedreich’s Ataxia

Medications

**DRUG(S) OF CHOICE**
- Muscle stiffness, spasms, and cramps might be treated with symptomatic medications, such as baclofen, diazepam, and gabapentin.
- Baclofen 10 mg 1-3 times per day is titrated up to an effective dose to maximum of 100 mg.
- Diazepam 2-10 mg three times daily.
- Neuropathic pain should be managed with gabapentin 100-900 mg tid, escalating up to a maximal dose of 3,600 mg/day.

**Contraindications**
- Worsening of gait unsteadiness and excessive sedation are major limitations related to use of these drugs.

**Precautions**
N/A

**ALTERNATIVE DRUGS**
- Tizanidine 2-8 mg qd-tid may be used as an alternative antispasticity agent. Gradual titration is required with monitoring for orthostasis, sedation, and LFT abnormalities.

Follow-Up

**PATIENT MONITORING**
- Careful patient monitoring and multidisciplinary approach with involvement of neurologists, psychiatrists, physical and occupational therapists, speech-Language pathologists, and, if needed, cardiologists, diabetologists, and orthopedic surgeons can be coordinated through a Muscular Dystrophy Association clinic.

**EXPECTED COURSE AND PROGNOSIS**
- Gradual worsening of the symptoms is expected. The speed of progression and the effect of FRDA on lifespan vary among patients. On average, people with FRDA live 3-4 decades after the diagnosis. Life expectancy is higher in patients with milder forms of the disease and later age of onset. Heart disease has the most significant impact on lifespan.

**PATIENT EDUCATION**
- Muscular Dystrophy Association has been a major sponsor of FRDA research and a vital source of services and education to patients affected by this disorder.
- Muscular Dystrophy Association-USA, 3300 East Sunrise Drive, Tucson, AZ 85718. Phone: 800-572-7171, website: www.mdausa.org
- National Ataxia Foundation, 2600 Fernbrook Lane, Suite 119, Minneapolis MN 55447-4752. Phone: 763-553-0020, website: www.ataxia.org

Miscellaneous

**SYNONYMS**
N/A

**ICD-9-CM:** 334.0 Friedreich’s ataxia

**SEE ALSO:** SPINOCEREBELLAR ATAXIAS

**REFERENCES**

Author(s): Lindenbaum Yelena, MD
**Gangliosidoses**

**Basics**

**DESCRIPTION**
- Gangliosidoses are a group of diseases that result from enzymatic block and subsequent neuronal ganglioside deposition. Gangliosides are present predominantly in the gray matter. The gangliosidoses include (i) $G_{M2}$ gangliosidosis (deficiency of hexosaminidase A), consisting of infantile $G_{M2}$ gangliosidosis or Tay-Sachs disease, juvenile $G_{M2}$ gangliosidosis, adult $G_{M2}$ gangliosidosis, and normal phenotype with hexosaminidase A deficiency; (ii) Sandhoff disease (deficiency of HEX A and HEX B); and (iii) $G_{M1}$ gangliosidosis, which has infantile, juvenile, and adult variants. A II of the gangliosidoses are autosomal recessive disorders.

**EPIDEMIOLOGY**
- The carrier rate of Tay-Sachs disease is between 1 in 30 and 1 in 40, with a disease incidence of 1 in 4,000 in Ashkenazi Jews; whereas in the non-Jewish population, the carrier rate is 1 in 167, with an incidence of 1 in 112,000. The carrier rate of Sandhoff disease is 1 in 500, with an incidence of 1 in 1,000,000 in the Jewish population. In non-Jewish populations, the carrier rate is 1 in 28, with a disease incidence of 309,000. The incidence of $G_{M1}$ gangliosidosis is 1 in 3,700.

**ETIOLOGY**
- There are two isoenzymes of $\beta$-hexosaminidase, HEX A and HEX B. Tay-Sachs disease is caused by gene mutations and complete deficiency of HEX A, with normal HEX B. Patients with juvenile and adult $G_{M2}$ gangliosidoses have partial deficiency of HEX A. Sandhoff disease is induced by mutant ions of the HEXB gene (encodes G subunit of HEX A and HEX B) with deficiency of HEX A and HEX B. $G_{M2}$ activator deficiency is due to mutations of the $G_{M2}$ A gene and deficiency of the $G_{M2}$ activator protein, with normal HEX A and HEX B.

**Genetics**
- All forms of $G_{M2}$ gangliosidoses are caused by mutations of the $\alpha$-galactosidase gene and severe deficiency of acid $\alpha$-galactosidase.

**RISK FACTORS**
- Tay-Sachs disease and Sandhoff disease are seen more frequently in the Jewish populations.

**PREGNANCY**
- The prenatal diagnosis of Tay-Sachs disease, Sandhoff disease, and other GM2 gangliosidoses can be made by quantifying HEX A and HEX B in the amniotic fluid (at 16-18 weeks) or the choronic villi (9-12 weeks) during pregnancy. Prenatal diagnosis of $G_{M2}$ gangliosidoses can be made by measuring acid $\beta$-galactosidase activity in amniocytes or chorionic villi.

**ASSOCIATED CONDITIONS**
- Myoclonic epilepsy, infantile spasms, and a variety of partial or generalized epilepsies are seen in Tay-Sachs disease and other GM2 gangliosidoses. Epilepsy is also present in infantile and juvenile $G_{M2}$ gangliosidoses.
- Progressive ataxia and dementia occur often in $G_{M2}$ gangliosidoses. Ataxia is also present in juvenile and adult GM, gangliosidoses.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Because myoclonic epilepsy, ataxia, loss of milestones, and dementia are all present in the gangliosidoses, the differential diagnosis includes neurodegenerative diseases such as neuronal ceroid lipofuscinosis, progressive myoclonic epilepsy syndrome, aminoacidopathies, organic acidopathies, fatty acid $\beta$-oxidation disorders, and mitochondrial cytopathies.
- Because adult and juvenile patients with gangliosidosis can have dystonia, psychosis, spinocerebellar degeneration, corticospinal tract degeneration, or spinal cord anterior horn cell dysfunction, the differential diagnosis includes Kugelberg-Welander disease, spinocerebellar ataxia, Friedreich's ataxia, amyotrophic lateral sclerosis, and other late-onset variants of lysosomal sphingolipidoses.

**SIGNS AND SYMPTOMS**
- In Tay-Sachs disease, hyperacusis, startle response, and severe irritability occur in the first few months. Developmental retardation, dementia, hypotonia, progressive weakness, poor head control, decrease in attention, visual decline and blindness, cherry-red spot (due to degeneration of ganglion cells around macular fovea centralis), and seizures (myoclonic seizures, infantile spasms, partial and generalized motor seizures) are frequently seen in the first year. Further deterioration in the second year of life results in decerebrate posturing, incoordinate swallowing, and a vegetative state.
- In juvenile $G_{M2}$ gangliosidosis, incoordination and ataxia become apparent between 2 and 6 years. Dementia, loss of speech, spasticity, seizures, and dysfunction of the basal ganglia, cerebellum, corticospinal tracts, and anterior horn cells then are noted over several years. Loss of vision occurs much later than in Tay-Sachs disease; cherry-red spot may not be seen. Optic atrophy and retinitis pigmentosa can occur in the later stages. Decerebrate rigidity and a vegetative state are frequently noted by 10-15 years of life.
- In chronic or adult onset $G_{M2}$ gangliosidosis, the onset is at puberty or early adulthood. Symptoms of spinocerebellar degeneration and lower motor neuron disease are often seen. Psychosis, depression, personality changes, dystonia, and extrapyramidal signs can occur.
- The presentation of infantile Sandhoff disease is similar to Tay-Sachs disease, including the onset and progressive deterioration of neurologic function; however, these patients have organomegaly and occasional bony deformities.
- $G_{M2}$ activator deficiency has a clinical phenotype similar to Tay-Sachs disease and infantile Sandhoff disease.
- In infantile $G_{M2}$ gangliosidosis symptoms are noted early, with severe motor and mental retardation evident in the first year. Feeding difficulty and poor appetite lead to weight loss. Cherry-red spots are seen in 50-60% of patients. Intractable seizures often occur.
- In juvenile $G_{M2}$ gangliosidosis, the onset is between 6 and 20 months. Psychomotor development is normal in the first year. Ataxia begins at age 1 year, along with strabismus, choreoatetosis, loss of speech, and generalized muscle weakness. Seizures and blindness often occur after age 2 years.
- In adult $G_{M2}$ gangliosidosis, initial symptoms are abnormalities of gait and dystonia, followed by progressive dystonia of the face and extremities. Mental impairment usually is mild and seizures are rare.

**LABORATORY PROCEDURES**
- EEG may reveal a variety of epileptiform abnormalities (e.g., hypsarhythmia). In adult $G_{M2}$ gangliosidosis, electromyograms frequently reveal chronic active denervation and reinnervation, and other changes consistent with anterior horn cell disease. Vacuolated lymphocytes and foam cells in the bone marrow can be detected in infantile and juvenile GM gangliosidosis.
**Gangliosidoses**

**IMAGING STUDIES**
- MRI of Tay-Sachs disease reveals low-signal lesions in areas of abnormal cerebral white matter and the basal ganglia. During later stages, diffuse brain atrophy and compensatory ventriculomegaly may be noted. Severe cerebellar atrophy and mild cerebral atrophy may be noted in juvenile and adult GM2 gangliosidoses.
- In all GM, gangliosidosis, diffuse brain atrophy is present on neuroimaging. Low-signal abnormalities of the basal ganglia and high-signal lesions of the white matter may be present in infantile and late-onset GM, gangliosidosis.
- In infantile GM, gangliosidosis, bone x-ray films may detect vertebral deformities, hypoplasia, anterior beaking at the thoracolumbar region, retarded bone age, short long bones, and bilateral dislocation of the hip joints.

**SPECIAL TESTS**
- Genetic testing of the gangliosidoses requires analysis of either blood or fibroblast samples. The HEXA gene is mapped to chromosome 3p21.33. Mutations include missense, nonsense, and insertion varieties.
- In GM1 gangliosidosis, the human beta-galactosidase gene is mapped to chromosome 4q24. HEXB gene to chromosome 5q13, and GBA gene to chromosome 5q32-33. At least 92 mutations in the HEXA gene have been reported in Tay-Sachs disease, and the most frequently seen mutation in Ashkenazi Jews is a fo message pair insertion in exon 11.
- The human beta-galactosidase gene is mapped to chromosome 3p21.33. Mutations include missense, nonsense, and insertion varieties.

**MEDICATIONS**

**DRUG(S) OF CHOICE**
- Anticonvulsants as required for seizure control. Spasticity of the extremities may benefit from antispasticity drugs such as oral diazepam, dantrolene, baclofen, or tizanidine. Intrathecal baclofen infusions and IM botulinum toxin injections may be effective.

**CONTRAINDICATIONS**
- N/A

**PRECAUTIONS**
- N/A

**ALTERNATIVE DRUGS**
- N/A

**REFERENCES**

**SYNONYMS**
- Tay-Sachs disease
- Sandhoff disease
- GM2 gangliosidosis
- GM1 gangliosidosis

**ICD-9-CM**
- 330.1 Tay-Sachs disease; 330.1 Gangliosidosis, 330.1 Sandhoff disease

**SEE ALSO**
- N/A

**PATIENT EDUCATION**

**Patient Monitoring**
- Patients need to be monitored for seizure control, neurologic function, psychosis or mental decline, and nutritional status.

**Expected Course and Prognosis**
- The majority of patients with Tay-Sachs disease survive to age 2-4 years. Aspiration pneumonia is often the cause of death. Patients with juvenile GM2 gangliosidosis also frequently die of intercurrent infection between 10 and 20 years of age. Adult patients with GM2 gangliosidosis may live beyond the third or fourth decade of life. Patients with infantile GM, gangliosidosis typically die of pneumonia by age 2 years. The average lifespan for juvenile GM, gangliosidosis varies between 3 and 10 years. Patients with adult GM, gangliosidosis may survive up to age 80.

**ADMISSION/DISCHARGE CRITERIA**
- Patients with exacerbation of epilepsy often need to be hospitalized for treatment. If severe infections occur (e.g., aspiration pneumonia), patients should be admitted for IV antibiotics and chest physical therapy.

**SYMPTOMATIC TREATMENT**
- Treatment of epilepsy with a variety of new antiepileptic drugs is available. Nutritional support, fluid and electrolyte maintenance, and infectious control with appropriate antibiotics are important. Constipation may be a significant problem and require stool softeners or laxatives.

**ADJUNCTIVE TREATMENT**
- Physical, occupational, and speech and language therapies are helpful for patients with muscle weakness, coordination difficulty, and language/speech problems.

**GENERAL MEASURES**
- There are no definitive treatment measures for the GM and GM2 gangliosidoses. Only symptomatic and supportive therapies are available.

**SURGICAL MEASURES**
- Gastrostomy tube placement and Nissen fundoplication may be needed for patients with feeding and swallowing difficulties, and gastroesophageal reflux.

**EXPECTED COURSE AND PROGNOSIS**
- Patients need to be monitored for seizure control, neurologic function, psychosis or mental decline, and nutritional status.

**Follow-Up**

**PATIENT MONITORING**
- Patients need to be monitored for seizure control, neurologic function, psychosis or mental decline, and nutritional status.

**EXPECTED COURSE AND PROGNOSIS**
- The majority of patients with Tay-Sachs disease survive to age 2-4 years. Aspiration pneumonia is often the cause of death. Patients with juvenile GM2 gangliosidosis also frequently die of intercurrent infection between 10 and 20 years of age. Adult patients with GM2 gangliosidosis may live beyond the third or fourth decade of life. Patients with infantile GM, gangliosidosis typically die of pneumonia by age 2 years. The average lifespan for juvenile GM, gangliosidosis varies between 3 and 10 years. Patients with adult GM, gangliosidosis may survive up to age 80.

**PATIENT EDUCATION**

**MEDICATIONS**

**DRUG(S) OF CHOICE**
- Anticonvulsants as required for seizure control. Spasticity of the extremities may benefit from antispasticity drugs such as oral diazepam, dantrolene, baclofen, or tizanidine. Intrathecal baclofen infusions and IM botulinum toxin injections may be effective.

**CONTRAINDICATIONS**
- N/A

**PRECAUTIONS**
- N/A

**ALTERNATIVE DRUGS**
- N/A

**REFERENCES**

**SANFORD-BEADET-SLY SYNDROMES**
- gangliosidosis
- Tay-Sachs disease
- Sandhoff disease
- GM1 gangliosidosis
- GM2 gangliosidosis

**SYNONYMS**
- Tay-Sachs disease
- Sandhoff disease
- GM2 gangliosidosis
- GM1 gangliosidosis

**ICD-9-CM**
- 330.1 Tay-Sachs disease; 330.1 Gangliosidosis, 330.1 Sandhoff disease

**SEE ALSO**
- N/A

**REFERENCES**

**Author(s): Chang-Yong Tsao, MD**
Giant Cell Arteritis

**Basics**

**DESCRIPTION**

Giant cell arteritis (GCA) is a systemic vasculitis characterized by focal granulomatous inflammation of medial and small arteries. Involvement of elastic-containing cranial vessels predominates, including the temporal arteries. Less commonly, vessels of the upper extremities and rarely the aortic arch and great vessels may be involved. Symptoms may include headache, temporal tenderness, jaw claudication, polyarthralgia rheumatica, fever, or general malaise. A high degree of suspicion should be maintained for GCA in patients age >60 years because of the risk of acute and severe visual loss. Ocular symptoms complicate 40%-50% of cases.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

- Annual incidence rate 50-59 years of age: 2.3/100,000; annual incidence rate 80-89 years of age: 44/100,000

**Race**

- Rare in African Americans and Asians

**Age**

- Generally individuals >60 years of age; incidence increases with age; majority will be in their eighth decade

**Sex**

- Female-to-male ratio of 2-3:1

**ETIOLOGY**

- The etiology of GCA is unknown, but an immune-mediated process is most widely suspected. A genetic predisposition may exist, as evidenced by an increased prevalence of HLA-DR4 antigen and occasional family clustering.

**PREGNANCY**

- There is no documented relationship.

**ASSOCIATED CONDITIONS**

- Polymyalgia rheumatica
- Rheumatoid arthritis

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Nonarteritic anterior ischemic optic neuritis
- Angle-closure glaucoma
- Migraine
- Temporomandibular joint syndrome
- Trigeminal neuralgia

**SIGNS AND SYMPTOMS**

- GCA is a syndrome that may present with any combination of the following:
  - Headache (initial manifestation in 50%-90% of cases)
  - Pain often gradual onset, diffuse and severe, may be unilateral, usually prominent if not intractable, may be perceived as superficial and may be unresponsive to analgesics
  - Temporal scalp tenderness
  - Point tenderness on palpation over superficial temporal artery
  - Temporal artery may be indurated or have a diminished pulse
  - Abrupt, progressive monocular visual loss with involvement of the fellow eye in 25%-50% of cases
  - Visual loss may be insidious or preceded by episodes of transient monocular loss of vision
  - Partial to complete blindness, largely irreversible
  - Anterior ischemic optic neuropathy (AION) is the most common cause of visual loss as observed in 71%-83% of cases in one series; less frequent causes include central and branch retinal artery occlusion, choroidal infarction, and retrobulbar ischemic optic neuropathy
  - Signs of optic neuropathy may include decreased visual acuity, decreased color vision, afferent pupillary defect, and visual field loss
  - Often atypical visual field defect (i.e., respecting the horizontal midline)
  - In cases of AION, the optic disc may show pallid swelling, although hyperemic disc swelling is occasionally seen; peripapillary hemorrhages and cotton wool spots may be noted; as optic disc swelling resolves, optic atrophy occurs
  - Less common ophthalmic presentations are diplopia secondary to cranial neuropathies, amaurosis fugax, orbital inflammation, ocular ischemic syndrome, and Horner's syndrome
  - Polymyalgia rheumatica (>50 years of age, proximal arthralgias and myalgias, morning stiffness, increased ESR >40)
  - Jaw claudication
  - Fever of unknown origin (generally low grade), weight loss, fatigue/malaise
  - Facial pain
  - Neurologic sequelae (ataxia, confusion, hearing loss, ischemic peripheral neuropathy)

- Hemorrhagic bullae, skin necrosis (over superficial temporal arteries)
- Extremity claudication
- Myocardial, renal, visceral, or cerebral infarction
- Large-vessel involvement (aortic aneurysm or rupture, most commonly thoracic)

**LABORATORY PROCEDURES**

- There is no specific laboratory test for the diagnosis of GCA, but the Westergren ESR often exceeds 10 mm/hour. A normal ESR does not rule out the diagnosis of GCA, however, as 6%-22% of biopsy-positive GCA cases will have ESR within “normal limits.” ESR is a general measure of systemic inflammation, as are C-reactive peptide, fibrinogen, and complement levels, which may also be elevated. Additionally, anemia (hypochromic, microcytic or normochromic, normocytic), polyclonal hypergammoglobulinemia, and a mild leukocytosis may be observed. Liver alkaline phosphatase levels may be elevated in GCA.

**IMAGING STUDIES**

- Fluorescein angiography (FA) of the fundus may demonstrate a delayed or absent choroidal filling pattern suggesting arteritic ischemic optic neuropathy. FA in cases of nonarteritic ischemic optic neuropathy may show delayed optic disc filling, yet the choroidal circulation is generally not affected. CT or MRI scans are generally not indicated but may be necessary to rule out compressive or infiltrative lesions in atypical cases (e.g., multiple cranial nerve deficits, proptosis, seizure).

**SPECIAL TESTS**

- Temporal artery biopsy (> 2 cm) should be taken from the affected side. A large biopsy is needed because of the commonly observed “skip” lesions in GCA. A positive biopsy is diagnostic and demonstrates granulomatous vasculitis with multinucleated giant cells near a fragmented internal elastic lamina (66% of cases); nonspecific leukocytic infiltration of vessel walls by neutrophils, eosinophils, and T lymphocytes; and intimal fibrosis with narrowing of the lumen. Some authors recommend bilateral temporal artery biopsies; however, biopsy of the symptomatic side usually is adequate. Baseline visual field testing is indicated even without visual symptoms. If large-vessel involvement is suspected, ultrasound and/or angiography should be pursued.
Giant Cell Arteritis

**Management**

**General Measures**
- Treatment of GCA focuses on the prevention of serious vascular complications, particularly blindness. Corticosteroids are the mainstay of therapy for GCA and should be instituted when the diagnosis is suspected, even in the face of normal ESR and prior to obtaining temporal artery biopsy. Unfortunately, visual loss often is permanent, and further damage to the affected eye and even in the previously unaffected fellow eye can occur despite high-dose IV methylprednisolone treatment. Therefore, prompt diagnosis and immediate corticosteroid intervention is paramount to preventing progressive visual loss. The proper corticosteroid regimen for treatment of GCA has not been established. Initial doses and extended taper schedules should be individualized by the clinical state of each patient. The prominent headache, which is so frequent in GCA, responds rapidly to corticosteroid treatment and typically resolves within 1-2 days. ESR, C-reactive protein, and other acute phase reactants may be used to monitor response to therapy and disease control. Duration of steroid therapy for treatment of GCA may range from 1-3 years.

**Surgical Measures**
- Temporal artery biopsy should be performed to confirm the diagnosis of GCA. It is performed under local anesthetic and on an outpatient basis. Biopsy should be completed within 7 days of starting corticosteroids, after which the results of the biopsy may be affected. A negative biopsy does not rule out the diagnosis of GCA.

**Symptomatic Treatment**
- Analgesics for headache

**Adjunctive Treatment**
- N/A

**Admission/Discharge Criteria**
- Visual symptoms/loss associated with GCA require the patient to see an ophthalmologist on an emergency basis and may involve admission. Admission for GCA is indicated for IV steroid therapy, unstable vitals, large-vessel involvement, ischemic limb, and renal, gastrointestinal, cardiac, or cerebral complication. Alternatively, IV therapy may be given on an outpatient basis.

**Follow-Up**

**Patient Monitoring**
- Patients should be seen every 4-6 weeks to assess the response to therapy. Clinical symptoms and signs, ESR, and other acute phase reactants should be followed as corticosteroids are tapered.

**Expected Course and Prognosis**
- Relapse most commonly occurs during the initial year of therapy, especially following reduction of steroid dose. Up to 50% of GCA patients may require corticosteroids for greater than 2 years. In general, patients have been reported to have the same life expectancy as age-matched controls. However, profound visual loss in GCA has been found to correlate with decreased quality and duration of life.

**Patient Education**
- It is necessary to educate each patient regarding the chronic nature of GCA, the spectrum of symptoms, the possibility of relapse, and possible sequelae of long-term steroid therapy.

**Miscellaneous**

**Synonyms**
- Temporal arteritis

**ICD-9-CM:** 446.3 Giant cell arteritis; 377.41 Ischemic optic neuropathy

**See Also:** N/A

**References**

Author(s): James A. McHale, MD; Steven E. Katz, MD
**Guillain-Barre Syndrome**

### DESCRIPTION
- **Basics**
  - **Description**
    - An acute, predominantly motor neuropathy of uncertain cause that is the most common cause of acute generalized paralysis in humans.

### ETIOLOGY
- **Precise cause is unclear but follows infection in most cases.** Infection is thought to produce an immune reaction resulting in cellular and humoral responses that attack unknown myelin components and result in macrophage-induced demyelination.
- **Axon may be attacked in severe cases, especially those following *Campylobacter jejuni* infection.**
- **Sporadic disease; some association with HLA types**

### RISK FACTORS
- **Infection precedes disease onset in two thirds of patients.** C. jejuni infection is the most common precipitating infection occurring in 30%-40%. It causes gastroenteritis and precedes weakness by 7-14 days. Other infections include influenza, *Epstein-Barr virus*, *cytomegalovirus*, *human herpes simplex virus*, *hepatitis A virus*, and certain drugs (e.g., heroin).

### AGE
- **All ages; mean age of onset ~40 years**

### EPIDEMIOLOGY
- **Incidence/Prevalence**
  - **Annual incidence 1-2/100,000**
  - **Race**
    - **All races affected**
  - **Incidence/Prevalence**
    - **1-2/100,000**

### SIGNS AND SYMPTOMS
- **Begin with numbness and tingling in fingers, toes, or trunk that may last 7-10 days.** Symmetric weakness follows, usually starting in legs and then going to arms (ascending pattern). Facial involvement in approximately 50%.
- **Peak weakness reached within 4 weeks of onset.** Extent of progression variable; approximately 30% require ventilatory assistance.
- **Sensory loss variable, particularly when compared to weakness.**
- **Dull, aching, burning pain involving low back or lower extremities occurs in approximately 90%.**
- **Autonomic involvement in 70% (blood pressure instability, bowel and bladder involvement, pupillary changes, cardiac arrhythmias) Can be life threatening.**
- **Variants of typical presentation account for about 15% of all Guillain-Barre syndrome patients.**
  - **Fisher syndrome (or Miller-Fisher syndrome) may account for 5%**, characterized by ophthalmoplegia, ataxia, and areflexia, often without weakness.
  - **Paraparetic weakness (1-2%)** present with rapidly progressive weakness and sensory loss with early respiratory insufficiency. Early electrophysiologic studies reveal axonal changes and little to suggest demyelination. Patients with a predominantly axonal picture are more likely to have had preceding *C. jejuni* infection.
  - **Pure sensory variant (<1%)** presents with large fiber, ataxic, areflexic sensory neuropathy with little or no motor involvement; tremor, and autonomic features. Electrophysiologic studies show severe involvement of sensory nerves with relatively few motor findings.
  - **Acute pandysautonomic variant (rare)** presents with GI disturbances (pain, vomiting, constipation), orthostasis, urinary retention, fatigue, impotence, diminished sweating and salivation, and occasionally pupillary abnormalities.

### DIFFERENTIAL DIAGNOSIS
- **Other neuropathies: chronic inflammatory demyelinating polyradiculoneuropathy, vasculitic, toxic, hereditary, porphyria, diptheria, critical illness neuropathy, subacute sensory neuropathy with cancer, malignant infiltration of nerve roots**
- **Muscle disorders: periodic paralysis, fulminant polymyositis**
- **Neuromuscular junction diseases: acute myasthenia gravis, botulism, organophosphate poisoning, prolonged neuromuscular blockade with anesthesia**
- **Spinal cord disorders: acute compressive lesions, transverse myelitis, multiple sclerosis**
- **Brainstem disorders: tumor infiltration, encephalitis**
- **Metabolic disorders: severe hypokalemia, hypophosphatemia**
- **Psychiatric disorders: conversion disorders, malingering**

### LABORATORY PROCEDURES
- **Spinal fluid analysis: elevated protein without Leuko cytosis (usually <10 cells/mm³) in ~90% at time of maximal weakness.** Cell count >50 cells/mm³ indicates alternate diagnosis unless in setting of HIV.
- **Anti-GQ1b antibody testing and serologic testing for *C. jejuni* usually not helpful in diagnosis and do not change therapy, but may indicate poor prognosis if positive.**
- **Anti-GQb antibodies helpful in confirming diagnosis of Fisher syndrome**

### IMAGING STUDIES
- **MRI may show nerve root or cranial nerve enhancement: usually not helpful in confirming diagnosis.**

### SPECIAL TESTS
- **Nerve conduction studies may be normal early in course, becoming abnormal by 2-3 weeks.** Changes in the motor nerves usually precede changes in the sensory fibers. Studies show prolonged distal motor latencies, slowed nerve conductions, temporal dispersion of motor response, conduction block, and prolonged F waves. EMG findings depend on extent of axonal involvement. Fibrillations and sharp waves develop if axonal disruption has occurred, usually after the second week. May be severe in some cases with "axonal variant"
Guillain-Barre Syndrome

**Management**

**GENERAL MEASURES**
- ICU hospitalization for all patients with respiratory compromise, autonomic instability, or complicating medical conditions. IV immunoglobulin or plasma exchange for all patients. Monitor ventilatory status closely with serial measurements of forced vital capacity (FVC) and negative inspiratory force (NIF). Consider ventilatory assistance if FVC falls below -15 to -20 mL/kg or NIF < -20 to -25 cm H2O. Neck flexor strength that is not at least antigravity often heralds ventilatory failure.
- Intubation for ventilatory failure or airway protection in patients with severe bulbar weakness.
- Cardiac monitoring for and treatment of arrhythmias or blood pressure instability.
- Aggressive management of neuropathic pain.

**SURGICAL MEASURES**
- Tracheostomy for patients requiring prolonged intubation.

**SYMPTOMATIC TREATMENT**
- Appropriate supportive care to include physical therapy, nutrition, deep vein thrombosis prophylaxis, pulmonary care, and psychological support.
- Tube feedings may be required for patients with severe bulbar weakness or those requiring ventilatory support.
- Letter boards or electronic devices are important for patients who cannot speak because of intubation or bulbar weakness.
- Pharmacologic treatment for depression.

**ADJUNCTIVE TREATMENT**
- N/A

**ADMISSION/DISCHARGE CRITERIA**
- Hospitalization for all but the mildest cases.

**Medications**

**DRUG(S) OF CHOICE**
- Plasma exchange (200-250 cc/kg total exchanged volume divided into 4-6 exchanges over 2-3 weeks) reduces time until initial improvement, return of ambulation, and time on the ventilator; increases percentage of patients improving at 1 and 6 months; and increases percentage of patients showing full recovery at 1 year.
- IV immunoglobulin 0.4 g/kg/day for 5 days is of equal efficacy, increasing the percentage of patients improved at 1 month, and reducing median time to improvement and time to reach independent ambulation.
- Both plasma exchange and IV immunoglobulin confers no additional benefits.

**Contraindications**
- Cardiovascular instability, congestive heart failure, hypotension, renal failure, or severe anemia are relative contraindications to plasma exchange. Theoretical risk of bleeding complications due to depletion of clotting factors, especially fibrinogen. For these patients, IV immunoglobulin probably is a better choice. Sepsis due to chronic indwelling central catheter may be a problem.
- For IV immunoglobulin, congenital IgA deficiency is relative contraindication, because these patients may develop antibodies to IgA that can result in anaphylactic-like reaction.

**Precautions**
- May need IV fluids if hypotension develops during plasma exchange. Hypocalcemia secondary to anticoagulants and during procedure may need treatment.
- Mild allergic reactions, including chills, itching, fevers, flushing, and tachycardia, usually respond to slowing of infusion rate, but antihistamines, steroids, or both occasionally are needed.

**FOLLOW-UP**

**PATIENT MONITORING**
- Periodic reassessments to ensure that relapse is not occurring.

**EXPECTED COURSE AND PROGNOSIS**
- Degree and extent of progression variable; approximately 75% of patients reach nadir within 7 days of presentation; essentially all by approximately 75% of patients reach nadir within 4 weeks. Some patients progress rapidly to ventilator dependence within days, whereas others have very mild progression for weeks and never lose ambulation.
- Approximately one third of patients eventually require ventilatory assistance. Recovery over weeks to months is usual (70% of patients).
- 10%-25% will have permanent weakness or other impairments that interfere with activities of daily living.
- 3°-7° -5% die, usually from respiratory distress syndrome, sepsis, or both.

**PATIENT EDUCATION**
- Careful explanation of the natural history of the disease and realistic goals for expected speed and degree of recovery.
- Guillain-Barre Syndrome Foundation International, P.O. Box 262, Wynnewood, PA 19096. Website: www.guillain-barre.com

**SYNONYMS**
- Landry-Guillain-Barre-Strohl syndrome
- Acute idiopathic polyneuritis
- Acute ascending paralysis
- Acute inflammatory demyelinating polyradiculoneuropathy

**ICD-9-CM: 357.0 Acute infective polyneuritis**

**SEE ALSO:** CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

**REFERENCES**

Author(s): John Kisset, MD

**Miscellaneous**

**SYNONYMS**
- Landry-Guillain-Barre-Strohl syndrome
- Acute idiopathic polyneuritis
- Acute ascending paralysis
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**ICD-9-CM: 357.0 Acute infective polyneuritis**

**SEE ALSO:** CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

**REFERENCES**

Author(s): John Kisset, MD
Headache, Acute

**Basics**

**DESCRIPTION**
- Headache is one of the most common symptoms seen in medical practice. Many headaches are chronic or fit readily into the most common patterns of headache. Headaches of new onset that do not fit into the description of migraine, cluster, or tension-type headache need to be analyzed carefully. A single severe headache lasting hours to days in a patient without a history of similar headaches can be classified as acute. Various processes may cause such headaches and may range from benign to life threatening. The acute headache is a particular problem for emergency room physicians, who have only one opportunity to diagnose headaches that require further evaluation and treatment.

**ETIOLOGY**
- Most acute headaches are migraine, tension-type headache, or cluster headache. Each of these entities is dealt with in its respective chapters. A variety of factors are red flags for more significant processes causing headache. The presence of one or more of the following factors is an indication for further evaluation:
  - Abrupt onset of headache
  - Anticoagulant use
  - History of head trauma within the past few months
  - Fever, immunosuppression, or other symptoms of infection, especially in a parameningeal focus
  - Prominent neck pain and stiffness, suggesting meningitis irritation
  - Progressive headache over hours or days
  - Altered consciousness (including syncope or seizures)
  - Focal neurologic complaints or findings — Age > 40, as the onset of primary headache disorders is rare in this age group and the prevalence of secondary headache disorders is higher
  - Exposure to products of combustion (or cohabitants/ coworkers with similar symptoms) suggesting carbon monoxide exposure

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Acute glaucoma: eye pain, visual blurring, tender orbit, conjunctival injection
- Brain mass lesion: brain tumor or abscess, usually progresses over days to weeks, and does not usually present as acute headache unless there is sphenopalatine arterial bleeding
- Carbon monoxide poisoning: exposure setting, others involved in same area, altered mental status, carbon monoxide, or arterial bleeding
- Encephalitis: hours to days, severe headache; focal neurologic signs (aphasia, hemiparesis), impaired consciousness, seizures, fever, chills
- Exertional headache: minutes, setting of exercise or straining (Valsalva), sudden, suboccipital, severe, pounding headache lasting minutes; may occasionally be associated with posterior fossa lesions, Arnold-Chiari malformations, or berry aneurysms
- Low-pressure headache: post lumbar puncture or trauma, operation, spontaneous; pancerebral, worse with standing, headache; associated with nausea
- Meningitis: hours to days, severe headache with neck stiffness, fever, chills, photophobia, possibly confusion
- Pheochromocytoma: days to weeks, intermittent acute headache, pounding, pancerebral, with acute hypertension
- Pseudotumor cerebri: days to weeks, progressive, pancerebral, worse with recumbency; associated with visual obscurations, occasional sixth nerve palsies, visual field constriction
- Sinusitis: acute sinusitis and other sinonasal problems can be a cause of a acute headache and/or facial pain. Less common than perceived by the public. Pain, tenderness over maxillary, ethmoid sinus, with purulent rhinorrhea, respiratory complaints. Vertex pain may occur with sphenoid sinusitis.
- Subarachnoid hemorrhage: immediate, "worst headache of my life," pancerebral, sometimes with loss of consciousness, confusion, mutism, focal neurologic findings, nuchal rigidity
- Temporal arteritis: days to weeks, persistent, aching headache, often temporal, unilateral, associated with malaise, low-grade fever, myalgias, nodular areas temporal arteries, jaw claudication, blindness

**RISK FACTORS**
- Dependent on the primary cause of a acute headache. Patients should be asked about medication and drug use, major medical problems, exposures to toxins, recent infections, trauma, and travel.

**PREGNANCY**
- New headaches in pregnancy may occur due to the onset of migraine. Rarely, cortical vein thrombosis, particularly in the peripartum period, may occur. Headaches may occur with eclampsia. Intracerebral and subarachnoid hemorrhages may occur in patients with berry aneurysms or intracranial malformations.

**ASSOCIATED CONDITIONS**
- See Etiology; Diagnosis

**ETIOLOGY**
- Approximately 6.6 million office visits are made for headache annually, representing 2% of all primary care visits made in the United States. Over 1.8 million emergency room visits are also made annually. This is 3% of all emergency room visits nationally. Resulting costs are estimated at $15 billion per year. In a single hospital study, of 455 patients screened primarily for headache, 76% were female, mean age 37 years, and 3% had subarachnoid hemorrhage.

**EPIDEMIOLOGY**
- New headaches in pregnancy may occur due to the onset of migraine. Rarely, cortical vein thrombosis, particularly in the peripartum period, may occur. Headaches may occur with eclampsia. Intracerebral and subarachnoid hemorrhages may occur in patients with berry aneurysms or intracranial malformations.

**SIGNS AND SYMPTOMS**

**Initial History**
- Description of the headache (nature, rapidity of onset, degree and quality of pain, location, relieving/exacerbating factors, prior headache history, change from prior headache)
- Associated symptoms (nausea, vomit ing, neurologic symptoms, fever, change in mental status, c/o pain or stiffness, dental and sinus symptoms, photophobia, nasal discharge)
- Current medications (including anticoagulants, monoamine oxidase inhibitors, pain medications, other medications)
- Past medical history (major medical or surgical disorders, trauma, infection, drug and alcohol history)

**Initial Examination**
- Vital signs (temperature, BP, pulse, respirations)
- Dental, sinus evaluation (oral examination, dental percussion, ear examination)
- Check for temporal artery nodularity, tenderness
- Neck examination (rigidity)
- Ophthalmologic examination (for corneal clouding, papilledema, subhyaloid hemorrhages, hypertensive changes)
• General medical examination (including ear, lymph nodes)
• Neurologic examination (level of consciousness, presence of aphasia or neglect, lateralizing signs, up-going toes)

LABORATORY PROCEDURES
• Depends on results of history and physical examination. Considerations include glucose (hypoglycemia or hyperglycemia), electrolytes, CBC (white count elevation in infection, anemia causing headache), PT/PTT (for coagulopathy causing bleeding), drug screen, carboxyhemoglobin (for carbon monoxide exposure), ESR and C-reactive protein (for temporal arteritis).

IMAGING STUDIES
• Any patient with a new headache should be considered for an imaging study. If the headache is suggestive of subarachnoid hemorrhage or intracerebral hemorrhage, a CT scan should be performed as soon. This is positive in subarachnoid hemorrhage in about 90% of patients, but more likely may be negative with a delay of days, with small amounts of blood, or with a low hematocrit. When there is a suspicion of subarachnoid hemorrhage despite negative CT, a lumbar puncture should be performed. MRI is less sensitive actively in subarachnoid hemorrhage but may show the presence of the aneurysm. Intracerebral hemorrhage is well imaged by CT, and the location and size may determine whether surgical approach is necessary.
• Imaging studies should be performed for other types of acute headache. MRI may be superior in some types of acute headache conditions. These include intracerebral infections (particularly with the use of gadolinium enhancement), cortical vein thrombosis, CNS inflammatory disorders, and encephalitis. MR angiography of the head and neck may be useful in patients with cerebral aneurysms or dissections of extracranial vessels, or with intracranial vascular anomalies. MR venography may assist in diagnosis of venous sinus thrombosis.

SPECIAL TESTS
• In patients with acute headache in whom there are red flags and initial evaluation is negative, or in which CT is negative and subarachnoid hemorrhage, meningitis, or encephalitis is considered, lumbar puncture is important and may be diagnostic. Lumbar puncture should be avoided in the presence of mass effect or lateralized processes to avoid precipitating cerebral herniation. • Cerebral arteriography is standard in patients with cerebral aneurysms and should be performed on all intracranial vessels to assess for secondary aneurysms, which occur occasionally.

Management

GENERAL MEASURES
• A warm, comfortable, quiet environment may be useful. Photophobia patients may be treated in a dark environment. Reassure the patient that effective analgesia will be provided and that appropriate diagnostic studies will be performed.

SURGICAL MEASURES
• Depends on primary cause of headache

SYMPTOMATIC TREATMENT
• Medications are the primary symptom therapy for acute headache.

ADJUNCTIVE TREATMENT
• See Medications

ADMISSION/DISCHARGE CRITERIA
• Patients considered to have a major cause for acute headache as outlined above should be admitted for definitive treatment. Any patient with a sudden, severe, unexplained headache may be considered for admission unless a rapid outpatient evaluation can be undertaken safely. Patients can be discharged when the primary diagnosis has been made and effective therapy is underway.

Medications

DRUG(S) OF CHOICE
• Analgesics may be used in acute headache. These include over-the-counter analgesics (aspirin, acetaminophen, ibuprofen, naproxen) with or without caffeine. Combination medications (e.g., acetaminophen, butalbital, caffeine) may be used. For more severe headache, opioids may be necessary (codeine and congeners, meperidine, morphine). In the emergency room setting, antiemetics may be useful at times effective for headache control (chlorpromazine). If the headache is migrainous, specific therapy with various vasoactive agents may be considered (sumatriptan, other “triptan” medications, isometheptene, dihydroergotamine).

Contraindications
• Depend on the individual medication considered. Although symptomatic therapy is important for patient comfort, the primary concern is effective diagnosis and treatment of the underlying cause of headache. Nonsteroidal agents are contraindicated in patients with renal failure or peptic ulcer disease. Vasoactive stbates are contraindicated with cardiac disease or intracranial vascular disease.

Precautions
• Antiemetic medications may cause symptomatic hypotension.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
• Patients should be followed carefully until their acute headache has resolved satisfactorily. Specific monitoring parameters depend on the etiology.

EXPECTED COURSE AND PROGNOSIS
• Depends on primary cause

PATIENT EDUCATION
• Depends on primary cause

Miscellaneous

SYNONYMS
• See specific diagnosis areas ICD-9-CM: See specific diagnosis areas

SEE ALSO: SPECIFIC DIAGNOSIS AREAS

REFERENCES
• Drexler ED. Severe headaches. Postgrad Med 1990;87:164-180.
• Silverstein SD, Marcelis J. Headache associated with changes in intracranial pressure. Headache 1992;32:84-94.

Author(s): Alexander D. Rae-Grant, MD, John Castaldo, MD
Headache, Chronic

**Basics**

**DESCRIPTION**
Headache occurring more than 15 days per month.
- Primary chronic headache
  - No identifiable cause
  - Nondemoral or correlation between the onset of an underlying disorder that causes secondary chronic headache and the headache onset.
- Secondary chronic headache: caused by an underlying disorder

**EPIDEMIOLOGY**
Incidence/Prevalence
Incidence unknown. Prevalence: 3.2% to 4.7%, versus 12% to 38% for episodic headaches

**ETIOLOGY**
- Development of chronic headache
  - 75% develop from episodic migraine
  - 8% develop from episodic tension-type headache
  - 16% develop without previous headache history ("new onset daily headache"); should be classified as chronic migraine or tension-type headache
- Medication overuse: frequently use episodic headache to evolve into chronic headache
- Genetics
  - Autosomal-dominant inheritance.
  - Chronic cluster headache exhibits autosomal-dominant inheritance.

**RISK FACTORS**
- Medication overuse
- History of episodic migraine
- Family history of chronic headache
- Coincident major depressive disorder
- Sex
  - Female predominance in chronic migraine, chronic tension-type headache, hemicrania continua, chronic paroxysmal hemicrania, and idiopathic stabbing headache
  - Male predominance cluster headache

**PREGNANCY**
N/A

**ASSOCIATED CONDITIONS**
- Psychiatric disorders: often remit following successful treatment of chronic headache
  - Anxiety disorders (23%-70%)
  - Mood disorders (25%-59%)
  - Somatoform disorders (6%)
- Medication overuse (30%-40%)
  - Defined as the use of:
    - At least three simple analgesic medications (e.g., single-agent, nonbarbiturate, nonsedative) per day at least 5 days per week

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Primary chronic headache
  - Chronic migraine
  - Chronic tension-type headaches
  - Hemicrania continua
  - Chronic cluster headache
  - Chronic paroxysmal hemicrania
  - Chronic hypnic headache
  - Idiopathic stabbing headache
- Secondary chronic headache
  - Posttraumatic headache
  - Cervical spine disorders
  - Cranial neuropathies
  - Ophthalmic disorders
  - Vascular disorders: arteriovenous malformation, arteritis, arterial dissection, subdural hematoma
  - Nonvascular disorders: increased or decreased CSF pressure, infection, neoplasm, Chiari malformation
  - Oromandibular disorders
  - Sinus and ear disorders

**SIGNS AND SYMPTOMS**

**Chronic Migraine/Transformed Migraine**
51% to 78% of chronic headache patients
- Present >1 month
- History of episodic migraine
- Period of increasing headache frequency with decreasing severity of migrainous symptoms (nausea, vomiting, photophobia, phonophobia) over 3 to 4 months
- Chronic tension-type headache with superimposed episodic migraine should be considered chronic migraine
- Triggers generally persist and can induce acute migraine attacks
- Pain is severe but patients attempt to sleep
- Chronic Tension-Type Headaches
  - Present >6 months
  - History of episodic tension-type headaches
  - At most one migrainous symptom
  - Two of the following pain characteristics:
    - Compressive quality
    - Mild to moderate intensity

**Chronic Cluster Headache**
- Present >1 month
- Headaches last 5 to 60 minutes
- Absence of autonomic symptoms
- One to three attacks per evening, waking patient from sleep
Headache, Chronic

- **ADJUNCTIVE TREATMENT**
  - Psychotherapy: stress management, relaxation therapy, and biofeedback proven efficacious
  - Physiotherapy: cervical spine manipulation, massage, TENS, and ergonomic review have limited evidence supporting for chronic tension-type headaches
  - Acupuncture proven ineffective

**ADMISSION/DISCHARGE CRITERIA**

- Emergency admission may be required for:
  - Complicated migraine
  - Suspicion of secondary chronic headache
  - Chronic headache with dehydration or vomit
  - Severe comorbid psychiatric disorders
  - Nonemergency admission may be required for:
    - Comorbid medical conditions requiring monitoring
    - Detoxification from opioids, barbiturates, benzodiazepines, or ergots
    - Failed outpatient detoxication

**MEDICATIONS**

**DRUG(S) OF CHOICE**

- Chronic migraine
  - Acute treatment: triptans
  - Prophylaxis: amitriptyline
- Chronic tension-type headache
  - Acute treatment: long-acting NSAIDs
  - Prophylaxis: amitriptyline
- Hemicrania continua
  - Indomethacin PRN for acute treatment, scheduled for prophylaxis
  - Reconsider diagnosis if no relief following indomethacin
- Chronic headache
  - Acute treatment: oxygen supplement, ergots
  - Prophylaxis: lithium
- Chronic paroxysmal hemicrania
  - Indomethacin
- Chronic hypnic headache
  - Lithium carbonate
- Idiopathic stabbing headache
  - Indomethacin

**PRECAUTIONS**

- Avoid ergots in patients with vascular disease, pregnancy, or coincidence of oral contraceptives
- Avoid triptans in patients with vascular disease or hypertension

**SYMPTOMATIC TREATMENT**

- Limit acute treatments, particularly short-acting NSAIDs, opioids, and ergots

**GENERAL MEASURES**

- Exclude secondary causes of chronic headache
- Identify comorbid factors
- Medication detoxification:
  - Gradually taper barbiturates, benzodiazepines, and opioids
  - Gradually switch from short-acting nonsteroidal antiinflammatory drugs (NSAIDs) (regular indomethacin, aspirin) to long-acting NSAIDs (sustained-release indomethacin, naproxen, ketoprofen, tolmetin, mefenamic acid, ibuprofen)

**SURGICAL MEASURES**

- Chronic cluster headache: gamma-knife radiosurgery, trigeminal rhizotomy, or trigeminal root transection for medically-refractory cases

**LABORATORY PROCEDURES**

**IMAGING STUDIES**

- Brain MRI or CT
  - Chronic migraine: not indicated if symptomatically stable unless abnormal neurologic examination
  - Chronic tension-type headache: identifies treatable abnormality in 0.5% to 2.4% of patients
  - Brain MR venogram: venous sinus thrombosis in 10% of chronic migraine and chronic tension-type headache patients

**SPECIAL TESTS**

- Lumbar puncture: opening pressure may be >20 cm H2O in 21% of chronic headache patients
- Only half of chronic headache patients with elevated intracranial pressure have papilledema

**REFERENCES**

- Prophylaxis: fluoxetine, doxepin, tizanidine, B-blockers, anticonvulsants (divalproex, topiramate)
- Chronic tension-type headache: tizanidine; botulinum toxin injection into tender points
- Hemicrania continua: aspirin, long-acting NSAIDs
- Chronic cluster headache
  - Acute treatment: DHE, intranasal lidocaine
  - Prophylaxis: verapamil, methysergide, valproate, topiramate
- May supplement with steroids
- Chronic paroxysmal hemicrania: aspirin, verapamil
- Chronic hypnic headache: flunoxipine, indomethacin
- Idiopathic stabbing headache: verapamil

**Follow-Up**

**PATIENT MONITORING**

- Per routine.

**EXPECTED COURSE AND PROGNOSIS**

- Response to preventative medications takes up to 10 weeks following detoxification.
- 4090 to 80% of patients with medication overuse revert to episodic headache following detoxification.
- Failure to improve following aggressive management is highly suggestive of psychiatric comorbidity.

**PATIENT EDUCATION**

- Encourage regular sleep habits and exercise.
- Diet: encourage regular meals.
- Dietary supplement iron with L-5-hydroxytryptophan (100 mg qd) may reduce anisocoria during ingestion detoxification.
- Organizations
  - International Headache Society. Website: www.i-h-s.org.

**SYNONYMS**

- Headache, Chronic
- Chronic daily headache

**SEE ALSO**

- Headache, Migraine
- Headache, Cluster
- Headache, Paroxysmal
- Headache, Trigeminal Neuralgia

**MISCELLANEOUS**

- International Headache Society. Diagnostic criteria URL:
- Author(s): Monique A. Anawis, MD, JD; Mark K. Borsody, MD, PhD

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- Headaches develop only during REM sleep, rarely during napping
- Maximum prevalence in 60- to 70-year-olds

**Idiopathic Stabbing Headache/Ice-Pick Syndrome/Ophthalmodynia**

- Attacks on 24 days/month at irregular per
- Pain lasting <1 second, sharp, causing shock-like response (“jolt”)
- Pain is typically unilateral, located in the orbit, forehead, and/or temple
- Absence of autonomic symptoms, triggers
- Additional headache in 58%
- High coincidence of ocular pathology

**LABORATORY PROCEDURES**

N/A

**IMAGING STUDIES**

- Brain MRI or CT
  - Chronic migraine: not indicated if symptomatically stable unless abnormal neurologic examination
  - Chronic tension-type headache: identifies treatable abnormality in 0.5% to 2.4% of patients
  - Brain MR venogram: venous sinus thrombosis in 10% of chronic migraine and chronic tension-type headache patients

**SPECIAL TESTS**

- Lumbar puncture: opening pressure may be >20 cm H2O in 21% of chronic headache patients
- Only half of chronic headache patients with elevated intracranial pressure have papilledema

**Management**

- Excluding secondary causes of chronic headache
- Identifying comorbid factors
- Medication detoxification:
  - Gradually taper barbiturates, benzodiazepines, and opioids
  - Gradually switch from short-acting nonsteroidal antiinflammatory drugs (NSAIDs) (regular indomethacin, aspirin) to long-acting NSAIDs (sustained-release indomethacin, naproxen, ketoprofen, tolmetin, mefenamic acid, ibuprofen)

**SURGICAL MEASURES**

- Chronic cluster headache: gamma-knife radiosurgery, trigeminal rhizotomy, or trigeminal root transection for medically-refractory cases

**SYMPTOMATIC TREATMENT**

- Limit acute treatments, particularly short-acting NSAIDs, opioids, and ergots

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- Hemicrania continua: aspirin, long-acting NSAIDs
- Chronic cluster headache
  - Acute treatment: DHE, intranasal lidocaine
  - Prophylaxis: verapamil, methysergide, valproate, topiramate
  - May supplement with steroids
- Chronic paroxysmal hemicrania: aspirin, verapamil
- Chronic hypnic headache: flunoxipine, indomethacin
- Idiopathic stabbing headache: verapamil

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- Prophylaxis: amitriptyline
- Chronic headache
  - Acute treatment: triptans
  - Prophylaxis: amitriptyline
- Hemicrania continua
  - Indomethacin PRN for acute treatment, scheduled for prophylaxis
  - Reconsider diagnosis if no relief following indomethacin
- Chronic headache
  - Acute treatment: oxygen supplementation, ergots
  - Prophylaxis: lithium
- Chronic paroxysmal hemicrania
  - Indomethacin
- Chronic hypnic headache
  - Lithium carbonate
- Idiopathic stabbing headache
  - Indomethacin

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- Avoid ergots in patients with vascular disease, pregnancy, or coincidence of oral contraceptives
- Avoid triptans in patients with vascular disease or hypertension

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- Toxicity with overdose of lithium and anticonvulsant medications
- Limit use of methysergide to less than 5 months due to retroperitoneal fibrosis

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- International Headache Society. Diagnostic criteria URL:
- Author(s): Monique A. Anawis, MD, JD; Mark K. Borsody, MD, PhD

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- Prophylaxis: amitriptyline
- Chronic headache
  - Acute treatment: triptans
  - Prophylaxis: amitriptyline
- Hemicrania continua
  - Indomethacin PRN for acute treatment, scheduled for prophylaxis
  - Reconsider diagnosis if no relief following indomethacin
- Chronic headache
  - Acute treatment: oxygen supplementation, ergots
  - Prophylaxis: lithium
- Chronic paroxysmal hemicrania
  - Indomethacin
- Chronic hypnic headache
  - Lithium carbonate
- Idiopathic stabbing headache
  - Indomethacin

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- Avoid ergots in patients with vascular disease, pregnancy, or coincidence of oral contraceptives
- Avoid triptans in patients with vascular disease or hypertension

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- Toxicity with overdose of lithium and anticonvulsant medications
- Limit use of methysergide to less than 5 months due to retroperitoneal fibrosis

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- International Headache Society. Diagnostic criteria URL:
- Author(s): Monique A. Anawis, MD, JD; Mark K. Borsody, MD, PhD
Headache, Cluster

Basics

DESCRIPTION
- Cluster headache is a primary headache disorder characterized by discrete repetitive attacks of unilateral headache with associated ipsilateral autonomic features (including lacrimation, rhinorrhea, ptosis, meiosis). The episodic form is most common and includes periods of attacks (clusters) followed by periods of remission lasting at least 14 days. Chronic cluster headaches occur when attacks occur for 1 year without a remission or when remissions last for <14 days.

EPIDEMIOLOGY
- Prevalence: Estimates vary from 0.17% to 0.4% of the population.
- Sex: More common in men than women, with the gender ratio varying from 6:1 to 2:1 in the 1960s to 1990s.

Age
- Peak age of onset is 25-50 years, although cluster headaches can occur in teens and children. Men tend to develop their first cluster headache at age 20-30, whereas women have two peaks of cluster onset: late teens/20s and 50-60 years of age.

Race
- Some authors report an increased incidence of cluster HA in African Americans.

ETIOLOGY

Pathophysiology
- Exact cause is unknown.
- One theory suggests involvement of the cavernous sinus portion of the carotid artery. It is here that the trigeminal nociceptive pathways and autonomic fibers are anatomically close together. Activation of these systems would result in the typical features of cluster headache: unilateral orbital pain, lacrimation and rhinorrhea (parasympathetic), ptosis, and meiosis (sympathetic).
- The periodicity of cluster attacks suggests involvement of the hypothalamus, specifically the suprachiasmatic nucleus, which is involved in regulation of circadian rhythms, and the posterior hypothalamus, which contains nuclei involved in autonomic function.
- Recent studies involving PET scans demonstrate activation of various parts of the brain in cluster patients: anterior cingulate gyrus, prefrontal cortex, insula, and contralateral thalamus (each a ‘hot associating pain’); ipsilateral hypothalamic gray (unique to cluster headaches); and extracerebral areas including the cavernous sinus (suggesting activation of the trigeminothalamic system).

Genetics
- Not known to have a genetic component, although recent studies suggest a 14-fold increased risk of cluster headaches in first-degree relatives.

RISK FACTORS
- Include smoking and alcohol use

PREGNANCY
- Women often experience remission while pregnant.
- Menopause, menstruation, menopause, oral contraceptives, and hormone replacement therapy have no known affect on cluster headaches.

ASSOCIATED CONDITIONS
- Leptin facies: sharp facial features, deep nasolabial furrows, telangiectasia, peau d’orange skin
- History of migraines
- Tall stature
- Dural ulceration/peptic ulcer disease, secondary to increased gastric acid production
- Psychological conditions (type A personality)

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Migraine headaches
- Trigeminal neuralgia
- Temporal arteritis
- Sinusitis
- Paroxysmal hemicrania
- Hemicrania continua
- SUNCT syndrome (short-lasting unilateral neuralgiform pain with conjunctival injection and tearing)
- Carotid or vertebral artery dissection
- Glaucoma
- Brain tumor
- Cervical cord tumor or infarction
- Arteriovenous malformation
- Intracranial or carotid aneurysms
- Tolosa-Hunt syndrome
- Pheochromocytoma
- Acute angle-closure glaucoma
- Corneal erosion
- Dental problem

SIGNS AND SYMPTOMS
- Cluster headache presents as a rapid-onset headache reaching its peak intensity within minutes.
- The pain often is continuous and is described as deep, boring, or explosive in quality. The phrase “like a hot poker in the eye” has been used to describe the attacks.
- Most patients are unable to remain in situ during an attack and may bang their heads against walls to relieve the pain.

Management

GENERAL MEASURES
- Early and accurate diagnosis is essential.
- Advise patients that cluster attacks are easily managed with fast-acting therapies and may be prevented with a variety of prophylactic medications.
- Prophylactic medications are often tapered near the end of the cluster period and may be restarted if symptoms recur.

SPECIAL TESTS
- CT and MRI are generally not useful in the diagnosis of cluster headache.

LABORATORY PROCEDURES
- May help rule out other causes of headache, such as an elevated ESR or C-reactive protein in temporal arteritis or abnormal endocrine studies with a pituitary tumor.

IMAGING STUDIES
- CT and MRI are generally not useful in the diagnosis of cluster headache.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Migraine headaches
- Trigeminal neuralgia
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- Unilateral headache, most often located around the orbit. May radiate to the face, ear, neck, hemicranium, jaw, or teeth.
- Patients have ipsilateral conjunctival injection, lacrimation, rhinorrhea, nasal congestion, sweating, ptosis, meiosis, pallor, or eyelid edema.
- Nausea, vomiting, photophobia, and phonophobia may occur. Auras are rare.
- Individual attacks last approximately 45-90 minutes. Cluster periods last 2-12 weeks, during which patients have 1-3 attacks per day. Remissions may last months to years.
- Patients commonly experience a cluster period at the same time each year, and cluster attacks at the same time each day.
- The attacks remain on the same side of the head during an individual cluster period but switch sides during the next cluster period in 15% of patients.
- Nocturnal attacks are more common, resulting in sleep deprivation, daytime napping, fatigue, and depression.

LABORATORY PROCEDURES
- May help rule out other causes of headache, such as an elevated ESR or C-reactive protein in temporal arteritis or abnormal endocrine studies with a pituitary tumor.

IMAGING STUDIES
- CT and MRI are generally not useful in the diagnosis of cluster headache.

SPECIAL TESTS
- N/A
**Symptomatic Treatment**

- Rapid onset and short duration of cluster headaches mandate fast relief of symptoms. Oxygen and subcutaneous sumatriptan achieve this quickly and effectively.

**Adjuvant Treatment**

- Some individuals may benefit from physical therapy, massage, acupuncture, or other relaxation techniques, although none of these alternative therapies has proven efficacy.

**Admission/Discharge Criteria**

- Patients rarely require hospitalization unless they have suicidal ideation.

**Medications**

**Drug(s) of Choice**

**Abortive Therapy**

- Oxygen given as 100% O₂ through a non-rebreather face mask at 7-10 L/min for 15 minutes. Effective in 70% of patients. Portable cylinders are available for patients, although some may find this to be cumbersome. Safe in patients with cardiovascular risk factors.

- Sumatriptan is currently the most rapid and effective treatment (75%-100% of patients achieve relief). May be self-administered as 6-mg SC injection.

**Contraindications**

- Sumatriptan is contraindicated in patients with uncontrolled hypertension, ischemic heart disease, or vascular disease. Dihydroergotamine should be avoided in patients with cardiovascular disease.

**Precautions**

- Patients using valproic acid should have baseline and routine CBC and LFTs checked; those on lithium must have renal and thyroid function tests monitored. Methysergide, when used for more than 3 months, may cause fibrosis of the pleural and pericardial linings and of the retroperitoneum.

**AlTERNATIVE DRUGS**

- Zolmitriptan 5-10 mg PO may be used for acute cluster attacks when patients prefer oral medications. Intranasal lidocaine may be useful as an adjunctive therapy in the setting of acute attacks. Other potential medications include topiramate, melatonin, capsaicin, methylphenidate, antidepressants, clonidine, diltiazem, histamine, and somatostatin.

**Follow-Up**

**Patient Monitoring**

- Patients should be followed closely to ensure that prophylactic medications are effective, to watch for signs of recurrence, and to monitor for potential side effects of medications.

**Expected Course and Prognosis**

- Natural history not well known
- Most often a lifetime disorder
- Estimated that 13% of episodic cluster patients progress to have chronic clusters, whereas the reverse occurs in 33% of patients
- Complete remissions occur rarely

**Patient Education**

**Activities**

- Practice proper sleep hygiene.
- Avoid afternoon naps.
- Avoid volatile substances (e.g., gasoline, paint).

**High altitudes (>5,000 feet) and airplane travel may precipitate attacks.
- Attacks may occur after bursts of anger, rage, anxiety, and excessive physical activity.

**Diet**

- Alcohol precipitates attacks during cluster periods but not during remissions.

**Organizations**

- American Headache Society. Website: www.aahsnet.org
- American Academy of Craniofacial Pain. Website: www.aahnfp.org
- National Headache Foundation. Website: www.headaches.org
- American Council for Headache Education. Phone: 800-255-ACHE

**References**

Headache, Migraine

Basics

DESCRIPTION
- The term migraine is used to describe a paroxysmal headache with some or all of the following features: unilateral, pulsating, of moderate or severe intensity, aggravated by routine physical activity, duration of 4-72 hours, nausea and/or vomiting, and photophobia and/or phonophobia. These symptoms help to distinguish migraine from tension-type headache, which typically lacks associated features. In practice, most recurrent and disabling headaches are likely to be a form of migraine and responsive to antimigraine therapy. Attacks should be separated by pain-free intervals.
- The most important factor in migraine classification is the presence or absence of aura. The classification system published in 1988 by the International Headache Society also includes several migraine variants.
  - Migraine without aura
  - Migraine with aura
  - Migraine with typical aura
  - Migraine with prolonged aura
  - Familial hemiplegic migraine
  - Basilar migraine
  - Migraine aura withot headache
  - Migraine with acute-onset aura
  - Ophthalmoplegic migraine
  - Retinal migraine
- Childhood periodic syndromes that may be precursors of or associated with migraine: Benign paroxysmal vertigo of childhood - Alternating hemiplegia of childhood - Cyclic vomiting - Paroxysmal torticollis - Alice in Wonderland syndrome - Complications of migraine
- Status migrainosus
- Migrainous infarction
- Unclassifiable migraine-Like disorder

Epidemiology
Incidence/Prevalence
- Prevalence is about 13% and peaks in the age range 25-55. Of migraineurs, 64% have migraine without aura, 18% have migraine with aura, 13% have migraine both with and without aura, and 5% have aura without headache.

RISK FACTORS
N/A

Pregnancy
- Approximately 70% of pregnant women experience improvement or remission of symptoms, but recurrence in the postpartum period is common. Pregnancy influences treatment options. Triptans are pregnancy category C, and ergots are contraindicated in pregnancy.

ASSOCIATED CONDITIONS
- Stroke, myocardial infarction, Raynaud's phenomenon, fatigue, depression, and anxiety have been associated with migraine.

Diagnosis

Differential Diagnosis
- Episodic tension-type headache
- Cluster headache
- Sinus headache
- Arteriovenous malformation
- Transient ischemic attack
- Arterial dissection
- Venous sinus thrombosis
- Vasculitis (including giant cell arteritis)
- Infection (meningitis/encephalitis)

Signs and Symptoms
- Some patients may experience stereotyped premonitory symptoms such as change in mood, change in energy level, or excessive yawning. An aura can be any transient visual, sensory, motor, or other focal neurologic symptom. The symptoms generally develop gradually over 5-20 minutes. Some of the most common auras are scintillating scotoma, photopsia, and paresthesias.
- Headache characteristics and accompanying features:
  - Moderate or severe intensity
  - Unilateral (can be bilateral)
  - Throbbing/pulsating pain
  - Aggravated by movement/activity
  - Anorexia/nausea/vomiting
  - Photophobia
  - Dizziness
  - Blurred vision
  - Lightheadedness

Laboratory procedures
- Laboratory tests are not routinely useful or necessary, but they may be performed to exclude secondary causes of headache (e.g., giant cell arteritis).

Imaging Studies
- MRI can show cortical abnormalities during or after attack, but findings are not specific. Appropriate imaging studies are warranted in the setting of a new-onset headache, a change in headache pattern (to rule out a secondary disorder), focal neurologic symptoms/signs, or a suspected seizure.

Special Tests
- EEG may show spikes or slowing during an attack, but it is not generally useful for diagnosis or management. Lumbar puncture is not indicated in routine cases.

Management

General Measures
- Avoid identifiable triggers.
- Maintain regular sleep and meal schedules.
- Stress-management techniques.
- Avoid analgesic overuse.
- Use headache calendar to monitor disability (e.g., missed work) and effect of therapy.

Surgical Measures
N/A
**SYMPTOMATIC TREATMENT**

- Use of analgesic/abortive medication as soon as headache attack is recognized.
- Rest in a dark quiet room.
- Ice pack on forehead may help.
- Caffeine may be effective.
- Control nausea/vomiting with medications.
- Sleep often resolves headache.

**ADJUNCTIVE TREATMENT**

- Preventive therapy is recommended for patients with frequent attacks, prolonged attacks, and/or attacks that significantly interfere with their daily routine.

**ADMISSION/DISCHARGE CRITERIA**

- Patients may require admission for symptomatic management of nausea/vomiting or for treatment of status migrainosus. Admission may be necessary for evaluation of focal neurologic deficits, impaired consciousness, or suspected secondary disorder.

**Medications**

**DRUG(S) OF CHOICE**

**Acute Therapy**

- Many migraines will respond to nonspecific medications. The triptans and DHE are considered "migraine-specific therapies" and have well-established efficacy. Triptans act predominantly as 5-HT1 receptor agonists, causing cranial vasoconstriction and decreasing the release of neuropeptides. Ergots act at the same receptor but are not as selective in their binding and, therefore, have more side effects than the triptans.
- Aspirin
- Nonsteroidal antiinflammatory drugs (NSAIDs)
  - Combination analgesics: aspirin and caffeine with or without acetaminophen
  - APAP/dichlorphenazone/ismethopentene (Midrin)
- Triptans
  - Almotriptan, naratriptan, frovatriptan, sumatriptan, rizatriptan, zolmitriptan
  - Available in multiple routes of administration (oral, nasal spray, rectal suppository, subcutaneous injection)
- Ergot derivatives
  - Ergotamine/caffeine (Cafergot)
  - DHE
- Antimetics
  - Prochlorperazine
  - Metoclopramide
  - Chlorpromazine

**Preventive Therapy**

- p-Blockers
  - Propranolol
  - Timolol
- Tricyclic antidepressants
  - Amitriptyline, Nortriptyline
- Calcium channel Mockers
  - Verapamil
- Anticonvulsants
  - Divalproex sodium; only FDA approved anticonvulsant for migraine prophylaxis — Gabapentin
  - Topiramate
  - Selective serotonin reuptake inhibitors; widely used but poor evidence of efficacy
  - Serotonin antagonists: methysergide
  - NSAIDs: most useful for nstural migraine prophylaxis

**Contraindications**

- Ergots are contraindicated in peripheral or coronary artery disease, uncontrolled hypertension, pregnancy, or breast-feeding.
- Triptans are contraindicated in coronary artery disease, Prinzmetal angina, uncontrolled hypertension, recent monoamine oxidase inhibitor use, severe liver disease, or presence of severe/prolonged neurologic deficits accompanying headache.
- p-Blockers are contraindicated in severe asthma.

**Precautions**

- Ergots may cause aggravation of asthma, bradycardia, hypotension, depression, or masking of hypoglycemia symptoms.
- Tricyclic antidepressants may cause cardiac arhythmias, sedation, or aggravation of angle-closure glaucoma.
- Divalproex sodium may cause weight gain, hair loss, tremor, liver dysfunction, or neural tube defects in developing embryos. Women of childbearing age should take supplemental folic acid.
- NSAIDs can cause renal dysfunction and should be used with extreme caution in patients with a history of GI bleeding.
- Methysergide can cause weight gain, vasoconstriction, or fibrosis (pulmonary, cardiac, retroperitoneal).

**ALTERNATIVE DRUGS**

- Butalbital-containing products or opioids have potential for habituation and are generally not recommended.
- Intranasal lidocaine is safe but efficacy has been underwhelmed.
- Toradol may be used in acute attacks.
- Recommended treatment of status migrainosus is repeated doses of DHE 0.5-1 mg parenterally every 8 hours, in combination with an antihistemic. Corticosteroids may also be used for refractory attacks.

**REFERENCES**


**Follow-Up**

- Patients should keep a headache calendar to document frequency of attacks.

**EXPECTED COURSE AND PROGNOSIS**

- The goal of therapy is to reduce headache frequency and minimize missed work or activities.

**PATIENT EDUCATION**

- American Council for Headache Education, 19 Mantua Road, Mount Royal, NJ 08061. Phone: 800-225-ACHE, website: www.achenet.org
- World Headache Alliance. Website: www.w-h-a.org

**SYNONYMS**

N/A

**ICD-9-CM**

- 346.0 Classic migraine
- 346.1 Common migraine
- 346.2 Variant of migraine (includes cluster, basilar, retinal) 346.8 Other forms of migraine (hemiplegic, ophthalmoplegic)
- 346.9 Migraine, unspecified; Fifth digit subclassification: 0 = withonit on ion of intractable migraine, 1 = with intractable migraine

**SEE ALSO:** N/A

**Miscellaneous**
Management

GENERAL MEASURES

• Needle design appears to be a provocative culprit in the occurrence of the disorder. The "pencil point" noncutting, atraumatic needles, such as Whitacre or Sprotte, have a duller tip and an oval opening just proximal to the tip, in contrast to the Quincke needle with sharp edges and an opening at the tip. There is convincing class I evidence in the anesthesiology literature for less PLPHA with noncutting needles compared to cutting needles with bevels parallel to dural fibers. Recently a large randomized trial of Sprotte versus Quincke 20-gauge needle for neurologic diagnostic taps showed considerably less headache in the patients assigned to receive the nontraumatic Sprotte needle for the procedure. Although anesthesiologists use smaller LP needles (usually 22-23 gauge), this size is inappropriate for neurologists who need to collect CSF for diagnostic purposes using larger-bore needle types, usually 20-21 gauge. Many neurologists believe that removing the needle from the CSF space while rolling the patient to the prone position, fluid replenishment, and caffeine use are important to prevent the syndrome, no matter which needle is selected.

SURGICAL MEASURES

• Not usually applicable. Rare case reports of PLPHA refractory to epidural blood patch have required open surgical closure.

SYMPTOMATIC TREATMENT

• The treatment of PLPHA is bed rest, caffeinated fluid and salt replacement, and time. Most often the syndrome resolves in 24-48 hours of bed rest, with bathroom privileges only.

ADJUNCTIVE TREATMENT

• When the problem becomes more prolonged and does not appear to be lessening in response to conservative methods, an epidural blood patch sometimes is warranted. This is performed by anesthesiologists/pain management physicians who take a small amount of blood from the patient's antecubital vein and infuse it in the lumbar epidural space in the region of the tap. Theoretically this provides a "blood patch" to the rent in the dural sac, allowing time for it to seal off, scar, and heal. Oddly, however, this technique of epidural blood patch also has been shown to be effective in spontaneous cervical dural tears, even when the blood is infused into the lumbar region.

This raises the question of the true pathophysiology of the PLPHA syndrome and whether elasticity of the dura may be more the problem than strict CSF hypovolemia, as some have suggested. The technique of epidural blood patch is safe and generally painless, and produces rapid "on the table" response in most patients.

ADMISSION/DISCHARGE CRITERIA

• Most patients with PLPHA do not require admission. Patients with refractory headache not responding to outpatient blood patch, with uncontrolled vomiting, or patients who are suspected of having meningitis or other illness should be considered for admission.

DRUG(S) OF CHOICE

• There is no specific drug therapy for PLPHA. Caffeinated beverages may be helpful in prevention. Either nonspecific pain medications (acetaminophen, aspirin, ibuprofen) or migraine medications (caffeinated medications, triptans) may be tried.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

• Patients should be monitored for resolution of headache.

EXPECTED COURSE AND PROGNOSIS

• Most patients can expect a full recovery in 1-2 weeks.

PATIENT EDUCATION

• Patients should be informed of the cause of the PLPHA. They should be educated about consumption of additional fluids, use of the recumbent position, and need to call the office for symptoms of progressive headache, fever, or chills.

Medications

REFERENCES

• Strupp M, Brandt T, Muller A. Incidence of post-lumbar puncture syndrome reduced by reinterting the stylet: a randomized prospective study of 600 patients. J Neurol 1998;245:50-59.

Author(s): John Castaldo, MD

Headache, Post Lumbar Puncture

GENERAL MEASURES

SYNONYMS

N/A

ICD-9-CM: 349.0 Post lumbar puncture headache

SEE ALSO: N/A

REFERENCES

Heavy Metal Poisoning, Neurologic Complications

**Basics**

**DESCRIPTION**
- Heavy metals associated with adverse neurologic effects include lead, mercury, manganese, arsenic, thallium, organotins (trimethyltin and triethyltin), and aluminum. Although iron and manganese are essential for the activity of certain enzymes, excessive levels can cause disruption of normal neuronal functioning. The toxic effects of heavy metal poisoning can present insidiously or abruptly, depending on the particular metal and the nature of exposure (i.e., acute or chronic; high or low level). Neurotoxicity of metals involves various mechanisms, including generation of free radicals that initiate lipid peroxidation and alter neuronal cell membranes and disruption of cellular respiration, oxidative phosphorylation, and ATP-dependent processes. Recognition of the signs and symptoms of metal poisoning is essential to minimize neuronal damage, remove at-risk persons from further exposure, and reduce accumulated levels of metal in tissue by therapeutic chelation.

**EPIEMIOLGY**

**Incidence/Prevalence**
- All races and ethnic groups can be affected.

**Race**
- All races and ethnic groups can be affected.

**Age**
- Two peaks are present, one in pediatric patients and the other in adults exposed to occupational hazards.

**Sex**
- Both sexes can be affected; most often diagnosed in mates.

**ETIOLOGY**
- Neurologic dysfunction of the central and/or peripheral nervous system (CNS, PNS) caused by excessive occupational or environmental exposure to one or more heavy metals.

**Genetics**
- N/A

**RISK FACTORS**
- Include occupation (e.g., welder, iron worker), hobbies (e.g., lead stained glass crafting), water supply (e.g., lead pipes), fish and seafood consumption, age (children at greater risk for lead and mercury encephalopathy), psychosocial factors (e.g., history of pica and object mouthing), nutrition (e.g., iron deficiency anemia susceptibility to lead poisoning), and concurrent medical problems (e.g., diabetes)

**PREGNANCY**
- Pregnancy has not been shown to affect the course of neurologic complications of heavy metal intoxication. Heavy metal intoxication during pregnancy may adversely affect the fetus.

**ASSOCIATED CONDITIONS**
- N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- The differential diagnosis is very extensive because heavy metal poisoning is often clinically nonspecific. Other common non-neurotoxic causes of the presenting symptoms should be evaluated (e.g., metabolic encephalopathy, tumor, stroke, diabetes mellitus, Parkinson's disease, and other idiopathic neurodegenerative disorders).

**SIGNS AND SYMPTOMS**
- Signs and symptoms are diffuse and nonspecific and may involve the CNS and/or PNS. All of the heavy metals can induce an encephalopathy syndrome; peripheral neuropathy can be noted in poisoning from aluminum, arsenic, lead, mercury, organotins, and thallium. Tremors and movement disorders can occur with poisoning from aluminum, lead, manganese, mercury, and thallium. Other significant symptoms include headache and cerebral edema (lead, organotins), nausea and emesis (thallium, arsenic, organotins), cranial neuropathy (thallium), psychosis (manganese, mercury, thallium, arsenic), loss of memory (lead, aluminum, thallium, arsenic), and seizures (lead, organotins, thallium, arsenic, aluminum).

**LABORATORY PROCEDURES**
- Screening for recent heavy metal exposure should be performed on blood and urine specimens. Hair or nail samples can be used to determine more remote exposures and may reveal abnormally elevated levels even if blood and urine are normal. Surat nerve biopsies may demonstrate wallerian-type dying back axonal degeneration with secondary demyelination (arsenic, thallium) or segmental demyelination (lead). S-Aminolevulinic acid (ALA) levels are elevated in blood and urine samples in lead poisoning cases.

**IMAGING STUDIES**
- MRI or CT, with and without contrast, is appropriate in patients with mental status changes, atypical seizures, or focal neurologic findings to rule out non-neurotoxic intracranial processes (e.g., subdural hematoma, abscess, tumor, stroke). Imaging may reveal atrophy of the cerebellum (mercury), hippocampus (organotin), or cerebral cortex (lead). Edema can be noted in lead poisoning. High-signal lesions in the globus pallidus may occur with manganese poisoning.
- In children, radiographs of long bones may reveal epiphyseal bands of increased density (i.e., lead lines) that can document remote exposures to lead.

**SPECIAL TESTS**
- EMG/nerve conduction testing and EEG can be of benefit to document the presence and pattern of peripheral neuropathy and seizure activity, respectively. Neuropsychological assessment can be helpful to document the extent and pattern of cognitive deficits. Serial neuropsychological testing can follow improvements in performance after cessation of exposure and can assist in determining prognosis.

**Management**

**GENERAL MEASURES**
- A comprehensive personal, occupational, and medical history is required to document potential past or current chemical exposures. All chemicals that the patient may have come in contact with must be determined. The home water supply and regional environment should be investigated. All further exposures to heavy metals must be avoided. All symptomatic patients should be considered for chelation therapy to reduce the body burden of accumulated metals.

**SURGICAL MEASURES**
- N/A
Heavy Metal Poisoning, Neurologic Complications

SYMPTOMATIC TREATMENT

- **Lead poisoning:** Mannitol should be administered to control cerebral edema associated with lead encephalopathy. Immediate chelation therapy is required for encephalopathic patients with serum levels >70 µg/100 mL; IV diazepam can be administered to control seizure activity associated with encephalopathy. Hemodialysis may be necessary in patients with renal failure. Chelation therapy may be helpful for patients with peripheral neuropathy due to chronic lead exposure. Chelation therapy is with BAL (British anti-Lewisite) or CaNa₂EDTA (calcium disodium ethylenediamine tetra-acetic acid).

- **Thallium poisoning:** Gastric lavage and whole bowel irrigation should be used to remove thallium from the GI tract following acute ingestion. Patients with acute poisoning should be monitored in the ICU. Traditional chelating agents are not effective in thallium poisoning. Prussian blue or activated charcoal should be administered instead to facilitate elimination. Diuretics can be used to enhance urinary excretion. Hemodialysis may be necessary in patients with thallium-induced acute renal failure.

- **Arsenic poisoning:** Gastric lavage and whole bowel irrigation should be used to remove arsenic from the GI tract following acute ingestion. Chelation therapy should be started immediately after acute ingestion with either BAL, DMSA (2,3-dimercaptosuccinic acid), or penicillamine. The patient should be monitored during initial treatment in the ICU. Activated charcoal can be administered to reduce further GI absorption. Hemodialysis may be necessary in patients with arsenic-induced acute renal failure.

- **Manganese poisoning:** Chelation is helpful to improve clinical symptoms and reduce the body burden in patients with encephalopathy; CaNa₂EDTA is the chelating agent of choice. Chelation therapy may reduce the high signal abnormality in the putamen-globus pallidus but may not improve parkinsonian symptoms. Levo-dopa and dopamine agonists have not been very effective in controlling manganese-induced tremor but are not contraindicated.

- **Mercury poisoning:** Symptomatic patients with serum mercury level of >15 µg/L should undergo chelation therapy with either BAL, DMSA, or penicillamine. Gastric lavage should be performed on patients who have ingested elemental or inorganic mercury. Hemodialysis with t-cysteine or DMSA infused into the dialyzer may be necessary to reduce body burden in patients with mercury-induced renal dysfunction.

ADJUNCTIVE TREATMENT

- Physical therapy and leg braces should be considered for patients with severe peripheral neuropathy. Nutritional supplements (including B vitamins) may hasten recovery from peripheral neuropathy. Cognitive and vocational retraining may be necessary for patients with permanent cognitive deficits.

ADMISSION/DISCHARGE CRITERIA

- Admission will generally be required for patients with acute neurologic events such as seizure activity, encephalopathy, severe weakness, persistent headache, and psychosis. Heavy metal tissue levels and history of exposure should be determined. Discharge is appropriate once the metal exposure has been determined and the patient has been stabilized with appropriate chelation and supportive therapy.

**Medications**

**DRUG(S) OF CHOICE**

- Chelation therapy with agents as listed for lead, thallium, arsenic, manganese, and mercury poisoning. Aluminum poisoning can be chelated with CaNa₂EDTA. Organotins can be chelated with BAL, DMSA, or penicillamine.

**Contraindications**

- None

**Precautions**

- BAL can frequently cause an elevation in SBP and DBP, accompanied by tachycardia. Penicillamine can induce renal dysfunction and should be used with caution in patients with impaired renal function.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

- Neurologic recovery from heavy metal intoxication and serum and/or tissue metal levels should be monitored. Serial testing with neuropsychological and neuropsychologic testing may be of benefit to follow recovery and determine prognosis.

**EXPECTED COURSE AND PROGNOSIS**

- Most patients improve with chelation therapy and supportive care. Pr ognosis and potential for permanent neurologic sequelae are variable and depend on the chronicity and severity of exposure. The most common residual deficits are memory loss and impaired cognition following encephalopathy, and persistent motor dysfunction in patients with severe peripheral neuropathy.

**PATIENT EDUCATION**

- Patients must be educated on strategies to avoid future exposures to heavy metals: protective clothing and masks/respirators, proper ventilation of the workplace, workplace monitoring of air levels of heavy metals, and individual body burdens. Materials Safety Data Sheets (MSDS) for materials used in the workplace should be reviewed. Advise patients on nonoccupational sources of exposure to heavy metals.

- Heavy metal poisoning support groups and resources. Website: www.medhelp.org/healthtopics/Heavy_Metal_Poisoning.html

- Heavy metal poisoning information. Website: www.waxaddict.com/g/conceptionpage/Poisoning_Heavymetals

**SYNONYMS**

N/A

ICD-9-CM: 984.9 Unspecified toxic effects of lead; 985.9 Unspecified toxic effects of other heavy metals

**SEE ALSO:** ENCEPHALOPATHY; NEUROPATHY; PARKINSON'S DISEASE

**REFERENCES**


Author(s): Robert G. Feldman, MD; Marcia H. Ratner, PhD

**Miscellaneous**
Herpes Zoster

**Basics**

**DESCRIPTION**
- Herpes zoster (shingles) is a painful vesicular rash that usually occurs in a dermatomal distribution. The infection occurs in individuals who have had chicken pox. The causative agent, varicella-zoster virus, lies dormant in the dorsal root ganglia following chicken pox. If reactivation of the virus occurs, herpes zoster will manifest along the involved ganglion’s distribution.

**ETIOLOGY**
- Affects both sexes with equal frequency.

**Incidence/Prevalence**
- Occurs in 600,000-1,000,000 persons annually in the United States. Incidence increases with increasing age.

**Race**
- More common in whites than blacks, with blacks 25% less likely than whites to develop zoster among those exposed to chicken pox.

**Sex**
- Affects both sexes with equal frequency.

**RISK FACTORS**
- The primary risk factor for herpes zoster is previous chicken pox infection. Other factors that may increase the risk of developing herpes zoster are those involving a depression of the patient’s immune system, including advancing age, AIDS, lymphomas, and chemotherapy.

**PREGNANCY**
- Herpes zoster is rare in pregnancy.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Appendicitis
- Bell’s palsy
- Cholecystitis and biliary colic
- Corneal ulceration
- Ulcerative keratitis
- Conjunctivitis
- Herpes simplex
- Renal calculi
- Trigeminal neuralgia

**SIGNS AND SYMPTOMS**
- Herpes zoster is preceded by approximately 2 days of pain, tingling, or burning in a dermatomal distribution. This prodromal phase results in a high incidence of misdiagnosis and is the reason herpes zoster is included in the differential diagnosis of many conditions whose symptoms may involve pain or sensory disturbances.
- The prodrome may be followed by symptoms including fatigue, malaise, low-grade fever, and headache. The most characteristic finding is that of a vesicular rash in a unilateral dermatomal pattern. The rash is rarely bilateral. The lesions progress from vesicles to pustules to crusts lesions until the rash resolves. The dermatomes of the thorax are the most commonly involved. The pain may or may not resolve with resolution of the rash. Zoster sine herpete is a form of zoster in which there is no rash, but there are pain and paresthesias in a dermatomal pattern.
- Pain lasting >1 month is described as postherpetic neuralgia.
- Herpes zoster ophthalmicus is defined as zoster involving the distribution of the ophthalmic division of the fifth cranial nerve and may involve the cornea. Herpes zoster ophthalmicus or Ramsay-Hunt syndrome is defined as zoster involving the distribution of the facial nerve and can cause severe ear pain as well as paralysis of the facial muscles.

**LABORATORY PROCEDURES**
- Monoclonal antibody tests
- A Tzanck smear of vesicular lesions can be done but will not distinguish between herpes simplex and varicella-zoster infections.
- Biopsy may be obtained and sent for direct immunofluorescence testing.
- Although Laboratory testing may be performed, the diagnosis is most commonly clinical.

**Management**

**GENERAL MEASURES**
- Therapy should be aimed at decreasing pain, shortening the duration of the disease, preventing complications, and minimizing the risk of postherpetic neuralgia. Although analgesics are indicated to treat the pain, antiviral agents also may be used and are most effective if given within the first 72 hours of onset of the patient’s symptoms. Studies involving antiviral agents suggest their primary benefit may be reducing the incidence and duration of postherpetic neuralgia. Oral steroids have been used to treat herpes zoster; however, there is conflicting evidence as to their efficacy.

**SURGICAL MEASURES**
- N/A

**SYMPTOMATIC TREATMENT**
- Herpes zoster usually causes severe pain. Analgesia should include nonsteroidal antiinflammatory drugs and/or narcotics. Dressings may be applied to the rash, including wet dressings with tap water or Burow solution (5% aluminum acetate). Discomfort also may be relieved by using certain lotions, including calamine lotion.

**ADJUNCTIVE TREATMENT**
- N/A

**ADMISSION/DISCHARGE CRITERIA**
- Herpes zoster is an outpatient disease in most cases; however, admission may be required in some instances, including some cases of herpes zoster ophthalmicus. Ophthalmologic consultation should be obtained in all cases of herpes zoster ophthalmicus. Another indication for admission is in the immunocompromised patient when evidence of dissemination exists. Dissemination should be suspected in the ill-appearing or toxic patient and in patients who have involvement of more than one dermatome.
Medications

DRUGS OF CHOICE:
- Antiviral agents given within the first 72 hours may reduce the duration and severity of postherpetic neuralgia. Although the most widely studied drug is acyclovir, famciclovir and valacyclovir share similar pharmacotherapeutic properties with acyclovir. Famciclovir and valacyclovir offer dosing regimens that are more convenient and easier to comply with. Whether or not the patient is treated with antiviral agents, a strong analgesic should also be prescribed.

Contraindications
- Caution should be used in administering antiviral agents in patients who have renal failure or who are taking nephrotoxic drugs because of the risk of inducing hemolytic uremic syndrome, which has been documented in patients receiving valacyclovir.

Precautions
- As above

Dosages
- Acyclovir 800 mg PO five times per day for 7 days
- Famciclovir 500 mg PO every 12 hours for 7 days
- Valacyclovir 1,000 mg PO every 8 hours for 7 days

ALTERNATIVE DRUGS
- Amitriptyline 25 mg PO qhs has been used for management of postherpetic neuralgia with some success.
- Narcotic analgesics
- Corticosteroids have been proposed by some authors to reduce acute pain, as well as the severity of postherpetic neuralgia. Although the literature suggests that corticosteroids have no effect on postherpetic neuralgia, there is some evidence supporting their use to reduce the acute pain of herpes zoster. There have been no studies examining the theoretical risk of corticosteroid-induced dissemination of localized zoster.

Follow-Up

PATIENT MONITORING
- Patients should be monitored for resolution of rash and cessation of pain. Patients with herpes zoster ophthalmicus should be monitored by ophthalmology for secondary ocular complications (corneal scarring, impaired vision).

EXPECTED COURSE AND PROGNOSIS
- Following the 1- to 3-day prodrome, acute herpes zoster typically resolves after 2 weeks.
- Postherpetic neuralgia presents in about 15% of patients following herpes zoster and is defined as pain that persists for >1 month following resolution of the rash. The incidence of postherpetic neuralgia increases significantly with age, approaching 70% in patients who develop herpes zoster after age 70 years.

PATIENT EDUCATION
- The vesicular lesions of herpes zoster contain the varicella virus; therefore, patients should be advised of that fact and avoid close contact with immunocompromised patients and patients who have not had chicken pox or the varicella vaccine.

Miscellaneous

SYNONYMS
- Shingles

ICD-9-CM: 053.9 Herpes zoster; 053.2 Herpes zoster with ophthalmic complications; 053.71 Herpes zoster oticus; 053.19 Postherpetic neuralgia

SEE ALSO: NA

REFERENCES

Author(s): Chris Melton, MD
Hemiballismus

Basics

DESCRIPTION

• Hemiballismus is a hyperkinetic movement disorder characterized by violent flailing movements involving mainly proximal limbs on the same side of the body. Hemiballismus is considered an extreme form of chorea because as ballistic movements subside with time, they have the appearance of classic chorea.

EPIDEMIOLOGY

Incidence

• Uncommon, with an annual incidence of around 1 per 500,000 in the general population. Of 3,084 patients seen at a tertiary care movement disorders clinic, only 21 had hemiballismus.

Age

• Mean age at presentation >60 years of age. It is rare in children; however, Sydenham’s chorea can be unilateral and of such large amplitude to resemble hemiballismus.

Sex

• Hemiballismus occurs equally in males and females.

Race

• There is no racial predisposition.

ETIOLOGY

• Hemiballismus typically is caused by a lesion involving the contralateral thalamic nucleus or its connections with the substantia nigra, putamen, caudate nucleus, globus pallidus or thalamus. The onset usually is acute, over minutes or hours, although evolution over weeks to months has been described depending on the mechanism of injury. Hemorrhagic and ischemic strokes account for about two thirds of all cases of ballism. Other potential etiologies include head trauma, space-occupying lesions, CNS infections, demyelinating disease, autoimmune diseases (especially systemic lupus erythematosus), hyperglycemia or hypoglycemia, medications (levodopa, oral contraceptives, phenytoin, tardive syndromes of dopamine-blocking agents), complications of surgical procedures for treatment of Parkinson’s disease, and calcification of the basal ganglia.

RISK FACTORS

• The list of potential risk factors is extensive. However, vascular risk factors, especially hypertension, are most important because stroke is the main cause of hemiballismus.

PREGNANCY

• There is no specific relationship to pregnancy except that chorea gravidarum occasionally can be severe and unilateral enough to resemble hemiballismus.

ASSOCIATED CONDITIONS

• Cerebrovascular disease: ischemic and hemorrhagic stroke, vascular malformations
• Autoimmune disorders: systemic lupus erythematosus, scleroderma, antiphospholipid antibody syndrome, Sydenham’s chorea
• Metabolic disorders: hypoglycemia, hyperglycemia
• Infectious diseases: syphilis, tuberculosis, toxoplasmosis, meningococcalitis, cryptococcosis, AIDS
• Tumors: primary CNS malignancies, metastatic tumors, cystic lesions, abscesses
• Drugs: levodopa, dopamine agonists, anticonvulsants (e.g., phenytoin), oral contraceptives (hormonal changes, e.g., pregnancy)
• Surgical procedures: thalamotomy, subthalamic deep brain stimulation, thalamotomy
• Head trauma

Differential Diagnosis

• Ballistic movements are unlikely to be confused with any other hyperkinetic movement disorders or focal seizures.

SIGNS AND SYMPTOMS

• Ballistic movements are large, proximal usually rotary throwing or kicking movements that often are violent and relentless. The movements may be voluntarily suppressed for brief periods of time. They interfere with motor activity and stress makes them worse. In half of patients, the leg and arm of the same side are equally affected. In about two thirds the face also is involved. For reasons that are unclear, the left side is more commonly affected. Other neurologic signs, such as cognitive or affective changes, hemiparesis, sensory impairment, and changes in tone and muscle stretch reflexes, suggest involvement of adjacent motor and sensory pathways.

LABORATORY PROCEDURES

• Laboratory procedures are directed at diagnosing the underlying cause. CBC, routine blood biochemistry, fasting and postprandial blood glucose, sedimentation rate, VDRL, ANA, PT, aPTT, pregnancy test, and urine analysis are first steps in the evaluation. In selected patients, the following tests may be obtained: HIV tests, anticonvulsant blood levels, throat culture, and antistreptolysin antibody titers.

IMAGING STUDIES

• Brain MRI or CT should be performed to search for the cause of hemiballismus. MRI is more sensitive, allows for anatomic localization of the causative lesion, and may show changes in the basal ganglia in patients with ballistic movements due to metabolic derangements.

SPECIAL TESTS

N/A

Management

GENERAL MEASURES

• Management requires identification of the cause of hemiballismus, mainly focusing on neuroimaging and identifying and treating risk factors, with special emphasis on vascular risk factors. Once the etiology has been established, the disorder causing the hemiballismus must be treated appropriately depending on its nature. In addition, supportive care directed at preventing self-injury and other complications, such as aspiration pneumonia, pulmonary embolism, and urinary tract infection, should be provided.

SURGICAL MEASURES

• Surgery usually is reserved for patients with refractory hemiballismus. Several surgical targets have been studied, but currently the one that has a putative benefit are the globus pallidus internus and zona incerta. The clinical results of different surgeries with different targets are difficult to compare. However, >80% of patients show significant postoperative improvement.

SYMPTOMATIC TREATMENT

• Medication, primarily dopamine receptor-blocking agents, is method of choice for symptomatic treatment. See Medications.

ADJUNCTIVE TREATMENTS

• Combination therapy is needed in some cases. ADMISSION/DISCHARGE

CRITERIA

• All patients should be admitted for diagnostic evaluation and started on treatment for the ballismus. Discharge criteria and workup depend on the underlying diagnosis.
Hemiballismus

**DRUG(S) OF CHOICE**

- **Neuroleptics:** These drugs are the first-line treatment for ballistic movements because of their proven efficacy. Antagonism of the postsynaptic D<sub>2</sub> dopamine receptor seems to be the common feature among agents effective in the treatment of hemiballismus.

  Chlorpromazine, promethazine, perphenazine, prochlorperazine, haloperidol, pimozide, and tiapride, among other neuroleptics, have been shown to be effective in the treatment of hemiballismus. Clozapine in low doses (50 mg/day) also is useful.

- **Sedative/hypnotics:** A variety of sedative drugs (e.g., barbiturates, chloral hydrate, benzodiazepines) have been used for treatment of hemiballismus. Their efficacy is very modest and related to their tendency to induce sleep.

- **Catecholamine-depleting agents:** Reserpine and tetrabenazine are effective for the treatment of hemiballismus, but the experience with these drugs is more limited than with neuroleptics.

- **GABA-ergic agents:** Valproic acid at various antiepileptic doses have been used with good results. Progabide 900 mg has been reported to be effective in patients who were unresponsive to neuroleptics.

**Contraindications**

- Neuroleptics should not be used in patients with prior history of hypersensitivity, neuroleptic malignant syndrome, and prolonged QT syndrome.

**Precautions**

- The main problems with the use of dopamine receptor-blocking agents is the development of extrapyramidal side effects, such as akathisia, drug-induced parkinsonism, neuroleptic malignant syndrome, and tardive dyskinesia. Other side effects include sedation, cardiac conduction abnormalities, weight gain, maculopapular rash, cholestatic jaundice, transient leukopenia, and photosensitivity.

**ALTERNATIVE DRUGS**

- If pharmacologic measures are ineffective, consider stereotaxic surgical options.

**Follow-Up**

- **Patient Monitoring**

  - Dependent on the etiology of the hemiballismus.

- **Expected Course and Prognosis**

  - The course and prognosis depend on the underlying cause. Overall, good prognosis for survival and recovery is expected, especially when the cause is vascular. In some patients, hemiballismus may evolve into a hemidystonia.

- **Patient Education**

  - There are no support groups or organizations providing information for patients with hemiballismus. The condition is mentioned briefly at www.wemove.org.

**Synonyms**

- Ballism
- Hemic horea

**ICD-9-CM:** 333.5 Hemic horea

**See Also:** N/A

**References**


**Author(s):** Xabier Beristain, MD; Joanne M. Wojcieszek, MD
## Hereditary Spastic Paraparesis

### Basics

#### DESCRIPTION
- Hereditary spastic paraparesis (HSP) represents a group of rare, genetically transmitted, neurodegenerative diseases characterized by the development of progressive weakness and spasticity of the lower extremities. A clinical classification distinguishes pure HSP from "complicated" HSP, in which other neurologic and non-neurologic abnormalities also are present.

#### EPIDEMIOLOGY

**Incidence/Prevalence**
- Reported prevalence rates for pure HSP vary from 1.0 to 2/2 per 100,000.

**Race**
- No ethnic predominance has been reported. Families with HSP have been identified in many parts of the world, with regional clusters.

**Age**
- Age of symptom onset varies widely (from infancy to >80 years) with a peak from the second through the fourth decades. The distinction between early onset (before 40 years) and late onset (after 40 years) is debated, because clinical features do not seem to be distinct.

**Gender**
- No gender difference was reported, except for X-linked forms of HSP.

#### ETIOLOGY
- Three modes of genetic transmission have been identified:
  - Autosomal dominant inheritance with complete or nearly complete penetrance is the most common mode of transmission. Linkage analysis identified loci on chromosomes 1q41, 2p, 15q, and 8q. CAG repeat expansions were identified in some families.
  - Autosomal recessive forms were linked to chromosomes 8, 16, and 15q.
  - X-linked inheritance is rare and has been linked to loci Xq28, Xq11, and Xq21.

#### RISK FACTORS
- Consanguinity increases the risk of expression of autosomal recessive forms.

#### PREGNANCY
- Prenatal genetic studies may be used to assess the risk that the fetus inherited HSP, but this testing is useful only in families with a known linkage to HSP loci. Results should be interpreted with caution.

### Diagnosis

#### DIFFERENTIAL DIAGNOSIS
- Clinical diagnosis of HSP requires the presence of progressive spastic paraparesis and a positive family history. However, other possible diagnoses should be ruled out in each patient (particularly in "complicated" forms) through complete neurologic examination and neuroimaging studies. Other causes of spastic paraparesis include:
  - Trauma
  - Malformations (Arnold-Chiari, tethered cord syndrome)
  - Acquired structural defects (her niated disc, spondylolisthesis)
  - Tumors
  - Vascular disorders (infarcts, hemorrhages, arteriovenous malformations)
  - Inflammation (transverse myelitis, multiple sclerosis)
  - Infections (spondylodiscitis, epidural abscess, tertiary syphilis, tropical [HTLV-1 associated] spastic paraparesis, AIDS)
  - Other neurodegenerative disorders (amyotrophic lateral sclerosis, spinocerebellar ataxias)
  - Metabolic disorders (B12 deficiency, leukodystrophies, mitochondrial diseases)
  - Familial peripheral neuropathies

#### SIGNS AND SYMPTOMS
- The main presenting complaint is progressive gait disturbance. Examination shows weakness and spasticity of the lower extremities with hyperreflexia and bilateral Babinski sign.
- In pure HSP, spastic paraparesis may be associated with sensory deficits of the lower extremities, bladder/bowel dysfunction, mild pyramidal involvement of the upper extremities (hyperreflexia, Hoffmann sign, decreased fine movements) and/or slight dysmetria on finger-to-nose testing.
- Amyotrophy of the lower extremities usually occurs late in patients with restricted mobility.
- Associated findings, which include ataxia, dystarthritis, extrapyramidal signs, sensory deficits, optic neuropathy, cluneal abnormalities, ophthalmologic abnormalities, and deafness, lead to the diagnosis of "complicated" HSP, particularly if there is a family history of pure HSP and other diseases have been ruled out.

### Management

#### GENERAL MEASURES
- There is no specific treatment for HSP. Management is primarily symptomatic.
- Goals of management:
  - Preserving function
  - Preventing medical complications
- Surgical measures:
  - Surgery (tenotomies and/or neurectomies) may be useful in the management of severe spasticity with contractures.

#### SYMPTOMATIC TREATMENT
- Spasticity requires daily stretching exercises and treatment of all potentially irritative factors (urinary tract infections [DTI], pressure sores, ingrown toenail). Multiple medications are available to treat spasticity (see below).

### Laboratory Procedures
- There is no laboratory diagnostic test for HSP. Genetic linkage studies are increasingly performed, but results must be used with caution because different mutations may be involved, and all HSP loci have not been identified yet.
- Other laboratory tests aimed at excluding other possible conditions:
  - VDRL
  - Serum vitamin B12
  - HIV and HMV-1 serologies
  - Plasma long-chain fatty acids

### Imaging Studies
- MRI of the brain and spinal cord is recommended for differential diagnosis. In patients with HSP, MRI is normal or shows atrophy of the spinal cord and/or corpus callosum. Cortical atrophy and foci of increased T2 signal in the cerebral white matter have been reported in some cases.

### Special Tests
- EMG is useful to rule out peripheral neuropathy. Nerve conduction velocity test are most often normal in HSP.
- Somatosensory evoked potentials obtained after stimulation of the median and tibial posterior nerves may be abnormal with delayed latency and decreased amplitude, even in the absence of clinical sensory deficits.

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**Image 39x712 to 67x742**

**Image 213x711 to 244x741**

**Image 393x370 to 424x399**

**Image 286x66 224**

**Image 398x415 472**

**Image 398x472 482**

**Image 398x482 506**

**Image 398x506 525**

**Image 398x525 544**

**Image 398x544 563**

**Image 398x563 582**

**Image 398x582 601**

**Image 398x601 620**

**Image 398x620 640**

**Image 398x640 660**

**Image 398x660 679**

**Image 398x679 698**

**Image 398x698 717**

**Image 398x717 736**

**Image 398x736 756**

**Image 398x756 775**

**Image 398x775 795**

**Image 398x795 814**

**Image 398x814 834**

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**Basics**

**Diagnosis**

**Differential Diagnosis**

**Symptoms and Signs**

**Risk Factors**

**Pregnancy**

**Associated Conditions N/A**

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Hereditary Spastic Paraparesis

• Bladder dysfunction: The most common complaints are urinary urgency and incontinence. Neurogenic bladder dysfunction is best evaluated by complete urodynamic assessment. It is at least recommended to measure postvoiding residual volumes (PVR), even when the patient does not complain of urinary hesitancy, in order to rule out onic retension, which might worsen with medications for incontinence. General measures include regular fluid intake and avoidance of irritants (coffee, sodas) Treatments for detrusor hyperactivity include oxybutynin 5 mg qd-tid, tolterodine (overtrate), and propantheline bromide. If PVR exceeds 100 mL, intermittent self-catheterization is recommended to prevent chronic bladder distention, recurrent UTIs, and vesicoureteral reflex. Indwelling bladder catheter is avoided as much as possible because of the risk of chronic infection.

• Sexual dysfunction is a common complaint. Erectile dysfunction can be managed through medications (sildenafil citrate [Viagra]), intracavernous injections, penile prosthesis.

• Bowel dysfunction: Management includes dietary recommendations, adequate fluid intake, regular physical activity, regular bowel schedule (using suppositories to trigger bowel movement or digital rectal evacuation if necessary), daily administration of bulk-forming agents, and cautious use of laxatives.

• Skin care: Prevention of decubiti is a concern mainly for patients with restricted mobility or for those wearing orthoses, particularly if sensation is decreased. Prevention includes frequent change of position, inspection of potential pressure points, use of adequate cushions/mattresses or padding, and avoidance of maceration due to incontinence. Agency for Health Care Policy and Research (HCPR) guidelines on pressure ulcers for adults can be found on the Internet at http://text.nlm.nih.gov/facts/gateway.

• Physical therapy in the ambulatory patient should be aimed at preserving and optimizing gait through aggressive stretching exercises, neuromuscular stimulation, muscle strengthening, endurance training, and appropriate use of technical aids. In the nonambulatory patient, rehabilitation should be oriented toward preserving range of motion and the ability to transfer. Occupational therapy should focus on upper extremity function, wheelchair assessment, instrumental activities of daily living, and home adaptations. Emphasis is placed on patient education and home exercises. Short periods of intensive rehabilitation may be useful during periods of rapid loss of function or after immobilization due to an intercurrent health problem.

ADMISSION/DISCHARGE CRITERIA

N/A

Medications

DRUGS OF CHOICE

• Oral baclofen is commonly used when spasticity is the cause of discomfort or interferes with function. The starting dose is low (10-20mg qd) and pr aggressively titrated up to 100 mg divided in 3-4 doses daily. Oral tizanidine may be used instead of, or in association with, baclofen at a dose of 2 mg up to 36 mg/day. Intrathecal baclofen pump implantation may be considered in cases of intractable spasticity despite oral treatment at maximum tolerated doses with caution in patients who are still ambulatory, considering the risk of losing function due to increased weakness.

Contraindications

N/A

Precautions

• Tizanidine may cause sedation or orthostatic hypotension and should be titrated up slowly. LFTs should be monitored periodically for chronic tizanidine treatment.

ALTERNATIVE DRUGS

• Other agents used in the treatment of spasticity include dantrolene and diazepam.

Follow-Up

PATIENT MONITORING

• Monitoring is focused on optimization of symptomatic treatment, preservation of function, and prevention or early treatment of complications, such as UTIs and pressure sores. Development of new neurologic symptoms or abrupt worsening of symptoms must raise the suspicion of misdiagnosis or sperr iron spastic condition (e.g., development of cervical spondylodiscitis in a patient with established HSP).

EXPECTED COURSE AND PROGNOSIS

• The rate of progression is highly variable among patients. For a given patient, progression may not be uniform over time. Patients with childhood onset and no or very slow progression have been reported. Many patients remain ambulatory for an extended period of time.

PATIENT EDUCATION

• HSPinfo.org (Hereditary Spastic Paraplegia/ Familial Spastic Paraparesis), 48 W Broadway, Salt Lake City UT 84101. Phone: 801-366-7348, e-mail: info@HSPinfo.org, website: http://www.HSPinfo.org

SYNONYMS

• Hereditary spastic paraplegia
• Familial spastic paraparesis/paraplegia
• Strumpell-Lorrain disease/syndrome

ICD-9-CM: 334.1 Hereditary spastic paraplegia; 344.1 Paraplegia SEE ALSO: N/A

REFERENCES


Author(s): Francois Bethoux, MD
Horner's Syndrome

Basics

DESCRIPTION

• In 1869, Johann Frederick Horner, the first professor of ophthalmology in Switzerland, published a case report of eyelid ptosis caused by a neck lesion. Horner's syndrome (HS) is characterized by a lesion of the oculomotoric pathway. This three-neuron sympathetic pathway runs from the brain to the pupil. The first-order (central) neurons run from the posterior hypothalamus through the brainstem into the spinal cord (via the intermediolateral column) to synapse at the ciliary ganglion located at the bifurcation of the cervical carotid artery, which is at the level of the thyroid cartilage. The third-order (postganglionic) neuronal axons leave the superior cervical ganglion to accompany the internal and external carotid arteries. Most third-order axons pass with the internal carotid artery to reach the ipsilateral cavernous sinus and then travel with fibers of the abducens (VI) nerve to pass to the nasociliary branch of the trigeminal nerve and enter the orbit through the superior orbital fissure. These long ciliary nerves pass through the ciliary ganglion (without synapse) and enter the eye in the sprachoidal space to innervate the radially oriented iris dilator muscle. Some orbital sympathetic fibers innervate Mueller's muscle, a smooth but minor elevator of the upper eyelid and a rudimentary analogus muscle of the lower eyelid. Both vasomotor (flushing) and edomotor (sweating) sympathetic fibers of the face travel with branches of the external carotid artery. Therefore, diseases that affect the brain, upper spinal cord, thorax, neck, and orbit can be diagnosed in patients who can present with miosis, partial (1-2 mm) ptosis (upper more than lower lid), and in some cases facial anhidrosis.

EPIDEMIOLOGY

• Nearly 2/3 of the population has at least 0.4 mm of anisocoria (unequal pupil diameter between the two eyes). The vast majority of such patients, however, have simple (essential, central, or physiologic) anisocoria in that they have equal amounts of anisocoria in bright and dim light. HS is an important diagnostic clue of a nisocoric patients. By taking a careful history, one can help localize the part of the three-order neuronal chain that is affected and thereby make an educated differential diagnosis of possible uterine ing diseases. Ancillary tests include office or bedside pharmacologic pupillary testing and targeted neuroimaging.

ETIOLOGY

• First-order lesions are associated with brainstem or upper spinal cord injury, such as stereotactic thalamotomy. Wallenberg's syndrome, polio myelitis, multiple sclerosis, syringomyelia, and complicated epidural blocks. Second-order lesions affect the spinal cord and sympathetic chain below the superior cervical ganglion and include apical lung cancer (e.g., bronchogenic carcinoma or so-called Pancoast tumor), birth injury involving the brachial plexus (Klumpke's paralysis), cervical carotid angiography, lymphoma, coronary artery bypass surgery, and radial neck surgery. Third-order lesions involve the superior cervical ganglion and higher and include disorders such as basilar skull fractures, nasopharyngeal carcinoma, cavernous sinus tumors, carotid cavernous fistulas, orbital tumors, and internal carotid artery dissections. In children, congenital cases can be idiopathic or associated with chiasmal plexus injuries. Acquired cases are presumed to result from a mediastinal tumor (e.g., neuroblastoma) until proven otherwise.

RISK FACTORS

• Risk factors are related to the underlying pathology. For example, smokers are at greater risk for bronchogenic carcinoma.

PREGNANCY

N/A

ASSOCIATED CONDITIONS

• Associated signs and symptoms are dependent on the underlying disease. For example, Wallenberg's syndrome is a lateral medullary infarct with ipsilateral H5, ataxia and facial loss of light touch, contralateral body loss of pain and temperature, dysphasia, hoarseness, nystagmus, and vertigo.

Diagnosis

DIFFERENTIAL DIAGNOSIS

• The differential diagnosis of anisocoria includes those cases of nonphysiologic anisocoria in which the anisocoria is greater in dim-light illumination and the abnormal pupil is the miotic pupil. Examples include pharmacologic causes such as miotic drops to treat glaucoma (e.g., pilocarpine) and intraocular inflammatory disease such as iritis or ocular trauma, both of which can lead to adhesions (posterior synechiae) between the iris and the lens. A careful ocular history and slitlamp examination will rule out the aforementioned examples. It also should be noted that chronic Adie's syndrome (post ciliary ganglinitis with initially large, relatively areflexic pupil that shows derangement hypersensitivity to dilute pilocarpine and is associated with reduced or absent deep tendon reflexes) can develop a small pupil with time, but such cases are unassociated with blepharoptosis. Also, ipsilateral miosis and ptosis can occur in a patient with essential anisocoria and levator aponeurosis dehiscence.

SIGNS AND SYMPTOMS

• The clinical features of HS are (i) anisocoria where the miotic eye being the affected eye as the parasympathetically innervated iris sphincters is unopposed) that is greater in dim light than in bright light; (ii) slower dilation of the affected pupil in dim light (dilation lag that can last up to 15 seconds) and (iii) ptosis of 1-2 mm of the upper lid and occasionally involving the lower lid (upside down ptosis) and apparent (pseudo) enophthalmos that is secondary to blepharoptosis. In some cases, conjunctival injection, reduced intraocular pressure, hemifacial anhidrosis, and lack of blushing are noted. In congenital cases, iris heterochromia (lighter iris color on the affected side) is present because the iris melanocyte development depends on sympathetic innervation. Such patients also may have hemifacial and hemicranial straighter hair.

LABORATORY PROCEDURES

• In children suspected of having a neuroblastoma, besides neuroimaging of the thorax and abdomen, a 24-hour urine collection for excessive catecholamine excretion (vanillylmandelic acid and homovanillic acid) is performed in conjunction with an evaluation by a pediatric oncologist.
Hornet's Syndrome

IMAGING STUDIES

• Targeted CT or MRI scanning is directed by the patient's history, clinical examination, and pharmacologic pupillary testing. Angiography (percutaneous or MR angiography) may be needed in patients with carotid cavernous fistulas or carotid dissections.

SPECIAL TESTS

• Pharmacologic testing is essential because it helps confirm the diagnosis of HS and aids in localizing the order of neuron affected. All pharmacologic pupillary testing should be done before any drops are placed in the patient's eye so that the corneal penetration of the drops is not altered. Oculosympathetic dysfunction is confirmed with topical cocaine (4%–10% in adults). Thereafter, allow 45 minutes before checking each pupil. Cocaine blocks the reuptake of the neurotransmitter norepinephrine at the neuromuscular junction; therefore, any order HS eye does not dilate (or does so minimally, <1 mm) whereas a normal pupil will dilate to cocaine. The Hornet's pupil does not dilate because norepinephrine is not being released into the third-order synaptic cleft. Thereafter, one should wait at least 24–48 hours before performing the hydroxyamphetamine (Paredrine 1%) test. Again, one drop is placed in each eye and repeated after several minutes. Hydroxyamphetamine causes release of the presynaptic norepinephrine vesicles. Third-order lesions cause presynaptic terminal degeneration and thereby a lack of norepinephrine vesicles. Unlike eyes that have first- or second-order HS, a third-order HS pupil fails to dilate in response to hydroxyamphetamine. The very good sensitivity and the specificity of pharmacologic testing are not 100%. There is no pharmacologic test to distinguish between first- and second-order HS. Oe may need to remind the patient that a urine drug screen will remain positive for 24–48 hours after such testing, which could be problematic with a drug toxicity screening for occupational hiring.

GENERAL MEASURES

• Depend on the underlying pathology

SURGICAL MEASURES

• Depend on the underlying pathology, see below

SYMPTOMATIC TREATMENT

• Ptosis repair (Fasanella-Servat or levator aponeurosis advancement) usually is not required because of its mild (1–2 mm) nature.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

• Some patients are diagnosed while they are hospitalized (e.g., for radical neck surgery); for others, the initial neuroimaging typically is done, if needed, as an outpatient. Acquired cases in childhood typically are admitted for a workup to rule out a neuroblastoma.

Medications

DRUG(S) OF CHOICE

N/A

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

• Once the diagnosis of HS is made, the underlying etiology is monitored on an individual basis.

EXPECTED COURSE AND PROGNOSIS

• HS typically is a permanent condition

PATIENT EDUCATION

• Directed to the underlying condition

References


Author(s): Thomas J. Mehelas, MD

ICD-9-CM: 337.9 Horner's syndrome; 379.41 Anisocoria; 374.43 Ptosis

SYNONYMS

• Claude Bernard-Horner syndrome

SEE ALSO: N/A

Miscellaneous
Huntington's Disease

**Basics**

**DESCRIPTION**
- Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by involuntary movements, psychiatric disturbance, and dementia.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- The worldwide prevalence of HD is approximately 5–10 per 100,000. Approximately 25,000 North Americans have manifest HD with an additional 125,000 at risk (parent with HD).
- Reduced prevalence has been reported for certain ethnic backgrounds (Japan, Norway, and individuals of African descent). The disease is endemic in and around Maracaibo, Venezuela.

**Age**
- The average age of symptom onset is during the third or fourth decade, although onset in childhood and in later life has been reported.

**Sex**
- No gender predisposition has been identified.

**ETIOLOGY**
- HD is caused by a mutation on the short arm of chromosome 4 in the first exon of the Huntington gene. Increase in the number of cytosine-adenine-guanine (CAG) triplets beyond 37 produces an expanded polyglutamine sequence that alters the conformation of the polypeptide and engenders a toxic gain of function.

**Genetics**
- HD is a fully penetrant, autosomal dominant disorder. In adult-onset HD, a CAG expansion of 40–50 is typical. Larger expansions result in juvenile-onset HD. Although the length of the triplet expansion correlates with age of onset, the relationship is imprecise and has limited prognostic value.
- The CAG repeat is unstable, expanding during meiosis. The largest increases occur during spermatogenesis. Meiotic instability provides a mechanism for the phenomenon of anticipation (earlier onset in offspring) and the association of juvenile-onset HD with an affected father.

**RISK FACTORS**
- N/A

**PREGNANCY**
- Although pregnancy and oral contraceptives can precipitate involuntary movements, the impact of pregnancy on HD is not well characterized.

**ASSOCIATED CONDITIONS**
- N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Hereditary
  - Benign familial chorea
  - Neuroacanthocytosis
  - Wilson's disease
  - Paroxysmal choreoathetosis
- Metabolic
  - Hypothyroidism
  - Hyperparathyroidism
  - Electrolyte disturbance
- Infectious/Immunologic
  - Sydenham's chorea (St. Vitus dance)
  - Viral encephalitis
  - Multiple sclerosis—Systemic lupus erythematosus
  - Polyneuropathy
- Cerebrovascular
  - Hemorrhage/Infarct (subthalamic nucleus)
  - Polycystic kidney disease

**SIGNS AND SYMPTOMS**
- Motor disorder
  - Involuntary movements (may include dystonia, athetosis, tics, as well as chorea).
  - Impaired pursuit and saccadic eye movements
  - Motor impersistence (inability to sustain eye closure or tongue protrusion)
  - Hyperactive tendon reflexes
  - Incoordination
- Mood disorder
  - Depression (may precede motor manifestations)
  - Higher frequency of suicide has been reported in HD
- Psychosis
  - Obsessive/compulsive behaviors
- Cognitive dysfunction
  - Elidation (partial loss of attention)
  - Paraneoplastic
  - Mental status changes

**LABORATORY PROCEDURES**
- Genetic testing: A CAG repeat expansion establishes the diagnosis of HD. The many implications of genetic testing must be carefully considered. Testing of at-risk, presymptomatic individuals must have established guidelines, with participation of a genetic counselor, psychologist, and neurologist. With rare exception, testing is restricted to individuals attaining the age of majority.
- Laboratory evaluation excluding alternative diagnoses
  - CBC with manual differential (neutrophils)
  - Electrolytes
  - LFTs (Wilson's disease)
  - Thyroid function studies
  - Sedimentation rate, antinuclear antibody
  - Antistreptolysin O (ASO) titers
  - Sydenham's Chorea
  - Ceruloplasmin, serum copper, 24-hour urine copper (Wilson's disease)
  - Pregnancy test (chorea gravidarum)

**IMAGING STUDIES**
- CT or MRI of the brain demonstrates progressive atrophy of the striatum (caudate nucleus and putamen) that parallels symptom progression. The roles for functional MRI and spectroscopy await definition.
- Functional imaging (PET and SPECT) may improve diagnostic sensitivity and specificity, but current use is restricted to research.

**SPECIAL TESTS**
- EEG can facilitate the management of seizures in juvenile HD.
- Neuropsychometric evaluation can be performed to assess the extent of cognitive dysfunction.

**Management**

**GENERAL MEASURES**
- Disease-modifying therapy has yet to be identified.
- Assistance from the social services department is frequently needed because wage-earning years are curtailed.
- Ensure a safe environment because gait disorder and poor balance increase the risk of falls and associated injury.

**SURGICAL MEASURES**
- Although several trials of fetal tissue transplantation have been reported, its role in surgery for HD awaits further investigation.
SYMPTOMATIC TREATMENT

- Treatment is aimed primarily at controlling involuntary movements and mood disturbance. See Medications.
- Stable environment and well-defined activities can help to control behavioral manifestations.
- Involuntary movements demand caloric intake that can be difficult to sustain, especially when dysphagia and aspiration complicate the management of advanced HD.

ADJUNCTIVE TREATMENT

- Behavioral and supportive psychotherapy can be useful in the management of HD.

ADMISSION/DISCHARGE CRITERIA

- Hospitalization does not occur frequently and usually is prompted by exacerbation of psychiatric/behavioral manifestations or to facilitate long-term placement.

DRUG(S) OF CHOICE

- Movement disorder: Typical and atypical neuroleptic medications dampen hyperkinetic movements. Dopamine-depleting compounds are used less commonly because of affective side effects. Treatment is deferred until dyskinesia presents an injury risk or interferes with daily activities, and the minimum dose yielding reasonable control is used. As symptoms progress, increasing akinesia and rigidity may respond to dopaminergic therapy. Response to the medicines listed may be enhanced by divided doses.
  - Typical neuroleptic
    - Haloperidol (Haldol) 0.5-5 mg qd
  - Atypical neuroleptic
    - Risperidone (Risperdal) 0.5-3 mg qd
    - Olanzapine (Zyprexa) 2.5-15 mg qd
  - Dopamine-depleting agent
    - Reserpine (Serpasil) 0.5 mg-2 mg qd
  - Dopaminergic agent
    - Carbidopa/levodopa (Sinemet) 25/100 mg bid-qid
    - Bromocriptine (Parlodel) 2.5-10 mg qd
  - Mood disorder: Selective serotonin reuptake inhibitors and tricyclic antidepressants can moderate the mood disturbance and obsessive-compulsive behaviors. Anticonvulsants are useful in mood stabilization and behavior control and may dampen dyskinetic movements. Neuroleptic medications effectively control psychotic features.
    - Sertraline (Zoloft) 25-200 mg qd
    - Amitriptyline (Elavil) 10-75 mg qd
    - Clomipramine (Anafranil) 25-250 mg qd

- Memory disorder: The efficacy of cognition-enhancing medications in HD awaits characterization.

Contraindications

- Other than known sensitivity or the experience of adverse effects, there are no specific contraindications to available treatments for HD.

Precautions

- When a family history is not readily available, diagnosis of HD often is dismissed. The implications of this diagnosis for the individual and for family members require continued diligence.

ALTERNATIVE DRUGS

- Although a source of great interest, nrit ional therapies have not been shown to provide symptomatic benefit or to alter the natural progression of HD. Intriguing results in a recent trial of coenzyme Q0 require additional study.

PATIENT MONITORING

- The frequency of follow-up is dictated by patient need. Semiannual visits provide an opportunity to address questions and obtain information on symptom progression and needed treatment modification.

EXPECTED COURSE AND PROGNOSIS

- Eventually hyperkinetic features are supplanted by increasing rigidity and akinesia. Aspiration pneumonia and other infectious complications are the ultimate cause of death. The interval separating initial symptom recognition and death varies between 15 and 20 years.

PATIENT EDUCATION

- Education is important through the many stages of HD, not only for the individual, but also for the immediate and extended family. Issues surrounding nutrition and the appropriateness of long-term management need to be regularly addressed.

Huntington's Disease

SYNONYMS

- Huntington's chorea
- Degenerative chorea
- Woody Guthrie's disease

ICD-9-CM: 333.0 Other extrapyramidal disease and abnormal movement disorders; 333.4 Huntington's chorea; 333.5 Other chorea's (i.e., hemiballism, paroxysmal chorea and rheumatic chorea); 333.9 Unspecified extrapyramidal disease and abnormal movement disorder

SEE ALSO: CHOREA

REFERENCES


Author(s): Donald S. Higgins, Jr., MD
Hydrocephalus

**Description**
- Hydrocephalus is a condition that results from an excess of CSF in the brain due to an increase in production of CSF or, more commonly, an obstruction of normal CSF flow or decreased absorption of CSF. The result of this overabundance of CSF is an increase in intracranial pressure (ICP) with corresponding enlargement of the ventricular system of the brain.

**Etiology**
- Hydrocephalus can be congenital or acquired, and communicating or obstructive (noncommunicating). Acquired hydrocephalus can occur after intracranial hemorrhage, especially intraventricular hemorrhage associated with prematurity, infection, or severe head trauma, or in association with brain tumors. In addition, normal pressure hydrocephalus (NPH) can occur in adults.

**Genetics**
- A number of genetic disorders are associated with hydrocephalus, such as X-linked hydrocephalus, cytogenetic abnormalities including trisomies 9, 13, and 18, and mendelian conditions such as Hurler syndrome, Walker-Warburg syndrome, and the craniosynostosis syndromes (Crouzon's and Apert).

**Risk Factors**
- Risk factors for hydrocephalus include prematurity (from intraventricular hemorrhage), several first-degree male relatives with congenital hydrocephalus, meningitis, intracranial hemorrhage (especially subarachnoid and intraventricular hemorrhage), and congenital brain malformations (spinal dysraphism, Chiari malformations).

**Pregnancy**
- Pregnancy is not contraindicated in women with treated hydrocephalus. Development of hydrocephalus during pregnancy is rare.

**Associated Conditions**
- Myelomeningocele (80%-90% require shunts), Chiari malformations, certain genetic disorders (see Genetics), brain tumors, intracranial hemorrhage, severe head trauma, CNS infections

**Diagnosis**

**Differential Diagnosis**
- Brain atrophy (resulting in ex vacuo hydrocephalus) secondary to brain ischemia and neurodegenerative disorders, benign intracranial hypertension, hydranencephaly, developmental anomalies (agenesis of the corpus callosum, septo-optic dysplasia).

**Signs and Symptoms**
- Headache, nausea and vomiting, decreased level of consciousness, confusion or difficulty concentrating, papilledema, abducted eyes, and upward gaze palsy, and gait changes. In young children, enlarging head circumference, a bulging and tense fontanel, splayed sutures, irritability, bradykinesia, and sunsetting eyes are commonly seen in hydrocephalus. In NPH, there is a classic triad of dementia, gait abnormalities, and urinary incontinence.

**Laboratory Procedures**
- There are no specific laboratory tests that diagnose hydrocephalus. With suspected infection, CSF should be sampled prior to placement of a CSF shunt. Placement of a CSF shunt requires CSF analysis and may provide the underlying cause of the hydrocephalus.

**Management**

**General Measures**
- Once the diagnosis is established and the need for treatment confirmed, one should proceed to the specifically indicated surgical option. In cases of acute hydrocephalus, where ICP is elevated to a life-threatening level, the usual emergency measures used to lower ICP can be done (elevate the head of the bed, administer 1 g/kg mannitol IV). These measures cannot be a substitute for prompt neurosurgical management of the underlying problem. In cases of neonatal intraventricular hemorrhage, serial LP or ventricular taps can be done until the child has grown large enough that a permanent shunt can be placed.

**Surgical Measures**
- Surgical treatment is the mainstay of therapy for hydrocephalus. Several surgical options are available, the goal of which is to bypass the regular CSF pathways.

**CSF Shunt**
- As a permanent solution to hydrocephalus, closed ventricular draining systems have been in use for >50 years. A, II CSF shunting systems consist of a proximal ventricular catheter, a one-way valve and reservoir; and a distal catheter terminat in another body compartment. The most common sites for termination of the distal catheter are (in order) the peritoneum, the pleural space, and the venous system (usually the right atrium or superior vena cava).

**Endoscopic Third Ventriculostomy**
- In selected cases of hydrocephalus, specifically aqueductal stenosis, where the forth ventricle is normal in size and the lateral and third ventricles enlarged, endoscopic third ventriculostomy (ETV) is a treatment option. In this procedure, a fiberoptic endoscope is passed into the lateral ventricle and then into the third ventricle through the foramen of Munro. A hole is made in the floor of the third ventricle, bypassing the obstruction at the aqueduct. A successful ETV will obviate the need for a permanent CSF shunt. EN is less successful in cases of hydrocephalus without aqueductal stenosis.

**Special Tests**
- In cases of suspected NPH, a number of ancillary tests to predict responsiveness of NPH to shunting are available. These include a nuclear medicine CSF flow study (using 99mTc-DPTA) and lumbar puncture (LP). A patient whose symptoms improve after withdrawal of CSF by LP may be more likely to respond to permanent CSF shunting.
External Ventricular Drainage

- In cases where placement of a permanent shunt is not feasible (e.g., infection or acute hemorrhage) or where drainage of CSF is required temporarily until CSF flow pathways are reestablished (e.g., posterior fossa tumor), placement of an external ventricular drain (EVD) can be a temporizing measure until a permanent shunt can be placed or the indication for CSF diversion is no longer present. The drain is passed into the lateral ventricle and tunneled out through the scalp, draining into an external system. Prolonged use of an EVD is associated with a high CSF infection rate.

SYMPTOMATIC TREATMENT

- The mainstay of symptomatic treatment is surgical therapy.

ADJUNCTIVE TREATMENT

- Supportive care, especially in children, involves monitoring of heart and respiratory rates. Bradycardia and periods of apnea can be ominous signs of increased ICP.

ADMISSION/DISCHARGE CRITERIA

- All patients with symptomatic hydrocephalus should be admitted for management of the condition. In asymptomatic cases where enlargement of the ventricular system is equivocal, it is reasonable to follow a patient both clinically and with serial neuroimaging studies (CT or MRI).
- Patients can be discharged within 1-3 days of surgery provided their symptoms of increased ICP have resolved and the surgeon is satisfied that the shunt is functioning properly. Many neurosurgeons obtain a CT scan of the brain before discharge to ensure that the ventricular catheter is in proper position and the ventricles reduced in size.

Medications

DRUGS OF CHOICE

- Prior to the widespread use of CSF shunts, medical treatment to limit CSF production with acetazolamide (a carbonic anhydrase inhibitor) and furosemide was used as a temporizing measure. These drugs did not provide a permanent solution for hydrocephalus and play no role in the modern management of the condition. Mannitol can be used to acutely lower ICP in an emergency situation.

ALTERNATIVE DRUGS

- No specific alternative drugs are used to treat hydrocephalus.

Patient Monitoring

- CSF shunt devices are associated with a high failure rate (40% at 1 year) and infection rate (5%-10%). As such, patients with shunt devices in situ require immediate attention should they develop symptoms of shunt failure. Symptoms of shunt failure or obstruction are similar to those of untreated hydrocephalus and include headache, nausea and vomiting, and a decreased level of consciousness. Evaluation of the patient with a suspected shunt malfunction includes a CT scan of the head and a "shuntseries" (a series of plain radiographs tracing the path of the shunt from the skull to the abdomen) in cases where shunt function is equivocal, a radionuclide shunt study can be undertaken to determine if the shunt is patent. Shunt infection can manifest as a shuntobstruction or as fever with no other identifiable source. Shunt infection can be diagnosed by sampling CSF from the shunt reservoir. When shunt malfunction or infection is suspected, immediate referral to a neurosurgeon is indicated. It is not uncommon for a shunted patient to develop subdural fluid collections, which can indicate CSF overdrainage. Many neurosurgeons monitor asymptomatic patients on an annual basis with a CT scan and shunt series.

Expected Course and Prognosis

- CSF shunting devices are associated with a high failure rate. Prior to the development of an adequate surgical treatment of hydrocephalus, the outcome was universally poor. With the use of shunts, mortality for infants with non-tumor-related hydrocephalus has dropped from 64% to 3%-10%. Seventy percent are socially independent and X10% are unemployable.

Patient Education

- Patients and families of those with treated hydrocephalus, either by a CSF shunting device or ETV, should be educated as to the signs and symptoms of shunt failure and to seek prompt medical attention should they develop. Patients with CSF shunts can pursue all regular activities.
- Hydrocephalus Association of America • Spina Bifida and Hydrocephalus Association of Canada
Hyperammonemia

**Basics**

**DESCRIPTION**
- Ammonia is present in all body fluids as ammonium ion. Excess ammonia is excreted as urea. Impaired metabolism; from various causes, leads to hyperammonemia, which can cause serious CNS toxicity. This chapter focuses on hyperammonemia due to defects in urea cycle enzymes N-acetylglutamate synthetase, carbamyl phosphate synthetase I (CPS I), ornithine transcarbamylase (OTC), argininosuccinate synthetase (citrullinemia), argininosuccinate lyase (argininosuccinic aciduria), and arginase (argininemia).

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Because the clinical presentation is nonspecific, differential diagnosis of hyperammonemia depends on laboratory studies.
- Hyperammonemia with respiratory alkalosis is caused by a urea cycle defect or transient hyperammonemia of the newborn. The presence of acidosis, ketosis, and low bicarbonate, along with hyperammonemia, suggests organic acidemia.
- Hyperammonemia, in addition to acidosis, ketosis, and increased lactate, indicates congenital lactic acidoses.
- Differential diagnosis for late-onset cases of hyperammonemia also includes liver disease and Reye syndrome. Hepatic transaminases would be elevated in both conditions, but in Reye syndrome bilirubin level would be within normal range.
- Determination of orotic acid and plasma citrulline: can help identify the enzyme deficiency. OTC deficiency is associated with elevated urinary orotic acid and trace citrulline level. Plasma citrulline level is very high in AS deficiency (>1,000 µmol/L) and moderately high (100-300 µmol/L) in AL deficiency.

**Symptoms and Signs**
- In neonates, the presentation is nonspecific. Symptoms include poor feeding, lethargy, and vomiting and can lead to coma.
- Patients with partial enzyme deficiencies have a delayed onset and may present with recurrent episodes of vomiting, lethargy, ataxia, and behavioral changes.
- Patients with argininemia present with spastic diplegia.
- Fragile hair (trichorrhexis nodosa) is seen in argininosuccinic aciduria.

**Laboratory Procedures**
- Plasma ammonia level (usually >300 µmol/L) arterial blood gas (shows respiratory alkalosis), plasma and urinary amino acid analysis, organic acid and orotic acid determination.

**Imaging Studies**
- CT or MRI of brain may show cerebral edema.

**Special Tests**
- Assay for specific enzymes on liver biopsy specimen. DNA analysis is available for OTC deficiency.

**Management**

**GENERAL MEASURES**
- Neonates should be admitted to a neonatal intensive care unit with hemodialysis facilities. Niprote in intake: Caloric intake in the form of hypertonic glucose and lipids. Monitor ammonia level. Treat any underlying infection.

**SURGICAL MEASURES**
- Liver transplantation for patients with cycle defects.
- Intravenous sodium benzoateOd phenylacetate. Hemodialysis if patient is comatose at presentation or if the avitronia level remains high after several hours of IV treatment.

**ADJUNCTIVE TREATMENTS**
- Arginine supplementation because it is an essential amino acid for parents with urea cycle defects.

**ADMISSION/DISCHARGE CRITERIA**
- Admission needed when patients present in hyperammonemic state with an altered mental status, dehydration, or not controlled by oral medications.

**Epidemiology**

**Prevalence**
- Estimated to be 1 per 30,000 live births.

**Age**
- Usually seen in neonates; however, can present in childhood.

**Sex**
- Seen in both sexes.

**Race**
- Cases have occurred in all races.

**Etiology**
- Excess ammonia causes activation of N-methyl-D-aspartate (NMDA) receptors, which then activates Na-ATPase leading to ATP depletion and ammonia toxicity. Several other metabolic changes also are involved, such as increased lactate and pyruvate, and decreased glycogen and glutamate.

**Risk Factors**
- N/A

**Pregnancy**
- N/A

**Associated Conditions**
- Urea cycle defects: include deficiencies of N-acetylglutamate synthetase, CPS I, OTC, argininosuccinic acid synthetase, argininosuccinate lyase and arginase.
- Other metabolic: organic acidemias, congenital lactic acidoses, fatty acid oxidation defects, dibasic amino acid transport defects.
- Transient hyperammonemia of the newborn.
- Reye syndrome.
- Hepatic dysfunction.

- Intravenous sodium benzoateOd phenylacetate. Hemodialysis if patient is comatose at presentation or if the avitronia level remains high after several hours of IV treatment.

- Arginine supplementation because it is an essential amino acid for parents with urea cycle defects.

- Admission needed when patients present in hyperammonemic state with an altered mental status, dehydration, or not controlled by oral medications.
**Medications**

**DRUG(S) OF CHOICE**
- Sodium benzoate, sodium phenylacetate, sodium phenylbutyrate. These drugs lower ammonia levels by conjugating with amino acids. Available in IV and oral formulation.

**Contraindications**
- Hypersensitivity

**Precautions**
- Due to high sodium content, avoid in congestive heart failure or renal insufficiency. Benzoate may worsen neonatal hyperbilirubinemia by competing with bilirubin for the binding sites on albumin.

**ALTERNATIVE DRUGS**
- N/A

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**Follow-Up**

**PATIENT MONITORING**
- Growth and development of children. Periodic levels of ammonia, arginine and glutamine.

**EXPECTED COURSE AND PROGNOSIS**
- Strict adherence to the dietary recommendations and compliance with medications should result in adequate growth and a decrease in episodes of acute hyperammonemia. Overall, there is considerable risk of mortality during acute episodes, and the majority of survivors will have significant cognitive delays.

**PATIENT EDUCATION**
- Depends on the specific disease entity

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**Miscellaneous**

**SYNONYMS**
- N/A

**ICD-9-CM:** 270.6 Hyperammonemia (congenital)

**SEE ALSO:** ENCEPHALOPATHY, HEPATIC ENCEPHALOPATHY, PROGRESSIVE PEDIATRIC

**REFERENCES**

Author(s): Kazi Imran Majeed, MD
Hypotonic Infant Syndrome

**Basics**

**DESCRIPTION**
- The term hypotonic infant refers to an infant with hypotonia or decreased muscle tone. Muscle tone is controlled by afferent muscle spindles and α- and γ-motor neurons in the spinal cord, but also is affected by upper motor neurons and corticospinal tract. Hypotonia is characterized by diminished resistance to passive movements and an excessive range of joint mobility. Hypotonic infant syndrome may be seen with severe muscle weakness, but also with only mild weakness or even without obvious weakness.

**EPIDEMIOLOGY**
- **Incidence**
  - Hypotonic infant syndrome is commonly seen in the clinical practice; however, its incidence is not known because it is seen with a large variety of diseases.
- **Race**
  - It is seen in all races.
- **Age**
  - Occurs more often in the newborn period and the first year of life.
- **Sex**
  - Both sexes are affected.

**ETIOLOGY**
- Lesions at any level of the nervous system, including upper and lower motor units, can cause hypotonia. Hypotonia combined with severe muscle weakness usually is associated with lower motor neuron disorders, including diseases affecting anterior horn cells of the spinal cord, peripheral nerves, neuromuscular junctions, and muscles. Hypotonia without obvious weakness often points to diseases of the central nervous system, connective tissue disorders, and chromosomal diseases, or those involving metabolic, endocrine, or innate problems.

**RISK FACTORS**
- N/A
- PREGNANCY
  - N/A
- ASSOCIATED CONDITIONS
  - N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Hypotonia with prominent weakness (lower motor unit disorders) spina muscular atrophy, congenital myotonic dystrophy, congenital muscular dystrophy, neonatal myasthenia gravis, congenital myasthenic syndrome, congenital myopathies, metabolic myopathies (Pompe’s disease, mitochondrial myopathy), hereditary motor and sensory neuropathies, Guillain–Barre syndrome, tic paralysis, infantile botulism
- Hypotonia with prominent weakness
  - Cerebral hypotonia: perinatal hypoxia, birth trauma, Down’s syndrome, Prader-Willi syndrome, Zellweger syndrome, Riley–Day syndrome, neonatal adrenoleukodystrophy, infantile GM gangliosidosis
- Intrauterine infections (toxoplasmosis, rubella, cytomegalovirus, herpes)
- Metabolic, endocrine, innate: hypothyroidism, organic acidosis, renal tubular acidosis, calcium abnormalities, hypothyroidism, celiac disease, malnutrition
- Connective tissue disorders: Ehlers-Danlos syndrome, Marfan syndrome
- Acute Illness
  - Benign congenital hypotonia

**SIGNS AND SYMPTOMS**
- Hypotonia with little or no weakness, normal or increased deep tendon reflexes, craniofacial dysmorphic features, Babinski sign, ankle or knee clonus, or other brain dysfunction such as language delay, mental retardation, progressive intellectual decline, seizures, aggressive behavior problems, or attention deficit hyperactivity often indicate upper motor unit diseases that affect the cerebral, cerebellum; brainstem, or spinal cord above anterior horn cells.
- In contrast, hypotonia with significantly severe muscle weakness and atrophy, decreased or absent deep tendon reflexes, and fasciculation, but without Babinski sign or clonus, frequently suggest lower motor unit diseases involving anterior horn cells, peripheral nerves, neuromuscular junction, or muscles. However, there are diseases with both upper and lower motor unit involvements, such as mitochondrial encephalomyopathy, congenital myotonic dystrophy, and metachromatic leukodystrophy.
- Medicaly treatable hypotonia refers to a condition that can be corrected with specific medical treatment. Hypothyroidism due to thyroid hormone deficiency may present with hypotonia, constipation, failure to thrive, developmental delay, jaundice, and retardation of bone growth. Left untreated, the infant with congenital hypothyroidism may develop mental retardation, and hypothyroidism may occur with hypothyroidism seizures, ataxia, alopecia, skin rash, developmental delay, sensorineural deafness, and lactic acidosis. With early treatment, the clinical features may be reversible. Neonatal myasthenia gravis may present with hypotonia, severe generalized weakness, and respiratory failure, but would be responsive to anticholinesterase treatment. Infantile botulism due to *Clostridium botulinum* toxins occurs in previously healthy infants in the first few months of life, with sudden generalized weakness, hypotonia; poor sucking and swallowing, constipation, ptosis, dilated pupils with sluggish light reflex, lethargy, and respiratory distress. With timely proper ventilatory support, complete recovery is possible; without it, the infant may suffer from respiratory arrest or even sudden death. Infantile Guillain-Barre syndrome is characterized by progressive generalized weakness and areflexia, hypotonia, and respiratory failure. It is immune induced and responsive to intravenous immunoglobulin and plasmapheresis. Tick paralysis is caused by the persistent tick bite with secretion of its toxin, leading to sudden generalized weakness and areflexia, and hypotonia in a formerly normal child. With timely removal of the tick, the child will rapidly and completely become normal.

**LABORATORY PROCEDURES**
- For lower motor unit diseases:
  - Serum creatine kinase may be increased in a variety of muscle disorders and some spinal muscular atrophy, and should be done before electromyography and nerve conduction studies.
- Blood DNA tests may detect survival motor neuron gene homozygous deletions for spinal muscular atrophy, abnormal CTG trinucleotide repeat expansion for congenital myotonic dystrophy, and mitochondrial DNA mutations of some mitochondrial encephalomyopathies such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.
- Other: stool for culture and toxoplasmosis detection, CSF for albuminocytologic dissociation in Guillain-Barre syndrome; serum acetylcholine receptor antibodies for myasthenia gravis
- For upper motor unit diseases:
  - Chromosomal studies for Down’s syndrome, Prader-Willi syndrome, and other chromosomal disorders
Hypotonic Infant Syndrome

—Serum studies: very long chain fatty acids for neonatal adrenoleukodystrophy; amino and organic acids, lactate, pyruvate, ammonia, carnitine for disorders of amino acids, organic acids, lactic acids, and urea cycle; lysosomal enzymes for lysosomal disorders; thyroid hormones for hypothyroidism; antibody titers for intrauterine infections (toxoplasmosis, rubella, cytomegalovirus, herpes)

IMAGING STUDIES
• Cranial MRI may detect intracranial ischemia or hemorrhage, increased T2 density of the white matter in the adrenoleukodystrophy or metachromatic leukodystrophy, penaventricular calcification for congenital cytomegalovirus infection, diffuse intracranial calcification in congenital toxoplasmosis, and a variety of other brain anomalies. In mitochondrial encephalomyopathy, it may reveal basal ganglia calcification, or cerebral or cerebellar atrophy. Cranial ultrasound study may be necessary at the bedside for neonatal birth asphyxia when MRI is impossible because of the intubation and respiratory support of critically sick and unstable neonates.

SPECIAL TESTS
For Lower Motor Neuron Diseases:
• Electromyography is abnormal in the muscle diseases. Motor and sensory nerve conduction velocity study is useful in the evaluation of peripheral neuropathy.
• Muscle or nerve biopsy may be indicated if there is evidence of myopathy or neuropathy and for more specific diagnosis of the muscle disorders and neuropathy. Muscles may be examined for the specific histochemical staining and special enzymes studies for Pompe's disease, mitochondria myopathy, specific congenital myopathies, muscular dystrophies, and other studies.
• Repetitive nerve stimulation with low frequency (2-3 Hz) often induces decremental response in myasthenia gravis, whereas stimulation with higher frequency (200 Hz often induces incremental response in infantile botulism.
• Electroencephalogram (Tensilon) IV infusion rapidly and dramatically improves the clinical features of myasthenia gravis, such as ptosis, extraocular ophthalmoplegia, and generalized weakness.

GUILLAIN-BARRE SYNDROME
Guillain-Barre syndrome may need plasmapheresis of intravenous immunoglobulin, or even respiratory support. Hypothyroidism requires treatment with thyroid hormone. Biotin replacement is needed for biotinidase deficiency. Tick paralysis requires removal of the tick from the skin of the patient.

SURGICAL MEASURES
• Gastrostomy tube placement and Nissen fundoplication may be required if the patients have severe feeding problems and gastroesophageal reflux. Tenotomy, and tendon transfer or lengthenignomy may be useful for the routine daily care of the patients.

SYMPTOMATIC TREATMENT
• Feeding problems may need special nipples, small and frequent feedings, gagging feedings, or even gastrostomy tube. Postural drainage, suctioning, or vigorous respiratory therapy would be necessary if hypotonia and muscle weakness impair cough reflex or pulmonary functions. Stool softener, laxatives, or dietary control may help constipation. Early infant intervention provides useful stimulation,

ADJUNCTIVE TREATMENT
• Physical, occupational, speech, and language therapy may be helpful when poor fine motor coordination, muscle weakness, and language delay are present.

ADMISSION/DISCHARGE CRITERIA
• Patients may need admission for acute evaluation and treatment of severe weakness associated with hypotonia, such as spinal muscular atrophy, congenital muscular dystrophy, neonatal myasthenia gravis, mitochondria (encephalomyopathy), and infantile botulism. They frequently also require long-term opioid rehabilitation or follow-up.

MEDICATIONS

DRUG(S) OF CHOICE
• Intravenous immunoglobulin is easier for infants with Guillain-Barre syndrome. Intramuscular neostigmine given 30 minutes before feeding is useful in neonatal myasthenia gravis. Biotin is indicated for biotinidase deficiency. Thyroid hormone replacement is necessary for hypothyroidism.

CONTRAINDICATIONS
• For intravenous immunoglobulin, congenital IgA deficiency, if complete, is a relative contraindication because these patients may develop antibodies to IgA that can result in anaphylactic-like reaction.

MANAGEMENT
SPECIFIC TREATMENT depends on the underlying cause of hypotonia. For example, myasthenia gravis patients will require anticholinesterase such as pyridostigmine neostigmine.

PRECAUTIONS
N/A

ALTERNATIVE DRUGS
• Plasma exchange may be useful if intravenous immunoglobulin fails to improve Guillain-Barre syndrome. Pyridostigmine or prednisone may be alternative drugs for myasthenia gravis.

PATIENT MONITORING
• Patients should be followed regularly after the underlying cause of hypotonia is identified. Patients with hypotonia may have progressive joint contractures or scoliosis and need proper treatment, such as physical therapy or braces. Other problems, such as seizures, may develop and require antiepileptic drug treatment.

EXPECTED COURSE AND PROGNOSIS
• The clinical course and prognosis depend on the underlying diseases of hypotonia.

PATIENT EDUCATION
• Many organizations associated with individual diseases exist to help support patients and their families and research to bring best treatments to the patients.

MISCELLANEOUS

SYNONYMS
• Floppy baby syndrome
ICD-CM: 781.9 Floppy infant; 781.3 Hypotonia
SEE ALSO: N/A

REFERENCES

Author(s): Chang-Yong Tsao, MD
### Immunizations Neurologic Complications

#### Basics

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
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<tr>
<td>Central and peripheral nervous system injuries occur in temporal relationship to immunization in a small number of patients. Nervous system vaccine-related injuries include acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), cerebellar ataxia, autism, encephalopathy/encephalitis, seizure disorder, deafness, mononeuropathy/multinerve myelopathy, brachial plexopathy, and Guillain-Barré syndrome (GBS). Virtually every vaccine has been reported to be associated with some form of nervous system injury. Although a causal role for vaccination is implied, such an association is rarely established.</td>
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<tr>
<th>EPIDEMIOLOGY</th>
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<tr>
<td><strong>Incidence</strong></td>
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<tr>
<td>The incidence of vaccine-related neurologic injuries is unknown and varies with the type of injury. The encephalopathy associated with diphtheria, pertussis, tetanus (DPT) immunization is reported to be 5 per 100,000 vaccinations in children &lt;age 2, and death related to vaccination in the same age group is reported to be 0 in &gt;29 million immunizations. Epidemiologic studies with prospective case-control designs have been most helpful in establishing or rejecting causality of vaccination to adverse events. In most of these studies, the overwhelming safety of vaccination has become apparent.</td>
</tr>
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</table>

| **Age** |
| Although generally a disorder of childhood, serious adverse events after vaccination have been reported in adults. |

| **Sex** |
| A preponderance in one gender has not been reported. |

| ETIOLOGY |
| Injury is considered to be due to the active components of the vaccine or neurotoxicity of adjuvants, preservatives, or contaminants. Generally, the basis of injury is considered to be due to autoimmun "anti-"genic mimicry” in which the viral/bacterial protein immunogen shares homology with nervous system proteins, usually myelin. In rare instances when the vaccine is inactivated and nonviralcutant, live virus/organisms, injury to the nervous system can result from reactivation of the pathogen as with oral polio virus vaccines. |

#### Risk Factors
- Congenital or acquired immuno deficiency states (various congenital immunodeficiency syndromes, cancer chemotherapy using cytotoxic drugs, pregnancy, chronic steroid therapy, HIV infection) can be associated with risk of injury to the nervous system. Most of these states are relative rather than absolute contraindications.

#### Pregnancy
- Vaccinations are generally avoided during pregnancy because adverse reaction may occur. Pregnancy is a state of relative immune suppression during which otherwise benign viral infections can become fulminant. Live viral vaccines should be avoided because their virulence during pregnancy can be indeterminant. Live vaccines, such as rubella, can be associated with teratogenic effects in the fetu.

#### Associated Conditions
- N/A

#### Diagnosis

<table>
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<tr>
<th>DIFFERENTIAL DIAGNOSIS</th>
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<tr>
<td>Includes acute infectious encephalitis, spongiform encephalopathies, metabolic encephalopathies, neoplastic and paraneoplastic disorders</td>
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<tr>
<th>SIGNS AND SYMPTOMS</th>
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<tr>
<td>The interval from vaccination to injury can range from minutes (anaphylaxis) to 2-3 weeks (ADEM). The more remote the onset, the less likely the symptoms are related to the immunization. Disorders that manifest &gt;6 weeks after immunizations are unlikely to be due to the vaccine, unless the early events after vaccination were clinically silent as is sometimes the case in demyelinating disorders. ADEM typically occurs within days or weeks after immunization. In its most fulminant form, alteration of consciousness can occur, leading to coma. Multifocal ocal neurologic deficits are the rule, and multifocal abnormalities can be seen on MRI studies of the brain and spinal cord. Pathologic evaluation identifies inflammatory lesions in a perivascular distribution in association with primary demyelination. Patients can develop clinical manifestations of meningoencephalitis, optic neuritis, focal solitary lesions that mimic neoplasms, and single or multifocal Level myelopathy.</td>
</tr>
</tbody>
</table>

#### Laboratory Procedures
- CSF studies: Spinal fluid studies are extremely helpful in diagnosis of ADEM. During the acute phase, CSF most often is normal for protein, cell count, and cultures. In fulminant cases, intracranial hypertension can be reflected in abnormally elevated opening pressures. A modest pleocytosis (50-100 cells) and mild elevation of proteins (always <100 mg/dL) may also be present. In children, predominantly lymphocytic pleocytosis is common, but a polymorphonuclear response can occur in the acute phase as well. In acute fulminant cases with hemorrhagic inflammation, RBCs can be present in the CSF with xanthochromia as well. Although inflammation is the hallmark of ADEM, evidence of intrathecal IgG synthesis usually is not observed, and oligoclonal G bands are distinctly absent. This feature often is helpful in distinguishing ADEM from MS. |
- CSF studies also are helpful in the diagnosis of GBS. The typical aluminocytologic dissociation (elevated protein without elevation of the cell count) can be useful for diagnosis. |

#### Imaging Studies
- MRI is the imaging modality of choice. If there are no lesions noted on MRI at the onset of suspected ADEM, imaging should be repeated in 3 weeks. If the MRI is consistently normal at 3 weeks or later, the diagnosis of ADEM should be questioned. Administration of gadolinium is useful in defining acute lesions. The lesions of ADEM can mimic the lesions of MS with a periventricular distribution, including corpus callosum lesions. Although complete resolution can occur clinically, demyelinated lesions can persist for life and result in subsequent confusion regarding diagnosis of MS. CT scan is helpful only if edema or herniation is present. |

#### SPECIAL TESTS
- Immunologic studies: Although generally not the standard of care, patients who experience an adverse event following vaccination should undergo testing for congenital or acquired immune deficiency, including immunoglobulin and complement levels, and T- and B-cell (including CD4 and CD8 subsets) quantitation. Delayed-type hypersensitivity should be examined, with skin tests for common antigens. Preferably, all of these studies should be performed prior to the use of corticosteroids or immunosuppressive agents. |
- There is good evidence that patients who develop ADEM have circulating lymphocytes sensitized to myelin basic protein and other myelin proteins.
**Admission/Discharge Criteria**

- Constitutional symptoms of headache, fever, malaise, and irritability are common in both children and adults with ADEM and should be managed using simple analgesics and antipyretics. Sleep disturbances may occur, particularly in children. Extreme irritability ("inconsolable crying of children"), well known to occur in encephalopathy following DPT, may require the use of sedatives. In general, however, narcotics and sedatives should be minimized because they can cloud assessment of mental status.

**Surgical Measures**

- In cases where solitary lesions are present and occur in encephalopathy following DPT, may require the use of sedatives. In general, however, narcotics and sedatives should be minimized because they can cloud assessment of mental status.

**Symptomatic Treatment**

- As above. Additionally, patients who develop GBS may require ventilator support during the acute phase of their illness.

**Adjunctive Treatment**

- Extensive rehabilitation with physical, occupational, and speech therapy may be necessary in patients with severe ADEM, GBS, brachial plexopathy, or severe mononeuritis multiplex.

**Admission/Discharge Criteria**

- There are no established criteria for admission or discharge; judgment should be used on an individual basis.

**Management**

**DRUG(S) OF CHOICE**

- Corticosteroids are the mainstay of treatment of ADEM. In particular severe cases with considerable edema can improve following steroid therapy. Pulse methylprednisolone, 1gm IV every day or every other day for 5-7 total dose is the standard treatment. Considerable improvement can occur in the following 2-4 weeks. Alternate therapies are best considered after a minimum of 3 weeks. In severe cases, where the response is suboptimal at the end of 2 weeks, consideration should be given for plasma exchange because there is good evidence that antibodies mediate the fulminant injury through activation of complement. Plasma exchange is carried out at exchange volumes of 10% body weight every other day for a total of seven treatments. Oral steroid taper is not necessary except in a few steroid responsive but steroid-dependent patients.

**Contraindications**

- N/A

**Precautions**

- Steroids should be administered with caution in patients with hypertension, diabetes, and peptic ulcer disease. Although rare, use of high-dose steroids can be associated with aseptic necrosis of the femur. Psychosis may occur in some patients during administration. In the few patients requiring long-term oral steroids, prophylaxis with trimethoprim/sulfamethoxazole is indicated for prevention of pneumonia secondary to Pneumocystis carinii.

**Alternative Drugs**

- Nontreatment is an acceptable alternative in any patient, especially patients with intolerance to steroids.

**Follow-Up**

**Patient Monitoring**

- Following recovery, long-term recurrences are rare. During steroid therapy, especially long-term oral steroid therapy, patients should be monitored regularly for steroid-related complications, including hypertension, glucose intolerance, infections, bone demineralization, GI discomfort, and weight gain.

**Expected Course and Prognosis**

- Majority of patients make an uneventful recovery; most show complete recovery by 3 months. In the few patients who experience fulminant disease, mortality or severe morbidity can occur. The incidence of such events is unknown.

**Patient Education**

- The Vaccine Adverse Event Reporting System (VAERS) is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a postmarketing safety surveillance program that collects information on adverse events (possible side effects) occurring after the administration of US licensed vaccines. The VAERS website also provides a vehicle for disseminating vaccine safety-related information. Website: www.vaers.org

**Miscellaneous**

- Postinfectious encephalomyelitis
- Postimmunization encephalomyelitis
- ICD-9-CM: 999.9 Complications, vaccination; 323.5 Encephalitis, encephalomyelitis, or myelitis

**See Also:** Multiple Sclerosis; Transverse Myelitis

**References**

- Author(s): Kottil W, Rammohan, MD

237
Inclusion Body Myositis

**Basics**

**DESCRIPTION**

- Sporadic inclusion body myositis (s-IBM) is an acquired idiopathic inflammatory myopathy of insidious onset. It often is characterized by a specific pattern of proximal and distal weakness demonstrating early involvement of forearm flexors and quadriceps muscles. Clinical history, laboratory studies, EMG, and muscle biopsy are used to diagnosis and distinguish s-IBM from polymyositis or dermatomyositis.

- Hereditary inclusion body myopathies (h-IBM) include a spectrum of hereditary myopathies, often within various ethnic groups, characterized by vacuolated myofibers containing filamentous inclusion, without inflammation. h-IBM may be autosomal dominant (limb-girdle distribution) or autosomal recessive (quadriiceps sparing) and have many of the histochemical and ultrastructural changes seen in s-IBM.

**EPIDEMIOLOGY**

**Incidence**

- Less than 1 per 100,000 population. s-IBM may account for 15%-28% of all idiopathic inflammatory myopathies. It is considered the most common myopathy in persons >50 years of age.

- h-IBM is much rarer than s-IBM in general, although among Iranian Jews the prevalence is estimated at approximately 1 per 1,500.

**Age**

- s-IBM typically affects persons >50 years of age, although some may be as young as 30 years. h-IBM symptoms begin in the second or third decade.

**Race**

- s-IBM: No data are available; most case reports have been of Caucasians.

- h-IBM: Most reports include isolated pedigrees within ethnic groups (Iranian Jews, Japanese, and Tunisian kindreds) although one family from India and another Caucasian family from the United States have been reported.

**Sex**

- s-IBM: Male-to-female ratio is 3:1. h-IBM: Males and females are affected equally.

**ETIOLOGY**

- Unknown for both s-IBM and h-IBM. The presence of amyloid deposits within the myofibers of muscle biopsy specimens suggests a degenerative process. Endomyositis inflammation in s-IBM, primarily CD8+ T cells, invades non-necrotic myofibers, but it is unclear whether cellular inflammation is primary or secondary. Additional biopsy findings of ragged red fibers and cytochrome oxidase (COX) negative fibers have suggested abnormal mitochondria. Mitochondrial DNA deletions have been detected in approximately 50% of 30 s-IBM patients studied. It is unclear whether these abnormalities are of pathogenic significance or are a secondary phenomenon.

**Genetics**

- s-IBM is associated with HLA-DR3, HLA-DR52 and HLA-B8 or HLA-DR3, HLA-DR52, and HLA-DQ2 and specifically (up to 77%) with DR1*0301, DR1*0101 (or DR3*0202), and DQ1*0201 alleles, suggesting an immunogenetic background. Human leukocyte antigen (HLA) testing currently is of no clinical utility.

- s*IBM has been seen among siblings of families and is thought to be related to genetic factors relating to the major histocompatibility complex (HLA system).

- Both autosomal dominant and autosomal recessive syndromes have been seen among h-IBM. The autosomal recessive forms seen among Iranian Jews and in Japanese distal myopathy both have been linked to the same locus on chromosome 9p1-1q.

**RISK FACTORS**

- Other than a possible HLA association, no known risks have been documented in s-IBM. h-IBM is often associated with consanguinity.

**PREGNANCY**

- No increased risk or associations

**ASSOCIATED CONDITIONS**

- Other immune-mediated conditions (e.g., Sogren's syndrome, rheumatoid arthritis) occur in approximately 10% of s-IBM cases. Nonspecific antibodies, such as positive ANA, rheumatoid factor, and SS-A, may be present in 40% of s-IBM cases and do not preclude the diagnosis of s-IBM.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

**Distal Myopathies**

- Welander distal myopathy

- Markesbery distal myopathy

- Nonaka distal myopathy

- Finnish distal muscular dystrophy

**Disorders with Rimmed Vacuoles**

- Desmin storage myopathy

- Acid maltase deficiency

- Lysoosomal storage disease with normal acid maltase

- McArdle syndrome

- Facioscapulohumeral dystrophy

- Oculopharyngeal muscular dystrophy

- Polymyositis

- Amyotrophic lateral sclerosis (ALS)

**SIGNS AND SYMPTOMS**

- s-IBM: Weakness >6 months, with selective involvement of biceps, triceps, subscapularis, shoulder adductors, and distal muscles of lower extremities. Amyotrophy may also involve these muscles. Pattern of involvement is quite variable from case to case.

- h-IBM: The hereditary inclusion body myopathies are a spectrum of myopathies whose classification is likely to undergo further revision with time. The two main patterns are an autosomal recessive diffuse weakness with quadriiceps sparing and an autosomal dominant limb-girdle weakness with characteristic histologic features on muscle biopsy.

**LABORATORY PROCEDURES**

- Creatine kinase (CK) may be normal or elevated to 10-12 times normal

**IMAGING STUDIES**

- MRI or CT demonstrate selective amyotrophy of particular muscle groups but is not necessary for diagnosis.

**SPECIAL TESTS**

- EMG: Sensory nerve and compound muscle action potentials usually are normal

- Needle EMG examination may reveal frequent fibrillation potentials and positive sharp waves, and low-amplitude, short-duration motor unit action potentials (MUAPs) or a mixed pattern of both low-amplitude, short-duration and high-amplitude, long-duration MUAPs (chronic myopathic changes).

**Muscle Biopsy**

**Requirements**

- Biopsy of involved but not end-stage muscle

- Use of frozen tissue; paraffin-embedded muscle fails to show the characteristic rimmed vacuoles within the myofibers

- Avoid biopsy of a muscle recently examined by EMG

**Features of s-IBM**

- Vacuolated myofibers (red-rimmed vacuoles on trichrome stain), central or subsarcolemmal 2- to 25-µm diameter, prominent in type I fibers, or evenly distributed between type I and II fibers

- Sparse-to-prominent endomyositis inflammation and invasion of non-necrotic myofibers by cytotoxic (CD8+) T cells
Inclusion Body Myositis

**Management**

**GENERAL MEASURES**
- Assistive devices (cane, walker) to prevent falls
- Occupational therapy to prevent contractures of the finger flexors

**SURGICAL MEASURES**
- Cricopharyngeal myotomy has been reported to relieve dysphagia in s-IBM if pharmacologic interventions fail.

**SYMPTOMATIC TREATMENT**

**N/A**

**ADJUNCTIVE TREATMENT**

**N/A**

**ADMISSION/DISCHARGE CRITERIA**
- These myopathies usually are assessed on an outpatient basis, although at end stage, morbidity associated with aspiration pneumonia or falls may necessitate inpatient admission.

**Medications**

**DRUG(S) OF CHOICE**
- Currently, no medications have been shown to be consistently effective for treatment of s-IBM. Several can be tried. Corticosteroids 1-2 mg/kg occasionally stabilize weakness or temporarily prevent progression (in approximately 10% of patients) A 3- to 6-month prednisone trial may be considered and tapered or discontinued if there is no benefit. A previous diagnosis of polymyositis refractory to corticosteroids should lead one to consider reevaluation for possible s-IBM.

**Contraindications**
- Corticosteroids are contraindicated in patients with known hypersensitivity.

**Follow-Up**

**PATIENT MONITORING**
- Patient strength may be monitored at intervals of 6-12 months, with symptomatic treatment for dysphagia or falls as needed.

**EXPECTED COURSE AND PROGNOSIS**
- In the absence of definitive treatment, weakness progresses slowly and insidiously. There is an increased risk for aspiration pneumonia with dysphagia.

**Patient Education**
- Patients are told to expect slow and relentless progression of weakness. There is no evidence that a particular diet or dietary supplement is of benefit. Activity is encouraged as tolerated.

**Synonyms**
- IBM, s-IBM, h-IBM
- Familial IBM, f-IBM

**ICD-9-CM:** 359.8 Inflammatory myopathy for s-IBM; 359.1 Hereditary progressive muscular dystrophy for h-IBM

**See Also:** N/A

**References**

**Author(s):** Boyd M. Koffman, MD, PhD
Incontinence, Neurogenic

**Basics**

**Description**

- Normal bladder function requires the coordinated action of the bladder muscle (detrusor, smooth muscle), internal sphincter (bladder neck, smooth muscle), and external (striated muscle) sphincter. Normal function includes the ability to store urine with limited increase in intraluminal pressure, to initiate voiding voluntarily and to empty the bladder completely. Neural bladder function control occurs primarily in the sacral spinal cord, as well as the pons, diencephalon, and cerebral cortex. Parasympathetic innervation promotes detrusor contraction and sphincter relaxation, whereas sympathetic stimulation results in detrusor relaxation and sphincter contraction.

- Neurogenic urinary incontinence is a symptom resulting from damage to the nerves involved in bladder relaxation or bladder contraction and the coordination of the bladder neck mechanism.

- Common bladder problems associated with neurologic disorders include inability to store (detrusor hyperreflexia), inability to empty (hypotonic bladder/detrusor areflexia) with or without overflow incontinence, or a combination of the two (detrusor sphincter dyssynergia [DSD]).

**Epidemiology**

- Common occurrence as a result of damage to the integrity of the control mechanisms of the bladder in the central nervous system or to the peripheral nervous system.

- Affects all ages, both genders, and people of all social and economic levels.

- At least 1.5 million individuals have neuropathic bladder.

**Etiology**

- Neurologic diseases result in damage to the innervation of the lower urinary tract. If innervation of the lower urinary tract is damaged, it can affect the detrusor, urethra, and sphincter. Often the lesion is combined. Neurologic deficit can occur abruptly or more slowly over time.

- Lesions above the sacral micturition center typically result in loss of inhibition from higher centers, causing detrusor hyperreflexia, with or without sphincter hypertonia and DSO. Lesions at or below the sacral center will result in detrusor areflexia.

**Risk Factors**

- Risk factors are associated with specific conditions known to cause neurogenic bladder.

- Surgery

- Diabetes

**Pregnancy**

- History of multiple pregnancies or obstetric trauma can lead to bladder dysfunction.

**Associated Conditions**

- Neurotrauma, brain tumor, meningitis-encephalitis, multiple sclerosis, Parkinson's disease, spinal cord injury, spinocerebellar degeneration, diabetes, stroke

**Diagnosis**

**Differential Diagnosis**

- Unitary tract infection
- Stress incontinence
- Bladder prolapse
- Constipation
- Enlarged prostate
- Surgical complications

**Signs and Symptoms**

- Neurogenic incontinence presents at any time during the course of an illness. Initial symptoms are urinary urgency, frequency, hesitancy, nocturia, and then leakage of urine.

- Feeling of incomplete emptying, double voiding, nocturia, or a combination symptoms may be indicative of retention or DSD.

**Laboratory Procedures**

- Urinalysis/culture and sensitivity test to rule out bladder infection
- Measurement of postvoid residual (bladder ultrasound/intermittent catheterization)
- Urodynamic testing
- Cystoscopy

**Imaging Studies**

- Ultrasound to identify the integrity of the organs (kidney, bladder, prostate)
- MR scan
- Intravenous pyelogram

**Symptomatic Treatment**

- Quick access to bathroom
- Absorbent products and devices
- Timed voidings
- External catheters
- Intermittent catheterization
- Indwelling urethral catheter

**Surgical Measures**

- Suprapubic catheter
- Urinary diversion
- Bladder augmentation
- Botulinum toxin injections (detrusor or sphincter)

**Adjunctive Treatment**

- Behavioral therapy/biofeedback to teach special exercises to help strengthen the pelvic floor muscle
- Physical therapy for mobility aids and equipment
- Occupational therapy for assistance with upper extremity function and manageable clothing and equipment (commode chair)

**Admission/Discharge Criteria**

- N/A

**Management**

**General Measures**

- Treatment requires identification of the underlying bladder dysfunction.

- Encouraging patients to keep a voiding diary can help identify symptoms.

- Adequate daily fluid intake (48-64 oz/day) is encouraged.

- Avoid caffeinated beverages, aspartame, and alcohol, which are bladder irritants.

- Treat constipation.

**Surgical Measures**

- Suprapubic catheter
- Urinary diversion
- Bladder augmentation
- Botulinum toxin injections (detrusor or sphincter)

**Symptomatic Treatment**

- Quick access to bathroom
- Absorbent products and devices
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- Physical therapy for mobility aids and equipment
- Occupational therapy for assistance with upper extremity function and manageable clothing and equipment (commode chair)

**Admission/Discharge Criteria**

- N/A
Incontinence Neurogenic

**DRUG(S) OF CHOICE**

- Anticholinergic and antimuscarinic agents (oxybutynin and tolterodine)
  - Oxybutynin: 5-10 mg po bid-qid if cost is an issue
  - Ditropan XL: begin at 5 mg po qd and increase as needed to 30 mg/day
  - Detrol LA: 2 mg/day and increase as needed to 4 mg bid
- DDAVP (desmopressin)
  - This synthetic antidiuretic hormone is useful in treating enuresis
  - Nasal spray (one puff per nostril qhs) or tablets 0.4-0.2 mg qhs
  - Caution required when prescribing DDAVP for patients >65. Additional concern about lower extremity edema.
- α-Blockers to relax sphincter
  - Terazosin (Hytrin): 1 mg qhs and increase as needed to 10 mg/day (reevaluate if no response after 6 weeks)
  - Quinazoline (Cardura): 1 mg qd, may double dose every 1-2 weeks to maximum 8 mg/day
  - Tamsulosin HCl (Flomax): initially 0.4 mg/day, then increase to 0.8 mg after 2-4 weeks

**Contraindications**

- Anticholinergics and antimuscarinics should be avoided if there is suspicion of inability to empty.
- DDAVP should be used with caution in the elderly and in patients with lower extremity edema.

**Precautions**

- Risk of hypotension with anticholinergts and α-blockers

**ALTERNATIVE DRUGS**

- Herbal remedies
- Cranberry juice or tablets

**PATIENT MONITORING**

- Patients are followed to monitor efficacy of intervention and overall symptom management.

**EXPECTED COURSE AND PROGNOSIS**

- Incontinence is relatively common and the clinical course may vary.
- There is risk of damage to the upper urinary tract, particularly in SCI.
- Worsening of neurologic symptoms with urinary tract infection usually is reversible after infection is treated.

**PATIENT EDUCATION**

- Support groups include disease-specific societies (e.g., MS Society, Parkinson's Support Group)
- National Association For Continence (NAFC)
  - P.O. Box 8310 Spartanburg, SC 29305-8310.
  - Toll-free: 800-BLADDER, phone: 864-579-7900, fax: 864-579-7902, e-mail: memberservices@nafc.org, website: www.nafc.org
- National Bladder Foundation, P.O. Box 1095, Ridgefield CT, 06877. Phone 203-431-0005, website: www.bladder.org
- Simon Foundation for Continence, Box 835-F, Wilmette, IL 60091. Phone: 800-23SIMON, website: www.simonfoundation.org

**SYNONYMS**

- Involuntary bladder
- Voiding dysfunction

**ICD-9-CM:** 596.54 Neurogenic bladder; 596.8 Bladder disorder, NEC; 596.9 Bladder disorder, NOS; 788.3 Incontinence (urinary incontinence); 788.43 Nocturia; 788.9 Bladder (urinary symptoms, NEC)

**SEE ALSO: NA**

**REFERENCES**


**Author(s):** Marie A. Namey, RN, MSN; Francois Bethoux, MD
Increased Intracranial Pressure

**Basics**

**DESCRIPTION**

- Increased intracranial pressure (ICP) is a result of the loss of the ability of the intracranial cavity to accommodate any further changes in the volume of its contents; with a subsequent rise in pressure within the skull. The increased ICP leads to a number of neurologic changes and may result in permanent neurologic injury or death. It is defined as a pressure >20 mm Hg when monitoring ICP.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

- Varies significantly depending upon the etiology. Tumors, trauma, infections, and other causes all may impact the incidence and prevalence of increased ICP.

**Race**

- No predilection

**Age**

- No predilection

**Sex**

- No predilection

**ETIOLOGY**

- The Monro-Kellie doctrine states that the skull is a rigid structure containing three compliant elements: blood, brain, and the spinal fluid. These elements are compressible, and the sum of the pressures of each element contributes to the total ICP. With lesions affecting the brain parenchyma, producing cerebral edema, or other lesions compressing the brain tissue, blood and spinal fluid are forced out of the intracranial cavity. Once the compliance limit has been reached, usually around an ICP of 20 mm Hg, no more fluid is able to be forced out of the skull and the brain tissue begins to become displaced. After this point, any small changes in the volume of the lesion produce significant increases in ICP. Etiologies include:
  - Obstruction of CSF pathways
    - Mass lesions, e.g., neoplasms, hematoma
    - Hemorrhages, e.g., subarachnoid hemorrhage, epidural, subdural, intraparenchymal
    - Venous obstruction, e.g., sagittal sinus thrombosis
  - Ischemic strokes
  - Brain injury
  - Infections, e.g., encephalitis, meningitis
  - Generalized seizures and status epilepticus
  - Hepatic encephalopathy
  - Malignant hypertension
  - Idiopathic, e.g., pseudotumor cerebri
  - Eclampsia

**RISK FACTORS**

N/A

**PREGNANCY**

- ICP is managed according to management principles outlined below, and the pregnancy is managed according to obstetric principles. Eclamptic states can lead to increased ICP.

**ASSOCIATED CONDITIONS**

N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Increased ICP is a sign of other pathology and does not have differential diagnosis in itself. The inciting etiology will require diagnosis. These etiologies have been:
  - Headache: common, may be positional, often worse after a period of recumbency. Tends to be generalized and nonfocal.
  - Nausea/vomiting: described as "projectile," but this is not reliable. Any persistent vomiting, particularly when headache is present, should prompt a neurologic examination.
  - Papilledema
  - Blurry vision
  - Ataxia
  - Cranial nerve palsies, particularly cranial nerves VI and III, with lateral rectus weakness and pupillary dilation
  - Diminished level of consciousness, coma
  - Hemiparesis
  - Cushing's triad: hypertension, bradycardia, and respiratory irregularity. A late finding, when a patient is in extremis. Classic triad seen only a third of the time, but any two of the findings should provoke concern for increased ICP.
  - Decerebrate/decorticate posturing

**SIGNS AND SYMPTOMS**

- Headache: common, may be positional, often worse after a period of recumbency. Tends to be generalized and nonfocal.
- Nausea/vomiting: described as "projectile," but this may not be reliable. Persistent vomiting, particularly when headache is present, should prompt a neurologic examination.
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**LABORATORY PROCEDURES**

- No specific blood work is indicated.
- If any neurosurgical intervention is required or pathology that may require rapid correction of coagulation parameters (such as intracranial hemorrhage) is present, blood should be drawn for a stat platelet count, PT, INR, and PTT, as well as a type and screen or type and cross
- Metabolic screen in cases of suspected metabolic disease.

**IMAGING STUDIES**

- CT scan
  - Method of choice
  - Performed on an urgent basis
  - Helps rule out surgically decompressible lesions
  - Provides information on the degree and location of cerebral edema, hemorrhage, ventricular size, and any bony abnormalities
  - ICP can only roughly be correlated to CT findings
- MRI
  - Little clinical value in the acute setting
  - Better definition of intraparenchymal lesions
- Angiography
  - Supplements above imaging studies
  - Useful in evaluating vasculitis, aneurysms, arteriovenous malformations, and other elderly vascular causes that may be contributing to increased ICP
- Skull films
  - Not useful

**SPECIAL TESTS**

- Lumbar puncture is contraindicated in cases of suspected increased ICP. The procedure can lead to cerebral herniation and death in a matter of seconds.
- Lumbar puncture may be performed once a CT scan has been obtained and no evidence impending brain herniation is present.
- Funduscopic examination to evaluate for papilledema.

**Management**

**GENERAL MEASURES**

- Remembering the Monro-Kellie doctrine assists greatly in medically managing increased ICP, because changing the pressure of any of the three components will decrease the overall ICP. Although the brain contributes 80% of the intracranial volume, the parenchyma is one of the least easily manipulated contributors to ICP. The vascular component, only 10% of the intracranial volume, contributes a significant portion of the ICP that can be manipulated, because regulation of the cerebral vasculature can be easily altered via clinical means.
- To diminish intracranial vascular congestion:
  - Straighten the head
  - Slightly elevate the head to 30 degrees
  - Avoid jugular vein compression, e.g.,' cervical collars, endotracheal tube tape
  - Reduce positive end-expiratory pressure if the patient is on a ventilator
- To diminish the overall volume of blood and hence extravascular fluid:
Increased Intracranial Pressure

**ADMISSION/DISCHARGE CRITERIA**

- Any patient with increased ICP should be admitted to the hospital for diagnostic procedures, acute intervention, and continuous neurologic assessment.

**ADJUNCTIVE TREATMENT**

- Pain/ agitation relief with narcotics, sedatives
- Seizure treatment
- Nausea/vomiting

**SYMPTOMATIC TREATMENT**

- Consult neurosurgery early in all cases of increased ICP
- Placement of ICP monitoring devices
- Nephrocalcinosis that placement of ICP monitor changes outcome, but only helps to titrate therapy of increased ICP
- Ventriculostomy for spinal fluid drainage
- Removal of mass lesions, and necrotic or damaged brain tissue

**SURGICAL MEASURES**

- To medically diminish the contribution of cerebral parenchymal pressure to ICP:
  - Maintain normothermia
  - Increases of 1°C increases cerebral metabolic rate and, therefore, ICP by 5%-7%
  - Maintain normal oxygenation
  - Hypoxia worsens clinical outcome
- Barbiturate coma
  - Antiepileptic medications when required
  - Seizures increase all cerebral metabolic parameters and adversely effect patient outcome

**EXPECTED COURSE AND PROGNOSIS**

- Signs of increased ICP that forebode a grave prognosis include:
  - Progressive increase in ICP despite aggressive medical management
  - Signs of hypothalamic dysfunction, especially diabetes insipidus
  - Progressive instability of blood pressure despite treatment and elimination of causes
  - Worsening or lack of recovery of neurologic function despite aggressive treatment

**PATIENT EDUCATION**

**REFERENCES**


Author(s): Scott W. Elton, MD

**DRUGS OF CHOICE**

- Mannitol 1 g/kg IV bolus, followed by 0.25-0.5 g/kg IV every 6 hours or more often as needed. Wean as clinical condition improves.
- Pentobarbital 5-10 mg/kg IV bolus, followed by 1-2 mg/kg/hour IV, titrated to burst suppression on continuous EEG
- Dexmethasone 6-10 mg IV, only indicated with increased ICP due to neoplasms and encephalitis states; wean according to improvement in patient status — Contraindications: diabetes, significant preexisting infection

**ALTERNATIVE DRUGS**

**PATIENT MONITORING**

- Patients should be monitored closely with frequent vital signs and neurologic examinations by trained personnel.
- Arterial line, central venous catheter, and Swan-Ganz catheter where required.
- ICP monitor when indicated by neurosurgery.

**SYMPTOMS**

- Signs of increased ICP due to neoplasms and encephalitis states; wean according to improvement in patient status
- Loss of the basal cisterns
- Progressive cerebral edema despite aggressive medical and surgical management

**ICD-9-CM:**

- 331.4 Obstructive hydrocephalus
- 348.2 Benign intracranial hypertension (pseudotumor cerebri)
- 348.4 Compression of brain

**SEE ALSO:** N/A
Lambert-Eaton Myasthenic Syndrome

Description

- Lambert-Eaton syndrome (LES; myasthenic syndrome) is an autoimmune disease that results in a defect of neuromuscular transmission. Patients present with symptoms of weakness and autonomic dysfunction.

Epidemiology

- Incidence/Prevalence
  - Formal epidemiologic studies have not been performed, but LES is a rare neuromuscular disease and is much less common than myasthenia gravis. Although about two-thirds of cases have an associated neoplasm (small cell lung carcinoma makes up 90% of these), only 1%-3% of patients with small cell lung carcinoma have LES.

- Race
  - No study has demonstrated any ethnic predominance.

- Age
  - LES is primarily a disease that occurs in older individuals. This is especially true for paraneoplastic cases. Cases of LES occurring before age 50 years are less likely to be associated with a tumor. There are case reports of children with LES.

- Sex
  - Males outnumber females by a 2:1 margin.

Etiology

- Paraneoplastic LES represents an autoimmune response against the presynaptic terminal of the neuromuscular junction. Antigenic similarity between the tumor (most often small cell lung carcinoma) and the presynaptic terminal results in antibody formation against the presynaptic voltage-gated calcium channels, which are responsible for the release of acetylcholine. The presynaptic terminal reduction in acetylcholine release produces the clinical symptoms. Decreased acetylcholine stimulation of nicotinic receptors on muscle results in weakness. Whereas diminished stimulation of muscarinic receptors produces the autonomic symptoms. Cases not associated with a neoplasm (non-paraneoplastic) are less common but also due to autoimmune dysfunction.

Risk Factors

- Smoking, small cell lung carcinoma, and age are the major risk factors. Other lung cancers, lymphoma, prostate cancer, cervical cancer, and thymomas are much less commonly associated with LES.

Pregnancy

- NA

Associated Conditions

- Cancer-related LES may have other paraneoplastic syndromes, including encephalomyelitis and cerebellar degeneration. Other autoimmune diseases are associated with LES, such as systemic lupus erythematosus, pernicious anemia, thyroid disease, and myasthenia gravis.

Diagnosis

Differential Diagnosis

- Myasthenia gravis
- Peripheral neuropathy
- Polyradiculopathy
- Inflammatory myopathy
- Cachexia
- Other paraneoplastic diseases

Signs and Symptoms

- LES presents with slowly progressive weakness and fatigue. Weakness is more prominent in proximal muscles, especially in the lower extremities. After a brief period of muscle activation patients may regain strength, although this is not found in many patients. Muscle stretch reflexes are diminished and typically absent in the lower extremities. It may be possible to enhance reflexes by asking the patient to briefly activate the muscle and then checking the reflex. Muscle pain and paresthesias also can occur, although the sensory examination usually is normal. Autonomic symptoms occur in more than two thirds of all patients and include dry mouth, constipation, impotence, blurred vision, and micturition difficulties. Unlike myasthenia gravis, ocular and bulbar symptoms (ptosis, diplopia, dysphagia) are less prominent and occur in about one third.

- Patients with paraneoplastic LES may have other signs and symptoms due to overlap with other paraneoplastic syndromes. The most common is paraneoplastic cerebellar degeneration and encephalomyelitis.

Laboratory Procedures

- Bloodwork: A very high voltage-gated calcium channel antibody is strongly supportive of the diagnosis of LES; low titers may be seen in normal patients. High levels do not correlate with disease severity, however. A search for other autoimmune diseases may be performed, including acetylcholine receptor antibody, anti-nuclear antibody (ANA), and thyroid analysis.

Imaging Studies

- In most cases of LES the symptoms precede the associated neoplasm by <18 months. For this reason, careful monitoring for a lung cancer is necessary, and it is recommended that older patients with a smoking history have a chest x-ray film, CT, or MRI at regular intervals.

Special Tests

- There are reports of bronchoscopy detecting a lung carcinoma in the absence of radiologic evidence.

Electrodiagnostic Studies

- EMG is the most helpful test in confirming the diagnosis of LES. Low-amplitude compound muscle action potentials are found at rest, often <10% of normal. This is followed by a >100%/s increase after a few seconds of exercise. In addition, a decremental response at low rates of stimulation (2-5 Hz) and an incremental response at high rates of stimulation (200 Hz) may be found. Needle electrode examination may reveal unstable motor unit action potentials. In mild cases of LES the electrodiagnostic findings may resemble those of myasthenia gravis.

Management

General Measures

- Treatment of LES is geared toward identification and treatment of a potential tumor, medications that enhance neuromuscular transmission, and alteration of autoantibodies. Early and successful treatment of a lung carcinoma usually results in clinical improvement.

Surgical Measures

- A lung carcinoma may benefit from surgical resection in some cases.

Symptomatic Treatment

- NA

Adjunctive Treatments

- If a carcinoma is identified, chemotherapy, radiation therapy, and other treatments are geared toward the lung carcinoma.

Admission/Discharge Criteria

- NA
Lambert-Eaton Myasthenic Syndrome

Medications

**DRUGS OF CHOICE**

- Pyridostigmine (Mestinon) inhibits acetylcholinesterase at the neuromuscular junction, resulting in more available acetylcholine for binding to receptors. Strength improvement is seen in some patients with LES, although usually to a mild degree. Dosages of 60 mg q4-6h are typically used. Cholinergic side effects are common and include abdominal cramps, diarrhea, and blurred vision.

- Guanidine hydrochloride increases the release of acetylcholine and may result in symptomatic improvement, especially when given with pyridostigmine. A beginning dose of 5-10 mg/kg/day is given, up to 30 mg/kg/day, divided throughout the day. Side effects include bone marrow suppression, chronic interstitial nephritis, renal tubular acidosis, arrhythmias, paresthesias, encephalopathy, and hepatic toxicity. CBC, LFT, and electrolytes need to be monitored periodically.

- 3,4-Diaminopyridine (DAP) enhances acetylcholine release by blocking potassium channels and results in strength improvement in most patients with LES. A dosage range from 5 mg tid to 25 mg gid is used. Higher dosages are associated with paresthesias, insomnia, and seizures. Cholinergic side effects are similar to those of pyridostigmine. Although DAP is beneficial and is more efficacious than pyridostigmine or guanidine, it is not yet available in the United States, except as on a compassionate-use basis. Pyridostigmine may enhance the effect of DAP. Side effects include paresthesias in the extremities and mouth, and seizures with higher dosages. Cholinergic side effects are common when used with pyridostigmine.

- Immunosuppressants such as prednisone and azathioprine often are used in the treatment of LES and are of benefit in some patients. Azathioprine can minimize the needed dose of prednisone due to its steroid-sparing effects.

- Patients with severe weakness or a rapidly progressive course may benefit from a course of plasmapheresis or intravenous immunoglobulin (IVIG). The effects are short lived, and repeated treatments may be necessary.

**Contraindications**

- Medications that interfere with neuromuscular transmission can worsen the symptoms of LES. This includes aminoglycoside antibiotics, penicillamine, 6-adrenergic Mockers, calcium channel blockers, anesthetic neuromuscular blocking agents, quinidine, and iodinated contrast agents.

**Precautions** N/A

**ALTERNATIVE DRUGS**

- Cyclosporine may be beneficial to patients who do not respond to prednisone or cannot tolerate azathioprine.

**Follow-Up**

**PATIENT MONITORING**

- Careful monitoring for a lung tumor is the most important factor for older individuals with LES. Young patients with other autoimmune diseases in whom a tumor is not found 5 years into the course are very unlikely to develop a lung cancer, and repeated testing is not necessary.

**EXPECTED COURSE AND PROGNOSIS**

- LES is a chronic disease. Identification of a tumor is the most important prognostic factor in paraneoplastic LES. Symptomatic treatment is less effective if a primary tumor is not identified and treated. Patients with nonneoplastic disease may have a clinical remission after immunosuppressive treatment.

**PATIENT EDUCATION**

- Information about LES and support groups is available through the Myasthenia Gravis Foundation of America, 123 W. Madison Street, Suite 800, Chicago, IL 60602. Phone: 312-853-0522; website: www.myasthenia.org

Miscellaneous

**SYNONYMS**

N/A

**ICD-9-CM:** 358.1 Myasthenic syndrome

**SEE ALSO:** N/A

**REFERENCES**


Author(s) Brad Cole, MD

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Leigh's Syndrome

DESCRIPTION
- Leigh's syndrome (LS) is a subacute necrotizing encephalomyelopathy caused by impaired oxidative energy production.

EPIDEMIOLOGY
Incidence/Prevalence
- Rare
- Race
- No ethnic predominance has been reported.

Age
- LS usually affects infants (<2 year old) or young children, although a few cases with adult onset have been reported.

Sex
- Male predominance related to mitochondrial DNA mutations (maternal inheritance)

ETIOLOGY
Biochemistry
- Several isolated or combined defects of the mitochondrial respiratory chain have been associated with LS: pyruvate dehydrogenase deficiency, cytochrome c oxidase deficiency, and complex I deficiency and complex II deficiency.

Genetics
- The mutation related to the syndrome can be found in up to two thirds of patients.

- Genomic DNA: Pyruvate dehydrogenase complex, subunit Eta in chromosome X (X-linked dominant);
- Complex I, subunit NADH ubiquinone oxidoreductase, in chromosome 11q13 (autosomal recessive inheritance);
- SURF1, in chromosome 9 (autosomal recessive inheritance), is a mitochondrial protein of unknown function; its mutation impairs cytochrome c oxidase activity;
- Nuclear encoded flavoprotein subunit gene of sulfamate dehydrogenase (complex II), in chromosome 5 (autosomal recessive inheritance).

- Mitochondria DNA: Several ATPase 6 subunit mutations and mitochondrial tRNA mutations have been associated with LS (maternal inheritance).

ELECTRONIC FOUNDATION
- The two most common mutations are T8993C and T8993G in the ATPase 6 subunit. Some of the mitochondrial mutations described in LS have been reported in association with other specific phenotypes in older patients: in NARP (neuropathy, ataxia, retinitis pigmentosa), MERRF (myoclonic epilepsy and ragged red fibers) and MELAS (mitochondria, Myopathy encephalopathy, lactic acidosis, stroke-like episodes).

RISK FACTORS
- Adult onset of LS is rare. In this event, females should avoid pregnancy due to the morbidity associated with IS.

ASSOCIATED CONDITIONS
- Pearson syndrome

DIFFERENTIAL DIAGNOSIS
- In children
- - Pearson syndrome
- - Infants: berberi
- - Lactic acidemia with mitochondrial deficiency
- In adults
- - Multiple sclerosis
- - Familial spastic paraplegia (coniplicated phenotype)
- - In sporadic cases, other causes of brainstem dysfunction

SIGNS AND SYMPTOMS
- LS is characterized by a variable combination of retarded motor and intellectual development, seizures, dystonia, swallowing and feeding difficulties, vomiting, ataxia, external ophthalmoplegia, impaired hearing and vision, and peripheral neuroopathy. Children may develop adult disorders. Isolated cases have undergone this procedure, and findings were not useful for the diagnosis.

- Differences in clinical presentation have been found associated with specific enzymatic defects:
- Cytochrome c oxidase associated-LS: Symptoms develop after 6 months and have a milder course. Patients rarely have seizures.
- Pyruvate dehydrogenase associated-LS and maternally inherited LS: Symptoms develop in the neonatal or early infantile period. Patients usually have seizures and recurrent apnea.

LABORATORY PROCEDURES
- Blood: Lactic acidosis and high pyruvate blood level are common findings that support the diagnosis of LS in the presence of typical MRI lesions. However, normal lactic acid and pyruvate blood levels do not rule out the diagnosis.
- CSF: CSF lactate and pyruvate levels usually are high (>2.2 mmol/L for lactate and 100 µmol/L for pyruvate) and are more sensitive and specific for the diagnosis of LS than blood levels when MRI lesions are typical.

IMAGING STUDIES
- MRI: T2 weighted cranial MRI is more sensitive than CT to detect lesions of subacute necrotizing encephalomyelopathy. Increased signal intensity and edema are commonly found in the substantia nigra, caudate, putamen, and globus pallidus bilaterally and sometimes in the tegmentum, and medullary olive. MRI scan is the most useful tool for pretreatment diagnosis of the disease.

SPECIAL TESTS
- Muscle biopsy: Muscle biopsy does not establish the diagnosis of the disease but may help in the identification of the biochemical defect. Cytochrome c oxidase activity and complex I can be investigated by histochemistry; complex I and pyruvate dehydrogenase activity should be assessed biochemically. Characteristically, ragged red fibers are hardly ever found in this disease.
- Biochemical analysis in other tissues: Skin fibroblasts, lymphocytes, and liver biopsy can be used for diagnosis of the biochemical defect. Skin biopsy is a less aggressive tool than muscle biopsy; however, the latter is more sensitive for detection of the biochemical deficiency. In addition, liver biopsy seems to be more sensitive than muscle biopsy for the diagnosis of IS, although no extensive data are available.
- Needle stereotactic brain biopsy: Only single cases have undergone this procedure, and findings were not useful for the diagnosis.
- Postmortem evaluation: Neuropathologic abnormalities include focal, bilaterally symmetric necrotic lesions extending from the thalamus to the pons, as well as involving the inferior olives and the posterior columns. The lesions are spongiform and characterized by cystic cavitation, vascular proliferation, neuronal loss, and demyelination. Postmortem neuropathologic findings are especially useful to confirm the diagnosis in affected siblings.
- DNA analysis: The identification of mutations known to be related to LS in genomic DNA usually is a research laboratory task; however, the study of some of the mitochondrial mutations, associated to LS, is routinely available, usually under the heading of mitochondrial DNA encephalomyelopathy profile or NARP, MERRF, or MELAS profiles.

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# Leigh's Syndrome

## Management

### General Measures

- Measures depend on the severity of the phenotype. In severe cases general support measures will be required: gastrostomy or feeding tube, ventilatory support, physical therapy, and symptomatic treatment of seizures and dystonia.

### Surgical Measures

N/A

### Symptomatic Treatment

N/A

### Admission/Discharge Criteria

- Admission for LS is recommended to treat concurrent complications.

### Medications

#### Drugs of Choice:

- In pyruvate dehydrogenase deficiency:
  - Thiamine 100-1,000 mg/day, lipoic acid 100 mg/day, and dichloroacetate 50 mg/kg twice a day
- In complex I deficiency:
  - High-dose riboflavin supplementation (40-300 mg/day) has been attempted with variable success
- For the other biochemical defects no specific treatment is recommended; however it is common practice to try thiamine 100-1,000 mg/day and/or dichloroacetate 50 mg/kg twice a day.

#### Contraindications

- In the event general anesthesia is needed, volatile anesthetic should be avoided.

#### Precautions

- If LS is related to mitochondrial mutations, general recommendations for mitochondrial diseases should be followed: vigorous use of antipyretics and avoidance of drugs that are known to inhibit the respiratory chain (phenytoin, barbiturates) or the mitochondrial protein synthesis (tetracyclines).

### Alternative Drugs

N/A

## Follow-Up

### Patient Monitoring

N/A

### Expected Course and Prognosis

- Prognosis seems to be related to the biochemical or genetic defect associated with LS:
  - In cytochrome c oxidase deficit, patients usually survive until age 5 or 6.
  - In pyruvate dehydrogenase defect, death commonly occurs between 6 and 12 months.
  - In complex I deficiency, prognosis depends on age of clinical presentation and the extent of organ involvement.
  - Transient spontaneous remissions have been reported in one fourth of the patients.

### Patient Education

- Activities: Avoid exhausting exercise.
- Diet: Ketogenic diet is recommended in pyruvate dehydrogenase deficiency.
- Organizations: Muscular Dystrophy Association, Website: http://mdausa.org

## Miscellaneous

### Synonyms

- Subacute necrotizing encephalomyelopathy
- ICD-9-CM: 330.8 Leigh's disease or subacute necrotizing encephalopathy

### References

- DiMauro S, Bonilla E, De Vivo DC. Does the patient have a mitochondrial encephalomyopathy? J Child Neurol 1999;14[Suppl1]:S23-S35.

Author(s): Carmen Serrano-Munuera MD
Leprous Neuropathy

Basics

DESCRIPTION
- Leprosy is an infectious disease that mainly affects the skin, the peripheral nerves, the mucosa of the upper respiratory tract, and the eyes. Leprous neuropathy is the most common type of peripheral neuropathy worldwide. It is caused by direct bacterial infiltration of small-diameter peripheral nerves.

EPIDEMOLOGY
- Leprosy is indigenous to Hawaii and portions of Florida, Louisiana, and Texas in the United States. It also is seen in immigrants from India, southeast Asia, and central Africa.

Incidence/Prevalence
- Prevalence of 0.9 million cases worldwide in 1996. It has been gradually but steadily declining over several decades.
- Prevalence exceeds 10 per 1,000 in endemic areas such as Asia and Africa.
- One hundred forty-four new cases in the United States in 1995. The majority of leprosy cases diagnosed in the United States are in immigrants from leprosy-endemic countries.

Race
- No racial predilection known

Age
- Leprosy can present at any age but is rare in infancy.

Sex
- Equal in children but 2:1 male preponderance in adults

ETIOLOGY
- The etiologic agent is Mycobacterium leprae, an acid-fast bacillus that grows best at 30°C (86°F), which explains its predilection for skin and peripheral nerves. Leprosy is transmitted via transfer of bacteria in nasal discharge of infected individuals to the respiratory tract of susceptible individuals, followed by hematogenous dissemination. The intensity of the cell-mediated immune response to the bacteria correlates with the type of disease expression. Patients with an intense cellular immune response to the bacteria develop disease types toward the tuberculoid end of the spectrum. Little or no cellular immune response is associated with development of lepromatous leprosy.

Genetics
- There is evidence that human leukocyte antigen (HLA)-associated genes influence the type of leprosy an individual develops.

RISK FACTORS
- Exposure to nasal discharge of individuals infected with leprosy

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Leprosy should be considered in presentations with the combination of a skin rash and peripheral neuropathy. The differential also includes the broad differential of peripheral neuropathy.
  - Lupus erythematosus
  - Lupus vulgaris
  - Sarcoidosis
  - Yaws
  - Dermal leishmaniasis other causes of leprosy

SIGNS AND SYMPTOMS
- Indeterminate leprosy (initial infection)
- Solitary hypopigmented macule, which may resolve (about 75%) or persist to progress to one of the other types of leprosy.
- Classification of leprosy types is based on a continuous spectrum based on clinico pathologic features: lepromatous, borderline lepromatous, borderline, borderline tuberculoid, and tuberculoid.

Lepromatous Leprosy
- Multiple symmetric skin lesions affecting face (especially cheeks and nose), limbs, and buttocks, initially macular and evolving into plaques and nodules, typically fairly symmetric. Lesions centers are convex and indurated, and margins are ill defined.
- Nasal congestions and epistaxis
- Ocular: pain, photophobia, loss of vision, glaucoma
- Testicular: atrophy, impotence, gynecomastia
- Sensory loss (especially pain, temperature) in distal limbs (palms and soles spared), pinnae of the ears, breasts, buttocks
- Nerve root enlargement, especially superficial nerves such as the greater auricular in the neck, ulnar, peroneal as it passes around the fibula, superficial radial, median
- Motor involvement is late: amyotrophy, clawhand, footdrop
- Reflexes preserved
- Cranial nerve involvement: preferentially V and VII (eye closure and palpebral musculature)
- Lucid reaction or phenomenon, a type of nercotizing vasculitis that can occur in lepromatous disease with high mortality

Tuberculoid Leprosy
- Sharply margined erythematous or hypopigmented macules or plaques that are solitary and asymmetric, occurring in the trunk, buttocks, and face. Tuberculoid leprosy lesions exhibit earlier sensory loss compared with lepromatous lesions.
- Nerve enlargement occurs early and involves nerves contiguous to skin lesions.
- Neuropathy pain
- Muscle atrophy, especially in the intrinsic hand muscles
- Resorption of phalanges (late)

Borderline Leprosy
- Skin lesions vary in number and character depending on whether the case is more toward the tuberculoid or lepromatous end of the spectrum.
- Nerve involvement may precede skin lesions in this type, with segmental enlargement and tenderness of nerve trunks.

LABORATORY PROCEDURES
- ELISA to serum antibody to phenolic glycolipid I (PGL-I), a capsular antigen of M. leprae, is positive in most patients with multibacillary disease (lepromatous or borderline lepromatous) and often negative in patients with paucibacillary forms of the disease (tuberculoid or borderline tuberculoid).
- Diagnosis is generally made from demonstration of acid-fast bacteria from smears from affected skin or nasal mucosa.

IMAGING STUDIES
N/A

SPECIAL TESTS
- Dermal scraping or slit-skin biopsy are sent for acid-fast stain or, alternatively, the Ziehl-Neelsen stain to identify M. leprae. In tuberculoid leprosy, noncaseating granulomas are present and bacilli often are scant or absent. In lepromatous leprosy, a diffuse granulomatous reaction is present, often with many demonstrable bacilli.
- Nerve biopsy is not usually necessary to make a diagnosis of leprous neuropathy, except in rare cases of isolated nerve involvement.
- Nerve conduction studies/electromyography are helpful to document neuropathy and delineate pattern of involvement.
**Management**

**GENERAL MEASURES**
- Treatment is given to eradicate the bacteria and to prevent secondary immune reactions that might cause further injury to the nerves. Patients should be evaluated by an ophthalmologist for ophthalmologic manifestations that might threaten vision. Family members should be evaluated for leprosy.

**SURGICAL MEASURES**
- Occasionally release of contractures and nerve and tendon transplants can improve function. Plastic surgery may be useful to correct or improve facial or other deformities.

**SYMPTOMATIC TREATMENT**
- Patients should be counseled about the risks of inadvertent injury, such as severe burns to areas rendered insensitive by peripheral neuropathy. Insensate limbs should be protected by good footwear, and patients should be warned about the risk of burns.

**ADJUNCTIVE TREATMENT**

**ADMISSION/DISCHARGE CRITERIA**
- Not generally required except in severe reactions to treatment (see Patient Monitoring)

**Medications**

**DRUG(S) OF CHOICE**
- Dapsone (diphenylsulphone), a folate antagonist, is the primary therapy.
- The regimen recommended by the US Public Health Service Hospital Long Hansen’s Disease Center in Louisiana is given below. These recommendations differ from the World Health Organization (WHO) recommendations, which include a broader regimen because of concerns of dapsone resistance.

**US Public Health Service Hospital Long Hansen’s Disease Center in Louisiana Regimen**

<table>
<thead>
<tr>
<th>Disease (Tuberculoid End of Spectrum)</th>
<th>Rifampin 600 mg PO daily</th>
<th>Cliformin 50 mg PO daily</th>
<th>Duration 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multibacillary Disease (Lepromatous End of Spectrum)</td>
<td>Dapsone 100 mg PO daily</td>
<td>Cliformin 50 mg PO daily</td>
<td>Duration 1 year</td>
</tr>
<tr>
<td>WHO-Recommended MDT Regimens</td>
<td>Rifampin 600 mg once per month</td>
<td>Dapsone 100 mg daily</td>
<td>Cliformin 300 mg once per month and 50 mg daily</td>
</tr>
<tr>
<td>Duration 6 months</td>
<td>Cliformin 300 mg once per month and 50 mg daily</td>
<td>Duration 12 months</td>
<td></td>
</tr>
</tbody>
</table>

**PRECAUTIONS**
- Adverse effects of dapsone are relatively uncommon but include hemolysis, agranulocytosis, hepatitis, and severe exfoliative dermatitis.
- CQ or CQ mine may cause reddish discoloration of the skin, diarrhea, and abdominal pain.
- Patients may actually have a worsening of their neuropathy or rash when treatment is initiated due to several types of reactions (see Patient Monitoring).

**ALTERNATIVE DRUGS**

**Patient Monitoring**
- Patients with leprosy must be followed closely for several types of adverse reactions to treatment.
- Lepre type 2 reaction (erythema nodosum leprosum) is a reaction that occurs in approximately 50% of patients with lepromatous leprosy during the first year of treatment and is attributed to immunologic reaction to massive death of M. leprae bacilli (Arthus reaction with deposition of immunoglobulin/complement in skin vessels). This leads to the development of multiple tender skin nodules, as well as fever, arthritis, iridocyclitis, edema, and new peripheral nerve injury in an acute, mononeuritis multiplex pattern. Prednisone is also used to treat this reaction. Thalidomide 100-300 mg Ohs is useful if prednisone does not quell the reaction.

**REFERENCES**
- Author(s): Joanne Lynn, MD
Lesch-Nyhan Disease

**Basics**

**DESCRIPTION**
- Lesch-Nyhan disease (LND) is an inherited metabolic disease characterized by overproduction of uric acid and a characteristic neurobehavioral syndrome. The overproduction of uric acid frequently leads to hyperuricemia, gouty arthritis, and kidney stones composed of uric acid. The neurobehavioral syndrome consists of mental retardation, severe motor handicap, and recurrent self-injurious behavior.

**EPIDEMIOLOGY**
- LND occurs in all ethnic groups with an estimated incidence of 1 per 380,000 births. Virtually all cases are males.

**ETIOLOGY**
- LND is caused by inherited mutations in the HPRT gene. This gene encodes hypoxanthine guanine phosphoribosyltransferase, an enzyme responsible for recycling the purine bases hypoxanthine and guanine into usable purine nucleotides. In LND, the rate of purine biosynthesis is increased, causing accumulation of uric acid in high concentrations in the blood, spinal fluid, and urine. Gouty deposits may occur in target tissues such as the joints and kidneys.

**RISK FACTORS**
- Because inheritance is X linked and recessive, female heterozygous carriers are completely asymptomatic, but their male offspring have a 50% risk of contracting the disease.

**PREGNANCY**
- Because there are no effective treatments for LND, prevention plays an important role in managing the disease. Any female relative of a patient with LND should be counseled regarding her risk of producing an affected child. Genetic tests are available for both carrier testing and prenatal diagnosis.

**ASSOCIATED CONDITIONS**
- Macrocytic anemia
- Growth retardation

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- The differential diagnosis for developmental delay includes a large number of inherited or acquired disorders. The differential diagnosis for self-injurious behavior also is broad and includes severe mental retardation, autism, and several other genetic syndromes. Hyperuricemia is unusual in children, often signifying a metabolic or lymphoproliferative disorder, or the effect of a medication.

**SIGNS AND SYMPTOMS**
- Developmental delay is followed by an extrapyramidal syndrome resembling cerebral palsy.
- Self-injurious behavior is characteristic, often with mutilation of the lips and fingers. Choreoathetosis starts early in life, and death usually occurs in the teens or 20s from renal failure.
- Renal colic may occur due to stones, and gouty arthritis may occur with joint inflammation.

**LABORATORY PROCEDURES**
- Serum uric acid
- 24-hour urinary uric acid

**IMAGING STUDIES**
- Imaging studies of the brain are largely unrevealing. Ultrasound and CT of the kidneys and urogenital system may disclose stones.

**SPECIAL TESTS**
- Evidence for overproduction of uric acid is a helpful clue but is not sufficient for definitive diagnosis. Diagnosis requires the demonstration of reduced HPRT enzyme activity in blood cells or fibroblasts. Alternatively, a gene test is available to screen for mutations (numerous point mutations mapped to Xg26.1 region). Prenatal testing possible in first trimester (chorionic villus sampling).

**Management**

**GENERAL MEASURES**
- A comfortable and engaging environment is essential for minimizing behavioral problems. Motor dysfunction and behavior problems often worsen with anxiety and stress, such as that associated with hospitalization.

**SURGICAL MEASURES**
- Patients with LND may undergo most routine surgical procedures with standard anesthetic agents.

**SYMPTOMATIC TREATMENT**
- Prevention of kidney stones requires generous hydration at all times and allopurinol to reduce the formation of uric acid. There are no consistently effective therapies for the neurobehavioral features. Prevention of self-hitting usually requires physical restraints and sometimes dental extraction to prevent self-biting. Medications sometimes helpful for reducing self-injury include gabapentin, carbamazepine, benzodiazepines, or risperidone.

**ADJUNCTIVE TREATMENT**
- Wheelchairs must be customized by covering all potentially dangerous parts within reach. Comfortable restraints usually are required in the wheelchair and sleeping environment.
- Behavior therapy can be very helpful to reduce the incidence of self-injurious behaviors.

**ADMISSION/DISCHARGE CRITERIA**
- N/A
Lesch-Nyhan Disease

**Medications**

**DRUG(S) OF CHOICE**
- Allopurinol

**Contraindications**
- Impaired renal function is frequent.

**Precautions**
- Good hydration must be provided.

**ALTERNATIVE DRUGS**
- N/A

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**Follow-Up**

**PATIENT MONITORING**
- Regular follow-up is needed to guard against nephrolithiasis and renal failure: Stones may arise even in well-hydrated patients taking allopurinol. The family may require assistance with managing self-injury and other counterproductive behaviors.

**EXPECTED COURSE AND PROGNOSIS**
- Developmental delay is apparent within the first few months of age. Extrapyramidal signs typically develop between 9 and 18 months of age. Self-injury typically begins between 24 and 36 months of age but may be delayed until late childhood or early adolescence, Although the condition is not progressively degenerative, few patients survive beyond 30 years of age. Most succumb to complications of renal failure or aspiration. A significant proportion experience sudden death of undetermined cause.

**PATIENT EDUCATION**
- Lesch-Nyhan Syndrome Children's Research Foundation, 210 South Greenbay Road, Lake Forest IL, 60045.
- Emedicine entry for Lesch-Nyhan syndrome.
  - Website: www.emed.com/neuro/topic630.htm

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**Miscellaneous**

**SYNONYMS**
- N/A

**ICD-9-CM:** 277.2 Lesch-Nyhan syndrome

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** H.A. Jinnah, MD, PhD

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**Leukodystrophies**

**Description**
- Leukodystrophies are inherited disorders of central myelination resulting in the destruction of white matter. Despite substantial progress in our understanding of inherited white matter disorders in recent years, approximately 10% of children with white matter abnormalities do not have a specific diagnosis even after extensive investigations to rule out well-defined leukodystrophies.

**Epidemiology**
- **Incidence**
  - Alexander's disease: rare, 1 in 10,000
  - Metachromatic leukodystrophy: 1 in 40,000 to 1 in 100,000
  - Krabbe leukodystrophy: 1 in 100,000
  - X-Linked adrenoleukodystrophy (ALD): 1 in 40,000
  - Pelizaeus-Merzbacher disease: 1 in 100,000

**Etiology**
- The leukodystrophies are inherited in an autosomal recessive pattern with the exception of Alexander's disease (autosomal dominant) and the X-linked recessive conditions (Winked ALD and Pelizaeus-Merzbacher), which affect males more severely. Biochemical abnormalities are:
  - Alexander's disease: de novo mutation in the aspartoacylase gene (GFAP) - Canavan's disease: mutations in the MLCP1 gene
  - Megalencephalic leukoencephalopathy with subcortical cysts (MLC1)
  - Krabbe leukodystrophy: mutations in the galactocerebrosidase gene
  - X-linked ALD: deficiency of peroxisomal membrane transporter
  - Pelizaeus-Merzbacher disease: deficient formation of proteolipid protein (PLP) in the central nervous system
  - Vanishing white matter disease: mutations in one of the five subunits of the translation initiation factor 2F2B

**Risk Factors**
- There are no known environmental risk factors.

**Pregnancy**
- Prenatal diagnosis available in some cases.

**Associated Conditions**
- In addition to leukodystrophy:
  - Metachromatic leukodystrophy: peripheral neuropathy, optic atrophy, gallbladder disease
  - Krabbe leukodystrophy: peripheral neuropathy, visual loss
  - X-linked ALD: Addison's (adrenal insufficiency)
  - Pelizaeus-Merzbacher disease: rotatory nystagmus

**Diagnosis**

**Differential Diagnosis**
- Multiple sclerosis
- Acute disseminated encephalomyelitis
- CNS vasculitis
- Toxic leukoencephalopathies (e.g., cyclosporine)
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Multiple subcortical infarctions
- Disorders of vitamin B12 and folate metabolism
- White matter abnormalities associated with other metabolic conditions, including organic acidurias, aminoacidopathies, and mitochondrial disorders

**Signs and Symptoms**

**Alexander's Disease**
- Infantile: macrocephaly, psychomotor regression, seizures, spasticity
- Juvenile: slower development of bulbar signs, ataxia, spasticity with relative preservation of intelligence
- Adult: heterogeneous, may mimic relapsing-remitting multiple sclerosis

**Krabbe's Disease**
- Infantile: macrocephaly, hypotonia, developmental delay - a seizures and spasticity
- Congenital: marked hypotonia, lethargy, dysphagia, early death
- Juvenile: onset after 5 years of cerebellar dysfunction, cognitive decline --> spasticity, optic atrophy

**Pelizaeus-Merzbacher Disease**
- Macrophagy prior to 1 year of age. Early development is normal with eventual development of ataxia, spasticity, and slow deterioration in motor functions. Intelligence remains relatively spared. Seizures may develop;

**Metachromatic Leukodystrophy**
- Late infantile: initial hypotonia - i progressive hypertonia, ataxia, intellectual regression, painful peripheral neuropathy, optic atrophy
- Juvenile: school difficulties, incontinence, and gait abnormalities -> extrapyramidal features, hypertonia, intellectual deterioration, pseudobulbar palsy
- Adult onset: initial neuropsychiatric symptoms with progressive frontal dementia --> gait disorder, peripheral neuropathy, hypertonia, optic atrophy, spastic tetraparesis, bulbar dysphonia

**Krabbe Leukodystrophy**
- Infantile: early irritability/hypersensitivity to stimuli --> marked hypertonia, loss of vision and hearing, peripheral neuropathy
- Juvenile and adult forms: mental deterioration, pyramidal signs, visual loss, peripheral neuropathy

**X-linked ALD**
- Six clinical phenotypes have been recognized for this condition:
  - Childhood cerebral ALD
  - Adolescent cerebral ALD
  - Adult-onset cerebral ALD
  - Amyeloneuropathy
- Addison's only Asymptomatic/presymptomatic
- The childhood cerebral form and amyeloneuropathy are the most common. The childhood cerebral form presents initially with behavioral changes and school difficulties at 2-10 years of age, followed by progressive neurologic dysfunction, visual loss, and adrenal insufficiency. The adolescent and adult-onset cerebral phenotypes have similar features to the childhood cerebral disease but a later age of onset. Amyeloneuropathy presents in the second to fourth decade of life as progressive spastic paraparesis. Up to half may develop cerebral symptoms, and two thirds develop adrenal insufficiency. Addison's alone may be present in 10%-25% of ALD patients with a high risk of later developing neurologic symptoms. Patients may remain asymptomatic for decades. Different clinical phenotypes can occur within the same family.

**Pelizaeus-Merzbacher Disease**
- Classic: rotatory eye movements and hypotonia --> very slowly progressive involuntary movements and spasticity
- Congenital: onset at birth with severe features and more rapid progression may have intractable seizures

- X-linked spastic paraparesis

**Vanishing White Matter Disease**
- Onset from infancy to adulthood
- Chronic progressive cerebellar ataxia, spasticity, optic atrophy, mild mental decline
- Episodes of rapid deterioration following febrile illnesses and minor head trauma
LEUKODYSTROPHY

LABORATORY PROCEDURES

- Alexander's disease: mutation analysis of GFAP gene
- Canavan's disease: elevated urinary excretion of N-acetylaspartic acid (NAA) decreased aspartoacylase enzyme activity; DNA mutation analysis
- Megalencephalic leukoencephalopathy with subcortical cysts: DNA mutation analysis
- Metachromatic leukodystrophy: arylsulfatase A assay on WBCs or fibroblasts; sulfatides in the urine
- Krabbe leukodystrophy: Galactocerebroside assay in WBCs or fibroblasts; mutation analysis
- X-linked ALD: deficiency of peroxisomal membrane transporter (ALDP); accumulation of very-long-chain fatty acids (VLCFA) in blood; DNA mutation analysis
- Pelizaeus-Merzbacher disease: mutations or duplication of the PLP gene
- Vanishing white matter disease: mutation analysis of five subunits of eIF2B

IMAGING STUDIES

- MRI is the study of choice for the evaluation of leukodystrophy:
- Alexander's disease: extensive frontal dominant white matter abnormalities
- Canavan's disease: diffuse hypodensity of white matter and increased NAA peak on magnetic resonance spectroscopy
- Megalencephalic leukoencephalopathy with subcortical cysts: diffusely abnormal; mildly swollen white matter with subcortical cysts in the anterotemporal region and often in the frontotemporal region.
- Metachromatic leukodystrophy: periventricular white matter abnormalities evolve into more extensive, symmetric involvement of the subcortical white matter
- Krabbe leukodystrophy: extensive white matter involvement precedes diffuse cerebral atrophy
- X-linked ALD: symmetric parieto-occipital white matter lesions
- Pelizaeus-Merzbacher disease: severe reduction or absence of myelin
- Vanishing white matter disease: diffusely abnormal white matter that vanishes over time and is replaced by CSF

SPECIAL TESTS

- Alexander's disease: histologic finding of Rosenthal fibers on brain biopsy is diagnostic but has been replaced by mutation analysis
- Metachromatic leukodystrophy: nerve conduction studies to assess for peripheral neuropathy; ultrasound to assess for accumulation of sulfatides in gallbladder wall
- Krabbe leukodystrophy: nerve conduction studies to assess for peripheral neuropathy
- X-linked ALD: adrenal function testing in patients with all forms of this disease

MANAGEMENT

GENERAL MEASURES
- Supportive therapy

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

- Bone marrow transplantation may result in long-term stabilization and sometimes improvement in clinical symptoms when performed early in cerebral X-linked ALD, juvenile and adult-onset forms of metachromatic leukodystrophy, and Krabbe disease. Once neurologic symptoms have progressed beyond the early stages, bone marrow transplantation has been shown to alter the natural course of these disease

ADJUNCTIVE TREATMENT

- Patients with ALD and amyeloneuropathy should be treated for adrenal insufficiency required.

ADMISSION/DISCHARGE CRITERIA

N/A

MEDICATIONS

DRUG(S) OF CHOICE

- Naffectve drugs are currently available.

ALTERNATIVE DRUGS

- Lorenzo's oil has been given to patients with X-linked ALD for more than a decade since it was initially shown to normalize plasma VLCFA. Recent studies, however, have demonstrated no beneficial effects of Lorenzo's oil on the natural course of the disease. Significant side effects, including elevated liver enzymes and thrombocytopenia, are frequently observed.

FOLLOW-UP

PATIENT MONITORING

- Presymptomatic boys with X-ALD should be monitored with serial neuropsychological assessments in order to detect early indications of cerebral disease and need for bone marrow transplantation.

EXPECTED COURSE AND PROGNOSIS

- Rate of progression of symptoms is dependent upon the age of onset and characteristics of each individual leukodystrophy.

PATIENT EDUCATION

- Genetic counseling should be provided to patients and their families. Presymptomatic testing of siblings may be offered for some conditions in view of the potential benefit of early bone marrow transplantation.
- United Leukodystrophy Foundation. Website: www.ulfd.org

SYNONYMS

- Leukoencephalopathies
- Metabolic white matter diseases

ICD-9-CM: 330.0, Leukodystrophy

SEE ALSO: N/A

REFERENCES


Author(s) Deborah L. Renaud, MD
Lyme Disease, Neurologic Complications (Lyme Neuroborreliosis)

**Description**
- Lyme disease is a multisystemic illness associated with both early and late-onset chronic neurologic syndromes.

**Epidemiology**
- **Incidence**: The incidence is much higher in the coastal New England, mid-Atlantic, and northern midwestern states.
- **Prevalence**: Up to 15% of treated patients develop early neurologic Lyme disease.
- **Race**: Vast majority are white; 2%-3% are black.
- **Age**: Children <15 years and adults >30 years are at greatest risk.
- **Sex**: Males and females are affected equally.

**Etiology**
- Spirochetal infection (Borrelia burgdorferi in the United States)
- Transmitted by deer tick (Ixodes scapularis in the United States)
- Most patients are infected in spring or summer when the Ixodes nymph feeds.
- Initial manifestation is typically the localized, slowly expanding skin rash, erythema migrans (EM).
- If localized disease is untreated, the infection may become disseminated, resulting in early neurologic or cardiac involvement and late manifestations such as oligoarticular arthritis or chronic Lyme neuroborreliosis.

**Risk Factors**
- Residence in, or visitation to, endemic areas during spring and summer

**Pregnancy**
- N/A

**Associated Conditions**
- Erythema migrans
- Lyme carditis
- Lyme oligoarticular arthritis

**Diagnosis**

**Differential Diagnosis**
- **Acute Lyme Cranial Neuropathy**
  - Idiopathic (Bell's) facial palsy
  - Guillain-Barre syndrome
  - Neurosarcoïdosis
- **Acute Lyme Radiculoneuropathy**
  - Herpes zoster
  - Cytomegalovirus (ebste in-Barr virus
  - Neurosarcoïdosis
  - Proximal diabetic neuropathy
  - Nonsystemic vasculitic neuropathy
- **Lyme Meningitis** or **Meningoencephalitis**
  - Viral meningitis or meningoencephalitis
  - Chronic meningitides
- **Chronic Lyme Radiculoneuropathy**
  - Distal sensory diabetic neuropathy
  - Other toxic-metabolic neuropathies
  - Idiopathic sensory polyneuropathy
  - Disc disease
  - Fibromyalgia
- **Chronic Lyme Encephalopathy**
  - Chronic fatigue/fibromyalgia
  - Toxic-metabolic causes
  - Depression
  - Early Alzheimer's disease
  - Neurosarcoïdosis
  - Other systemic inflammatory disease

**Signs and Symptoms**
- **Acute Lyme Neuropathy; Cranial Neuropathy, Radiculoneuropathy, Meningitis**
  - In summer/fall, within days to weeks after the onset of infection, cranial neuropathy and/or radiculoneuropathy may develop. A CSF lymphocytic pleocytosis is frequently present; meningeal signs and symptoms may be subtle or absent.
  - Other less common syndromes are encephalitis, encephalomyelitis, transverse myelitis, or myositis.
  - Any cranial nerve can be affected (most commonly facial palsy in 50%-45% of patients and bilateral in one third). Facial palsy is typically noted within 4 weeks of EM.
  - Acte Lyme radiculoneuropathy usually presents with severe sharp, jabbing, or boring pain in the distribution of peripheral nerves or nerve roots. Within days to weeks, neurologic deficits appear, including sensory loss, weakness, or hyporeflexia. Symptoms and signs may be focal or multifocal.

**Chronic or Late Lyme Radiculoneuropathy**
- Presents months to years after disease onset with sensory symptoms, particularly distal paresthesia or radicular pain. Muscle weakness is slight or absent, and tendon jerks are normal or slightly hyporeactive.
- Compared to acute Lyme neuropathy, chronic Lyme radiculoneuropathy is less severe and does not include cranial neuropathy or CSF pleocytosis.
- Patients with distal paresthesia present with symmetric or asymmetric sensory and signs in a “stocking glove” distribution or truncal paresthesia. The radicular form is less common.

**Chronic or Late Lyme CNS Syndromes:**
- **Encephalopathy or Encephalomyelitis**
  - Lyme encephalopathy presents primarily with memory and concentration difficulty.
  - Headache, mild depression, irritability, fatigue, or excessive daytime sleepiness may occur.
  - Encephalomyelitis usually presents with progressive limb weakness and spasticity, urinary urgency, and occasionally cranial neuropathy.

**Laboratory Procedures**
- **Serology**: Within 3-4 weeks, a serum IgM response is detectable and by 6-8 weeks an IgG response develops as the IgM response declines. During early disease (e.g., EM), the patient often is seronegative. Once the disease becomes disseminated, serological and neurologic complications develop, however, the vast majority has a positive IgM or IgG titer.
- **Western blot**: All borderline or positive titers should be confirmed with Western blots to differentiate false- from true-positive titers.
- **CSF analysis**: Lymphocytic pleocytosis typically is found in acute radiculoneuritis, meningitis, encephalitis, encephalomyelitis, transverse myelitis, and sometimes isolated cranial neuritis. Elevated CSF protein is found in Lyme encephalopathy. Selective concentration of Lyme antibody in CSF is found in most patients with CNS Lyme disease.
- **Neuropsychologic tests**: Typically discloses subtle verbal or visual memory problems. EMG/nerve conduction studies: Patients with acute or chronic Lyme radiculoneuropathy show sensorimotor axon loss, polyradiculoneuropathy with low-amplitude action potentials (sensory more than motor), and slight slowing of conduction velocities and demyelination of distal and proximal muscles. In contrast to the axonal neuropathy in the limbs, patients with acute Lyme facial palsy may show demyelinating physiology With conduction block of facial motor fibers.
- **Evoked potential**: EEG usually is normal in CNS neuroborreliosis. Seizures, focal sharp activity and focal slowing or dysrhythmia may be seen with encephalomyelitis.
Lyme Disease, Neurologic Complications (Lyme Neuroborreliosis)

**IMAGING STUDIES**
- Brain MRI: Nonspecific white matter lesions are seen in about 75% of patients with subacute or chronic Lyme encephalomyelitis. Only about 25% of adults or pediatric patients with Lyme encephalopathy have cerebral, nonenhancing, white matter lesions.

**SPECIAL TESTS**
- CSF culture: Culture of *B. burgdorferi* is technically demanding and positive in <10% of patients with known CSF infection.
- CSF polymerase chain reaction (PCR): Positive in <50% of patients with CNS or meningeval Lyme disease. Technically demanding, numerous controls required, not standardized.
- Single photon emission computed tomography (SPECT): Multifocal areas of cortical and subcortical hypoperfusion are often seen in Lyme encephalopathy.

**GENERAL MEASURES**
- Once the diagnosis of Lyme neuroborreliosis is made, antibiotic therapy should be begun promptly. If there is evidence of CNS invasion (e.g., CSF pleocytosis, selective concentration of antibody in CSF, positive CSF PCR), IV antibiotics (e.g., IV ceftriaxone) should be started. If not, oral antibiotics (e.g., PO amoxicillin) suffice, particularly for isolated cranial neuropathy.

**SURGICAL MEASURES**
N/A

**SYMPTOMATIC TREATMENT**
- Neuropathic pain control in patients with acte or chronic radiculoneuropathy
- Corneal protection for facial palsy
- Treatment of headache, sleep disorder, depression, spasticity, or seizures if necessary

**ADJUNCTIVE TREATMENT**
- Physical therapy for limb weakness
- Cognitive rehabilitation for patients with memory disturbance

**ADMISSION/DISCHARGE CRITERIA**
- Outpatient management is the rule with admission for patients with significant progressive neurologic deficits.

**EXPECTED COURSE AND PROGNOSIS**
- In acute Lyme radiculoneuropathy, radicular pain often improves over hours to days of IV antibiotic administration. Whereas sensory and motor deficits generally resolve completely over weeks to a few months.
- The prognosis for facial and other cranial nerve palsies is excellent.
- In acute or chronic Lyme encephalomyelitis, neurologic function improves, but residual deficits are common.
- In chronic Lyme radiculoneuropathy, symptoms resolve more slowly than in acute Lyme neuropathy over many months, usually with mild residual deficits. The outcome is better than in Lyme encephalopathy than encephalomyelitis.
- Improvement in symptoms **BECOMES** beginning 2-3 months after completion of antibiotic therapy and continuing for 6 to 9 months.

**PATIENT EDUCATION**
- Tick avoidance: Beware of high grass, brush, woods in endemic areas in spring/summer

**SYNONYMS**
- Neuroborreliosis
- Banwarth’s syndrome (acute Lyme radiculoneuropathy)

**ICD 9 CM:** 088.81 Lyme disease; 088.81 [320.7] Meningitis-Lyme disease, meningencephalitis-Lyme disease; 323.9 Encephalitis; 348.3 Encephalopathy; 351.9 Facial neuropathy; 357.0 Polyneuritis, infective (acute); 356.9 Polyneuritis (peripheral); 723.4 Radiculitis, Arm; 724.4 Radiculitis, leg or thoracic

**REFERENCES**

**Author(s):** Eric L. Logigian, MD

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**Management**

**Medications**

**DRUG(S) OF CHOICE**
- For CNS disease, the third-generation cephalosporin, ceftriaxone, is superior to high-dose penicillin because it easily crosses the blood-brain barrier, requires once per day dosing, and has high spirochetalic activity against *Borrelia*.
- For: early neurologic involvement with CSF pleocytosis: 2-4 weeks of IV ceftriaxone 2 g/day in adults (75-100 mg/kg/day in children).
- For isolated facial palsy with normal CSF: 4 weeks of tetracycline 100 mg PO bid or amoxicillin 500 mg PO tid in adults.
- For late central or peripheral neurologic involvement: 4 weeks of IV ceftriaxone 2 g/day in adults (75-100 mg/kg/day in children).
- For encephalomyelitis: 4-6 weeks of IV ceftriaxone therapy

**Contraindications**
- Known drug allergy
- Patients with penicillin allergy should be skin tested prior to initiating ceftriaxone therapy.

**Precautions**
- Administer initial dose of IV antibiotic under direct medical supervision.
- Observe for diarrhea (pseudomembranous colitis), right upper quadrant pain (biliary), line sepsis, or phlebitis.
- Treatment duration beyond 4-6 weeks almost never is necessary.
- Symptoms that are unresponsive to prolonged courses of intravenous antibiotics are most likely due to another cause.

**ALTERNATIVE DRUGS**
- For adults with CNS disease who have penicillin and cephalosporin allergy, consider doxycycline at higher dose (200 mg PO bid). Other alternatives are chloramphenicol, vancomycin, or imipenem.

**Follow-Up**

**PATIENT MONITORING**
- If elevated initially, expect Lyme antibody titer to remain elevated despite adequate therapy and resolution of symptoms.
- Follow-up CSF studies: pleocytosis resolves, protein declines, CSF/PCR returns to negative.
- Consider follow-up neuropsychologic testing to document improved memory.
- Brain MRI abnormalities may not improve; SPECT abnormalities do improve.
Malignant Hyperthermia

DESCRIPTION
Malignant hyperthermia (MH) is a condition characterized by elevated calcium concentration in the sarcoplasm after exposure to triggering agents, causing an uncontrolled increase in muscle metabolism.

EPIDEMIOLOGY
Incidence/Prevalence
Incidence of acute MH is approximately 1/15,000 anesthetics in the pediatric population, and 1/50,000 to 1/150,000 in adults.

Sex
Acute MH is more prevalent in males, even prior to puberty.

ETIOLOGY
The ryanodine receptor is the calcium release channel from the sarcoplasmic reticulum. Release of calcium from the sarcoplasmic reticulum normally occurs after depolarization via an action potential. The subsequent calcium release into the myoplasm allows actin-myosin cross-bridge cycling (contraction), which is terminated by calcium reuptake into the sarcoplasmic reticulum (relaxation). Abnormal stimulation of calcium release by triggering agents, possibly combined with abnormal reuptake, causes continuous cross-bridge cycling and consumption of energy stores, both by the contraction apparatus and by sarcoplasmic adenosine triphosphatase (ATPase).

Genetics
The genetics of MH is characterized as autosomal dominant with variable penetrance. Between 26% and 70% of MH susceptible patients have a genetic mutation in the ryanodine receptor. The MH phenotype may be dependent on other proteins that modulate the ryanodine receptor or calcium reuptake.

RISK FACTORS
• Malignant hyperthermia is most commonly caused by exposure to triggering agents including all halogenated inhalation anesthetics, such as sevoflurane and desflurane, and the depolarizing neuromuscular blocker succinylcholine. MH-susceptible patients may not have an episode with their first exposure to a triggering anesthetic; 30% of patients may have had up to three previous anesthetic experiences. Triggering and severity of an episode may be ameliorated by mild hypothermia (consistent with the comparatively greater incidence in children as mild hypothermia is less common during pediatric anesthesia).

DIAGNOSIS

SIGNS AND SYMPTOMS
• The first sign may be masseter muscle spasm, during succinylcholine administration; tills may be severe enough to prevent intubation. Approximately 50% of patients with masseter spasm after succinylcholine are found to be MH susceptible. When presented with a patient with masseter spasm after succinylcholine administration, consideration should be given to aborting the anesthetic. If the anesthetic is continued with nontriggering drugs, then consideration should be given to what must be done to facilitate early diagnosis and treatment should MH develop.
• Increased muscle metabolism increases CO2 production because aerobic metabolism increases in muscle, and lactic acid produced by muscular anaerobic metabolism is neutralized. Metabolic and respiratory acidosis results. Severe muscle rigidity may be caused by uncontrolled stimulation of actin-myosin cross-bridge cycling by increased intracellular Ca++ and by muscle temperature above 43.5°C, which causes irreversible sible contraction. The rigidity of MH is not affected by neuromuscular blockade. In spontaneously breathing patients, tachypnea will be noted; in ventilated patients, increases in end-tidal CO2 occur despite increasing minute ventilation. Tachycardia and hypertension may be caused directly by hypercarbia, and indirectly by hypercarbic stimulation of catecholamine release. Hyperthermia associated with MH is secondary to muscle hypermetabolism and depends on both the ability to dissipate heat produced and the rapidity of definitive treatment. High concentrations of catecholamines, hypercarbia, and Catechol-1-o-sulfotransferase lead to flushed, diaphoretic, cyanosis, local hypothermia, acidosis, and depletion of adenosine triphosphate (ATP), cause increased membrane permeability and release of potassium. Increased membrane permeability and release of potassium leads to tachycardia, muscle hyperkalemia leads to arrhythmia, decreased cardiac output, and cardiac arrest. Continued hypermetabolism, decreased energy stores, local temperature rise, and decreased perfusion lead to death from fatal hyperthermia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
Sepsis, thyrotoxic crisis, pheochromocytoma, metastatic carcinoma, serotonin syndrome, neuroleptic malignant syndrome, inadequate ventilation, light anesthesia, cocaine intoxication, iatrogenic overheating, central fever, anaphylactoid reactions.
Malignant Hyperthermia

LABORATORY PROCEDURES

• Arterial and venous blood samples, serum potassium and other electrolytes, urinalysis.
• If urine dipstick is positive for blood, then obtain microscopic analysis for RBCs and quantitative analysis for myoglobin.
• If urine pH is low, consider alkalization.
• Baseline CK, clotting studies, and creatinine.
• Repeat CK 12 to 24 hours later and until the diagnosis of MH.
• If urine pH is low, consider alkalization.

REPEATED CLINICAL FINDINGS

Respiratory acidosis secondary to muscle MH. It is available in five centers in the U.S. in hypermetabolism, along with signs of muscle only approved diagnostic test for susceptibility to hypermetabolism, along with signs of muscle hypermetabolism, along with signs of muscle breakdown and resolution with dantrolene, favor the diagnosis of MH.

IMAGING STUDIES

SPECIAL TESTS

The halothane-caffeine contracture test is the only approved diagnostic test for susceptibility to MH. It is available in five centers in the U.S. in 2003, and requires 1 g of fresh muscle. Although the test is very sensitive, it lacks specificity. Therefore, the index patient should undergo contracture testing to maximize the predictive value for other family members.

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GENERAL MEASURES

The definitive treatment of a known or suspected MH episode is administration of dantrolene as soon as possible and immediate discontinuation of triggering agents. Ventilation with high-flow O2 through the anesthesia ventilator should be sufficient, as the concentration of inhalational agent in this ventilator will be less than that in the patient.

SURGICAL MEASURES

When an episode occurs during surgery, the procedure should be terminated as soon as possible.

SYMPTOMATIC TREATMENT

Standard treatment of hyperkalemic dysrhythmias should be initiated. Hyperventilation to approach normocarbia, and bicarbonate or tris(hydroxymethyl)-aminomethane (TRAM) administration for initial treatment of the metabolic and respiratory acidosis should be titrated. Hyperthermia should be treated with safe cooling, intraperitoneal lavage, ice packs in the axillae and groin, and intravascular administration of cold solution. Aggressive hydration to prevent myoglobin-induced renal failure should be started and monitored by urine output and central venous pressure (CVP).

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Patients should be closely monitored until all vital signs and laboratory parameters have been normal for 24 hours. Speed of recovery is dependent on severity of the episode, rapidity of treatment, and development of other sequelae.

MEDICATIONS

DRUG(S) OF CHOICE

Dantrolene sodium inhibits Ca2+ release from the sarcoplasmic reticulum. The dose is 2.5 mg/kg up to 10 mg/kg in the acute period, then 1 mg/kg every 6 hours for 24 to 36 hours. Intravenous dantrolene may be administered intraoperatively. Side effects include muscle weakness, drowsiness, nausea, and phlebitis. Respiratory compromise is uncommon without preexisting or concurrent causes of muscle weakness.

Contraindications

N/A

Precautions

Dantrolene is an antiarrhythmic, increasing atrial and ventricular refractory periods and increasing action potential duration. Administration of dantrolene in the presence of calcium channel blockers may cause hyperkalemia and profound depression of cardiac contractility, but administration for a suspected MH episode should not be held for this reason.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

Creatine kinase measurements are recommended 6, 12, and 24 hours after the initial episode, because CK often peaks 24 to 36 hours after treatment of MH. CK values of greater than 20,000 are almost always associated with an MH episode or other severe myopathy.

EXPECTED COURSE AND PROGNOSIS

Administration of dantrolene and cessation of triggering agents halts the syndrome, Hyperkalemia, associated arrhythmias, and respiratory/metabolic acidosis typically resolve. If rhabdomyolysis was extensive, there may be muscle pain and weakness for weeks to months after resolution of acute MH.

PATIENT EDUCATION

Patients who have an MH episode should be counseled regarding the seriousness and heritability of their condition and should wear a "Ned-alert" bracelet to inform other health-care professionals. First-degree relatives should be considered susceptible. The Malignant Hyperthermia Association of the United States. Phone: 203-847-0407, website www.mhaus.org. 24-hour hotline 800-MH-HYPER.

Miscellaneous

SYNONYMS

N/A

ICD-9-CM: 995.86 Malignant hyperthermia

SEE ALSO: N/A

REFERENCES


Author(s): Miriam Anixter, MD; Barbara W. Brandom, MD
McArdfte's Disease (Myophosphorylase Deficiency, Glycogenosis Type V)

**DESCRIPTION**
McArdfte's disease is a metabolic muscle disease caused by deficiency of the enzyme myophosphorylase.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
McArdfte's disease is a rare condition. No data are available about the exact incidence of the disease. In tertiary neuromuscular clinics one or two new cases are diagnosed every year.

**Race**
No ethnic predominance has been reported.

**Age**
McArdfte's disease can become symptomatic at any age. In most individuals onset of symptoms occurs prior to age 10 years. Rarely the disease affects infants leading to progressive muscle weakness, respiratory insufficiency, and death.

**Sex**
Male predominance.

**ETOLOGY**
McArdfte's disease is caused by the lack of myophosphorylase, the phosphorylase isoenzyme in muscle:

—Myophosphorylase activity is undetectable in muscle biopsies (either by immunohistochromy or direct biochemical analysis) in most patients with McArdfte's disease. Up to 10% of residual enzyme activity can be seen in some cases.

—Myophosphorylase initiates glycogen breakdown by removing 1,4-glucosyl residues from outer branches of the glycogen molecule, resulting in formation of glucose-1-phosphate. In McArdfte's disease the block of this process leads to:
  - Shortage of glycogen-liberated glucose as a source of adenosine triphosphate (ATP), ultimately impairing the operation of adenosine triphosphatases (ATPases) (sodium-potassium ATPase, calcium ATPase, and myosin ATPase) that couple the hydrolysis of ATP to cell work.
  - Lack of normal pH fall during exercise with consequent impaired CK reaction equilibration and exacerbarated rise of adenosine diphosphate (ADP), which, among other actions, can also inhibit ATPases.

—Exactly how these metabolic changes lead to clinical symptoms is unclear.

**Genetics**

The disease is in most cases inherited in an autosomal-recessive fashion. The gene for the muscle phosphorylase has been located in chromosome 11q13. Up to 17 different nonsense, missense, and splice junction mutations have been reported. The Arg49Stop mutation is the most common in North America and Europe, accounting for 63% to 81% of the mutations. The incidence of these mutations varies among ethnic groups. Familes with apparent autosomal-dominant transmission have been described, although these may in fact represent partial expression of disease in heterozygote carriers.

**RISK FACTORS**
N/A

**PREGNANCY**
Labor may constitute an exhausting exercise leading to rhabdomyolysis.

**ASSOCIATED CONDITIONS**
Rhabdomyolysis
Vitamin B₄ deficiency

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

Inherited metabolic myopathies:

—Disorders of carbohydrate metabolism:
  - Abnormal glycolysis metabolism: debrancher enzyme deficiency; phosphorylase bkinase deficiency; Abnormal glycolysis: phosphofructokinase deficiency; Pyruvate kinase deficiency; phosphoglycerate mutase deficiency; lactate dehydrogenase deficiency;
  - Disorders of lipid metabolism: carnitine palmitoyltransferase deficiency; muscle carnitine deficiency
  - Disorders of purine metabolism: myoadenylate deaminase deficiency

—Secondary metabolic myopathies —
  - Endocrine: acromegaly; hypothyroidism; hyperthyroidism; hypoparathyroidism
  - Electrolyte imbalance: hypox- and hypernatremia; hypox- and hypercalcemia; hypokalemia; hyperphosphatemia; hypomagnesemia

—Mitochondrial myopathies

**SIGNS AND SYMPTOMS**
The cardinal symptom of McArdfte's disease is exercise intolerance with myalgia, early fatigue, painful cramps (metabolic contractures) and weakness of exercising muscles. Symptoms typically resolve with rest. Although many different physical activities may precipitate this clinical picture, two types of exercise are likely to cause symptoms: brief efforts involving isometric contraction (e.g., lifting weights) or less intense but sustained dynamic exercise (e.g., walking up a long hill). Walking, on level ground is usually well tolerated. Most affected individuals function well once they adjust their activities to a level below their individual threshold for symptoms and learn they can exercise longer if they allow a brief rest immediately after the first sensation of muscle pain. This phenomenon is called the "second-wind phenomenon" and is attributed to the combination of increased blood flow stimulated by the activity and the ability to mobilize alternative sources of energy (i.e., fatty acids) for muscle work. Exercise-induced muscle necrosis and rhabdomyolysis eventually manifest in -50% of patients; 25% to 50% of these will develop renal failure due to acute tubular necrosis from myoglobinuria. Uncomplicated episodes of myoglobinuria are followed by complete recovery.

There are many variations to this typical presentation. The severity of the symptoms in particular may vary, with some patients complaining only of excessive tiredness and progressive weakness late in life, without cramps or myoglobinuria.

**LABORATORY PROCEDURES**

—Blood work: There is no specific blood test to diagnose McArdfte's disease. However, creatinine kinase (CK)resting level should be obtained since it is moderately increased in 90% of patients. This helps distinguish McArdfte's disease from carnitine palmitoyltransferase deficiency, another major metabolic myopathy causing myoglobinuria, where resting CK is usually normal. Serum electrolytes should be checked to rule out electrolyte imbalance as a cause of the symptoms. Endocrine studies such as thyroid function, parathyroid function, and growth hormone levels should be performed only if the systemic clinical picture suggests these diagnoses.

If rhabdomyolysis is suspected, serum myoglobin, CK, Lactate dehydrogenase, electrolytes, and renal function studies should be monitored.

—Urine studies: urine volume, urine sediment, and myoglobin levels are required only if rhabdomyolysis is suspected.
McArdle’s Disease (Myophosphorylase Deficiency, Glycogenosis Type V)

IMAGING STUDIES
No specific imaging studies are useful in the diagnosis of McArdle’s disease.

SPECIAL TESTS

• Electromyogram (EMG): EMG is often normal between episodes of myoglobinuria but up to half of the patients may show some nonspecific myopathic abnormalities. The muscle tightness is electrically silent, indicating the presence of true contractures.
• Forearm exercise test: This test is performed by having the patient perform repetitive maximum grip sustained for periods of 1.5 seconds separated by rest periods of 0.5 seconds for a total of 1 minute. Venous blood should be drawn for lactate and ammonia levels prior to exercise, and at 1, 2, 4, 6, and 10 minutes after completion of the exercise. In normal subjects, forearm exercise increases venous lactate to three- to fivefold at the first and third minutes of the test. In patients with muscle disorders affecting the glycolytic or glycogenolytic pathways, lactate cannot be released into the circulation and venous levels do not change. Myophosphorylase deficiency is the most common cause for the lack of production of lactate during this test.
• Muscle biopsy: The diagnosis of McArdle’s disease is made by the absence of histochemical staining for myophosphorylase in muscle fibers, while it remains positive in vessel walls. False-positive results can be found in patients with low residual activity or when the fetal phosphorylase isoform is transiently expressed in regenerating fibers after rhabdomyolysis. Additionally, in light microscopy, subsarcolemmal or intermyofibrillar deposits of periodic acid-Schiff (PAS)-stained glycogen can be seen. The muscle can also be sent for direct biochemical assay of myophosphorylase.
• P-31 magnetic resonance spectroscopy: Concentrations of ATP and creatine phosphate are normal at rest but, with exercise, the expected decrease in pH is not seen due to the lack of production of lactate, and the recovery of energy-rich metabolites to baseline is delayed. This tool is essentially used in research protocols.

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
The diagnosis is usually made in the outpatient setting, and no emergency conditions are associated with the disease except for acute rhabdomyolysis following periods of intense exercise with the consequent risk for acute tubular necrosis.

DRUGS OF CHOICE
Myophosphorylase is the major repository of vitamin B6 in the body, accounting for 80% of the total body pool. Some patients with McArdle’s disease may show signs of subclinical vitamin B6 deficiency and have reported greater resistance to fatigue with oral vitamin B6 supplementation.

ALTERNATIVE DRUGS
None

Follow-Up

PATIENT MONITORING
No specific monitoring is required.

EXPECTED COURSE AND PROGNOSIS
Fixed proximal weakness, especially in the shoulder girdle, will appear in up to one third of patients later in life.

PATIENT EDUCATION
Patient should be instructed, especially in childhood, to avoid intense exercise because of the risk of acute rhabdomyolysis. Patients can contact the Muscular Dystrophy Association for educational programs and updates in research and treatment.


MANAGEMENT

GENERAL MEASURES
There is no specific therapy for McArdle’s disease but combined aerobic exercise programs and high-protein diets have had positive effects in some cases.

SURGICAL MEASURES
Not applicable

SYNONYMS
Myophosphorylase deficiency
Glycogenosis t o V

ICD-9-CM: 330.8 Glycogenosis, myophosphorylase deficiency, or McArdle’s disease
SEE ALSO: RHABDOMYOLYSIS

REFERENCES

Author(s): Carmen Serrano-Munuera, MD
Meniere's Disease and Syndrome

**DESCRIPTION**

Meniere's triad of vertigo, hearing loss, and tinnitus is associated with swelling of the endolymphatic space. Meniere's disease denotes idiopathic endolymphatic hydrops; Meniere's syndrome denotes secondary endolymphatic hydrops.

**EPIDEMIOLOGY**

Incidence and Prevalence

Incidence estimates vary widely from 15 to 50 per 100,000, with prevalence about 220 cases per 100,000.

- **Age**: Characteristically an affliction of adults, and quite unusual in children.
- **Sex**: It has very modest female predominance, slight left ear predominance, and often positive family history. Confusion between disease and syndrome confounds the epidemiology.

**ETIOLOGY**

Typical early endolymphatic distention in the scala media extends to the saccule. Later hydrops occurs in the utricle and vestibular labyrinth. Rupture of the membranous labyrinth admixes perilymph with endolymph. Thereupon a transient improvement of hearing (Lemoyez phenomenon) may occur. Etiopathogenic possibilities include vascular insufficiency, endolymph overproduction, electrolyte or osmotic pressure shifts, impaired endolymphatic flow, or inadequate endolymph resorption. Current consensus favors the latter. The etiology remains controversial.

**Genetics**

Heterogenous Meniere's disease families have been described: These rare clusters likely make a minor contribution to overall disease burden.

**RISK FACTORS**

- Trauma (labyrinthine concussion, acoustic trauma; temporal bone fracture; fenestration of the otic capsule)
- Inflammation (autoimmune ear disease; Cogan's syndrome)
- Infection (otosyphilis; viral labyrinthitis)
- Infiltration (leukemia, as in Meniere's original patient; Paget's disease; von Hippel-Lindau-associated neoplasms; histiocytosis)
- Effusion (chronic otitis media; serous labyrinthitis)
- Malformations (Mondini's cochlear dysplasia)
- Endocrine/metabolic (thyroid; diabetes)
- Electrolyte/osmolality shifts

**PREGNANCY**

Attacks associated with decreased serum osmolality in gravid women and premenstrual attacks associated with fluid retention have been well reported.

**ASSOCIATED CONDITIONS**

N/A

**SIGNS AND SYMPTOMS**

Episodes of vertigo lasting from minutes to hours are superimposed on fluctuating hearing loss, aural fullness, and tinnitus. This tetrad varies between patients and over time. Patients often confine true vertigo, with an after-going sense of instability. Cross-coupled accelerations in the semicircular canals (Coriolis effect) may exacerbate vertigo, lightheadedness, suggesting other, disorders. Hydrops starting in the basilar cochlea and leading to rupture of Reissner's membrane at the innercochlea gives the auditory illusion of deafness. Convulsive sensory disturbances may result in palpitations, inappropriate sensitivity to loud sounds, Cacophonous distortion, muffling, and sometimes diplopia occur. Abnormal pressure dynamics in the membranous labyrinth may cause the "otolitic crisis" of Tumarkin, a sudden drop attack in which the fully conscious patient is thrown to the floor. Pneumatic pressure—induced nystagmus (Hennebert's sign) may be seen. Valsalva or pressure-induced dizziness (Hennebert's symptom) and sound-induced dizziness (Tullio phenomenon) can also occur. In late-stage symptoms become chronic and urmitt. Atypical Meniere's disease denotes predominantly vestibular or auditory variants. Presumably str'uctures in the ductus reuniens or ucricular duct result in isolated cochlear or vestibular hydrops. Unilateral onset is typical. Over time bilateral disease features emerge in 10% to 60%. Contralateral fast-phase nystagmus is seen with attacks. Brief ipsilateral recovery nystagmus" sperevens in attack resolution.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

Episodic vertigo occurs with perilymph fistula, migraine, vestibular neuritis, benign paroxysmal positioning vertigo, viral labyrinthitis, and vestibular ataxia. Semeiogomy, otosyphilis, endolymphatic sac tumors, brain tumor mass, presbycusis, and otosclerosis can masquerade as Meniere's disease. Rarely cerebellar degenerations and familial episodic ataxia must be considered. Ataxic seizures mimic otolithic crises.

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**LABORATORY PROCEDURES**

No laboratory tests confirm Meniere's disease. Autoimmune disease panel, systemic inflammation markers, RAST, FTA-ABS, thyroid studies, metabolic panel, and CBC evaluate the differential possibilities.

**IMAGING STUDIES**

MRI and MRA are appropriate for suspected vertebrobasilar insufficiency, neurovascular compression, acoustic neuroma, multiple sclerosis, etc. High-resolution temporal bone CT may show dehiscence of the superior semicircular canal. High-resolution MRI visualized the endolymphatic duct significantly less often in Meniere's patients than in controls. Focused temporal bone MRI detected swelling of the scala media. The primary role of imaging is to exclude other structural pathology.

**SPECIAL TESTS**

- Pure tone audiometry is important. Few causes of low-frequency sensorineural hearing loss give an up-sloping audiogram like early Meniere's disease. With progressive disease, the audiogram becomes peaked about 2000 Hz. Thereafter it becomes uniformly depressed or "flat." Speech audiometry is worse than predicted because of distortion and correlates well with subjective complaints.
- Electrocochleography (ECoG) is a very promising short latency evoked response to auditory clicks, in which the summing potential (SP) is sensitive to cochlear basilar membrane distortion. An elevated ratio of SP to action potential (AP) appears to be quite specific but not very sensitive for endolymphatic hydrops.
- Electroencephalography (ENG) with bi-thermal caloric testing may show vestibular paresis (>25% decrease in the affected ear), but is not very sensitive and less specific than ECoG. Caloric responses vary with disease stage and the recency of the last attack.
- Rotational chair testing may show decreased gain, increased phase lead, and sometimes an asymmetry toward the affected side, as in any peripheral vestibular paresis.
- Spontaneous nystagmus can be seen on ENG or with Frenzel goggles. Nystagmus may be elicited by rapid back-and-forth head shaking for 30 seconds, abruptly stopping in the central position and viewing through Frenzel lenses.
- Marching in place with eyes closed and arms extended forward will result in a gradual rotation of the patient toward the paretic labyrinth.
- Osmotic diuresis test seeks improvement in baseline audiometry 1 to 3 hours after ingestion of a powerful diuretic (typically glycerol), suggesting endolymphatic hydrops.
Meniere's Disease and Syndrome

Management

GENERAL MEASURES
A strict low-sodium diet (1.5 to 2.0 g/d) is universally recommended. Stricter restrictions are arguably more effective. Some advocate avoiding caffeine, chocolate, tobacco, stimulants, stress, and alcohol.

SURGICAL MEASURES
• Nondestructive surgery includes endolymphatic sac stent or shunt procedures. Still quite popular, fibrous overgrowth and success rates indistinguishable from placebo are concerns. Endolymphatic duct stent and cochleosacculectomy have been advocated. Myringotomy and tympanic ventilation tubes have been supplemented by pressure chamber treatments. Recently pressure oscillation through a tympanostomy tube has been used.
• Destructive (ablative) surgery: For medically intractable disease, vestibular neurectomy, intratympanic injection of ototoxic drugs (usually gentamicin or streptomycin), and surgical labyrinthectomy (for those without functional hearing in the affected ear) have all been used. Surgical oto logic consultation is recommended only after medical therapy has failed. Since Meniere's disease can become bilateral, destructive procedures require appropriate circumspection.

SYMPTOMATIC TREATMENT
During attacks vestibular suppressants (diazepam or medazepam and antiemetics [prochlorperazine, promethazine, dimenhydrinate, and trimethobenzamide]) are useful. Glycopyrrolate is helpful in milder cases.

ADJUNCTIVE TREATMENT
Vestibular rehabilitation may augment central compensation for peripheral vestibular loss in the late chronic stage. Some advocate extension to early disease, although dysequilibrium often substantially remits between attacks.

ADMISSION/DISCHARGE CRITERIA
Medical admission rarely may be indicated to investigate worrisome alternate diagnoses.

Medications

DRUG(S) OF CHOICE
Diuretics: Mild diuresis with hydrochlorothiazide/triamterene or similar regimen is customary. Acetazolamide should be optimal since dark cells in the labyrinth and the stria vascularis use carbonic anhydrase, but usually it is less clinically useful.

Histamine: Betahistine is a first-line European agent, ostensibly to provide vasodilatation in the labyrinth.

Medical ablation: Historically a selective vestibular toxin was advocated to ablate noisome vertigo.

Contraindications
Anuria or renal failure; elevated serum potassium; avoid combination with multiple potassium-sparing diuretics.

Precautions
Gout; lupus; diabetes; hepatic, renal, or chronic pulmonary disease. Pregnancy category D.

ALTERNATIVE DRUGS
Only diuretics and betahistine have controlled randomized trial support. Local and systemic corticosteroids have been used, as well as other immunosuppressives (azathioprine and methotrexate). No controlled trials support frequently used antihistamines. Empirically, vasodilators and calcium channel blockers have been tried.

PATIENT MONITORING
Symptomatic treatment during attacks and regular office visits for dietary and medical management may be combined with periodic audiometry and bithermal caloric ENG.

EXPECTED COURSE AND PROGNOSIS
Unilateral onset of a fluctuating auditory and vestibular decline is punctuated by repeated vertiginous attacks of generally declining frequency. Some contralateral involvement increases from 10% to 15% at 2 years to 30% to 60% at 15 years. Medical treatments do not alter the prognosis for hearing or vestibular loss. Likewise, surgical procedures ablating vertigo do nothing to preserve hearing and may impair it. Some patients have only a few vertiginous spells, mild hearing loss, and a stable course. Others have lifelong relapsing attacks with gradual decline. A minority have an aggressive, unrelenting course with only brief remissions until profound deafness and dysequilibrium ensue. The course of auditory and vestibular symptoms can be independent. Isolated vestibular variants usually, but not always, evolve into more typical forms. Consider other diagnoses if no auditory features emerge after a reasonable time.

PATIENT EDUCATION
Nutritional counseling and repeated encouragement of a low-sodium diet are suggested.

DIZZINESS/VERTIGO

SYNONYMS
Endolymphatic hydrops

ICD-9-CM: 386.00 (01 cochleovestibular; 26.00 (02 cochlear; 03 vestibular; 04 in remission)

SEE ALSO:

REFERENCES

Author(s): Robert W. Jensen, MD, JD
Meningitis, Acute Bacterial

DESCRIPTION
Acute bacterial meningitis (ABM) is an inflammation of the meninges due to bacterial infection, which, if not treated promptly and appropriately, results in neurologic morbidity and high mortality.

EPIDEMIOLOGY
Incidence/Prevalence
In 1995, a report showed that a total of 5,755 cases of ABM were caused by five major pathogens in the United States: Streptococcus pneumoniae (1.1 cases/100,000 persons), Neisseria meningitidis (0.6/100,000), group B streptococcus (0.3/100,000), Listeria monocytogenes (0.2/100,000), and Haemophilus influenzae (0.2/100,000).

Race
There is no evidence of any ethnic predominance.

Age
The disease occurs in all ages.

Sex
Males and females are equally affected.

ETIOLOGY
The most common pathogens responsible for ABM vary by age group. Among neonates, group B streptococcus (Streptococcus agalactiae) is the most common pathogen. While H. influenzae type B (HIB) was formerly the most common among children of ages 1 month to 4 years, widespread use of the HIB vaccine has dramatically reduced the incidence of this pathogen; and S. pneumoniae (pneumococcus) and N. meningitidis (meningococcus) are now the predominant pathogens in this age group. In older children, ages 5 to 18 years, and adults, pneumococcus and meningococcus are most common, while pneumococcus, L. monocytogenes, and Gram-negative bacilli are most common in older adults over age 50.

• A subset of patients who have had head trauma, neurosurgery, or CSF shunt are at risk for ABM secondary to Staphylococcus spp., Gram-negative bacilli, as well as pneumococcus.

• ABM pathogens generally colonize the nasopharyngeal mucosa of the host, enter the intravascular space, cross the blood–brain barrier, and multiply aggressively in the CSF. There is a paucity of antibody and complement in the CSF, resulting in inefficient phagocytosis of the bacteria. Cytokines contribute to brain edema and elevated intracranial pressure.

Genetics
Complement deficiency is a risk factor for meningococcal disease. Late complement deficiency (C5, C6, C7, C8, or C9) is associated with recurrent meningococcal disease.

RISK FACTORS
Cases of ABM are generally sporadic, though close contact may play a role in some cases. For example, close contacts of patients with meningococcal meningitis may be at risk for developing the disease. One study did suggest that college students residing on campus may be at higher risk of ABM due to N. meningitidis. Rifampin, ciprofloxacin, or ceftriaxone may be used to eradicate nasal carriage of this organism. The meningococcal vaccine may also be useful in this population. Children under age 2 who have not been vaccinated with the HIB vaccine are at risk of ABM secondary to this organism. Rifampin or ceftriaxone in children and adults, and ciprofloxacin, rifampin, or ceftriaxone in adults, may be used as prophylaxis if a patient comes into contact with a child with HIB ABM. Other risk factors may include the following:

• Closed head injury with skull fracture or disruption of the cribiform plate

• Parameningeal infections such as sinusitis, chronic otitis, and mastoiditis

• Anatomic defects such as pilonidal sinuses, meningomyeloceles, and meningial disruption

• Sickle cell anemia and splenectomy may predispose to meningitis due to encapsulated organisms

PREGNANCY
Little is known regarding ABM in pregnancy.

ASSOCIATED CONDITIONS
N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

• Infectious etiologies:
  —Viral meningitis
  —Encephalitis
  —Brain abscess
  —Fungal meningitis
  —Mycobacterial meningitis
  —Primary HIV infection

• Noninfectious etiologies:
  —Benign or malignant brain tumor
  —Cerebrovascular accident
  —Sarcoidosis
  —Systemic lupus erythematosus
  —Wegener’s granulomatosis
  —CNS vasculitis
  —Arachnoiditis
  —Migraine
  —Drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole, and OKT3

SIGN AND SYMPTOMS
The classic signs and symptoms of ABM are fever, headache, photophobia, and nuchal rigidity. Less common is vomiting, focal neurologic changes (particularly cranial nerves III, IV, VI, and VII), seizures, and somnolence. Symptoms generally develop rapidly, and ABM should be considered a medical emergency.

LABORATORY PROCEDURES
Baseline blood work should include CBC and differential, blood cultures, serum electrolytes and glucose, liver function tests, and an HIV test.

IMAGING STUDIES
Head CT is useful in patients with coma, papilledema, or focal neurologic signs, but is otherwise not indicated. Obtaining an imaging study should not prevent immediate blood cultures and prompt administration of antibiotics. If no mass effect is seen on imaging, an immediate lumbar puncture should be done.

SPECIAL TESTS
• CSF obtained by lumbar puncture is the most important and accurate diagnostic tool. Opening pressure, Gram stain, CSF culture, protein, glucose; and cell count and differential should be done at a minimum. Latex agglutination for bacterial antigens, may be useful if the patient has had prior antibiotic therapy. Opening pressure is typically elevated. In 80% of cases, the organism should be visible on Gram stain. There is usually a neutrophilic pleocytosis (>1,000 WBC cells/mm³), with a predominance of neutrophils. CSF protein is almost always elevated, and hypoglycorrhachia is common. Very rarely, CSF may be normal, particularly in immunocompromised patients, neonates, or in those patients very early in the course of their disease.

• Gram stain is very useful for tailoring antibiotic therapy, although prior antibiotic therapy may make it difficult to interpret.
Meningitis Acute Bacterial

Management

**GENERIC SELF-ASSESSMENT**

- Prompt administration of empiric antibiotics is the most important therapeutic modality. Delay of antibiotic administration has been related to increased neurologic morbidity and mortality. Antibiotic therapy should initially be directed at the most likely pathogens, then tailored specifically to the Gram stain or culture data when available. Infectious disease specialists should be consulted, as antibiotic resistance patterns, particularly of Staphylococcus aureus and HIB, vary widely from region to region.

- Close monitoring is essential, and many of these patients may need endotracheal intubation for airway protection. In patients with elevated intracranial pressure, high-dose dexamethasone, hyperosmolar agents, or hyperventilation may be needed.

- In patients over 2 years of age with ABM due to known or suspected HIB, dexamethasone therapy should be started just prior to antibiotics, because it has been shown to decrease neurologic morbidity. Dexamethasone may also be useful in adults with ABM, but only if there is evidence of elevated intracranial pressure.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

Symptomatic treatment includes management of fevers, antiepileptic drugs for secondary seizures, analgesics for headache, and hydration.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

Patients are admitted for parenteral antibiotics when the diagnosis of meningococcal meningitis is classified; 320.89 Meningitis due to other bacterial diseases not elsewhere classified elsewhere; 320.3 Streptococcal meningitis; 320.4 Staphylococcal meningitis; 320.7 Meningitis in other bacterial diseases classified elsewhere; 320.81 Anaerobic meningitis; 320.82 Meningitis due to Gram-negative bacilli not elsewhere classified; 320.89 Meningitis due to other species of bacteria.

**Symptoms**

- Fever
- Photophobia
- Nuchal rigidity
- Headache
- Seizures

**Follow-Up**

**PATIENT MONITORING**

Once hemodynamically and neurologically stable, close monitoring is not indicated. Follow-up lumbar puncture and MRI or CT may be useful in patients who have uncommon pathogens (e.g., Gram-negative bacilli, Staphylococcus aureus, etc.) or whose clinical course does not improve as expected. These may aid in evaluation of possible parameningeal focus of infection, and evaluate for complications such as cortical vein thrombosis or subdural empyema.

**EXPECTED COURSE AND PROGNOSIS**

Overall morbidity in adults in 1995 was 25%. In another recent study, 81% of children had developmental delay and neurologic sequelae after Gram-negative bacillary meningitis. These two reports emphasize the need for the rapid use of antibiotics in patients suspected of having ABM. Despite appropriate therapy, many of these patients will have high morbidity and a variety of neurologic sequelae. Many will require physical and occupational therapy after their illness, and some will have massive neurologic deficits.

**PATIENT EDUCATION**

Information is available on the World Wide Web at http://www.cdc.gov/ncidd/dhdx/education or http://www.meningitis.org. Also, the Meningitis Foundation of America Inc. may be contacted for information at 7155 Shadeland Station, Suite 190 Indianapolis, Indiana 46236-3922. Phone 800-668-1129.

**Medications**

**DRUGS OF CHOICE**

Empiric Antibiotics

- Age <3 months: ampicillin 100 mg/kg IV q8h plus broad-spectrum cephalosporin such as cefotaxime 50 mg/kg IV q8h or ceftriaxone 50–100 mg/kg IV q24h
- Age 3 to <18 years: broad-spectrum cephalosporin such as cefotaxime 50 mg/kg IV q8h or ceftriaxone 50–100 mg IV q24h
- Age 18 to <50 years: broad-spectrum cephalosporin such as cefotaxime 2 g IV q8h or ceftriaxone 2 g IV q24h plus vancomycin 1 g IV q24h
- Age 50 and above: ampicillin 2 g IV q4h plus broad-spectrum cephalosporin such as cefotaxime 2 g IV q8h or ceftriaxone 2 g IV q24h plus vancomycin 1 g IV q24h
- Patients with impaired cellular immunity: ampicillin 2 g IV q4h plus ceftazidime 2 g IV q8h
- Patients who have head trauma, are neurosurgical patients, or who have a CSF shunt: vancomycin 1 g IV q24h plus ceftazidime 2 g IV q8h
- Dexamethasone dosing is 0.15 mg/kg IV q6h for 4 days for both children and adults.

**Contraindications**

History of allergic reaction to specific antibiotics is a contraindication to their use.

**Precautions**

None

**ALTERNATIVE DRUGS**

Space is too limited to list alternative regimens for each suspected pathogen; consultation with an infectious disease specialist is recommended.

**REFERENCES**


**AUTHORS:** Thomas C. Keeling, MD; Susan L. Koletar, MD

**SYNONYMS**

Bacterial meningitis

**ICD-9:CM:** 306.0 Meningococcal meningitis; 320 Bacillary meningitis; 320.1 Haemophilus meningitis; 320.2 Pneumococcal meningitis; 320.3 Streptococcal meningitis; 320.4 Staphylococcal meningitis; 320.7 Meningitis in other bacterial diseases classified elsewhere; 320.81 Anaerobic meningitis; 320.82 Meningitis due to Gram-negative bacilli not elsewhere classified; 320.89 Meningitis due to other species of bacteria.
Meningitis, Aseptic

DESCRIPTION
Aseptic meningitis is a generic term encompassing a range of conditions that is characterized by an inflammation of the meninges without a readily identifiable bacterial cause after initial stains and culture of the CSF. It is most commonly viral in etiology.

ETIOLOGY

Incidence/Prevalence
Approximately 10,000 cases of aseptic meningitis are reported in the United States each year. There is summertime predominance, corresponding to enterovirus infections, the primary cause of aseptic meningitis.

Race
There is no evidence of any ethnic predominance.

Age
There is no known age predominance.

Sex
Males and females are equally affected.

ASSOCIATED CONDITIONS
N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Infectious etiologies
  - Viral meningitis
  - Partially treated bacterial meningitis
  - Encephalitis
  - Brain abscess
  - Fungal meningitis
  - Mycobacterial meningitis
  - Primary HIV infection
- Noninfectious etiologies — Benign or malignant brain tumor — CNS vasculitis — Systemic lupus erythematosus — Wegener's granulomatosis — Arachnoiditis — Medications

SIGNS AND SYMPTOMS
The classic signs and symptoms of aseptic meningitis are fever, headache, photophobia, and nuchal rigidity. Also common is vomiting. Focal neurologic deficits, seizures, and significant lethargy are unusual in aseptic meningitis. Usually the symptoms are acute, but occasionally may begin after several days or even weeks of fever or systemic illness.

LABORATORY PROCEDURES
Baseline blood work should include CBC and differential, blood cultures; serum electrolytes and glucose, liver function tests, and an HIV test.

IMAGING STUDIES
Head CT is useful in patients with coma, papilledema, or focal neurologic signs, but is otherwise not indicated. Obtaining an imaging study should not prevent immediate blood cultures and prompt administration of antibiotics if the patient is critically ill. If no mass effect is seen on imaging, an immediate lumbar puncture should be done.

SPECIAL TESTS
- CSF obtained by lumbar puncture is the most important and accurate diagnostic tool. Opening pressure; Gram stain; CSF culture for bacteria, fungi, and virus; and protein and cell count and differential should all be done. Opening pressure is typically elevated. CSF WBC is usually less than 500 cells/µL, and can be less than 200 WBC/mm³. Mononuclear cells are the most common leukocyte found in the CSF pleocytosis of aseptic meningitis. CSF glucose is generally normal, and CSF protein is usually normal to slightly elevated.
- Latex agglutination for bacterial antigens may be useful if the patient has had prior antibiotic therapy, and partially treated bacterial meningitis is being considered as the diagnosis. If warranted by the physical exam, other tests that may be useful include CSF cryptococcal antigen, acid-fast stain and culture, serum RPR and CSF VDRL, wet mount for amebic trophozites, viral culture of CSF, and HSV polymerase chain reaction (PCR). If the patient continues to deteriorate, a meningococcal or brain biopsy may be necessary.
Management

GENERAL MEASURES

Treatment is primarily supportive. Many patients can be treated symptomatically at home, but others may require admission. Criteria for admission may include profound headache, nausea, vomiting, or CSF pleocytosis with a polymorphonuclear leukocytes predominance that may require empiric treatment for acute bacterial meningitis. Oral acyclovir may be useful if herpes meningitis secondary to primary HSV infection is suspected.

SURGICAL MEASURES

There are no surgical measures for aseptic meningitis.

SYMPTOMATIC TREATMENT

Symptomatic treatment addresses pain control, relief of fever, and gentle rehydration.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

Patients are admitted if the clinician feels the symptoms are severe enough to warrant admission, or if there is concern about bacterial meningitis with CSF pleocytosis and polymorphonuclear leukocyte predominance. Patients are discharged when their symptoms allow.

Medications

DRUG(S) OF CHOICE

- Analgesics and antipyretics as necessary
- Herpes: acyclovir 200 mg PO 5x/day for 10 days.
- Partially treated bacterial meningitis: ceftriaxone 2 g IV q12h or cefotaxime 2 g IV q6.
- Other pathogens, if found, should be treated with the appropriate therapy.

Contraindications

Known hypersensitivity to a particular agent.

Precautions

N/A

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

If hemodynamically and neurologically stable, close monitoring is not indicated.

EXPECTED COURSE AND PROGNOSIS

Prognosis is excellent. Most cases of aseptic meningitis are self-limited with no sequelae. In other cases, prognosis is dependent on the underlying etiology.

PATIENT EDUCATION

The Meningitis Foundation of America Inc. may be contacted for information at 7155 Shadeland Station, Suite 190 Indianapolis, Indiana 46256-3922. Phone 800.668-1129, website http://www.musa.org. You may also contact your local health department for more information.

Meningitis, Aseptic

SYNONYMS

Viral meningitis
Aseptic meningitis
Meningitis

ICD-9-CM: 047 Meningitis due to enterovirus (includes aseptic meningitis and viral meningitis)

This excludes the following: 049.1 Meningitis due to enterovirus; 060.0-066.9 Meningitis due to arbovirus; 054.72 Meningitis due to herpes simplex virus; 053.0 Meningitis due to varicella zoster virus; 049.0 Meningitis due to lymphocytic choriomeningitis virus; 072.1 Meningitis due to mumps virus; 047.0 Meningitis due to coxsackie virus; 047.1 Meningitis due to ECHO virus; 047.9 Meningitis due to virus not otherwise specified

SEE ALSO: MENINGITIS, ACUTE BACTERIAL; AND MENINGOENCEPHALITIS, CRYPTOCOCCAL

REFERENCES


Author(s): Thomas C. Keeling, MD; Susan L. Kol etar, MD

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Meningoencephalitis, Cryptococcal

**DESCRIPTION**
Cryptococcal meningoencephalitis is caused by fungal infection of both the meninges and underlying brain parenchyma by Cryptococcus neoformans. It is the most common cause of fungal meningitis in the United States and an increasingly important opportunistic infection in immunosuppressed patients.

**Epidemiology**
Cryptococcal meningoencephalitis is rare in individuals without impaired cellular immunity. The incidence of cryptococcal meningitis among HIV-infected individuals ranges from 6% to 10%. Cryptococcosis is an AIDS-defining illness in about 40% of these cases.

**Risk Factors**
Conditions associated with defects in cell-mediated immunity such as HIV infection, organ transplantation, prolonged corticosteroid treatment, malignancy, and sarcoidosis.

**Pregnancy**
N/A

**Associated Conditions**
As above.

**Diagnosis**

**Differential Diagnosis**
- Infectious
  - Viral meningitis
  - Encephalitis
  - Brain abscess
  - Fungal meningitis
  - Mycobacterial meningitis
  - Toxoplasmosis
  - Primary HIV infection
  - Syphilis
  - Progressive multifocal leukoencephalopathy
- Noninfectious
  - Malignancy
  - CNS vasculitis
  - Cerebrovascular accident
  - Lymphomatous meningitis
  - Leukoencephalopathy

**Onset**
Onset of CNS cryptococcosis may be acute or insidious. Autoimmune phenomena are more common in the immunosuppressed patient. Immune compromise such as in AIDS results in a higher burden of organisms and diminished inflammatory response. Most common symptoms are fever, malaise, and headache. There is typically minimal or no nuchal rigidity. Clinical illness is rarely fulminant, and the subacute onset of symptoms and nonspecific presentation can make it difficult to diagnose. In the immunocompetent host, symptoms may follow a more chronic course over weeks to months. Most present with signs and symptoms of subacute meningitis or meningoencephalitis.

**Laboratory Procedures**
- CSF examination including examination with India ink. Opening pressure may be markedly elevated (>200 mm H2O), especially in patients with AIDS, and India ink smears show typical encapsulated yeast forms. Gram stain is usually not sufficient since the organisms can be confused with host cells. Cell counts are characteristically low (<50/µL) in AIDS associated infection and higher in non-AIDS cases with lymphocyte predominance.
- Protein and glucose levels are usually only slightly abnormal; with elevated protein and depressed glucose more common in normal hosts. Culture is needed to confirm the diagnosis. Negative cultures do not absolutely rule out infections as only small numbers of organisms are present in some CSF and may be missed. Therefore, large specimens of CSF may be required for diagnosis.
- Extraneural disease is more common in the immunocompromised host. Urine, sputum, and blood cultures should be obtained and any suspicious skin and soft tissue lesions should be cultured and/or biopsied.

**Imaging Studies**
Any immunocompromised patient with central neurologic dysfunction should undergo CT scan or MRI to exclude possible space-occupying lesions and/or detect hydrocephalus. CT scan of the head is abnormal in up to 30% of AIDS patients with cryptococcal meningitis. Most common abnormalities are cortical atrophy and varying degrees of ventricular enlargement without focal lesions or enhancement. Cryptococcomas can be either single or multiple and occur in up to 25% of patients.

**Special Tests**
Cryptococcal antigen assay is highly sensitive and specific for detection of C. neoformans infection. Antigen can be detected in both serum and in CSF, and may be positive before identification of the organism in culture. Antigen presence implies extrapulmonary involvement and necessitates careful evaluation for site of infection. The height of the antigen titer correlates with the burden of organisms. Serial measurement of antigen titers may be useful in following therapy and to predict relapse in immunocompetent patients, but of limited value in AIDS patients.
Management

GENERAL MEASURES
Treatment involves initiation of antifungal therapy and supportive care. Treatment options depend on the host immune status. In the non-HIV infected, goal is cure of the infection with CSF sterilization and prevention of long-term neurologic sequelae. In those with coexisting HIV, therapeutic goals are to achieve clinical remission and to prevent relapse with chronic suppressive therapy.

SURGICAL MEASURES
Surgery is rarely required in patients with mass lesions.

SYMPTOMATIC TREATMENT
Supportive care.

ADJUNCTIVE TREATMENT
Systemic corticosteroids may be given for mass lesions with significant edema. Patients with increased intracranial pressure (>200 mm H₂O) may respond to removal of large volumes of CSF with daily lumbar punctures. Lumbar drains or ventricular shunts may be necessary for patients who require more frequent fluid removal for symptom control. Corticosteroids, acetazolamide, and mannitol have no benefit in the management of elevated intracranial pressure.

ADMISSION/DISCHARGE CRITERIA
Patients are admitted for further evaluation, parental antibiotics, and careful monitoring.

Medications

DRUG(S) OF CHOICE
HIV-negative: induction course of amphotericin B (0.5-1 mg/kg/d) with flucytosine (100 mg/kg/d) for 2 weeks, followed by consolidation therapy with fluconazole (400 mg/d) for an additional 8 to 10 weeks. Optimal duration of consolidation therapy varies from 3 to 6 months.

HIV-positive: induction course of amphotericin B (0.7-1 mg/kg/d) combined with flucytosine (100 mg/kg per in four divided doses) for 2 weeks, followed by consolidation therapy with fluconazole (400 mg/d) for 8 to 10 weeks or until CSF sterile. In conjunction with antiretroviral therapy, lifelong maintenance therapy with fluconazole (200 mg/d) should be administered. Contraindications None except systemic allergy.

Precautions
Adverse side effects of amphotericin B include renal injury, nausea, vomiting, chills, fever, and rigors. Fluconazole dosage must be adjusted on basis of hematologic toxicities. It is necessary to carefully monitor serum electrolytes, renal function, and bone marrow function.

ALTERNATIVE DRUGS
In the setting of significant infusional toxicities or renal failure on conventional amphotericin B, liposomal preparations have been shown to be effective and less toxic. For patients unable to tolerate fluconazole, itraconazole (200 mg twice daily) may be substituted. Salvage therapy with intrathecal or intraventricular amphotericin B may be used in refractory cases.

Follow-Up

PATIENT MONITORING
All patients should be monitored for evidence of elevated intracranial pressure. Treatment decisions should not be based routinely or exclusively on CSF or serum cryptococcal antigen titers. In HIV-negative patients, lumbar puncture is recommended after 2 weeks of treatment to assess the status of CSF sterilization. Patients with cryptococcosis involving any site should be evaluated every few months for at least 1 year after therapy. Relapses are more common in chronically immunosuppressed patients, so prolonged therapy is often indicated and close follow-up throughout initial and maintenance therapy is crucial.

EXPECTED COURSE AND PROGNOSIS
Overall mortality has improved with recommended antifungal treatment regimens. However, certain immunosuppressed patients remain at increased risk for more rapid mortality or treatment failure. The most important prognostic factor is the level of immunocompetence. Most patients with no apparent immunosuppression can expect to be cured of the infection with no significant impact on survival. In HIV-negative patients, increased mortality is associated with the following: (a) positive India ink examination of the CSF, (b) CSF WBC count >200/cuL, (c) initial CSF or serum cryptococcal antigen titer >1:128, (d) extraneural sites of infection, and (e) high opening pressure on lumbar puncture. Furthermore, those who relapse after treatment typically have one or more of the following: (a) persistently low CSF glucose concentrations after 4 weeks of therapy, (b) low initial CSF WBC, (c) posttreatment CSF or serum antigen titers of >1:8, and (d) treatment with at least 20 mg of prednisone or its equivalent after completion of therapy. In HIV-positive patients, significant predictors of death during initial therapy are (a) abnormal mental status, (b) CSF antigen titer >1:1024, and (c) CSF WBC >20/cuL.

PATIENT EDUCATION

REFERENCES


Author(s): Jennifer L. Klaus, MD
**Mental Retardation**

**Basics**

**DESCRIPTION**
- Mental retardation (MR) is defined as:
  - Intelligence quotient (IQ) <70.
  - At least 2 of 10 areas of impaired adaptive functioning such as social, occupational, health/safety skills [see Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), for complete list]. Onset <18 years.
- DSM-IV subclassifies MR by IQ:
  - Mild MR: 50-55 to 70
  - Moderate: 50-55 to 35-40
  - Severe: 35-40 to 20
  - Profound: <20
- Note:
  - Mixed population, etiologically and clinically.
  - A given IQ score/severity does not imply similar abilities across all cognitive/functional domains.
  - MR may not be lifelong/static
- Borderline intellectual functioning (BIF): IQ of 70 to 90

**EPIEIDEMIOLOGY**

**Prevalence**
- For MR (after DSM-IV): 1% or less

**Race**
- Affects all races.

**Age**
- Grade-school age (97/1,000 MR children)
- Infancy-preschool age (1/1,000)
- Note: Borderline/mild MR may not be detected until school-age years.

**Sex**
- Male/female ratios:
  - Severe MR, 1.4-1.8:1
  - Mild MR, 2:5:1
- Perhaps due to possible greater male predominance in:
  - Fetal neonatal mortalities
  - Phenotypic expression of X-linked disorders

**ETIOLOGY**

Two-group model (may be oversimplified):
- Mild MR (75%-80% of the MR population) is more often familial, cultural or polygenic, idiosyncatic, and without physical stigmata/comorbidity
- Severe MR (5%-10%) is most often sporadic, due to identifiable brain injury/causae and a associated with physical stigmata/comorbidity

**Time and Cause of Injury**
- Unknown timing/causae: 12% to 55%
- Prenatal: 2% to 73%
  - Genetic: 32%
    - Maldistribution/aneuploidy: most common genetic cause (e.g., trisomy 21)
  - Inborn errors of metabolism, neurocutaneous disorders
  - Malformations (genetic, structural, migration disorders, unknown): 8% (e.g., neural tube defects)
  - Environmental/Exogenous: 12%-17% (Rubella, HIV, cytomegalovirus, eclampsia, placental abnormalities, teratogens, radiation exposure, malnutrition, etc.)
- Perinatal: 10% to 20%
- Environmental/exogenous:
  - Delivery complications
  - Infections (e.g., herpes simplex, toxoplasmosis, syphilis, HIV)
- Unknown/other
  - Postnatal: 2% to 10%
- Environmental/exogenous/acquired
  - Toxins (e.g., lead, pica, carbon monoxide, medications, substance/alcohol abuse)
- Infections (e.g., meningitis/encephalitis) - Malnutrition
  - Other (e.g., psychosocial, trauma)
  - Unknown/other causes

**RISK FACTORS**
- Social deprivation/neglect/abuse
- Poverty
- Familial MR
- Gestational folate deficiency (neural tube defects)

**PREGNANCY**
- Severe/profound MR less likely to reproduce
- Possible congenital/developmental anomalies of the gonads (as in Turner’s syndromes)
- Possible neuroendocrinopathies

**ASSOCIATED CONDITIONS**

**Congenital Anomalies**
- Cephalic features (shape, size)
- Eyes (hypertelorism, almond shaped, epicanthal folds)
- Lens/retina (subluxed lenses, retinal pigmentation)
- Midfacial/oral (cleft palate, high arched palate)
- Ears (malformed, low-set)
- Neck (webbed, short)
- Skin/hair (fibromas, angiomata, pigmented hair texture/whorls)
- Digits (long middle toe, syndactyly, gaps)
- Dermatoglyphic (palmar crease)
- Cardiac anomalies
- Gastrointestinal system (esophageal atresia)
- Renal/anurete anomalies
- Urogenital system
- Musculoskeletal system (subluxed atlantoaxial joint, hip joint dislocation)
- Medical comorbidity is common:
  - Non-CNS involvement due to congenital anomalies or biochemical/physiologic factors
  - Visual/auditory deficits: 10%
  - Abnormal body fat distribution (e.g., central)
  - Seizures: 9% to 19%
  - Cerebral palsy: 20%
  - Psychiatric comorbidity: 14% to >70%

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- It is important to ascertain time of onset of cognitive/functional impairment, any precipitating events, course and any family history (consanguinity, familial pattern of MR, learning disabilities, spontaneous abortions, difficulties with conceiving, neurologic disorders, childhood psychiatric disorders)
- CNS specific causes (e.g., artemovirus malformation, neoplasmia, hydropsphalus)
- Seizures
- Neurosensory deficit
- Sleep disorders
- Endocrinopathies
- Psychiatric illnesses (e.g., depression, eating disorders)
- Childhood psychiatric disorders (see DSM-IV)
- Learning disabilities
- Developmental disorders
- Autistic and Asperger’s disorders
- Rett’s and childhood disintegrative disorders (loss of acquired milestones/skills by 5 to 48 months old and by 2 to 10 years old, respectively)

**SIGNS AND SYMPTOMS**
- Cognitive/developmental/functional deficits
  - Possible abnormal neonatal sleep/feeding patterns
  - Delay or loss of milestones
  - Poor school performance
  - Impaired social/self-care or other skills
  - Abrupt growth pattern
  - Physical exam findings such as:
    - Stigmata/congenital anomalies
    - Urine odor (mousy, maple syrup, etc.)
    - Cephalofacial features
    - Sit or focal neurologic signs
    - Signs of cerebral palsy
    - Cerebellar signs
    - Cranial nerve signs
    - Abnormal higher cortical function
- Syndrome/genetic disorder specific features

**LABORATORY PROCEDURES**
- Neonatal lished diagnostic protocol—generally based on clinical presentation
- Some typical blood tests: electrolytes, BUN, Cr, fasting blood sugar (FBS) CBC differential, ammonia, uric acid, calcium, magnesium, phosphate, copper, ceruloplasmin, lead, viral titers, RPR
• Endocrine blood/urine tests such as serologic thyroid function test
• Arterial blood gases (ABGs)
• Routine urinalysis

Consider consulting with a geneticist regarding tests for inborn error of metabolism (IBEM) or chromosomal studies

• Results rarely positive unless:
  — Clinical presentation suggests IBEM
  - A neonatal presentation with any of the following: hypoglycemia, acidosis, coma, seizures, physical stigmata
• Least helpful if precipitating event is identified/absent physical stigmata
• Some tests for IBEM (see Jones, 1997):
  — Blood levels of carnitine, pyruvate, lactate, amino acids, organic acids, very long chain fatty acids
  — ABG and ammonia level
  — Urine analyses of amino and organic acids, mucopolysaccharides
  — Fibroblast or white cell culture studies for lysosomal enzyme disease
Consider chromosomal studies, particularly if:
  — Prenatal onset
  — Familial pattern
  — Physical stigmata
  — Severe MR
  — Idiopathic (according to some experts)

IMAGING STUDIES
• No established protocol, and the cost-to-benefit ratio in idiopathic MR is controversial
• Consider MRI in specific cases such as:
  — Cephalic abnormalities
  — Neurofocal defects
  — New-onset seizures
  — Cerebral palsy
  — Degenerative course
  — Features of neurocutaneous disorders, neural tube defects, etc.

SPECIAL TESTS
• Neuropsychological assessment
• Also consider:
  — Electroencephalogram
  — Evoked potentials (e.g., for neurosensory deficits)
  — Audiometry/ophthalmologic evaluation
  — Cerebral fluid spinal studies

SURGICAL MEASURES
Sometimes for congenital anomalies/medical complications.

SYMPTOMATIC TREATMENT
• Bladder dysfunction:
  — Consider postvoid residual and cystometric studies
  — Anticholinergic agents may be helpful. Consider imipramine for an enuretic insomniac patient
• Seizures: anticonvulsant treatment
• Behavioral problems or functional/cognitive decline:
  — Thorough physical examination by primary physician to rule out underlying medical condition
  — Thorough neurologic exam to rule neurologic condition (if over 50 years old or an adult with Down syndrome consider dementia)
• Treatments to consider: behavioral, cognitive, supportive, group, family psychotherapies, patient/family psychopharmacology
• Obesity/overweight (common in MR): dietary consultant, psychologist, psychiatrist

ADJUNCTIVE TREATMENT
Multidisciplinary approach:
  — Family and patient counseling
  — Psychologist, behaviorist, or psychotherapist
  — Psychiatrist (if suspect psychiatric disorder)
  — Neurologist (such as for seizures)
  — Primary care physician
  — Genetics consultant and counselor
  — Nutritionist/dietitian
  — Speech/physical/occupational therapists

ADMISSION/DISCHARGE CRITERIA
• Patients not previously assessed for MR may require admission for rapidly deteriorating course, unstable conditions, or medical/neurologic complications or surgery
• Most severe cases present at birth/perinatal period and are generally hospitalized for assessment/treatment
• Children or adults previously diagnosed with MR may require admission for:
  — New-onset seizures, unstable or treatment resistant seizures
  — Severe behavioral or psychiatric problems — Other unstable medical conditions

ADDITIONAL CONSIDERATIONS
• Life span is thought to be inversely correlated with severity of MR.
• Adults may be more prone to age-related conditions/disorders.

PARENTAL MONITORING
• Annual assessments of vocational/educational/functional skills
• Many require annual blood/urine analyses for syndrome specific condition.
• Consider annual neurosensory assessments in patients with deficits.

EXPECTED COURSE AND PROGNOSIS
• Developmentally delayed
• Life span is thought to be inversely correlated with severity of MR.
• Adults may be more prone to age-related conditions/disorders.

ICD-9-CM: 319 Mental retardation, unspecified; 317 Mental retardation, mild (IQ 50-70); 318.0 Mental retardation, moderate (IQ 35-49); 318.1 Mental retardation, severe (IQ 20-34); 318.2 Mental retardation, profound (IQ under 20); V62.89 Mental retardation, borderline; 758.0

Mental Retardation

Management

GENERAL MEASURES
If an underlying reversible etiology is identified, appropriate treatment should be implemented accordingly. Management often involves a multidisciplinary approach that addresses educational/training needs and psychosocial issues, provides advocacy, and maximizes level of independence/functioning.

PRECAUTIONS
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Generally requires:
• Annual assessments of vocational/educational/functional skills
• Many require annual blood/urine analyses for syndrome specific condition.
• Consider annual neurosensory assessments in patients with deficits.

EXPECTED COURSE AND PROGNOSIS
• Developmentally delayed
• Life span is thought to be inversely correlated with severity of MR.
• Adults may be more prone to age-related conditions/disorders.

PATIENT EDUCATION
• Government: Department for MR
• National Down Syndrome Congress, 7000 Peachtree-Dunwoody Rd., Building #5, Suite 100, Atlanta GA 30328. Phone 800-232-6372.
• Special Olympics

Miscellaneous

SYNONYMS
• Developmentally delayed
• Life span is thought to be inversely correlated with severity of MR.
• Adults may be more prone to age-related conditions/disorders.

ICD-9-CM: 319 Mental retardation, unspecified; 317 Mental retardation, mild (IQ 50-70); 318.0 Mental retardation, moderate (IQ 35-49); 318.1 Mental retardation, severe (IQ 20-34); 318.2 Mental retardation, profound (IQ under 20); V62.89 Mental retardation, borderline; 758.0

SEE ALSO: N/A

REFERENCES

Author(s): Karen Brugge, MD

Medications

DRUG(S) OF CHOICE
There are no established medications

Contraindications N/A

Precautions
N/A

Mitochondrial Diseases

Basics

DESCRIPTION
Mitochondria) diseases are clinically, biochemically, and genetically heterogeneous diseases associated with primary mitochondrial dysfunction. Neurologic, systemic, or both manifestations can be seen in the disorders.

EPIDEMIOLOGY
Incidence/Prevalence
The incidence/prevalence for most mitochondrial diseases is unknown. However, the prevalence of mitochondrial DNA (mtDNA) disease has been estimated to be 1 in 10,000 to 1 in 50,000.

Race
All races are affected.

Age
All ages can be affected.

Sex
Both sexes are affected.

ETIOLOGY
The causes of mitochondrial disorders can be due to nuclear DNA defects, which include defects of substrate transport (such as carnitine palmitoyl transferase deficiency, carnitine deficiency), defects of substrate utilization (such as defects of O2- oxidation, pyruvate dehydrogenase complex deficiencies), defects of the Krebs cycle (such as fumarase deficiency), defects of oxidation-phosphorylation coupling (such as Luft's disease), and defects of respiratory chain (complex I-V deficiencies). They can also be due to mtDNA defects, which include sporadic large-scale deletions or duplications, point mutations affecting structural genes and synthetic genes, as well as defects of communication between both genomes, which consists of autosomal-dominant multiple mtDNA deletions and autosomal-recessive mtDNA depletion.

Genetics
Genetically inherited mitochondrial diseases may result from defect of mitochondrial or nuclear genome. The former is characterized by maternal inheritance and the latter by mendelian inheritance. Among nuclear DNA defects, most are inherited as autosomal-recessive diseases except pyruvate dehydrogenase deficiency and ornithine transcarbamylase deficiency, which are x-linked diseases. Maternal inheritance is transmitted from the mother to all of her sons and daughters, but only her daughters can pass the mutation to their children. The clinical manifestations are determined by the threshold effect (phenotype occurs when the content of mutated mtDNA reaches certain percentage, for example, the threshold may be 60% to 70% in chronic progressive external ophthalmoplegia) and mitotic segregation (the contents of mutated mtDNA are changed randomly during cell division).

RISK FACTORS
AZT treatment for AIDS may induce mtDNA depletion. Exposure to methyl-phenyl-tetrahydropridine (MPTP) can cause brain respiratory chain complex I defect and a Parkinsonian syndrome.

PREGNANCY
N/A

ASSOCIATED CONDITIONS
• Alzheimer's disease: complex IV and pyruvate dehydrogenase deficiencies.
• Huntington's disease: defects of complex II, III, IV in caudate nucleus have been reported.
• Parkinson's disease: complex I defect in substantia nigra has been shown.
• Huntington's disease: defects of complex II, III, IV in caudate nucleus have been reported.
• Alzheimer's disease: complex IV and pyruvate dehydrogenase defects have been described in the brain.

Diagnosis

DIFFERENTIAL DIAGNOSIS
The following mitochondrial disorders need to be differentiated from other diseases.
• Chronic progressive external ophthalmoplegia: myasthenia gravis, oculopharyngeal muscular dystrophy, thyroid oculomypathy
• Mitochondria) encephalomyopathy, lactic acidosis, stroke-like syndrome (MELAS): viral encephalitis, brain tumor, stroke
• Myoclonic epilepsy and ragged red fibers syndrome: Lafora body disease, progressive myoclonic epilepsy of Unverricht-Lundborg type
• Leber hereditary optic neuropathy: optic neuritis, alcohol-tobacco amblyopia, multiple sclerosis, anterior ischemic optic neuropathy

SIGNs AND SYMPTOMS
The clinical symptoms and signs that may suggest mitochondrial diseases include developmental delay, hypotonia, microcephaly, depression, dementia, mental retardation, central hypoventilation, short stature, seizures; ataxia, migraine headache, sensorineural deafness, ptosis, ophthalmoplegia, optic atrophy, pigmentary retinopathy, cataract, stroke, muscle weakness, exercise intolerance, cardiomyopathy, cardiac arrhythmia, peripheral neuropathy, renal tubulopathy, hepatopathy, pancytopenia, sideroblastic anemia, pancreatic insufficiency, diabetes mellitus or other endocrinopathies, movement disorders, gastrointestinal disorders such as malabsorption, myoglobinuria, multiple lipomas.

LABORATORY PROCEDURES
Elevated serum or CSF lactate, associated with lactate/pyruvate ratio above 20, strongly suggests respiratory chain defects. However, normal serum or CSF lactate with lactate/pyruvate ratio below 20 does not exclude respiratory chain defects. In contrast, increased serum or CSF lactate with lactate/pyruvate ratio below 20 may indicate pyruvate dehydrogenase complex or pyruvate carboxylase deficiencies.

IMAGING STUDIES
Brain MRI or CT may show basal ganglia calcification in mitochondrial diseases. MRI may also reveal multifocal hyperintense T2 signal in the cortex of cerebrum, cerebellum, or subjacent white matter, which is not confined to a single vascular territory, especially in the posterior temporal and occipital areas in MELAS. The increased inorganic phosphate-to-phosphocreatine ratio has been shown in the muscle of mitochondrial myopathy patients. EMG and nerve conduction studies may detect myopathy and neuropathy.

SPECIAL TESTS
Muscle biopsy may reveal ragged red fibers, which represent proliferation of subsarcolemmal mitochondria, and cytochrome c oxidase negative muscle fibers, which indicate mitochondrial diseases. Muscles also may show respiratory chain defects. Molecular genetic studies may be performed for most common mtDNA point mutations, and most can be done with the blood; however, muscle may be needed to detect mtDNA deletions or deletions. Blood and skin may permit detection of pyruvate "enzyme defects. Muscles are needed for the diagnosis of carnitine palmitoyl transferase and carnitine deficiencies.
Management

GENERAL MEASURES
- Because mitochondria are virtually present in all organs and systems, mitochondrial diseases often affect multiple organs and systems. Once this disease is suspected, audiograms may detect progressive sensorineural deafness. ECG or echocardiogram may be needed for the diagnosis of cardiomyopathy. Brain MRI may reveal basal ganglia calcification, progressive cerebral or cerebellar atrophy, or other abnormalities.
- During clinical follow-up, other screening for complications of these illnesses may be needed for the diagnosis of mitochondrial diseases. Brain MRI may reveal basal ganglia calcification, progressive cerebral or cerebellar atrophy, or other abnormalities.
- During clinical follow-up, other screening for multisystem involvement in mitochondrial diseases may include muscle weakness, intestinal dysfunction, hepatocellular dysfunction, renal tubulopathy, visual loss or retinitis pigmentosa, pancytopenia, anemia, exocrine pancreatic dysfunction, hyperglycemia, hypocalcemia, growth hormone or sex hormone abnormalities.

SURGICAL MEASURES
- For ptosis due to mitochondrial diseases, surgery to elevate upper eyelids to improve vision may be needed.
- For severe cardiac conduction defects, cardiac pacemaker implantation may be lifesaving.

SYMPTOMATIC TREATMENT
- Seizures may benefit from anticonvulsant treatment; migraine headache requires proper medications.
- Diabetes mellitus or other endocrine abnormalities should be treated if present and sensorineural deafness may require hearing aids.

ADJUNCTIVE TREATMENT
- Moderate aerobic exercise may be useful; prolonged fasting and overexertion should be avoided.
- Optimal nutritional support is also needed.

ADMISSION/DISCHARGE CRITERIA
Patients are sometimes admitted for muscle biopsy when significant sedation is required or for severe complications of these illnesses.

Medications

DRUG(S) OF CHOICE
- Biotin 5-10 mg/d is needed in biotinidase deficiency.
- L-carnitine 50-100 mg/kg/d is life-saving for carnitine transporter defect and is also prescribed for most patients with secondary carnitine deficiency associated with mitochondrial diseases.
- Coenzyme Q10 is beneficial for coenzyme Q deficiency and is usually prescribed in respiratory chain defects at 4.3 mg/kg/d but may need much higher dosage with coenzyme Q10 deficiency associated with cerebellar ataxia and other encephalopathies.

Contraindications
Chloramphenicol and tetracycline are inhibitors of mitochondrial protein synthesis; barbiturates can inhibit respiratory chain; valproic acid can sequestrate carnitine. These medications should be avoided.

Precautions
During surgery, halothane or other halogenated anesthetic drugs and succinylcholine should also be avoided to prevent malignant hyperthermia when anesthetic drugs and succinylcholine are used.

ALTERNATIVE DRUGS
Dichloroacetate can stimulate pyruvate dehydrogenase complex and has been reported useful in severe lactic acidosis due to pyruvate dehydrogenase complex defects and respiratory chain defects.

Follow-Up

PATIENT MONITORING
Patients should be monitored regularly for multiple organ/system disorders, which are often seen in mitochondrial diseases, and receive appropriate treatment.

EXPECTED COURSE AND PROGNOSIS
Prognosis of mitochondrial diseases varies tremendously from mild to severe, especially for mtDNA disease because the level of mutant mtDNA in the organs may increase or decrease with time. The clinical course may be static, or rapidly or slowly progressive.

Mitochondrial Diseases

PATIENT EDUCATION
Patients with mitochondrial diseases can be referred to the lay organization, United Mitochondrial Disease Foundation, P.O. Box 1151, Monroeville, PA 15146-1151. Phone/fax 412-856-1297, email: 74743.2705@compuserve.com; http://biochemgen.ucsd.edu/umd; and another website: http://www.gen.emory.edu/mitomap.html.

Miscellaneous

SYNONYMS
Mitochondrial cytopathy

ICD-9-CM: 359.9 Mitochondrial disease

SEE ALSO: N/A

REFERENCES

Author(s): Chang-Yong Tsao, MD, FAAN, FAAP
Mucolipidoses

**DESCRIPTION**

The term mucolipidoses was initially coined to denote a group of lysosomal storage diseases with clinical features common to both the mucopolysaccharidoses and sphingolipidoses but lacking mucopolysacchariduria and sphingolipiduria. These diseases are characterized by variable storage of mucopolysaccharides, glycoproteins, sphingolipids, and/or glycolipids in various tissues, including neurons. A wide spectrum of genetic and metabolic defects, from a mutation in the gene encoding a specific lysosomal hydrolase to defective targeting and endocytosis of multiple hydrolases into lysosomes, underlies this heterogeneous group of disorders.

**ETIOLOGY**

**Genetics**

All the disorders are autosomal recessive. Carrier detection and prenatal testing are available.

**RISK FACTORS**

N/A

**PREGNANCY**

N/A

**ASSOCIATED CONDITIONS**

N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

Other degenerative disorders.

**SIGNS AND SYMPTOMS**

- **Mucolipidosis I** (three types)
  - Sialidosis type 1: cherry-red spot myoclonus variant. Onset in the teen years with progressive visual loss associated with a cherry red spot and nonpigmentary retinal degeneration. Myoclonus and generalized seizures.
  - Sialidosis type 2: congenital and infantile/childhood forms described and characterized by progressive mental retardation, hepatosplenomegaly, and coarsened facial features. A macular cherry red spot, hearing loss, peripheral neuropathy, ataxia, myoclonus, seizures, and dysostosis multiplex may occur. Patients with the congenital form may present with hydrops fetalis. Patients with kidney involvement have been described.
  - Galactosialidosis: infantile, late infantile, and juvenile/adult onset. Intellectual deterioration, macular cherry red spot, hearing loss, myoclonus, and corneal clouding. Visceromegaly, coarsening of the facial features and skeletal dysplasia. Mucolipidosis I or I-cell disease: psychomotor retardation evident by 6 months of age, hepatomegaly, coarse facial features, severe dysostosis multiplex, gingival hyperplasia, and recurrent respiratory infections. [Many features similar to mucopolysaccharidosis (MPS) I H/Hurler syndrome, but onset is earlier, course is more rapid, and there is an absence of mucopolysacchariduria.]

- **Mucolipidosis II or pseudo-Hurler polydystrophy** (a milder form of mucolipidosis I): onset 2 to 4 years of age with a slowly progressive course. Fifty percent of patients have a learning disability or mental retardation. Stiffness of the hands and shoulders with subsequent claw hand deformity, scoliosis, dysostosis multiplex, and coarsening of facial features. Carpal tunnel syndrome. Ophthalmologic triad of corneal clouding, mild retinopathy, and hyperopic astigmatism. (Many features similar to mild to moderately severe MPS I and VI but without mucopolysacchariduria.)

- **Mucolipidosis IV** (three types)
  - a-Mannosidosis: a-mannosidase
  - b-Mannosidosis: b-mannosidase
  - b-Mannosidosis: b-mannosidase

- **Fucosidosis**
  - a-L-fucosidase
  - a-L-fucosidase

- **Aspartylglucosaminidase**
  - Aspartylglucosaminidase

- **Galactosidosis**
  - Combined, B-galactosidase

- **a-Mannosidosis**
  - a-Mannosidase

- **b-Mannosidosis**
  - b-Mannosidase

- **Aspartylglucosaminuria**
  - Aspartylglucosaminidase

**EPIDEMIOLOGY**

**Incidence/Prevalence**

The mucolipidoses are rare disorders.

**Race**

The following mucolipidoses have a predilection for a particular subpopulation of the population:

- Cherry-red spot myoclonus variant of sialidosis: Italians
- Galactosialidosis: Japanese
- Mucolipidosis IV: Ashkenazi Jews
- Fucosidosis: Italians and the Mexican-Indian population of New Mexico and Colorado
- Aspartylglucosaminuria: Finnish

**Age**

See Signs and Symptoms, below.

**Sex**

Because of autosomal-recessive inheritance, there is an equal number of male and female cases.

**LABORATORY PROCEDURES**

See Special Tests, below.

**IMAGING STUDIES**

Bone x-rays to look for skeletal dysplasia.

**SPECIAL TESTS**

Excessive excretion of oligosaccharides is found in urine. Specific diagnosis is suspected on clinical grounds and confirmed by enzymatic testing.

- Mucolipidosis I: sialidosis type 1 and 2—glycprotein acid a-neuraminidase
- Galactosialidosis: combined, B-galactosidase/ a-neuraminidase deficiency due to absence of "protective protein"
- Mucolipidosis II or I-cell disease: multiple lysosomal enzymes due to deficiency of UDP-N-acetylgalactosamine: lysosomal enzyme N-acetylgalactosamine phosphotransferase
- Mucolipidosis III or pseudo-Hurler polydystrophy: same as mucolipidosis II
- Mucolipidosis IV: ganglioside sialidase
- Fucosidosis: a-L-fucosidase
- a-Mannosidosis: a-mannosidase
- b-Mannosidosis: b-mannosidase
- Aspartylglucosaminuria: aspartylglucosaminidase
Mucolipidoses

Management

GENERAL MEASURES
Bone marrow transplantation for fucosidosis, a-mannosidosis, and aspartylglucosaminuria is experimental.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
Treatment is individualized and aimed at treating complications of the disease.

ADJUNCTIVE TREATMENT
Physical therapy may improve quality of life.

ADMISSION/DISCHARGE CRITERIA
Patients are usually admitted for evaluation and treatment of the complications of their disease.

Follow-Up

PATIENT MONITORING
Patient follow-up is guided by the predicted course and potential complications of the disease.

EXPECTED COURSE AND PROGNOSIS
- Mucolipidosis I or sialidosis type 1: survival into middle age without dementia but with a devastating and virtually untreatable myoclonus.
- Type 2: death in infancy in the congenital form, survival to the second decade in milder forms.
- Galactosialidosis: early death to survival into adulthood.
- Mucolipidosis II or 1-cell disease: cardiorespiratory complications usually lead to death in early childhood.
- Mucolipidosis III: survival into adulthood is possible.
- Mucolipidosis IV: few patients survive into their teens and beyond. A milder variant has been reported.
- Fucosidosis: severe form with death in the first decade. Survival into the third decade in milder forms.
- a-Mannosidosis: infantile onset with rapid progression and death between 3 and 12 years of age. Later-onset disease more slowly progressive with survival into adulthood.
- β-Mannosidosis: severe form with death by 15 months of age. Milder forms with survival to adulthood.
- Aspartylglucosaminuria: survival to adulthood.

Medications

DRUG(S) OF CHOICE
No specific drug treatment is available.

ALTERNATIVE DRUGS
N/A

Patient Education

National Tay-Sachs and Allied Diseases. Association, 2001 Beacon St., Ste. 204; Brighton, MA 02135; phone 800-90-NTSAD.
ML4 Foundation, 714 E. 17th St., Brooklyn, New York 11230. Phone 718-434-5067.

ICD-9-CM: 272.7 Mucolipidosis I, II, III; 271.8 Fucosidosis, mannosidosis

SEE ALSO: N/A

REFERENCES

Author(s): Eveline C. Traeger, MD
Mucopolysaccharidoses

DESCRIPTION

Mucopolysaccharidoses (MPSs) are chronic and progressive multisystem disorders caused by deficiency of lysosomal enzymes to degrade mucopolysaccharides with resultant marked lysosomal accumulation of one or a combination of the following: dermatan sulfate, heparan sulfate, keratan sulfate, chondroitin sulfate. This accumulation results in cell, tissue, and organ dysfunction. Ten known enzyme deficiencies give rise to six disorders. Residual enzyme activity correlates with clinical course of disease as illustrated by the variable phenotypes due to α-L-iduronidase deficiency in Hunter syndrome and Scheie syndrome. In contrast, Sanfilippo syndrome can result from four distinct enzyme deficiencies, all of which result in the accumulation of heparan sulfate. Neurologic symptoms are a prominent feature of some MPSs and occur to some degree in all. Profound mental retardation, which is characteristic of MPS I H, severe MPS II, and all subtypes of MPS III, may be absent in other MPSs.

EPIDEMIOLOGY

Incidence/Prevalence

A study of MPS in the Netherlands reported an incidence of 1.19 cases per 100,000 births for MPS I; 1.16 cases per 100,000 births for MPS III; 0.67 cases per 100,000 births (1.30 cases per 100,000 male births) for MPS II. Incidence of type IVA is estimated at 1 cases per 200,000 births. Type IVB is rare, as are types VI and VII.

Race

MPS is diagnosed in patients from many ethnic/racial backgrounds.

Age

See Signs and Symptoms, below.

Sex

Because of X-linked inheritance, patients with Hunter syndrome (MPS II), which is X-linked. Prenatal diagnosis by enzyme determination following chorionic villus biopsy or amniocentesis is available.

RISK FACTORS

N/A

PREGNANCY

N/A

ASSOCIATED CONDITIONS

N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS

Other degenerative disorders.

SIGNS AND SYMPTOMS

- Hunter syndrome or MPS I H: developmental delay apparent by 12 to 24 months of age. Psychomotor retardation characterized by a maximum functional age of 2 to 4 years followed by progressive deterioration. Corneal clouding, dysostosis multiplex (constellation of radiographic abnormalities), hepatosplenomegaly, and heart disease.
- Scheie syndrome or MPS I S: normal intelligence. Corneal clouding, stiff joints, aortic valve disease.
- Hunter-Scheie compound or MPS I H/S: intermediate between MPS I H and MPS I S.
- Severe Hunter syndrome or severe MPS II: onset of disease occurs between 2 and 4 years of age. Progressive psychomotor retardation, dysostosis multiplex, hepatosplenomegaly, respiratory, and heart disease.
- Mild Hunter syndrome or mild MPS II: normal intelligence. Short stature, heart disease.
- Morquio syndrome types A and B or MPS IV types A and B: normal intelligence, spondyloepiphyseal dysplasia (which is specific to this disorder), and corneal clouding.
- Maroteaux-Lamy syndrome or MPS VI: normal intelligence, dysostosis multiplex, corneal opacities, heart disease.
- Sly syndrome or MPS VII: wide spectrum of severity with mental retardation in severe form and normal intelligence in mild form. If present, mental retardation is evident by 3 years of age. Dysostosis multiplex, hepatosplenomegaly.

LABORATORY PROCEDURES

See Special Tests, below.

IMAGING STUDIES

Bone x-rays to look for skeletal dysplasia.

SPECIAL TESTS

MPS may be diagnosed by finding excessive urinary excretion of mucopolysaccharide degradation products. The diagnosis is confirmed by measuring specific enzyme activity in serum, leukocytes, or fibroblasts. Patients with MPS have less than 10% and often less than 1% of residual enzyme activity.

- MPS I H, I S, and I H-S: α-L-iduronidase deficiency
- Severe and mild MPS II: iduronate sulfatase deficiency
- MPS III type A: heparan N-sulfatase deficiency
- MPS III type B: α-N-acetylgalactosaminidase deficiency
- MPS III type C: N-acetyl transferase deficiency
- MPS III type D: α-N-acetylgalactosaminide-6-sulfatase deficiency
- MPS IV type A: galactose 6-sulfatase deficiency
- MPS IV type B: 0-galactosidase deficiency
- MPS VI: galactosamine-4-sulfatase (aryl sulfatase B) deficiency
- MPS VII: β-glucuronidase deficiency

GENERAL MEASURES

- The chronic and progressive course of the MPS warrants periodic evaluation for potential complications, the management of which may improve quality of life. Evaluations should be performed in the following areas: neurologic, cardiovascular, respiratory (including evaluation for obstructive sleep apnea), and joint function.
- Neurologic complications and possible medical and surgical interventions are presented in more detail. It is important to note that patients with MPS I, II, IV, and VI may be at high risk for anesthesia complications because of atlantoaxial instability and presence of a narrowed airway.

SURGICAL MEASURES

Bone marrow transplant (BMT) for patients with MPS I, MPS IV, MPS VI, and MPS VII may lessen visceral and joint symptoms and improve quality of life. BMT can stabilize the CNS in MPS I. BMT performed in patients with MPS I H prior to 24 months of age with a Mental Developmental Index >70 can result in continued cognitive development and prolonged survival. Results of BMT for MPS II and MPS III are unsatisfactory.
Mucopolysaccharidoses

**SYMPTOMATIC TREATMENT**

- Progressive communicating hydrocephalus due to failure of reabsorption of CSF in the arachnoid granulations may be seen in MPS I H, MPS II, severe and MPS VI. VP shunt placement may be indicated.
- Corneal clouding leading to significant visual impairment can occur in MPS I, MPS IV, MPS VI, and MPS VII. Consider corneal transplant.
- Glaucoma may develop in patients with MPS I and MPS VI.
- Screening for conductive and sensorineural hearing loss in all patients with MPS. Deafness has been attributed to three causes: frequent middle ear infections, deformity of the ossicles, and probable abnormalities of the inner ear. Hearing aids and myringotomy tubes may improve hearing.
- Development of carpal tunnel syndrome in all MPS patients except those with MPS III and VII. Surgical nerve decompression may be indicated.
- Seizures may develop in patients with severe MPS II and MPS III. Antiepileptic medication should be used to control seizures.
- C1-C2 subluxation/cord compression as a result of a narrowed spinal canal and storage within the meninges (pachymeningitis cervicalis) in patients with MPS I H, MPS IV, MPS VI, and MPS VII. Occipitocervical fusion and laminectomy may be required.

**ADJUNCTIVE TREATMENT**

Range of motion exercises may help preserve joint function.

**ADMISSION/DISCHARGE CRITERIA**

Patients are generally admitted for evaluation and treatment of the neurologic, cardiovascular, and respiratory complications of their disorder.

**Medications**

**DRUG(S) OF CHOICE**

No specific drug treatment is available.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

Patients should be periodically evaluated for complications of their disorder as described in the management section.

**EXPECTED COURSE AND PROGNOSIS**

Death is usually due to heart failure but may be secondary to respiratory failure in MPS II or cervical cord compression in patients with MPS IV.
- MPS I H: death by 10 years of age.
- MPS I S: normal life span.
- MPS I H-S: intermediate between I H and I S.
- Severe MPS II: death between 10 and 15 years of age.
- Mild MPS II: survival to adulthood and beyond.
- MPS III: death in teens or early adulthood.
- MPS IV: patients with severe disease may not survive beyond their twenties.
- MPS VI: survival to teens in severe form, adulthood in mild form.
- MPS VII: wide spectrum including hydrops fetalis and survival to adulthood.

**PATIENT EDUCATION**


**Miscellaneous**

**SYNONYMS**

N/A

**ICD-9-CM:** 277.5 Mucopolysaccharidosis

**SEE ALSO:** N/A

**REFERENCES**


**Author(s):** Eveline C. Traeger, MD
## Multiple Sclerosis

### Basics

#### DESCRIPTION

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of unknown etiology that involves demyelination of the CNS with resultant neurologic dysfunction. The manifestations are extremely variable in type and severity.

#### EPIDEMIOLOGY

Incidence/Prevalence

Approximately 400,000 persons in the U.S. Prevalence varies with latitude: northern U.S. is a high-risk area (prevalence >30 per 100,000); southern U.S is a medium-risk area.

Age

Onset usually between 10 and 59 years (between 20 and 40 years in approximately 70% of patients).

Sex

Female/male ratio of 2:1

Race

Prevalence is higher in Caucasians than blacks or Asians.

#### ETIOLOGY

- Etiology uncertain but evidence suggests an autoimmune process directed against the protein components of myelin. T lymphocytes are activated against myelin antigens, axons, and/or oligodendrocytes and enter the CNS, triggering an immunologic cascade with recruitment of inflammatory cells and local release of lymphokines and cytokines with resultant injury to myelin and the underlying axon.
- A multitude of environmental factors has been proposed to trigger an autoimmune process. One theory is that an infection triggers the autoimmune response through molecular mimicry. Many infectious agents have been studied; evidence of a link to any particular agent remains inconclusive.

#### Genetics

Most cases are sporadic; 25% concordance rate in monozygotic twin studies and studies of first-degree relatives (children of patients with MS have 30 to 50x increased risk). Multiple candidate weak MS-susceptibility genes are currently being studied including the gene for CTLA-4 (a molecule expressed on the surface of activated T cells). HLA-DR15, DQ6 haplotype linkage has been demonstrated.

#### RISK FACTORS

- Female preponderance 2:1
- Caucasian/Northern European
- Temperate latitudes
- Family history of MS

### PREGNANCY

The relapse rate decreases significantly during the third trimester. Many studies show an increase in relapse rate in the first 6 months postpartum. Pregnancy does not appear to have a detrimental effect on long-term course or disability.

#### ASSOCIATED CONDITIONS

- Bell’s palsy
- Optic neuritis
- Trigeminal neuralgia
- Uveitis
- Transverse myelitis
- Devic’s syndrome

### Diagnosis

#### DIFFERENTIAL DIAGNOSIS

- Acute disseminated encephalomyelitis
- Behcet’s disease
- Hereditary ataxias
- Lyme disease
- Metastatic neoplasm
- Migraine
- Neurosyphilis
- Paraneoplastic neurologic syndromes
- Primary CNS lymphoma
- Progressive multifocal leukoencephalopathy
- Sarcoidosis
- Sjogren’s syndrome
- Somatization disorders
- Spinal cord compression from tumor or disc
- Strokes in the young
- Syphils
- Syringomyelia
- Systemic lupus erythematosus
- Transverse myelitis
- Tropical spastic paraparesis/HTLV-1
- Vasculitides
- Vitamin B12 deficiency

#### SIGNS AND SYMPTOMS

- Afferent pupillary defect (Marcus Gunn pupil)
- Ataxia
- Babinski sign
- Bowel dysfunction: constipation, urgency, incontinence
- Cognitive impairment
- Depression
- Diplopia
- Facial palsy or myokymia
- Fatigue
- Gait disorder
- Hyperreflexia
- Incoordination
- Intracranial ophthalmoplegia
- Lhermitte’s sign
- Numbness
- Nystagmus
- Pain
- Paralysis
- Paresthesias
- Sexual dysfunction
- Spasticity
- Tonic spasms
- Tremor
- Trigeminal neuralgia
- Urinary frequency, retention, incontinence
- Vertigo
- Visual disturbance or blindness
- Weakness in one or more limbs

### LABORATORY PROCEDURES

There is no definitive laboratory test that is conclusive for MS. Blood work (to exclude other disorders):

- ANA (can be positive in low titer in up to 80% of MS patients)
- Anti-SSA antibody (if sicca symptoms)
- HTLV-1 antibody (in myelopathic presentation)
- Vitamin B12 level
- FTA-ABS
- Serum Lyme antibody titer

### IMAGING STUDIES

- MRI is the most powerful diagnostic tool, abnormal in 90% of patients with clinically definite MS, 60% to 70% probable MS, 30% to 50% possible MS. Cranial MRI: white matter lesions in paraventricular distribution and infratentorial lesions. Acute lesions may enhance with gadolinium.
- The International Panel on the Diagnosis of Multiple Sclerosis convened in 2000 and made recommendations for new diagnostic criteria. The details of these criteria cannot be covered here but may be summarized by maintenance of the traditional requirement to obtain objective evidence of dissemination in time and space of lesions typical of MS. MRI can be useful to demonstrate dissemination in both time and space. Serial MRI scans can be used to demonstrate dissemination in time by the appearance of new T2 or gadolinium-enhancing lesions at least 3 months after an initial scan without a second clinical exacerbation.
- Spinal MRI of cervical and/or thoracic levels is useful to rule out compressive lesions in myelopathic presentation and may demonstrate cord hypertensions when cranial MRI is not diagnostic. May show cord atrophy in chronic cases.
- Cranial CT is not sensitive enough to detect most MS lesions.
SPECIAL TESTS
- CSF exam may provide additional support for diagnosis if cranial MRI not deemed typical or diagnostic.
  - WBC: normal or modest lymphocytic pleocytosis (<5 cells/mm³).
  - Total protein should be normal.
- Protein electrophoresis: presence of oligoclonal bands or elevated IgG index reflect activation of immune cells within CNS, present in 80% with definite MS.
- CSF Ig abnormalities are not required for the diagnosis of RR MS but are required to meet the new diagnostic criteria for a diagnosis of PP MS (in which MRI abnormalities are often less conspicuous).
- Evoked potentials (visual, somatosensory): less helpful than MRI or CSF but may occasionally be used to demonstrate slowing of conduction through central pathways and presence of second lesion.

Symptomatic Treatment
- Fatigue—naps, energy conservation, assistive mobility devices, conditioning exercise programs, optimization of sleep, minimization of sedating medications and pharmacotherapy
- Spasticity—conditions that may cause reflex increase in spasticity, such as urinary tract infections, decubiti, cellulitis; physical therapy with emphasis on ROM, daily stretching, exercise, and medications
- Weakness—rest, physical therapy, exercise, energy conservation, cooling vest
- Depression—psychotherapy, antidepressants, exercise
- Dysesthetic pains—medications and TENS units, acupuncture
- Tonic spasms—carbamazepine, phenytoin, gabapentin
- Bladder dysfunction—medications, intermittent self-catheterization, difficult to differentiate several possible patterns of bladder dysfunction based on symptoms alone. Should check postvoid residual to rule out retention? or if serious problem with incontinence or frequent UTIs, refer for more detailed urologic evaluation.
- Bowel dysfunction—increased fluid intake to 2 to 2.5 L/day, stool softeners, peri-stimulants, increased dietary fiber, enemas, bulking agents, rectal stimulation
- Cognitive dysfunction—cognitive rehabilitation, address fatigue and depression, treat underlying MS
- Tremor—wrist weights, benzodiazepines, primidone, carbamazepine, ondansetron, thalamotomy, or thalamic electrostimulation
- See Medications, below, for appropriate medications

ADJUNCTIVE TREATMENT
- Orthotics—cane and instruction in proper use, walker, ankle-foot orthosis for foot drop, motorized scooter to maintain mobility, conserve energy
- Cooling devices

Admission/Discharge Criteria
- MS is managed on an outpatient basis except when abrupt decline prevents the patient from performing normal activities of daily living such asambulation or transfers, when a serious complication occurs such as unresponsiveness or deep venous thrombosis/pulmonary embolism, or rehabilitation or chronic long-term care is required. High-dose intravenous corticosteroids generally can be given at home except when close monitoring of hypertension or hyperglycemia due to diabetes mellitus is required.
- Discharge criteria—patients with acute exacerbation should be discharged to home once able to care for self or adequate services are available or to rehabilitation facility if appropriate.

Management

General Measures
- Resist temptation to attribute all symptoms, especially pain, to MS.
- Evaluate for infections when a patient presents with exacerbation and intervene early.
- Aggressively treat fever, which may worsen neurologic function.
- Prescribe stress avoidance/management.
- Prescribe skin care for insensate skin or areas prone to decubitus seat cushions, frequent pressure area changes, sheeplin, water/foam mattress.
- Prescribe physical therapy, including range of motion (ROM), stretching exercises, strengthening, exercises, gait assessment.
- Prescribe occupational therapy to assist with upper extremity weakness and incoordination, exercise, and assistive devices.
- Prescribe speech therapy to evaluate dysarthria, and problems with deglutition.

Surgical Measures
- Placement of intrathecal baclofen pump or tenotomy, myotomy, myelotomy for intractable spasticity
- Placement of gastric or jejunal feeding tube for severe swallowing dysfunction
- Urinary diversion procedures for severe voiding problems
- Implantation of deep brain stimulator, gamma knife thalamotomy for intractable tremor

Multiple Sclerosis

Medications

Drug(s) of Choice

Acute Exacerbations
- Mild exacerbations, e.g., sensory symptoms, do not require treatment.
- For more severe exacerbations, methylprednisolone 1 g IV qd x 3 to 5 days with or without an oral prednisone taper starting at 60 mg, reduced over approximately 9 to 14 days (restores blood-brain barrier, reduces edema, shortens duration of relapse, and accelerates recovery).
- The Optic Neuritis Treatment Trial results suggest that moderate doses of oral steroids alone may result in a higher subsequent relapse rate; therefore, intravenous steroids with or without oral taper are now preferred. Studies of the use of high-dose oral steroids equivalent to IV doses are underway.

Symptomatic Treatment

- Fatigue
  - Amantadine 100 mg PO bid-tid
  - Modafinil 200-400 mg PO qd; pemoline has been used but less frequently due to concerns about hepatotoxicity.
  - Methylphenidate, and other stimulants.
- Spasticity
  - Baclofen—start 10 mg to bid and titrate up to 100 mg or even 200 mg/qd if severe in three to four doses per day
  - Tizanidine 4 mg—start with 2 mg qd and gradually increase by 2 mg q3-qd until maximum of 32 mg/day. May cause less weakness than baclofen. LFT's must be monitored.
  - Diazepam or clonazepam may relieve spasticity especially at night; use limited by sedation.
  - Baclofen pump, which delivers intrathecal baclofen, may be helpful in severe spasticity not relieved by oral medications.
- Other approaches to severe refractory spasticity include botulinum toxin injection, intrathecal phenol injection, dorsal root section, myelotomy, or even cordectomy.
- Vertigo
  - Medication 12.5-25 mg up to qid; diazepam 2 mg bid to qid PRN
- Bladder dysfunction
  - Hypertonic bladder: avoid caffeine, oxybutynin 2. 3 to 5 mg bid to tid; tricyclic antidepressants
  - Hypotonic bladder: bethanechol may improve detrusor contractions; intermittent self-catheterization
  - Bladder-sphincter dyssynergia: anticholinergics and self-catheterization
- Constipation
  - Glycerin or Dulcolax suppositories
  - Theracyn mini-enemas
Multiple Sclerosis

- Tremor
  - Often very difficult to treat
  - Weights on the limbs sometimes helpful
  - Propranolol may help action component of tremor (80 mg or more per day)
- Primidone: start with low doses such as 25 to 50 mg/d and gradually increase to 250 mg bid and further as tolerated. Limited by sedation.
- Isoniazid 600-1,200 mg/d with pyridoxine may reduce intention tremor
- Thalamotomy or chronic thalamic stimulation investigational
- Dysesthetic pain
  - Carbamazepine 100 to 200 mg/d to start and gradually increase to 600-1,600 mg/d in 3 to 4 doses for lancinating, sharp pain, e.g., trigeminal neuralgia
  - Gabapentin in doses of 100-1,200 mg tid; other agents that may be helpful include phenytoin, clonazepam, baclofen
  - Tricyclic antidepressants may be helpful for burning, gnawing, aching pains.
- Sexual dysfunction
  - For males, sildenafil, vacuum/tumesence constriction therapy, intracorporeal injections, penile implantation
  - For females, adequate lubrication and stimulation

Disease-Modifying Treatments

Several therapies are available in the U.S. for treatment of MS including three forms of interferon-beta, glatiramer acetate, and mitoxantrone.

- Interferons are natural cytokines that have a wide spectrum of immunomodulating activities. These activities include effects on T-cell activation, alteration of Th1 versus Th2 cytokine production, blood-brain barrier, and antiviral effects. Well-designed studies have been performed with several forms of interferon-beta and have each showed reduction of the exacerbation rate in the range of one third and reduction of new and gadolinium-enhancing lesions on MRI scans. In various trials, the interferons have also demonstrated delayed time of progression in relapsing or secondary progressive disease. The three interferon-beta products are:
  - Interferon-beta 1b (Betaseron)—8 million units (0.25 mg) SC qos
  - Interferon-beta 1a (Avonex)—30 µg IM q week
  - Interferon-beta 1a (Rebif)—22 or 44 µg SC 3 times a week

- Glatiramer acetate (Copaxone) is a synthetic protein that causes inhibition of myelin-reactive T cells and induction of antiinflammatory Th2 cells as well as some bystander suppression of inflammation in the CNS. It is administered as 20 mg SC qd and has been shown to decreases relapse rate by approximately one third and to decrease new MRI lesions.

Treatment of Progressive Disease

- Studies of interferon-beta for the treatment of secondary progressive MS have had mixed results. However, several studies have shown a reduction in acute exacerbations superimposed on a deteriorating baseline and a slowing of progression. Interferon-beta 1b has been FDA approved for secondary progressive MS.
- Slight benefit has been shown with methotrexate 7.5 to 12.5 mg PO q week.
- Mitoxantrone (Novantrone), an anthracenedione antineoplastic agent with immunosuppressive activity, has been shown in one phase III trial to reduce relapse rate and slow progression of neurologic disability. It has been approved for these purposes in SP MS and worsening RR MS.
- The recommended dose is 5 to 12 mg/m² IV infusion every 3 months. Side effects include nausea and alopecia. Lifetime exposure to this medication is limited to 2 to 3 years (cumulative dose of 120-140 mg/m²) due to dose-related cardiotoxicity. Patients should be monitored with periodic assessments of heart function such as ejection fraction by echocardiogram during their course of mitoxantrone.

Contraindications

- See manufacturer’s package insert for each drug.
- No known drug interactions with other agents.
- Pernone has been associated with hepatotoxicity.

Precautions

- Interferon-beta side effects: flu-like symptoms (fever, chills, myalgias, headaches) starting 2 to 6 hours and lasting 24 to 48 hours after injection. These gradually lessen over several months. Injection site tenderness, swelling, and occasional skin necrosis as well as LFT abnormalities, leukopenia, anemia, exacerbation of depression. Patients should have a baseline CBC/diff and LFTs then be monitored approximately 1 and 3 months after initiation of interferon therapy and then every 3 to 6 months. Management of interferon side effects—dose administration before bed so greatest side effects while sleeping; acetaminophen 650 mg q4-6 hrs for 24 hours; nonsteroidal antiinflammatory drugs (NSAIDs) with longer half-life on shot day if acetaminophen not effective; prednisone 10 mg with injection and q6h for 1 to 3 doses on injection day for interferon-beta 1b if above not helpful; pentoxifylline 400 mg bid in addition to acetaminophen; dose reduction and gradual re-escalation, ice or topical anesthetic such as lidocaine 2.5% and prilocaine 2.5% combination for injection site pain.

- Glatiramer acetate is associated with a self-limited postinjection reaction shortly after injection that may include flushing, palpitations, dyspnea, and chest pain or tightness lasting up to 30 minutes. This may be quite alarming to patients unless they are warned about the potential for this reaction ahead of time.

- Tizanidine may cause light-headedness. Many of these medications may cause sedation.

ALTERNATIVE DRUGS

- Other agents used to treat severe relapsing or progressive disease include azathioprine, cyclophosphamide, intermittent intravenous methylprednisolone, intravenous immunoglobulins, plasma exchange, and cladribine. Studies are ongoing on total lymphoid irradiation, bone marrow transplantation, and other agents.

- There is a new emphasis in MS centers to consider trials of treatment with various combinations of therapy such as interferon and methotrexate. However, there is a paucity of phase 3 trials to support efficacy.

Follow-Up

Optimal care with primary care physician sharing care with neurologist with intermittent consultation by urology, psychology, physical medicine and rehabilitation, physical therapy, and occupational therapy as needed. Motor function should be assessed regularly in follow-up visits, and some recommend assessment of time to walk 25 feet as a reliable measure to follow as well as other measures of hand function. Patients should be screened for depression (as depression is very frequent in this population as well as suicide), urinary and sexual dysfunction, fatigue, and cognitive dysfunction at each visit as these problems are not reliably reported as active problems. This condition can also put strains on family relationships, including the primary caregiver, and support should be offered.
EXPECTED COURSE AND PROGNOSIS

• The course is highly variable with several common patterns:
  — Relapsing-remitting—episodes of acute worsening of neurologic symptoms followed by variable recovery and stable period between relapses
  — Secondary progressive—relapsing course that evolves into a gradual course of deterioration with or without superimposed relapses
  — Primary progressive—gradual neurologic deterioration without relapses or remission

• For approximately one third, the disease is relatively benign with minimal disability 10 to 15 years after onset. Approximately one half of MS patients are unable to walk without assistance within 15 years of the initial diagnosis.

• Prognostic factors for severe disease: age of onset >40 years (because older onset patients have higher likelihood of early progressive course), progressive course from disease onset, motor and cerebellar involvement from time of presentation, multiple cranial T2-weighted MRI lesions, poor recovery from relapses, short interval between initial two relapses, and incomplete remissions.

• Approximately 50% of those who present with isolated optic neuritis go on to develop MS.

PATIENT EDUCATION

• National Multiple Sclerosis Society, 205 E. 42nd Street, New York, NY 10017. Phone: 800-344-4867 (FIGHTMS), which can also connect patient to nearest local chapter. Website: www.nmss.org.

• Routine vaccinations are safe and appropriate for MS patients.

• Patients should be warned about potential deleterious effects of heat and fever on neurologic function.

References


SYNONYMS

Disseminated sclerosis

ICD-9-CM: 340 Multiple sclerosis

SEE ALSO: OPTIC NEURITIS, TRANSVERSE MYELITIS
Multiple System Atrophy

DESCRIPTION
Multiple system atrophy (MSA) is the prototype of a Parkinson’s plus syndrome. Sharing clinical similarities with typical idiopathic Parkinson’s disease (IPD), MSA nevertheless presents with a constellation of additional neurologic symptoms. Three major classes of MSA have been described:
- **MSA-P (parkinsonism)** or striatoniigral degeneration (SND): typically presents with parkinsonian features (bradykinesia, rigidity, postural instability, and/or rest tremor), which are virtually resistant to dopaminergic therapy. This syndrome is notoriously difficult to distinguish from IPD at initial evaluation due to transient response to dopaminergic agents.
- **MSA-C (cerebellar)** or sporadic olivopontocerebellar atrophy (OPCA): sometimes presenting initially with parkinsonian features, individuals afflicted with this disorder develop concomitant or subsequent cerebellar features, which usually predominate as the disease progresses. Patients usually manifest multiple symptoms of cerebellar dysfunction including ataxia of limb movement, gait and speech, dysarthria, dysdiadokokinesis, titubation, impaired check response, nystagmus, and other eye movement abnormalities associated with cerebellar dysfunction. Bulbar symptoms such as dysphagia may develop.
- **MSA-A (autonomic)** or Shy-Drager syndrome (SDS): typically presents with parkinsonian features and concomitant autonomic dysfunction including orthostatic hypotension without a compensatory tachycardia (defined as a 20 mm Hg drop in systolic BP or a 10 mm Hg drop in diastolic BP from recumbent to standing position without an alternative cause), urinary retention or incontinence, and/or impotence (in males). Other possible features of autonomic insufficiency include anhidrosis, constipation, and reduced/absent pupillary reactivity. While patients with MSA-C and MSA-A may present without parkinsonian features, once manifest, the parkinsonian features may initially respond significantly to dopaminergic therapy, suggesting at least partial preservation of striatal integrity and primary loss of dopaminergic afferents from the substantia nigra. These benefits from dopaminergic treatment are not typically sustained with time, however, especially as the cerebellar and/or autonomic features advance clinically.

Classical Pathologic Changes in Multiple System Atrophy
Neuropathologic changes in SND include neurodegeneration and glial cytoplasmic inclusions (GCIs) in multiple subcortical structures including globus pallidus, striatum, substantia nigra, inferior olivary nucleus cerebellum,pons, intermediolateral columns of the spinal cord, and autonomic nuclei of the brainstem. The GCIs are composed of α-synuclein and are common to all varieties of MSA, suggesting a common pathophysiologic process with disorders in which α-synuclein is deposited in the Lewy bodies of IPD and diffuse Lewy body disease (DLBD).

EPIEMIOLOGY
Incidence/Prevalence
Incidence in individuals past the age of 50 may approach 3/100,000. The prevalence has been estimated at 3 to 5 per 100,000 in the general population.

Race
No known ethnic predilection.

Sex
Some authors suggest a mild male predominance.

ETIOLOGY
There are no clear genetic or environmental causes of MSA. The cerebellar variant must be distinguished from the hereditary multiple system degenerations.

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

Diagnosis

Differential Diagnosis
Idiopathic Parkinson’s disease Diffuse
Lewy body disease Corticobasal
ganglionic degeneration Progressive
supranuclear palsy Hereditary ataxias

Signs and Symptoms
Differentiating MSA in its early stages from other akinetic-rigid syndromes such as IPD is difficult, even for specialists. The clinical diagnosis relies on the development of distinct signs and symptoms, none of which is unique to MSA. However, consensus criteria have been developed, which allows for some degree of confidence for antemortem diagnosis (summarized by Gilman, 2002). The criteria and their corresponding levels of clinical confidence are as follows:

- **Possible MSA:** one criterion plus two features from other separate domains. If parkinsonism is the criterion, poor levodopa response qualifies as one distinct feature.
- **Probable MSA:** criterion for autonomic failure/urinary dysfunction plus levodopa-unresponsive parkinsonism or cerebellar dysfunction.
- **Definite MSA:** pathologic confirmation of pertinent neurodegenerative changes accompanied by the presence of high density of GCIs.

The clinical domains referred to by these criteria include:

- **Autonomic and urinary dysfunction**
  - Features - Orthostatic hypotension blood pressure drop of >20 mm Hg systolic or >10 mm Hg diastolic
  - Occasional urinary incontinence or incomplete bladder emptying
  - Criteria
  - Severe orthostatic hypotension—>30 mm Hg systolic or >15 mm Hg diastolic drop in blood pressure or
  - Persistent urinary incontinence accompanied by impotence in men
  - Both orthostatic changes and urinary incontinence
- **Parkinsonism**
  - Features
  - Bradykinesia
  - Rigidity
  - Postural instability
  - Tremor
  - Criteria
  - Bradykinesia, plus
  - Rigidity, or
  - Postural instability, or
  - Tremor
- **Cerebellar dysfunction**
  - Features -
  - Gait ataxia
  - Ataxic dysarthria
  - Limb ataxia
  - Sustained gaze-evoked nystagmus
  - Criteria
  - Gait ataxia, plus
  - Ataxic dysarthria, or
  - Limb ataxia, or
  - Sustained gaze-evoked nystagmus
- **Corticospinal tract dysfunction**
  - Features
  - Extensor plantar responses with hyperreflexia
  - No criteria

Other associated clinical features include
(a) peripheral neuropathy, especially affecting sphincter musculature; (b) sleep disorders, especially REM sleep behavior disorder and sleep apneas; (c) relative absence of cognitive decline; and (d) multiple other motor and sensory symptoms including severe antecollis, spasticity, myoclonus, Raynaud’s phenomenon, and pain.
Multiple System Atrophy

LABORATORY PROCEDURES
There are no specific blood tests to diagnose PSP, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism: serum vitamin B12 level, thyroid function tests, serum ceruloplasmin, 24-hour urine copper excretion, and serum a-tocopherol (vitamin E) levels.

IMAGING STUDIES
Functional neuroimaging using PET and SPECT scanning using markers for neuronal activity (fluorodeoxyglucose), dopaminergic terminals, and dopamine receptors may distinguish MSA from PD, but does not distinguish MSA from other Parkinson's plus syndromes such as PSP. These methods are not being widely implemented. There is some evidence to suggest that MRI can assist in the diagnosis of MSA. Specifically, brain MRI may reveal hypointensity and/or atrophy in the putamen or, alternatively, hyperintensity and/or atrophy in the cerebellum and brainstem. MRI may also reveal evidence of other causes of parkinsonism such as vascular insults, mass lesions, calcium or iron deposition in the striatum, and cortical atrophy patterns suggestive of other dementing illnesses.

SPECIAL TESTS
Routine studies of autonomic function may help distinguish MSA-A from cases of primary autonomic failure. Cardiac imaging studies visualizing the autonomic innervation of the heart using a SPECT ligand has consistently distinguished MSA-A from IPD with autonomic involvement.

Management

GENERAL MEASURES
There is no effective treatment for MSA. Management is aimed at alleviating the consequences of the motor and autonomic changes associated with MSA.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
The extrapyramidal symptoms of bradykinesia and resultant loss of mobility may be overcome by the use of four-wheeled walkers, although the tendency of patients with MSA, especially MSA-C, to fall usually limits the effective duration of this intervention. Dysarthria and dysphagia may benefit from speech pathology intervention. Percutaneous endoscopic gastrostomy (PEG) may be performed to provide life-sustaining nutrition.

ADJUVANT TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
MSA is usually managed in an outpatient setting. Rarely, concomitant illnesses, especially aspiration pneumonia, can lead to an acute exacerbation of MSA symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility.

DRUG(S) OF CHOICE

Rarely, extrapyramidal symptoms seen in MSA may respond to carbidopa/levodopa administration, sometimes requiring supratherapeutic (i.e., greater than 600-800 mg of levodopa per day) doses. Anticholinergic agents and amantadine may also be of limited usefulness. These responses are usually minimal and short-lived.

Orthostatic hypotension may be treated with increased salt intake, fludrocortisone (0.1-0.4 mg/d in two divided doses), or midodrine (5-10 mg up to three times daily).

Urinary incontinence may be treated with peripheral anticholinergic therapy (oxybutynin 5-10 mg at bedtime, and other formulations).

Constipation is treated with advancing doses of fiber supplements, stool softeners, fruit and vegetable preparations, and/or lactulose. The ataxia seen in MSA sometimes responds to clonazepam 0.5-1.0 mg at bedtime. Antidepressants, especially selective serotonin reuptake inhibitors, have helped in cases of depression.

Contraindications
Individuals with a history of congestive heart failure or renal insufficiency should not be prescribed a high-salt diet and should be carefully monitored if given a volume-expanding agent such as fludrocortisone.

Precautions
Severe hypertension can result from aggressive treatment with volume expanding or vasoactive therapies. Careful monitoring of blood pressure during titration of these agents is mandatory.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Like other Parkinson’s plus syndromes, the progression of MSA is relentless and refractory to most common treatment modalities, resulting in death within an average of 6 to 9 years after symptom onset. Patients are monitored in the outpatient setting, usually at 4- to 6-month intervals. Judicious use of antidepressant medications and timely discussion of PEG tube placement are recommended to assist patients and their families prepare for future decline.

EXPECTED COURSE AND PROGNOSIS
Due to its progressive nature, the symptoms of MSA always worsen with time. Over time, the limited responsiveness of MSA patients to dopaminergic therapy typically deteriorates. Death usually occurs as a consequence of cardiac arrhythmia or aspiration pneumonia.

PATIENT EDUCATION
The postural instability characteristic of MSA syndromes prevents the use of ambulatory exercise, although stretching and strengthening exercises in a sitting position may be useful. Aquatic therapy with close supervision may help forestall some of the immobility issues associated with this illness. Speech therapy is useful for speech and swallowing disturbances. Frequently, patients continue to be classified as IPD patients, confounding their understanding and expectations of treatment options and prognosis.

Miscellaneous

SYNONYMS
None

ICD-9-CM: 333.0 Shy-Drager syndrome

SEE ALSO: PARKINSON’S DISEASE, DIFFUSE LEWY BODY DISEASE, PROGRESSIVE SUPRANUCLEAR PALSY

REFERENCES

Author(s): Lawrence W. Elmer, MD, PhD
Muscular Dystrophy, Congenital

Basics

DESCRIPTION
Congenital muscular dystrophies refer to a group of rare heterogeneous muscle diseases presenting in the neonatal period or early infancy (<6 months) with diffuse muscle weakness and atrophy, hypotonia with or without joint contractures, variable brain abnormalities and mental retardation, and dystrophic changes in the muscle. Included in the congenital muscular dystrophies are Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome, muscle-eye-brain disease, laminin-a2 (merosin)-deficient and -positive congenital muscular dystrophy, rigid spine congenital muscular dystrophy, Ulrich congenital muscular dystrophy, and other unlinked congenital muscular dystrophies.

EPIDEMIOLOGY

Incidence/Prevalence
Merosin-deficient congenital muscular dystrophy consists of 50% of congenital muscular dystrophies. The incidence of Fukuyama congenital muscular dystrophy is 1/18,000 in Japan; that of laminin-a2-positive congenital muscular dystrophy is 1/60,000. The incidence of other types of congenital muscular dystrophies is unknown.

Race
Fukuyama congenital muscular dystrophy is seen in Japan and Taiwan, and rare in other areas. Muscle-eye-brain disease is described most often in Finland. Other types of congenital muscular dystrophies are reported in all races.

Age
Onset is from birth to first few months of life in all types of congenital muscular dystrophies.

Sex
Males and females are equally affected in all types of congenital muscular dystrophies.

ETIOLOGY

Genetics
All of the above congenital muscular dystrophies are autosomal-recessive diseases. Laminin-a2 (merosin)-deficient congenital muscular dystrophy is linked to chromosome 6p22-23 (gene product: merosin). Fukuyama congenital muscular dystrophy is linked to chromosome 9q31-q33 (gene product: fukutin). Muscle-eye-brain disease is linked to chromosome 1p32-p34 (gene product: glycosyltransferase). Integrin-a7-deficient congenital muscular dystrophy is linked to chromosome 12q13 (gene product: a7 integrin). Rigid spine congenital muscular dystrophy is linked to chromosome 1p35-36 (gene product: selenoprotein Nt). Ulrich congenital muscular dystrophy 1-2 is linked to chromosome 218q (gene product: collagen VI A1-2); Ulrich congenital muscular dystrophy 3 is linked to chromosome 2q3 (gene product: collagen VI A3). Other congenital muscular dystrophies are unlinked.

RISK FACTORS

N/A

PREGNANCY

N/A

ASSOCIATED CONDITIONS

- Forebrain abnormalities including cobblestone lissencephaly and mental retardation are seen in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, and Walker-Warburg syndrome.
- Cerebral white matter abnormalities are also frequently seen in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome, and laminin-a2 (merosin)-deficient congenital muscular dystrophy.
- Eye abnormalities are present in muscle-eye-brain disease and Walker-Warburg syndrome.
- Seizures and epilepsy may occur in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome, and laminin-a2 (merosin)-deficient congenital muscular dystrophy.
- Early spine contractures, rigidity, and scoliosis are seen in rigid spine congenital muscular dystrophy.
- Distal joint laxity is seen in all types of Ulrich congenital muscular dystrophies.
- Severe cardiac involvements are reported in muscle-eye-brain disease and Fukuyama congenital muscular dystrophy.
- In the classical or pure form of congenital muscular dystrophy, which is merosin positive, there are no ophthalmologic abnormalities and the patients are usually mentally normal. Congenital muscle dislocation or sublimation is frequently seen. In merosindeficient congenital muscular dystrophy, no abnormal ophthalmologic findings are demonstrated, but severe weakness with inability to ambulate independently is shown in complete merosin deficiency.
- Fukuyama congenital muscular dystrophy, seen mostly in Japan, typically consists of severe congenital muscular dystrophy, mental retardation, and mild cobblestone lissencephaly. Muscle-eye-brain disease, seen predominantly in the Finnish population, reveals congenital muscular dystrophy, mental retardation, retinal hypoplasia, and cobblestone lissencephaly. In Walker-Warburg syndrome, congenital muscular dystrophy, severe mental retardation, retinal abnormalities, and severe cobblestone lissencephaly are present. Although mental retardation is seen in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, and Walker-Warburg syndrome, marked eye abnormalities are present in muscle-eye-brain disease and Walker-Warburg syndrome but not in Fukuyama congenital muscular dystrophy. Seizures and epilepsy are also reported in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome, and laminin-a2 (merosin)-deficient congenital muscular dystrophy.

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Mitochondrial encephalomyopathy
- Congenital myopathies
- Congenital myasthenic syndrome
- Congenital myotonic dystrophy
- Metabolic myopathies

SYMPTOMS

- In all types of congenital muscular dystrophies, there are generalized hypotonia, diffuse muscle weakness and atrophy, variable early and multiple joint contractures, and onset from birth or the first few months of life.
- In the classical or pure form of congenital muscular dystrophy, which is merosin positive, there are no ophthalmologic abnormalities and the patients are usually mentally normal. Congenital muscle dislocation or sublimation is frequently seen. In merosindeficient congenital muscular dystrophy, no abnormal ophthalmologic findings are demonstrated, but severe weakness with inability to ambulate independently is shown in complete merosin deficiency.
- Fukuyama congenital muscular dystrophy, seen mostly in Japan, typically consists of severe congenital muscular dystrophy, mental retardation, and mild cobblestone lissencephaly. Muscle-eye-brain disease, seen predominantly in the Finnish population, reveals congenital muscular dystrophy, mental retardation, retinal hypoplasia, and cobblestone lissencephaly. In Walker-Warburg syndrome, congenital muscular dystrophy, severe mental retardation, retinal abnormalities, and severe cobblestone lissencephaly are present. Although mental retardation is seen in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, and Walker-Warburg syndrome, marked eye abnormalities are present in muscle-eye-brain disease and Walker-Warburg syndrome but not in Fukuyama congenital muscular dystrophy. Seizures and epilepsy are also reported in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome, and laminin-a2 (merosin)-deficient congenital muscular dystrophy.
**Muscular Dystrophy, Congenital**

**IMAGING STUDIES**

Brain MRI demonstrates a variety of congenital brain abnormalities, including polymicrogyria, pachygyria cobblestone lissencephaly, and diffuse or patchy prolonged T1 and T2 signals in cerebral white matter in Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome, muscle-eye-brain disease, and laminin-a2 (merosin)-deficient congenital muscular dystrophy. Brain MRI is normal in laminin-a2 (merosin)-positive congenital muscular dystrophy and all other congenital muscular dystrophies.

**SPECIAL TESTS**

- Complete or partial muscle and skin laminin-a2 (merosin) deficiency is detected in laminin-a2 (merosin)-deficient congenital muscular dystrophy by immunohistological staining. Secondary partial laminin-a2 deficiency is also shown in Fukuyama congenital muscular dystrophy and muscle-eye-brain disease.
- Normal laminin-a2 (merosin) is seen in the muscles of classic or pure form of congenital muscular dystrophy, Walker-Warburg syndrome, rigid spine congenital muscular dystrophy, integrin-a2—deficient congenital muscular dystrophy, and other congenital muscular dystrophies.

**SURGICAL MEASURES**

Tenotomies, tendon transfer, and tendon lengthening may be necessary for some patients to help in standing and ambulation. Progressive scoliosis may require spinal fusion to preserve pulmonary function and respiratory failure. Those with severe cardiac conduction defects may need pacemaker placement to prevent sudden death.

**SYMPTOMATIC TREATMENT**

Antiepileptic drugs are needed to treat seizures and epilepsy. Physical, occupational, speech and language therapy, braces, and special education are often necessary because muscle weakness, joint contractures, learning problems, and mental retardation are often present in many patients with congenital muscular dystrophies. Special eyeglasses may be needed in patients with visual problems. Antispastic drugs such as baclofen, diazepam, dantrolene, or botulinum toxin injection often reduce spasticity of the extremities.

**ADJUNCTIVE TREATMENTS**

Passive stretching to improve contractures, night splints, and serial plaster casts may be useful.

**ADMISSION/DISCHARGE CRITERIA**

Patients are admitted for diagnostic evaluations and treatments such as muscle biopsy, brain MRI, and speech, occupational, and physical therapy.

**PATIENT EDUCATION**

In general, all types of congenital muscular dystrophies are rare diseases and the patients need to be referred to muscular dystrophy association clinics or multiple specialty clinics for education and proper care.

**SYNONYMS**

Muscular dystrophy

**ICD-9-CM**

359.0 Congenital muscular dystrophy.

359.1 Hereditary progressive muscular dystrophy

**SEE ALSO:** N/A

**REFERENCES**


**Author(s):** Chang-Yong Tsao, MD, FAAN, FAAP
Muscular Dystrophy, Duchenne's and Becker's (Dystrophin-Related Disorders)

Basics

DESCRIPTION
Muscular dystrophies are progressive neuromuscular diseases that are genetic myopathies, caused by defects in structural proteins resulting in muscle degeneration and weakness. Dystrophopathies are muscular dystrophies in which the primary abnormality involves dystrophin. Dystrophin is an intracellular protein localized to the subsarcolemmal region of skeletal and cardiac muscle. Duchenne's and Becker's muscular dystrophies are the most common dystrophopathies that share the same gene defect but have variable phenotypic expressions. Less common dystrophopathies are Duchenne outlier, female Duchenne muscular dystrophy (DMD), and female Duchenne carrier.

EPIDEMIOLOGY
Incidence/Prevalence
- Duchenne's
  - Incidence: 1:3,500 male births
  - Prevalence: 1:25,000
  - 30% spontaneous mutation rate
  - Inheritance: x-linked recessive
  - Defect: absent dystrophin (may be up to 3% of normal)
- Becker's
  - Incidence: 1:16,000 to 1:33,000 of male births
  - Inheritance: x-linked recessive
  - Defect: decreased or defective dystrophin (3%-20% of normal)

Race
All races are affected equally.

Age
- Duchenne's
  - Onset by 3 years of age
- Becker's
  - Onset after age 5 to 7 years

ETIOLOGY
Genetics
- Duchenne's and Becker's are x-linked recessive disorders; hence they occur primarily in boys. They are caused by a mutation in the dystrophin gene, which is located on chromosome Xp21.
- An out-of-frame mutation causes Duchenne's. The mutation disrupts dystrophin production. No dystrophin, but rarely 3% of normal dystrophin content may be present.
- An in-frame deletion causes Becker's.
  - Shortened but semifunctional dystrophin (20% of normal)
  - Reduced expression of normal dystrophin results in outlier DMD.

- Carrier female
  - Heterozygotes with normal dystrophin gene on one X chromosome, a mutant gene on the other, and are asymptomatic
  - By Lyon hypothesis, when more than half of X chromosome in a muscle fiber express a mutant gene for dystrophin, the muscle fiber is prone to degeneration and can cause clinical symptoms in female carriers.
  - 30% to 35% of dystrophopathies have a point mutation and may not be detectable by routine clinical testing.
  - Female Duchenne phenotype presents occasionally in Turner syndrome and has clinical features similar to the male Duchenne.

RISK FACTORS
- Family history of maternal uncles with DMD
- Female carrier donates anochrome to a susceptible son and also to carrier daughters.
- Spontaneous mutation—30% to 35%

PREGNANCY
Prenatal diagnosis is possible in the first trimester by chorionic villi sampling to determine deletion and may be more accurate if a family member is known to be involved.

ASSOCIATED CONDITIONS
- Contractures, particular in Achilles' tendon
- Obesity
- Nonprogressive mental retardation with mean IQ = 85
- Cardiomyopathy
- Gastrointestinal tract disorders, including malabsorption, megacolon, volvulus, cramping, and dysmotility
- Emotional disorders, including depression

Diagnosis

Differential Diagnosis
- Congenital myopathies—group of myopathies with abnormal muscle histology and fiber-type abnormalities presenting mostly as infantile hypotonia
- Congenital muscular dystrophy—present at birth, unpredictable, slow progressive course, with CNS anomalies
- Mitochondrial myopathies—with or without ragged red fibers, multigorgan involvement, and respiratory pathway enzyme deficiencies
- Metabolic myopathies—usually with abnormal muscle lysosomal storage diseases due to enzyme deficiencies, e.g., acid maltase deficiency
- Facioscapulohumeral muscular dystrophy—autosomal dominant face, shoulder, and upper limb involvement; slow progression

- Emery-Dreifuss-X-linked, onset age 5 to 15 years, upper arms and peroneal muscles, slow progression
- Limb girdle—autosomal recessive, onset age 10 to 20 years, shoulder or pelvic girdle

SIGNS AND SYMPTOMS
- Duchenne's
  - Delayed motor development and delayed walking
  - Onset of gait abnormalities evident by 3 to 5 years
  - Call hypertrophy can be as early as 1 to 2 years
  - Waddling gait
  - Gowers's sign—child "climbs up by his thighs"
  - Toe walking
  - Lordosis and later kyphoscoliosis
  - Proximal, and later distal, limb weakness
  - Difficulty in climbing stairs and frequent falls
  - Contractures later
  - Bulbar weakness may be late
  - Cardiomyopathy
  - Wheelchair-bound by 12 years
  - Death by second or third decade
  - Absent tendon reflexes later
- Becker's
  - More slowly progressive than Duchenne's
  - Muscle weakness usually after 5 years
  - Still ambulant at 20 years, shoulder or pelvic girdle
  - Death in adulthood as late as 50 years
- Duchenne outlier
  - Clinically presents like Duchenne's dystrophy with same early symptoms, but with a slower course.
  - Residual dystrophin in 10% of muscle fibers.
  - Still ambulatory by 16 years.
  - Life expectancy may be more than 25 years.
- Female Duchenne muscular dystrophy
  - Normal dystrophin gene on one X chromosome and a mutant gene on the other.
  - According to Lyon hypothesis random inactivation of one X chromosome may leave more than half of mutant X chromosomes to be operant, resulting in various degrees of muscle weakness.
  - Such a scenario leaves these females with clinical signs and symptoms similar to male Duchenne, with laboratory findings of partial absence of dystrophin, elevated creatine phosphokinase (CPK), and Duchenne-type muscle biopsies.

LABORATORY PROCEDURES
- Serum creatine kinase up to 10,000-30,000 IU early but is lower when disease progresses
- Serum aldolase increases
- Restriction fragment length polymorphic markers for carrier detection

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Muscular Dystrophy, Duchenne's and Becker's (Dystrophin-Related Disorders)

- Muscle biopsy—histology reveals fiber size variation, fiber degeneration and regeneration, endomysial fibrosis
- Absent dystrophin staining for Duchenne's
- Partial dystrophin staining for Becker's
- Chorionic villus sampling in first trimester reveals muscle pathology

**IMAGING STUDIES**

- Plain-x-ray: useful for scoliosis detection. Chest x-ray may reveal cardiac enlargement

**SPECIAL TESTS**

- ECG: Many patients exhibit ECG abnormalities such as tall right precordial R waves with increased R/S amplitude in V1, and deep Q waves in left precordial leads. ECG is useful to monitor for evidence of conduction system abnormalities including arrhythmias, ectopy, and intraventricular conduction defects.
- EMG can be avoided if clinical features, history, and CPK rule in the diagnosis.

**Management**

**GENERAL MEASURES**

- There is no cure, and management is largely symptomatic.
- Early detection and genetic counseling
- Testing of other family members
- Early information to family members/parents
- Multidisciplinary approach involving neurologist, geneticist, cardiologist, orthopedist, pulmonary medicine, psychologist, nutritionist, nursing coordinator, physical therapist, and social worker
- Encouragement of active exercise as much as tolerated

**SURGICAL MEASURES**

- Scoliosis prevention, detection, and management to keep correct posture
- Achilles tendon stretching and cord release
- Orthopedic care, e.g., scoliosis and contracture surgery

**SYMPTOMATIC TREATMENT**

- Physical and occupational therapies may be beneficial. Contractures occur early and emphasis should be placed on aggressive stretching regimens for heel cords, illocordial bands, and hips. Nighttime ankle/foot orthoses may prevent or lessen development of heel-cord shortening.
- Calcium supplementation to prevent decreased bone density

**ADJUNCTIVE TREATMENT**

- Cardiac care, e.g., arrhythmias, cardiomyopathy, and congestive heart failure

**ADMISSION/DISCHARGE CRITERIA**

- Admit patients with pulmonary and cardiac complications.

**ADMISSION/DISCHARGE CRITERIA**

- Pulmonary care, e.g., pneumonia prevention, postural drainage, and pulmonary toileting in end stage
- Psychiatric and psychological care

**MEDICATIONS**

**DRUGS OF CHOICE**

- Prednisone initiated at 0.75 mg/kg/day improves muscle strength, pulmonary function, and functional ability with maximal improvement attained within 3 months of initiation. Chronic prednisone doses of 0.65 mg/kg/d will maintain these improvements, slow worsening, and may prolong ambulation for up to 2 years. Side effects include weight gain, growth retardation, development of cushingoid features, behavioral changes, and excessive body hair. The weight gain may be enough to secondarily impair ambulation.

**Contraindications**

- Avoid anticholinergics and ganglion-blocking agents, which can cause decreased muscle tone.
- Avoid cardiotoxic drugs such as halothane.

**Precautions**

- Proper evaluations prior to general anesthesia to reduce neuromuscular blockade.

**ALTERNATIVE DRUGS**

- Deflazacort 1.2 mg/kg/d; this is a corticosteroid that has benefits similar to prednisone but with fewer side effects.

**Follow-Up**

**PATIENT MONITORING**

- Early genetic consultation and counseling with multidisciplinary team and evaluations
- 3- to 6-month clinic visits depending on severity and need for services

**EXPECTED COURSE AND PROGNOSIS**

- Duchenne's
  - Long leg braces by 9 years
  - Wheelchair-bound by 12 years
  - Death in second decade
- Becker's
  - May reach adult life
  - Outlier DMD
  - May reach 25 years or more

**PATIENT EDUCATION**

- Other support groups
- Housing is very important; avoid houses with stairs.
- Educational and school planning
- Special camps
- Modification of educational activities

**REFERENCES**


**SYNONYMS**

- Arran Duchenne muscular dystrophy
- Becker's: Late-onset x-linked muscular dystrophy

**ICD-9-CM:** 359.4 Hereditary progressive muscular; dystrophy/Duchenne/Becker type; 359.1 Muscular dystrophy/other than Duchenne/Becker type; 359.8 Other myopathies

**SEE ALSO:** N/A

**AUTHOR(S):** Samuel Dzodzozeny, MD
DESCRIPTION

Facioscapulohumeral muscular dystrophy (FSHD) is a chronic progressive myopathy that is characterized by weakness initially restricted to the facial and shoulder girdle muscles. Though the clinical presentation is typical in the majority of cases, there is considerable heterogeneity both in the pattern and severity of muscular weakness.

EPIDEMIOLOGY

Incidence/Prevalence
The prevalence of FSHD is 1 in 20,000, making it the third most common dystrophy after Duchenne and myotonic dystrophy. It is an autosomal-dominant disorder.

Race
There is no clear evidence of a racial predilection.

Age
Most affected individuals showing signs of FSHD by age 20. The frequency of sporadic mutations is approximately 30%.

Sex
There is high penetrance in both sexes.

Genetics

The FSHD genetic defect consists of deletion of a critical number of a 3.3-kb DNA tandem repeat unit localized to the long arm of chromosome 4 (4q35). Individuals with FSHD have fewer than 10 repeats, whereas normal individuals have 15 or more. The deletion on 4q35 does not contain an expressed sequence of DNA (i.e., a functional gene). Furthermore, chromosomal aberrations that result in loss of the entire 4q35 region do not cause FSHD. The current hypothesis is that expression of nearby genes is influenced by a critical reduction in the number of the 3.3-kb repeats caused by the FSHD-associated deletion, causing a toxic gain of function.

RISK FACTORS

The genetic mutation described above.

PREGNANCY

Approximately 30% may experience a worsening of symptoms during pregnancy. Patients should be cautioned that proximal lower extremity weakness may increase fall risk. There is no clear evidence of increased fetal loss in patients with FSHD.

ASSOCIATED CONDITIONS

As listed below.

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Idiopathic brachial plexopathy: a prominent history of acute onset of severe shoulder and/or neck pain, followed by weakness and atrophy of shoulder girdle muscles, usually separates idiopathic brachial plexopathy from FSHD.
- Atypical presentations of inflammatory myopathies (e.g., polymyositis) are suggested by marked neck flexor weakness. Patients with FSHD usually have relative sparing of the neck flexors while the neck extensors may be quite weak.
- Other dystrophies (e.g., limb-girdle dystrophy): patients with limb-girdle dystrophies may have significant scapular winging resembling FSHD though typically with only minimal facial weakness. Emery-Dreifuss muscular dystrophy, an X-linked condition, has a scapuloperoneal distribution of weakness resembling FSHD. However, unlike FSHD, they also have prominent contractures, minimal facial involvement, and a characteristic cardiac rhythm disturbance (atrial standstill).
- Spinal muscular atrophy syndromes may rarely present with a scapuloperoneal distribution of weakness. These are readily differentiated on electrodiagnostic studies by the finding of neuropathic rather than the myopathic motor unit potentials seen in FSHD.

SIGNS AND SYMPTOMS

In general, close attention to specific features of the history, inheritance pattern, and careful attention to the pattern of muscle weakness is key in accurate diagnosis. The presence of slowly progressive facial weakness, scapular winging, and proximal upper extremity weakness sparing the deltoids is characteristic of FSHD. Most patients present during the first or second decade with slowly progressive proximal upper extremity weakness and are usually unaware of facial weakness. However, on specific inquiry a history of sleeping with eyes open, inability to whistle, or difficulty drinking with a straw is usually elicited. Examination reveals facial weakness in essentially all patients (an inability to bury the eyelashes fully, pout the lips, or whistle, and dimples may be noted at the corners of the mouth with resultant reduction in facial expressivity). Expiratory, bulbar, and respiratory muscles are characteristically spared. The pectoral muscles are often atrophic, leading to axillary creasing; the clavicle angle is flattened. The scapula is prominent and deviates outward and upward on shoulder abduction and elevation. The deltoid is spared, but the biceps and triceps are often affected. This, in combination with relative preservation of the forearm muscles, gives the arm a distinctive "Pop-eye" appearance.

Frequently, there is prominent abdominal muscle weakness with an exaggerated lumbar lordosis, and a deviation of the umbilicus in the vertical direction (usually upward) upon attempting a sit-up (Beevor sign). This is a feature uncommon in other myopathies. Initially, lower extremity involvement is less impressive and is typically confined to the distal muscles, particularly the anterior compartment. However, as the disease progresses, patients usually develop hip-girdle as well as knee extensor and flexor weakness. Side-to-side asymmetry of muscle weakness is characteristic and often striking. Disease progression is typically descending, starting in the facial and scapular fixator muscles and later involving the upper arm, distal lower extremity, and hip-girdle muscles. Most patients relate a slow, steady progression, although some patients describe a stuttering course with periods of slow or no progression interrupted by periods of more rapid loss of muscle strength.

Extramuscular Manifestations

- Retinal telangiectasias are seen commonly on retinal fluorescein angiography.
- Retinal detachment, usually in the setting of severe exudative retinopathy, occurs only rarely (Coats’ disease).
- Atrial conduction abnormalities including atrial tachycardia, and mild conduction delay occur frequently, and there is believed to be a higher susceptibility to inducible atrial arrhythmias. High-grade atrioventricular block requiring a pacemaker is unusual and suggests an alternative diagnosis such as myotonic dystrophy, or rarely, Emery-Dreifuss muscular dystrophy.
- High-frequency deafness appears to be a frequent accompanying feature, and is usually mild.
- Some patients, usually those with severe infantile onset FSHD, may suffer from mental retardation and seizures.

LABORATORY PROCEDURES

Serum creatine kinase (CO is normal or elevated, and is typically not greater than 3 to 5 times normal. A higher level suggests an alternative diagnosis (e.g., inflammatory myopathy).

IMAGING STUDIES

N/A
Muscular Dystrophy, Fascioscapulohumeral

GENERAL MEASURES
Treatment is largely symptomatic.

SURGICAL MEASURES
Surgical fixation of the scapula to the chest wall in an attempt to improve functional strength of proximal shoulder muscles is successful but is associated with a number of complications if not performed by experienced surgeons. Moreover, bilateral surgical fixation of the scapula also reduces overall shoulder mobility. Careful consideration of residual muscle strength, rate of disease progression, and the presence of limitation of the shoulder joint should be made before this surgical procedure.

SYMPTOMATIC TREATMENT
Other beneficial supportive interventions include ankle-foot orthoses for foot drop and various forms of knee bracing. Several bracing techniques have been devised to improve shoulder mobility with variable success. In general, such bracing has to be tightly fitting making it impractical for prolonged daily use.

ADJUNCTIVE TREATMENT
Physical therapy is of benefit to maintain range of motion and prevent joint contractures. The role of exercise in FSHD has not been fully studied. In general, a low- to moderate-intensity exercise program is felt to be safe in FSHD.

Foll ow-Up

PATIENT MONITORING
Follow-up at 3-month intervals is a reasonable approach; this should be individualized based on degree of functional disability.

EXPECTED Course AND PROGNOSIS
Because of the slow progression of FSHD, most individuals adapt remarkably well to their disabilities and remain relatively functional. However, about 20% of patients become nonambulatory.

ADMISSION/DISCHARGE CRITERIA
Admission is generally not required except for rare cardiac complications.

Medications

DRUG(S) OF CHOICE
No specific pharmacologic recommendations can be made at present. Albuterol has been suggested as a potential treatment based on its presumed effect in upregulation of muscle protein synthesis. However, a randomized trial failed to show benefit. Corticosteroids and other immunosuppressive agents have not been shown to be helpful.

Contraindications
N/A

Precautions
N/A

ALTERNATIVE DRUGS
N/A

Miscellaneous

SYNONYMS
None

ICD-9-CM: 359.1 Hereditary progressive muscular dystrophy
SEE ALSO: N/A

REFERENCES

Author(s): James C. Cleland, MBChB; Rabi Tawil, MD
Muscular Dystrophy, Myotonic Dystrophy

Basics

DESCRIPTION

Myotonic dystrophy (DM) is an autosomal-dominant inherited disorder characterized by progressive skeletal muscle weakness, wasting, myotonia, and other nonmuscular features, such as cardiac conduction defects, cataracts, frontal balding, and intellectual impairment.

EPIDEMIOLOGY

Incidence/Prevalence

Myotonic dystrophy is the most common adult muscular dystrophy with an incidence of 13.5/100,000 living births and a prevalence of 5/100,000 in the Western population.

Race

No data show an ethnic predilection. However, this disease was found to have high incidence in certain regions, such as Quebec, Canada (1:500).

Age

The median age of patients at the onset of symptoms is 20 to 25 years, although a form of congenital myotonic dystrophy can affect neonates. A very mild form of congenital myotonic dystrophy with late onset also occurs.

Sex

Males and females are equally involved.

ETIOLOGY

An expansion of CTG trinucleotide repeats is believed to cause this disease. However, the precise mechanism by which these excessive repeats induce the phenotype of the myotonic dystrophy remains to be clarified.

Genetics

Myotonic dystrophy is an autosomal-dominant disorder. The affected person carries an abnormal gene (myotonic dystrophy protein gene) with an expansion of trinucleotide repeats (CTG), which is located on the 3' noncoding region of the myotonin protein kinase gene on chromosome region 19q13.2. The number of CTG repeats in the myotonic dystrophy protein gene in normal subjects varies from 4 to 37. The inducing threshold for the myotonic dystrophy is around 50 CTG repeats. The myotonic dystrophy protein gene in normal subjects varies from 40 to threefold elevated. Myotonia, the diagnosis of myotonic dystrophy is most likely.

RISK FACTORS

Positive family history.

PREGNANCY

Congenital DM occurs in 25% of children born to mothers affected by DM. These pregnancies may be complicated by polyhydramnios and poor fetal movements.

ASSOCIATED CONDITIONS

- Sleep apnea; hypersomnia
- Cardiac conduction defects
- Mitral valve prolapse
- Testicular atrophy
- Frontal balding
- Cataracts
- Insulin resistance

DIFFERENTIAL DIAGNOSIS

- Proximal myotonic myopathy (PROMM)
- Paramyotonia congenita
- Myotonia congenita
- Potassium sensitive periodic paralysis
- Myotonia induced by drugs (clofibrate, diazoxide)
- Isaac’s syndrome
- Stiff-person syndrome
- Dystonia

SIGNS AND SYMPTOMS

- Classical myotonic dystrophy has its onset from adolescence to the 50s. The majority of DM patients have a slow and progressive course with distal muscles predominantly affected. Weakness and atrophy in the face, tongue, pharynx, masseter, temporalis, and distal limb muscles are characteristic. Myotonia is an impairment of muscle relaxation that occurs in patients with DM but rarely causes significant complaints. It can be elicited by percussion of thenar, wrist extensor, or lingual muscles or by requesting release after sustained hand grip. When this pattern of weakness and atrophy occurs in association with myotonia, the diagnosis of myotonic dystrophy is most likely.
- The recognition of manifestations in nonmuscular systems is very important. These include cardiac conduction disturbances, impaired respiratory drive, personality changes, hypogonadism, posterior subcapsular cataracts, and frontal balding. The impairments in cardiac conduction and respiration are the leading causes of mortality of DM patients.
- Other signs/symptoms
  - Infertility
  - Sleep apnea/hypersomnia
  - Dysphagia/esophageal dysmotility
  - Colonic hypomotility/megacolon
  - Retinal and macular pigmentary degeneration

SPECIAL TESTS

- Serum creatine kinase (CK) in DM subjects is normal to threefold elevated. However, this test is nonspecific for the disease. Needle EMG may reveal myotonic discharges with other myopathic features, such as low-amplitude, short-duration, and polyphasic motor unit potentials. This technique is helpful for identifying other affected family members with minimal symptoms. Muscle biopsies are largely avoidable as the DNA test is now available. The typical muscle biopsy would show type I fiber atrophy, excessive central nuclei, small angular atrophic fibers, and nuclear clumps.
- The DNA test is the confirmatory test with a sensitivity and specificity approaching 100%. If the CTG trinucleotide repeats exceed 50, the subject is considered to have myotonic dystrophy.

IMAGING STUDIES

N/A

SPECIAL TESTS

N/A

Management

There is no specific treatment demonstrated to reverse the progression of DM. Symptomatic treatments are the primary focus of DM management. Optimal care includes a multidisciplinary approach to monitor for and manage manifestations of nonmuscular involvement. Patients with DM often have significantly compromised pulmonary function due to weakness of respiratory muscles and impaired ventilatory drive. Many DM patients have hypersomnia, which is frequently caused by nocturnal sleep apnea. Bilevel positive airway pressure (Bi-Pap) may be effective to reduce these symptoms. Weakened bulbar muscles may cause dysphagia and an increased risk for aspiration pneumonia. A high index of suspicion for these complications is required to detect these problems in their early stage.

GENERAL MEASURES

- Congenital myotonic dystrophy is a severe form of DM affecting children, which is almost always inherited from a DM mother. These patients usually manifest neonatal hypotonia, feeding difficulties, failure of development, mental retardation, and respiratory compromise.
**Muscular Dystrophy, Myotonic Dystrophy**

**Surgical Measures**
- Posterior subcapsular cataracts may require excision.
- Cardiac pacemaker implantation for significant conduction disturbances.

**Symptomatic Treatment**
A footdrop may be benefited by an ankle-foot orthosis.

**Adjunctive Treatment**
- Weight reduction instruction
- Pulmonary hygiene, cough and deep breathing exercises, postural draining
- Children with congenital myotonic dystrophy require intervention if developmental delay and/or mental retardation exists.

**Admission/Discharge Criteria**
DM patients are usually admitted for ventilation failure and significant disturbances of cardiac conduction.

**Medications**

**Drugs of Choice**
The symptom of myotonia usually does not require pharmacologic treatment. Phenytoin does not shorten the P-R interval and is the preferred agent.

**Contraindications**
Although effective agents to treat myotonia, quinine and procainamide can impair cardiac conduction and should be avoided.

**Precautions**
Similarly, other antiarrhythmic agents should be used with caution for cardiac ectopy because of the possibility of precipitating heart block. Patients with DM may be more sensitive to sedative medications and have prolonged effects of anesthetics.

**Alternative Drugs**
N/A

**Follow-Up**

**Patient Monitoring**
- Periodic cardiac examination is very important. Conventional ECG and/or long-term cardiac monitoring is needed to detect the disturbances of cardiac conduction. Cardiac pacemaker implantation should be considered for patients with unexplained syncope, second-degree heart block, and trifascicular conduction disturbance in conjunction with significant prolongation of the PR interval.
- Patients should be questioned regarding symptoms of hypersomnia and referred for sleep evaluation when appropriate.
- Regular eye examination in DM patients is required to detect cataracts and other ophthalmologic complications.

**Expected Course and Prognosis**
Although there are exceptions, the number of trinucleotide repeats predicts the severity of DM. For example, patients with congenital myotonic dystrophy may have more than 750 repeats in their leukocytes. The affected children usually have a high risk of death in the neonatal period. The classical DM patients have 100 to 750 repeats in their leukocytes. These patients generally have significantly progressive muscle weakness and other nonmuscular involvement. In contrast, patients with minimal DM have only 50 to 80 repeats. They have very slow progression of muscle weakness without cardiac involvement. In a 10-year longitudinal study in 367 DM patients, the life expectancy was shown to be greatly reduced. The mean age at death was 53.2 years (range, 24-61 years). Death was caused by respiratory problems in 70% of patients. Cardiovascular complications caused death in 20% of patients. The patients with early onset and proximal muscle involvement had greater reduction in their life expectancy.

**Patient Education**
Genetic counseling should be recommended for all considering reproduction, especially when the affected person is female due to the risk of congenital myotonic dystrophy.


**References**

**Author(s): Jun Li, MD, PhD**

**Miscellaneous**

**Synonyms**
Steinert's disease

**ICD-9-CM:** 359.2 Myotonic disorders

**See Also:** N/A
Myasthenia Gravis

**Basics**

**DESCRIPTION**
Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies directed against the acetylcholine receptor of skeletal muscle. Its main feature is muscular weakness, which is made worse by continuing activity, relieved by rest, and improved by the administration of anticholinesterase drugs.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
Prevalence is 14 per 100,000 population

**Race**
No ethnic predominance.

**Age and Sex**
The most common age at onset is the second and third decade in women and the sixth and seventh decade in men.

**ETIOLOGY**

MG is an autoimmune disease of the neuromuscular junction with production of antibodies directed against the acetylcholine receptor protein of the skeletal muscle. These antibodies reduce the number of available acetylcholine receptors. Seventy-five percent of patients have thymic hyperplasia, while 80% have thymic tumors. MG is e-like (myoid) cells in the thymus gland that bear surface acetylcholine receptors, and a break in immune regulation interferes with tolerance and initiates antibody production.

Although MG is not transmitted by mendelian inheritance, family members of patients are 1,000 times more likely to have the disease than the general population, and asymptomatic first-degree relatives show EMG abnormalities. There is a moderate association with human leukocyte antigens (HLAs) B8 and DRw3. This suggests that a genetically determined predisposition to develop MG exists.

**Risk Factors**

There are no specific risk factors for MG.

**Pregnancy**

Effects of pregnancy on MG are variable. It can remain unchanged, worsen, or improve. Worsening in the first trimester is more common in primigravids. Exacerbations in the third trimester and in the postpartum period are more common in subsequent pregnancies.

**ASSOCIATED CONDITIONS**

- Graves’ disease and autoimmune thyroiditis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyositis
- Aplastic anemia

**Diagnosis**

**Differential Diagnosis**

Patients presenting with ocular or bulbar involvement may be misdiagnosed with stroke, motor neuron disease, multiple sclerosis, or cranial nerve palsies. Patients with acute generalized weakness can be misdiagnosed with botulism or Guillain-Barré syndrome. Diseases characterized by excessive fatigability like Lambert-Eaton myasthenic syndrome (LEMS) or fibromyalgia may be diagnosed as MG.

**Signs and Symptoms**

The ocular muscles are the most commonly involved, with ptosis and diplopia being the initial symptom in 70% of the cases, and present in 90% of cases at some time. Bulbar muscle weakness is the initial symptom in 15% of patients with eventual involvement in 70% to 80% of cases. Presentation as limb weakness is seen in only 15%, and proximal muscles are primarily involved. With severe disease, diaphragm and chest muscles become weak. Weakness is fluctuating, usually mildest in the morning. Testing of muscle strength during maximal effort and after brief periods of rest shows fluctuation. There are two main types of MG: (a) ocular, in which the manifestations are confined to the ocular muscles for 2 years or more; and (b) generalized, in which disease spreads beyond the ocular muscles.

**Laboratory Procedures**

Acetylcholine receptor antibodies are measured in the serum. These are seen in 85% of patients with generalized MG and in 50% of patients with ocular myasthenia. Another antibody is the anti-striated muscle antibody, which is thought to have a strong association with thymoma. Thyroid function test should be performed to rule out associated autoimmune thyroid diseases, as myasthenic patients respond best to treatment in the euthyroid state. Systemic infections are a common cause of exacerbations, and chest x-ray as well as urine, sputum, and blood cultures may be needed.

**Imaging Studies**

CT scan/MRI of the chest are performed to rule out thymic enlargement and thymoma.

**Special Tests**

Edrophonium hydrochloride (Tensilon) test: Tensilon prevents the breakdown of acetylcholine at the neuromuscular junction and improves muscle weakness in myasthenic patients. Tension is preferred for diagnostic testing as it can be given intravenously, and has rapid onset (30 seconds) and a short duration of action (about 5 minutes). The test is considered positive when there is unequivocal improvement in an objectively weak muscle. A fractionated test is performed in which 2 mg are given initially, and two further doses of 4 mg are then given at 5-minute intervals if required. EMG and nerve conduction: repetitive nerve stimulation and single-fiber EMG demonstrate defective neuromuscular transmission.

**Management**

**General Measures**

In an acute exacerbation, respiratory function should be monitored closely with forced vital capacity (FVC) and negative inspiratory force (NIF) measurements every 4 hours. FVC of less than 1 L and an NIF of less than 20 are indications for elective intubation. The patient’s list of medications should be screened for drugs that can exacerbate myasthenia, and these should be discontinued or changed whenever possible. Such drugs include aminoglycoside antibiotics, beta-blockers, quinidine, d-penicillamine, etc.

**Surgical Measures**

Elective thymectomy is performed in patients who have generalized MG and are younger than age 60 and in all patients with thymomas. Patients with disease onset after age 60 rarely show improvement after thymectomy. Thymectomy is not recommended for patients with ocular myasthenia. Prior to thymectomy, effective immunosuppressive treatment must be used to render the patient asymptomatic, as this greatly reduces postoperative morbidity and mortality.

**Symptomatic Treatment**

Pyridostigmine (Mestinon) may be helpful for the symptoms of weakness of MG (see below).

**Adjunctive Treatment**

**N/A**

**Admission/Discharge Criteria**

Most patients with MG can be treated on an outpatient basis. Patients with rapidly progressive weakness or with respiratory insufficiency should be admitted to an intensive care unit setting until they show improvement in weakness and respiratory function.
**Myasthenia Gravis**

### Medications

**DRUG(S) OF CHOICE**

- **Anticholinesterases:** pyridostigmine (Mestinon) is preferred because of its long duration of action (4 to 6 hours). It is available in 60-mg tablets and is started in a dose of 30 mg tid and increased according to response. Mestinon may be the only treatment required for ocular myasthenia, but immunosuppressive drugs must be added in patients who do not respond to corticosteroids.

- **Corticosteroids:** prednisone is most often used, in a dose of 1.5-2 mg/kg/d. More than 75% of patients show improvement within 2 weeks and are then switched to an alternate-day schedule. The dose is slowly reduced over many months to the lowest dose necessary to maintain improvement; 25% of patients show a transient initial worsening when prednisone is started, and this requires an increase in the dose of Mestinon or, in more severe cases, plasmapheresis.

- **Cyclosporine:** a useful alternative when steroids are contraindicated or are producing unacceptable side effects. The dose is 5-6 mg/kg/d given in two divided doses 12 hours apart. The dose is adjusted to maintain a trough of serum cyclosporine concentration between 75 and 150 ng/mL. Improvement is seen within 1 to 2 months after starting the drug.

- **Azathioprine:** can provide relief of symptoms in most patients, but its effect is delayed by 4 to 8 months. It is usually started in a dose of 50mg/d and increased every week by 50 mg to a total of 150 to 200 mg/d. It is indicated in patients who do not respond to corticosteroids.

**Contraindications**

Cytotoxic agents cannot be used during pregnancy.

**Precautions**

Major side effects from steroid therapy include weight gain, hypertension, and osteoporosis. Postmenopausal women are especially at risk. If osteoporosis, and Fosamax (alendronate sodium) should be given with steroids. Cyclosporine can be nephrotoxic and patients should have periodic monitoring of urea and creatinine. Blood pressure may rise and need appropriate treatment. Azathioprine causes leukopenia and liver damage and this requires regular monitoring of CBC and liver function tests. A non-idiosyncratic reaction with flu-like symptoms can occur in the first 2 weeks of treatment and requires discontinuation of the drug. Serum IgA should be measured before intravenous immunoglobulin (IVIG) administration, as patients with selective IgA deficiency may develop anaphylaxis to the drug.

**Other Therapeutic Measures**

- **Plasmapheresis** provides the most rapid therapeutic benefit and is the treatment of choice in patients with severe generalized disease and respiratory embarrassment. A typical protocol consists of removing 2 to 3 L of plasma three times a week for a total of five to six exchanges. Improvement is usually seen within 48 hours of the first exchange. IVIG produces improvement in 50% to 100% of patients. Effects are seen within a week and can last for several weeks or months. The dose is 400 mg/kg/d for 5 days.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

After starting treatment the weak muscles should be evaluated on serial examinations. % el nmm rent vs Tuveh, re rose steroids can be reduced. Patients younger than 60 years of age with generalized myasthenia should have an elective thymectomy when they are minimally symptomatic.

**EXPECTED COURSE AND PROGNOSIS**

If MG remains confined to ocular muscles for 2 years or longer, there is little chance it will generalize. Generalized MG responds to immunosuppressive therapy in 80% of patients. Early thymectomy can produce a remission in 35% of nontumor cases and lead to improvement in another 50%. With optimal care most patients lead normal lives.

**PATIENT EDUCATION**

Patients can obtain information on MG from the Myasthenia Gravis Foundation of America, 123 W. Madison Street, Suite 800, Chicago, IL 60602. Phone: 312-853-0522, website: www.myasthenia.org.

**Miscellaneous**

**SYNONYMS**

N/A

**ICD-9-CM:** 358.0 Myasthenia gravis

**SEE ALSO:** LAMBERT-EATON SYNDROME

**REFERENCES**


**Author(s):** Noor A. Pirzada, MD
Myoadenylate Deaminase Deficiency

DESCRIPTION
Myoadenylate deaminase (mAMPD) deficiency is a clinically diverse disorder of skeletal muscle adenosine triphosphate (ATP) catabolism due predominantly to inherited defects in the AMPD1 gene. Most individuals with this metabolic derangement are asymptomatic, while others are grouped according to clinical, biochemical, and molecular criteria. Exertional myalgia and intolerance without other clinical complications typically characterize symptomatic inherited mAMPD deficiency. Acquired and coincidental mAMPD deficiencies are both secondary to a wide variety of other definable clinical diseases but differ in molecular criteria.

EPIDEMIOLOGY
Incidence/Prevalence
Common, with an incidence of approximately 2/100,000 in the entire Caucasian and African-American populations.

Age
Most individuals are asymptomatic. Affected individuals can present as young as 18 months old and up to age 76. Most commonly, clinical features have appeared in over half of all reported cases in the teenage and young-adult years.

Sex
Affects both males and females consistent with the location of the AMPD1 gene on the short arm of chromosome 1 (p13-p21). The inheritance follows an autosomal-recessive pattern.

Race
Prevalent in Caucasians and African Americans, but rare in Japanese owing to the apparent absence of a common mutation found in the former populations.

ETIOLOGY
All individuals with inherited forms of mAMPD deficiency have identified defects in the AMPD1 gene. Independent of grouping, the predominant mutant allele in Caucasians and African Americans is defined by double C to T transitions at nucleotide +34 and +143 in the AMPD1 open reading frame. The former is the dysfunctional mutation and results in a QD1 nonsense codon and premature termination of mAMPD polypeptide translation. Prevalence of the common AMPD1 mutant allele in Caucasian sample groups (10%-14%) is sufficient to account for the combined incidence of all forms of mAMPD deficiency in this population. Other rare mutations have also been identified that result in single amino acid substitutions (Q156H in Caucasians and R388W and R425H in Japanese). Individuals with acquired mAMPD deficiency are simple heterozygotes for AMPD1 mutations in which pathology related to the associated disorder reduces AMPD1 expression from the normal allele into the deficient range.

RISK FACTORS
Other than inheritance of AMPD1 mutant alleles, additional risk factors related to symptomatic inherited mAMPD deficiency, although suspected, have not been identified.

PREGNANCY
A normal pregnancy, labor, and delivery without complications have been reported in a woman with symptomatic inherited mAMPD deficiency.

ASSOCIATED CONDITIONS
Coincidental inherited and acquired mAMPD deficiencies have been reported secondary to a wide variety of other definable clinical disorders too numerous to list. The relationship of mAMPD deficiency to clinical involvement in most of these individuals is unknown and may simply reflect the prevalence of AMPD1 mutations in the general population. Consequently, the number of associated disorders in these two groups of mAMPD-deficient individuals should not be limited to those already described. Notably, clinical symptoms can be more severe than either condition alone when a coincidental inherited mAMPD deficiency is combined with another defect in energy metabolism (termed “double trouble”). In addition, clinical symptoms have been observed in patients with documented multiple partial defects in energy metabolism (including AMPD1), a condition referred to as synergistic heterozygosity.

DIFFERENTIAL DIAGNOSIS
Symptomatic inherited mAMPD deficiency
Exertional myalgia (undefined) Fibromyalgia

SIGNS AND SYMPTOMS
Symptomatic inherited mAMPD deficiency presents with diffuse symptoms that can include exercise intolerance, fatigue, muscle aches, and pain. This form of the disease is generally not progressive, although some individuals do experience more persistent symptoms over time. Exercise-induced myoglobinuria has been exceptionally reported. Limb muscles, particularly lower ones, are most symptomatic. Cranial, truncal, and respiratory muscles are spared. Even in symptomatic patients, clinical weakness is unusual. Clinical complications of coincidental inherited and acquired mAMPD deficiency are generally defined by the associated disorders that are typically more severe.

LABORATORY PROCEDURES
Serum CK level may be slightly elevated. EMG is often normal, but may reveal small-amplitude, short-duration, motor unit potentials in symptomatic proximal muscles. Serum uric acid elevation has been described. A blunted venous ammonia response during ischemic forearm exercise provides a relatively noninvasive and sensitive diagnostic test for mAMPD deficiency. However, the subject has to perform enough work to prevent a false-negative diagnosis. Adequate effort should produce a concurrent rise in venous lactate of 2.5 to 4 mM (approximately 20 to 35 mg/dL). If mAMPD deficiency is indicated, the diagnosis can be confirmed from muscle biopsy material using enzyme assay or histochemical stain.

IMAGING STUDIES
N/A

SPECIAL TESTS
Polymerase chain reaction (PCR)-based tests are available to identify the C34T mutation in genomic DNA from fresh whole blood.
Myoadenylate Deaminase Deficiency

Management

GENERAL MEASURES
Individuals with symptomatic inherited mAMPD deficiency tend to adopt a more sedentary lifestyle in response to their exertional myalgia. However, mild to moderate exercise should be encouraged in these patients since it may promote exercise tolerance. Management of coincidental inherited and acquired mAMPD deficiencies is dictated by treatments appropriate for the associated disorder.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
There is no reliable treatment available for individuals with symptomatic inherited mAMPD deficiency. Oral administration of 5-carbon sugars, such as ribose and xytitol, reportedly have minimized exertional myalgia in some individuals with symptomatic mAMPD deficiency, whereas this strategy has been ineffective for others. These sugars are reasonably well tolerated at doses of 15–20 g/d without significant side effects. Treatment of coincidental inherited and acquired mAMPD deficiencies follows courses appropriate for the associated disorder.

EXPECTED COURSE AND PROGNOSIS
Although symptomatic inherited mAMPD deficiency is generally not progressive, some individuals experience a worsening of symptoms, such as cramping and pain even at rest. Emotional issues can also develop over time due to patient or physician frustration arising from a lack of reliable treatment. The course and prognosis of coincidental inherited and acquired mAMPD deficiencies should be dictated by the associated disorder.

PATIENT EDUCATION
The Muscular Dystrophy Association maintains a website related to mAMPD deficiency: http://www.mdausa.org/disease/mad.html.

Follow-Up

PATIENT MONITORING
Individuals with symptomatic inherited mAMPD deficiency may seek follow-up if they perceive a change in their generally diffuse symptoms or become frustrated with their modified lifestyle. Monitoring of those with coincidental inherited and acquired mAMPD deficiencies will be dictated by the associated disorder.

REFERENCES

Author(s): Richard L. Sabina, PhD; Safwan S. Jaradeh, MD

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
N/A

DRUG(S) OF CHOICE
No medications are currently available for symptomatic inherited mAMPD deficiency.

ALTERNATIVE DRUGS
N/A

Miscellaneous

SYNONYMS
MDD
MADD
Muscle adenylate deaminase deficiency
Muscle adenylic acid deaminase deficiency
Muscle adenosine monophosphate deaminase deficiency
ICD-9-CM: 359.803 Myoadenylate deaminase deficiency
SEE ALSO: N/A
**Myoclonus**

### Basics

**DESCRIPTION**

Myoclonus is a brief sudden muscle jerk. It is caused by either active muscle contractions (positive myoclonus) or a brief interruption of tonic muscle activity (negative myoclonus), as is seen in asterixis. It may involve the face, trunk, or extremities.

**ETIOLOGY**

Males and females are equally affected.

**Incidence/Prevalence**

Myoclonus is considered a common movement disorder. Myoclonus is not a disease entity in itself, but can be a sign of a wide variety of different illnesses. For this reason, its epidemiology is largely unknown.

**Race**

No study has demonstrated any ethnic predominance.

**Age**

Myoclonus may occur at any age, and there is no predisposition for any specific age group.

**Sex**

Males and females are equally affected.

### Risk Factors

Myoclonus is a physiologic manifestation that can be caused by a long list of associated neurologic illnesses. Essential myoclonus is familial (autosomal dominant); thus a positive family history predisposes to the condition. Cortical or spinal cord lesions may produce myoclonus. Degenerative diseases such as Creutzfeldt-Jakob disease, Alzheimer's disease, multiple system atrophy, or corticobasal ganglionic degeneration are associated with myoclonus. Metabolic derangement secondary to liver or renal failure and toxins such as bismuth can cause myoclonic jerks.

### Associated Conditions

- Cortical, brainstem, or spinal cord lesions such as tumors, arteriovenous malformations, encephalitis, ischemia (as in palatal myoclonus), or inflammation
- Progressive myoclonic epilepsies, epilepsy partialis continua, juvenile myoclonic epilepsy, and other childhood myoclonic epilepsies
- Spinocerebellar degeneration
- Basal ganglia degenerations such as multiple system atrophy, corticobasal ganglionic degeneration, and Parkinson's disease
- Dementias such as Creutzfeldt-Jakob disease and Alzheimer's disease
- Encephalitides such as subacute sclerosing panencephalitis, herpes simplex encephalitis, and others
- Metabolic derangements such as a hepatic and renal disease, hyponatremia, hypoglycemia, and mitochondrial encephalomyopathies
- Toxic encephalopathies such as a bismuth, heavy metal, methyl bromide poisoning, or medications such as a levodopa or serotonin reuptake inhibitors
- Posthypoxic encephalopathy (Lance-Adams syndrome)
- Startle syndromes (hypermimicla)

### Diagnosis

**DIFFERENTIAL DIAGNOSIS**

- Tics: in contrast to myoclonus, tics are voluntarily suppressible and are often associated with a premonitory feeling of urgency prior to the tic and a sense of relief afterwards.
- Chorea: consists of quick jerk-like movements, which are in a continuous flow.
- Tremor: tends to be repetitive, whereas myoclonus has a sudden definable onset and end.
- Dyskinesia: consists of often painful twisting and turning movements that cause abnormal postures.

**SIGNS AND SYMPTOMS**

Myoclonus may affect one or two adjacent body parts (focal or segmental myoclonus), different noncontiguous body parts (multifocal myoclonus), or the entire body (generalized myoclonus). It may be present at rest, while maintaining a posture, or when a particular movement is performed (action myoclonus). Reflex myoclonus can be triggered by visual, auditory or somesthetic stimuli, such as pinpricking or flicking the fingers or toes. Negative myoclonus consists of a short interruption of tonic muscle activity (asterixis). Asterixis is usually multifocal. When axial muscles are affected, the patient experiences postural lapses that manifest in a bouncy, unsteady gait.

**LABORATORY PROCEDURES**

N/A

**IMAGING PROCEDURES**

N/A

**SPECIAL TESTS**

**Electrodiagnostic Studies**

- EMG recordings from involved muscles may sometimes be helpful in characterizing the myoclonus.
- EEG can distinguish cortical from brainstem myoclonus, which has no preceding cortical discharge.
- Somatosensory evoked potentials show an enlarged P25/N33 component in cortical myoclonus, and a cortical correlate may be back-averaged in the simultaneously recording EEG.
- The presence of a Bereitschaftspotential prior to the EMG discharge on the back-averaged EEG suggests the possibility of psychogenic myoclonus.
**Myoclonus**

**Management**

**GENERAL MEASURES**

The most important measure is to correctly subclassify myoclonus and treat the underlying disease process. Essential myoclonus, like essential tremor, responds very well to small doses of alcohol (e.g., a glass of red wine), a feature that is not found in other types of myoclonus.

**SURGICAL MEASURES**

Myoclonus is generally treated successfully with medications, and surgical treatment is rarely recommended. However, there are reports of successful surgical management of myoclonus. Spinal myoclonus may respond to removal of a compressive lesion in or adjacent to the spinal cord. A recent study demonstrated alleviation of hereditary essential myoclonus by neurostimulation of the ventral intermediate thalamic nucleus. Older studies show improvement of myoclonus with destructive lesions of the lateral ventral nucleus of the thalamus.

**SYMPTOMATIC TREATMENT**

Myoclonus secondary to cortical lesions and epileptic myoclonus respond best to valproate, clonazepam, or a combination of these. Piracetam has also been shown to be effective in the treatment of myoclonus; however, it is not readily available in the United States at this time. Primidone has been tried successfully as well. In several cases, combinations of the above medications are needed. Negative myoclonus is much more resistant to treatment than positive myoclonus. The above medications may be tried, but are much less effective. Clonazepam appears to be most effective for brainstem myoclonus. N-acetylcysteine has been shown to be beneficial in the symptomatic treatment of myoclonus. A combination of 5-hydroxytryptophan and carbidopa has been found to be successful in the treatment of Lanz-Adams syndrome (postanoxic myoclonus).

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

The criteria for admission depend, in general, on the underlying disease and not the myoclonus itself. However, rarely, action myoclonus or negative myoclonus of the lower extremities can be so severe as to affect the patient’s ability to walk or feed himself, which may necessitate hospitalization.

**Medications**

**DRUG(S) OF CHOICE**

Aside from the symptomatic medications discussed above, amelioration of myoclonus depends largely on treating the underlying cause for the myoclonic syndrome.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

Patients should be followed on an individualized basis, depending on the severity of the myoclonus. Most of the time, the underlying disorder that causes the myoclonic syndrome dictates the frequency of follow-up and the need for hospitalization.

**EXPECTED COURSE AND PROGNOSIS**

In general, the prognosis depends on the underlying disorder that causes the myoclonic syndrome. Myoclonus itself does not tend to cause complications, unless associated with seizures, which may lead to hypoxia, aspiration, or traumatic injuries.

**PATIENT EDUCATION**


**REFERENCES**


**Author(s):** Dorothee Cole, MD

**SYNONYMS**

Jers, Lighting-fast movements, Involuntary movements

**ICD-9-CM:** 333.2 Myoclonus

**SEE ALSO:** TREMOR

**Misellaneous**

**REFERENCES**


**Author(s):** Dorothee Cole, MD
Myopathy, Congenital

Basics

DESCRIPTION
Congenital myopathies, rare heterogeneous groups of muscle disorders, are characterized by muscle weakness and hypotonia presenting at birth or in the first few months and usually with very slow or lack of progression. However, rare onset in later childhood or even adulthood has been reported. Common congenital myopathies are initially referred to as those with obvious structural abnormalities, including central core disease, nemaline rod myopathy, and myotubular myopathy. There are also uncommon forms of congenital myopathies, including multicore myopathy, fingerprint body myopathy, congenital fiber type disproportion, and protein surplus myopathies due to accumulation of abnormal proteins, such as desmin-related myopathies and actinopathies.

ETIOLOGY
Both sexes are equally affected.

EPIDEMIOLOGY
Incidence/Prevalence
Incidence of nemaline myopathy is 0.02 in 1,000 live births. Incidence of other congenital myopathies is unknown.

Race
No ethnic predilection is noted.

Age
Onset mostly at birth or in the first few months; recently, adult onset has been reported in some patients.

Sex
Both sexes are equally affected.

ASSOCIATED CONDITIONS
- Malignant hyperthermia, especially with central core disease and multicore disease
- Skeletal abnormalities including congenital hip dislocation, scoliosis, clubfoot
- Ophthalmoplegia, ptosis, especially with myotubular myopathy
- Respiratory failure, especially with myotubular myopathy, multicore disease, nemaline rod myopathy, and desmin-related myopathies
- Seizures, especially with myotubular myopathy
- Cardiomyopathy, especially with myotubular myopathy, nemaline rod myopathy, and desmin-related myopathies
- Exercise intolerance, especially with desmin-related myopathies
- Mental retardation, especially fingerprint body myopathy
- Gastroesophageal reflux

DIAGNOSIS
- Also a newly recognized congenital myopathy, actinopathies is due to accumulation of thin filaments of muscle fibers, actin.

RISK FACTORS
N/A

PREGNANCY
N/A

LABORATORY PROCEDURES
- Nerve conduction studies are normal;
- Serum creatine kinase is usually normal or mildly increased.
- EMG shows either normal or myopathic features.
- Nerve conduction studies are normal; repetitive nerve stimulation is normal.

SPECIAL TESTS
- Muscle biopsy is necessary to diagnose specific congenital myopathy. In central core disease, central cores appear as central or eccentric areas of muscles devoid of oxidative enzyme activity. In nemaline myopathy, nemaline rods are seen as red cytoplasmic or perinuclear clusters on modified trichrome staining. In myotubular myopathy, central nuclei are detected in many muscle fibers. In the multicore disease, multiple small fusiform lesions without mitoticochondria are present. In the fingerprint myopathy, ovoid inclusions are seen. In congenital fiber type disproportion, type 1 fiber smallness and predominance and type 2 fiber hypertrophy are seen. Recently, the demonstration of desmin, the intermediate filament protein of the muscle fibers, in the cytoplasmic bodies, and of a-actinin in the intranuclear rods, expands the spectrum of the congenital myopathies to protein surplus myopathies, which include desmin-related myopathies and actinopathies.

ETIOLOGY
- Myotubular myopathy is inherited as an X-linked recessive disease in neonatal cases, as autosomal-recessive disease in late infancy and early childhood cases, but as autosomal-dominant disease in late childhood cases.
- Nemaline rod myopathy is inherited as autosomal-dominant disease, linked to chromosome 1q, but also as sporadic diseases.
- Central core disease is usually inherited as autosomal-dominant disease, linked to chromosome 19, with the mutation of ryanodine receptor gene as the molecular marker of the disease that is associated with susceptibility to malignant hyperthermia. However, it also can be a sporadic disease.
- Multicore disease is inherited as autosomal-dominant disease.
- Congenital fiber type disproportion is usually sporadic.
- Recently recognized desmin-related myopathies are usually autosomal-dominant, because of autosomal-recessive or sporadic diseases.

DIFFERENTIAL DIAGNOSIS
- Spinal muscular atrophy
- Congenital muscular dystrophy
- Congenital myotonic dystrophy
- Pompe’s disease
- Debranching enzyme disease
- Mitochondrial myopathy
- Carnitine deficiency
- Congenital peripheral polyneuropathy
- Congenital myasthenic syndrome

SIGN AND SYMPTOMS
Most patients with congenital myopathy present with generalized hypertonia, delayed motor milestones, and generalized muscle weakness and atrophy. Respiratory failure, ptosis, or ophthalmoplegia may be seen. Sudden body habitus, long narrow face, and skeletal abnormalities such as clubfoot, congenital hip dislocation, and kyphoscoliosis are often noted. However, some patients with congenital myopathies can be asymptomatic or only present with mild muscle weakness. Occasionally, cardiomyopathy is seen in the patients with nemaline rod myopathy and myotubular myopathy. Mental impairment is reported in fingerprint myopathy, Desmin-related myopathies, a newly recognized group of disorders, may present in late adolescence or adulthood, with scapuloperoneal or distal muscle weakness, and some patients may also have respiratory insufficiency, cardiomyopathy, and cardiac arrhythmia.

LABORATORY PROCEDURES
- Serum creatine kinase is usually normal or mildly increased.
- EMG shows either normal or myopathic features.
- Nerve conduction studies are normal; repetitive nerve stimulation is normal.

IMAGING STUDIES
Sonographic, CT, or MRI studies of muscles are not useful to recognize specific congenital myopathy.
**Myopathy, Congenital**

**Management**

**GENERAL MEASURES**
In general, only supportive treatment is available for all types of congenital myopathies.

**SURGICAL MEASURES**
Associated congenital hip dislocation, scoliosis, or clubfoot may require surgical treatment:

**SYMPTOMATIC TREATMENT**
- Ankle-foot orthoses may be needed for footdrop.
- Back bracing may help scoliosis.
- Respiratory support or gastrostomy feeding may be necessary in respiratory failure or gastroesophageal reflux.

**ADJUNCTIVE TREATMENT**
- Physical therapy often is needed to prevent joint contractures.
- Wheelchair may be needed.

**ADMISSION/DISCHARGE CRITERIA**
Patients may be admitted for muscle biopsy for diagnosis and surgical treatment of scoliosis, gastrostomy tube placement, and then discharged to home.

**Medications**

**DRUG(S) OF CHOICE**
No specific drugs are available for any type of congenital myopathies.

**Contraindications**
Because malignant hyperthermia is associated with central core and multicore myopathies, these patients should avoid halothane or other halogenated anesthetic agents and succinylcholine, which may precipitate malignant hyperthermia.

**Precautions**
Patients should wear medical alert bracelet or necklace indicating their risk of malignant hyperthermia associated with anesthesia.

**ALTERNATIVE DRUGS**
N/A

**Follow-Up**

**PATIENT MONITORING**
Patients should be followed regularly for respiratory insufficiency, cardiomyopathy, or cardiac arrhythmia if present in some congenital myopathies, and the need of braces, physical therapy, nutritional support, or scoliosis treatment.

**EXPECTED COURSE AND PROGNOSIS**
- Central core disease is usually mild, nonprogressive, but with rare exceptions.
- Nemaline myopathy may run mild to severely progressive course with some fatal outcome, especially those with neonatal onset.
- Myotubular myopathy may also run mild to severely progressive course, even fatal outcome, especially with neonatal onset.
- Congenital fiber-type disproportion usually has mild, nonprogressive/course.
- Desmin-related myopathies may be fatal in the infancy or early childhood due to respiratory failure.

**PATIENT EDUCATION**
Because all types of congenital myopathies are rare, the patients should be referred to the Muscular Dystrophy Association clinics for care, education, and support: Muscular Dystrophy Association, 3300 E. Sunrise Dr., Tucson, AZ 85718-3208. Phone: 1-800-572-1717, website www.mdausa.org.

**Miscellaneous**

**SYNONYMS**
Myopathy

**ICD-9-CM**: 359.0 Congenital myopathy; 359.1 Nemaline myopathy; 359.9 Central core myopathy; 359.0 Myotubular myopathy

**SEE ALSO**: N/A

**REFERENCES**

**Author(s)**: Chang-Yong Tsao, MD, FAAN, FAAP
Myopathy, Metabolic

**DESCRIPTION**

Metabolic myopathies are a group of muscle disorders stemming from defective energy utilization due to abnormalities in glycogen, lipid, purine, or mitochondrial metabolism.

**Incidence/Prevalence**

Rare. Prevalence rates between 1:40,000 and 1:1,000,000 for each individual disorder. However, collectively they are not uncommon.

**Race**

No known difference.

**Age**

Age of onset varies from infancy through middle age.

**Sex**

No known difference except for the two X-linked disorders of carbohydrate metabolism.

**ETIOLOGY**

Skeletal muscle is highly energy dependent and uses three major sources of adenosine triphosphate (ATP): high-energy phosphate compounds such as phosphocreatine; glycogen; and fatty acids. The intensity and length of exertion determines which energy source is used:

- At rest—fatty acids
- During exercise
  - First few minutes—high-energy phosphate compounds
  - Minutes to an hour—glycogen
- Hours—fatty acids

**Genetics**

Inheritance patterns vary by disease. Most disorders are autosomal recessive. Others follow X-linked, mitochondrial, or, rarely, autosomal-dominant modes of transmission.

**RISK FACTORS**

None

**PREGNANCY**

No known relationship.

**ASSOCIATED CONDITIONS**

The following conditions occur with some of the metabolic myopathies:

- Disorders of carbohydrate metabolism: hepatomegaly, cardiomyopathy, **ketotic** hypoglycemia, anemia
- Disorders of lipid metabolism: cardiomyopathy, c cirrhosis, hypoketotic hypoglycemia
- Disorders of mitochondrial function: deafness, neuropathy, retinopathy, seizures, stroke

**Clues to Metabolic Pathway Affected**

- Carbohydrate metabolism
  - "Second wind" phenomenon—when muscle symptoms develop, a brief rest results in improved exercise tolerance.
  - Symptoms are associated with brief, vigorous, isometric exercise such as squatting or lifting a heavy weight, or with short duration, vigorous aerobic activity such as sprinting 100—800 m.
- Lipid metabolism
  - Symptom onset associated with fasting, illness, cold, or anesthesia
  - Onset of symptoms with prolonged (4-12 hours) exertion
  - Episodes mimicking a Reye-like syndrome or coma
  - Family history of sudden infant death syndrome
  - Mitochondrial
    - Multisystem involvement
    - Central and/or peripheral nervous system involvement
    - Ptosis, external ophthalmoplegia

**SPECIAL TESTS**

- **Nerve conduction studies**—exclude acquired demyelinating polyneuropathies.
- **Repetitive nerve stimulation**—excludes neuromuscular junction disorders in cases with ptosis or ophthalmoplegia.
- **Needle electromyography (EMG)**—confirms myopathy with findings of abnormal spontaneous activity (fibrillation potentials and positive sharp waves) and/or short duration, low amplitude motor units that recruit early seen in some cases. EMG is often normal in metabolic myopathies with permanent weakness.
- **ECG and echocardiography**—evaluate symptomatic cardiac involvement and exclude presymptomatic disease.
- **Forearm exercise test (FET)**—a useful screening tool for carbohydrate and purine metabolism disorders. Collect baseline CK, pyruvate, lactate, and ammonia (NH₃) levels.
  - Have the patient squeeze a ball or hand dynamometer vigorously for 1 minute intermittently squeezing for 3 seconds and relaxing for 1 second.
  - Draw blood samples for lactate and NH₃ at 1, 2, 4, 6, and 10 minutes after exercise. All blood samples should be placed on ice.
—Interpretation of FET results
  - In normal subjects, both the lactate and NH₃⁺ levels should rise at least 2X to 5-fold within 1 to 4 minutes (lactate) and 2 to 6 minutes (NH₃⁺) after exercise.
  - In disorders of carbohydrate metabolism, lactate levels should not rise or be blunted (less than twofold elevation), while NH₃⁺ levels should rise normally, by at least 2X-fold.
  - In disorders of purine metabolism, such as myoadenylate deaminase deficiency, the rise in NH₃⁺ levels is blunted, while the lactate response is normal, at least a 2X-fold rise.
  - If both the lactate and NH₃⁺ levels do not rise by at least 2X-fold, this suggests inadequate effort and the test should be repeated.

• Muscle biopsy—allows sampling of the muscle for histologic review, histochemical analysis, biochemical assays, and genetic analysis. An open biopsy is preferable to needle biopsy.
  - Carbohydrate metabolism
    - History—vasoconstriction and accumulation of glycogen staining positive with periodic acid-Schiff (PAS) stain.
    - Histochemical—diminished or absent staining for the enzyme on the muscle tissue sections in myophosphorylase, phosphofructokinase, or acid maltase deficiencies. Biochemical—quantitative enzyme function assays can be performed on muscle tissue.
    - Commercial testing is available for deficiencies of all the glycolytic defects (AMP, debrancher, brancher, MyoP, PFK, PBK, PGK, PGM, LDH) except aldolase A and 13-enolase.
    - Mutation analysis—genetic testing is available commercial for the most common mutations causing myophosphorylase deficiency (McArdle's disease).

—Lipid metabolism
  - History—vasoconstriction and accumulation of glycogen staining positive with oil-red-o (ORO) stain.
  - Biochemical—commercially available assays can be performed on muscle tissue for free and total carnitine levels along with CPT II.

—Mitochondrial metabolism
  - History—"ragged red fibers" and diminished muscle staining for oxidative enzymes (NADH, SDH, and CDX).
  - Biochemical—analysis for mitochondrial enzyme deficiencies.
  - Mutation analysis—testing is commercially available for some disorders (MELAS, MERRF, NARP, LHON, KSS/CPEO) via blood and/or muscle tissue. In mitochondrial myopathies, disease-causing mutations may segregate disproportionately with muscle tissue rather than other tissues during embryogenesis. Therefore, mutation analysis on muscle tissue provides a higher diagnostic yield for mitochondrial myopathies.

### Management

#### GENERAL MEASURES

The major therapeutic goal in metabolic myopathies is avoidance of provocative factors such as brief bursts of exertion for carbohydrate disorders and fasting for disorders of lipid metabolism. In the future, treatment will consist of enzyme replacement and/or genetic therapy.

#### SURGICAL MEASURES

None

#### SYMPTOMATIC TREATMENT

Most patients with a metabolic myopathy derive benefit from a low-intensity, graduated exercise program with emphasis on aerobic exercise. Dietary modification may benefit some patients. A diet high in protein and fats benefits some patients with carbohydrate metabolism disorders. The obverse is true for disorders of lipid metabolism. These patients benefit from frequent meals and a low-fat, high-carbohydrate diet.

#### ADJUNCTIVE TREATMENT

Co-management of concomitant cardiac, hepatic, and hematologic dysfunction improves quality of life and may be lifesaving. Seizures in mitochondrial disorders usually respond to conventional anticonvulsant drugs. Malignant hyperthermia, especially prevalent in disorders of carnitine processing, responds to dantrolene.

### Medications

#### DRUGS OF CHOICE

No medical regimen is yet known.

**Contraindications**

None

**Precautions**

None

**ALTERNATIVE DRUGS**

Some patients with mitochondrial myopathies improve after treatment with coenzyme Q10, 50-100 mg tid, and L-carnitine, 1,000 mg tid, plus an antioxidant vitamin regimen.

### Follow-Up

**PATIENT MONITORING**

Patients should be seen every 6 to 12 months to monitor disease progression. These visits also facilitate patient education about advances in care.

**EXPECTED COURSE AND PROGNOSIS**

The clinical course and prognosis are highly variable. Influencing factors include the distinct enzyme involved, the percentage reduction in enzymatic activity, the unique compensatory genetic milieu of each patient, and the environment in which these features play out. Some infantile forms of these disorders cause death due to cardiorespiratory failure prior to the first birthday, while adult-onset forms may present late in life with mild symptoms such as myalgias, cramps, and fatigue.

**PATIENT EDUCATION**

Muscular Dystrophy Association, 3300 E. Sunrise Drive, Tucson, AZ 85718. Phone: 800-572-1717, website: www.mdausa.org. Distinct patient organizations exist for many of the individual metabolic myopathies and may be found by searching the Internet.

### Miscellaneous

**SYNONYMS**

Myophosphorylase deficiency = McArdle's disease
Phosphofructokinase deficiency = Tarui's disease
Infantile form of acid maltase deficiency = Pompe's disease

**ICD-9-CM**: 359.89 Other myopathies; 728.89 Rhabdomyolysis (idiopathic); 995.86 Hyperthermia, malignant (due to anesthesia)

**SEE ALSO: N/A**

**ACKNOWLEDGMENT**

The views expressed herein are those of the author and do not reflect the official policy of the United States Air Force or the Department of Defense.

**REFERENCES**


**Author(s):** Matthew P. Wicklund, MD
Myopathy, Toxic

ASSOCIATED CONDITIONS
Hereditary myopathies associated with malignant hyperthermia
• Evans myopathy
• King-Denborough syndrome

Potential sequelae of rhabdomyolysis include myoglobinuria and renal failure.

Diagnosis

DIFFERENTIAL DIAGNOSIS
There should be no other identifiable cause of myopathy present. Differential diagnoses are listed by clinical and pathologic findings and may be listed more than once if more than one mechanism of presentation has been described.

Hyperthermia
• Malignant hyperthermia
• Neuroleptic malignant syndrome

Painful Toxic Myopathies
• Myopathic disorders: inflammatory myopathy, mitochondrial myopathy
• Medications: D-penicillamine, procainamide, didanosine, geranium, zidovudine; possibly phenytoin, levodopa, cimetidine, leuprolide, propylthiouracil, streptokinase
• Cholesterol lowering agents:
  — Fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil)
  — Nicotinic acid
• Combinations of medications: lovastatin and gemfibrozil may induce a myopathy in up to 5%.
• Antimicrotubular myopathy: colchicine, vincristine
• Drug-induced lysosomal storage myopathy (amphiphilic cationic drug myopathy)
  — Antimicrobial: chloramphenicol, plasmocid
  — Cholesterol lowering: lovastatin
  — Antimicrotubular myopathy: colchicine, vincristine

Toxic focal myopathies
—Ethanol (acute)
— Intramuscular injections
  — Acute: cephalothin, lidocaine, diazepam - Chronic: antibiotics (children), intravenous drug abuse, meperidine, pentazocine, pethidine
• Toxic myopathies associated with drugs of abuse
  — Amphetamines
  — Cocaine
  — Heroin
  — Phencyclidine
  — Volatile inhalation (e.g., toluene, gasoline)

SIGNS AND SYMPTOMS
Myopathic weakness begins after a suitable duration of exposure to a presumed toxin. There is usually no preexisting neuromuscular condition, and symptoms of weakness resolve following removal of the offending agent. Deep tendon reflexes and appreciation of primary sensory modalities are preserved.

LABORATORY PROCEDURES
Laboratory procedures to consider when a toxic myopathy is suspected should be based on suspicions elicited from the history.
• Serum: CK, potassium, serum toxicology screen
• Urine: 3-methylhistidine, myoglobin, urine toxicology screen

IMAGING STUDIES
N/A

SPECIAL TESTS
• In vitro contracture test (IVCT)—a bioassay that indicates susceptibility to malignant hyperthermia uses increasing concentrations of halothane or caffeine to measure contraction of biopsied skeletal muscle; contraction
Management

GENERAL MEASURES
Removal of the offending agent—most cases of toxic myopathy require removal of the potentially offending agent. Neuroleptic malignant syndrome can be caused by removal of a dopaminergic agent or use of neuromuscular junction blockers.

MUSCLE BIOLOGY

- Muscle biopsy—should be done if there is an alternate cause of weakness such as demyelinating neuropathy or demyelinating neuropathy or neuromuscular junction defect. Some agents can cause a neuropathy as well as a myopathy, and nerve conduction studies may also be affected. Such is the case with the anticholinergic agents colchicine and vinblastine, and possibly with chloroquine and amiodarone. EMG is normal in acute corticosteroid myopathy and demonstrates normal insertional and spontaneous activity with short duration and low-amplitude voluntary motor units in chronic corticosteroid myopathy.

- Muscle biopsy—should be done if there is incomplete or no resolution of weakness following removal of the suspected offending agent. Neuromuscular junction blockers may be done sooner to exclude causes of weakness other than toxin-induced myopathy. Knowledge of the pathologic findings and medications that the patient takes can help narrow the differential or confirm a diagnosis.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
N/A

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA

Admission Criteria
- Rhabdomyolysis or myoglobinuria—risk of renal failure
- Hyperthermia following anesthesia or use of neuromuscular blockers
- Impaired ambulation
- Impending respiratory failure

EXPECTED COURSE AND PROGNOSIS

Complete or at least partial resolution of symptoms after treatment.

MEDICATIONS

DRUGS OF CHOICE
- Malignant hyperthermia—dantrolene (1 mg/kg) IV as a continuous rapid infusion as needed up to a total dose of 10 mg/kg. The regimen may be repeated if symptoms recur.
- Neuroleptic malignant syndrome—dantrolene (1 mg/kg) IV as needed up to a total dose of 10 mg/kg.

CONTRAINdications
None. Only one case of anaphylaxis has been reported through 1999.

PRECAUTIONS
The intravenous formulation of dantrolene has a high pH and care should be taken to prevent extravasation. If mannitol will be used to prevent or treat late renal complications of malignant hyperthermia, mannitol, 3 g, is required to dissolve each 20 mg vial of dantrolene.

REPORTING
The Food and Drug Administration encourages voluntary reporting of adverse events, defined as any undesirable experience associated with the use of a medical product in a patient. The event should be reported when USE of a medication or product causes death or hospitalization. Reports can be submitted by the patient, their family members, or health care professionals.

ADDITIONAL DRUGS

Neuroleptic malignant syndrome: bromocriptine.

ALTERNATIVE DRUGS

Neuroleptic malignant syndrome: bromocriptine 2.5-10 mg IV or enterally by NG tube every 4 to 6 hours.

PATIENT MONITORING

Do not neglect other supportive measures of oxygenation, cooling, and management of metabolic acidosis for malignant hyperthermia or neuroleptic malignant syndrome.

EXPECTED COURSE AND PROGNOSIS

Complete or at least partial resolution of symptoms after treatment.

PATIENT EDUCATION

- Activities—as tolerated
- Diet—N/A
- Organizations—Malignant Hyperthermia Association of the U.S., 32 South Main Street, PO Box 1069, Sherburne, NY 14870; phone: 800-966-4287, 607-674-7901; fax 607-674-7910; email: mhas@nordrnb.com, website: http://www.malignanthyperthermia.org/RE Đối tác: Boyd M. Koffman, MD, PhD
Narcolepsy

**DESCRIPTION**

Narcolepsy is a chronic and disabling neurologic disorder characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations primarily related to abnormal regulation of rapid eye movement (REM) sleep.

**EPIDEMIOLOGY**

**Incidence**

Not determined, because the disorder is chronic. Prevalence has been ascertained in the adult Finnish population (0.026%) and estimated to be 0.05% in the general U.S. population.

**Race**

No known racial predominance.

**Age**

Develops around adolescence. Onset may be bimodal (mid-teens and mid-thirties). It then persists lifelong. Excessive daytime sleepiness often develops first with delay in the development of other features; this may lead to a delay in diagnosis.

**Sex**

Equally common in men and women.

**ETIOLOGY**

The etiology is uncertain. A strong association with certain human leukocyte antigen (HLA) haplotypes (DR15, DQB1*0602) suggests an autoimmune mechanism. It is likely that narcolepsy results from a deficiency of a neurotransmitter, possibly hypocretin (Orexin). Hypocretins are neurotransmitters whose cell bodies are located in the hypothalamus. Some propose that the pathogenesis likely includes a loss of hypocretin-producing neurons or of hypocretin receptor function, perhaps due to an autoimmune mechanisms.

**Genetics**

The etiology of narcolepsy is considered to be multifactorial. The 1% to 2% prevalence of narcolepsy within families with an index case does represent a genetic predisposition compared to the 0.05% rate in the general population. Monozygotic twins are concordant for narcolepsy in 25% to 31% of cases. The hypocretin gene was found to be abnormal in narcoleptic dogs in 1999 and a murine model has been produced by knocking abnormal in narcoleptic dogs in 1999 and a murine model has been produced by knocking out the genes that produce hypocretins.

**RISK FACTORS**

None are known. Rarely, narcolepsy has been reported after head trauma.

**PREGNANCY**

There is no known relationship to pregnancy.

**ASSOCIATED CONDITIONS**

- Obesity
- Type 2 diabetes
- Multiple sclerosis
- Pituitary-hypothalamic pathology (anterior pituitary tumors, craniopharyngiomas, dienrophic sarcoma)
- Brainstem lesions

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

Obstructive sleep apnea

Insufficient sleep syndrome (shift work, jet lag)

Delayed sleep-phase syndrome

Major depression

Chronic fatigue syndrome/fibromyalgia MS-related fatigue

Familial sleep paralysis

Periodic paralysis

Alcohol or other drug dependence

Restless legs/periodic movements of sleep

Idiopathic hypersomnia

**SIGNS AND SYMPTOMS**

Narcolepsy is manifested as a classic tetrad of symptoms, most of which may occur in people without narcolepsy. Cataplexy, sleep paralysis, and hypnagogic hallucinations are the result of partial intrusion of REM sleep physiology into wakefulness.

- Excessive daytime somnolence—the most frequent and disabling symptom is an abnormal tendency to rapidly fall asleep during falling asleep. Evidence of narcolepsy consists of exhibit evidence of REM sleep within minutes of asleep. However, many patients with, narcolepsy exhibit evidence of REM sleep within minutes of falling asleep. Evidence of narcolepsy consists of an abnormal tendency to rapidly fall asleep during an MSLT nap opportunity (within 5 minutes) plus occurrence of two or more episodes of REM sleep during MSLT naps. Such REM-containing naps are especially significant if they take place late in the day, when the propensity for REM sleep is normally low. Approximately 85% of patients with narcolepsy will have a positive MSLT. HLA haplotyping is useful for ruling out narcolepsy in cases of excessive daytime sleepiness attributed to obstructive sleep apnea or other causes.

**LABORATORY PROCEDURES**

- EDS may be assessed by the Epworth Sleepiness Scale.
- Polysomnography (PSG), an overnight sleep recording (with EEG, EMG, electrooculography, ECG, pulse oximetry, and respiratory monitoring) should be performed to rule out symptomatic sleep apnea or movement disorders as the cause of EDS. PSG should ideally be performed when the patient has been tapered off of sleeping medications and drugs that might affect sleep onset or REM latency (sedatives, stimulants, or antidepressants).

**MULTIPLE SLEEP LATENCY TEST (MSLT)** should be performed the next day. REM sleep normally does not occur until 90 minutes after initially falling asleep. However, many patients with narcolepsy exhibit evidence of REM sleep within minutes of falling asleep. Evidence of narcolepsy consists of an abnormal tendency to rapidly fall asleep during an MSLT nap opportunity (within 5 minutes) plus occurrence of two or more episodes of REM sleep during MSLT naps. Such REM-containing naps are especially significant if they take place late in the day, when the propensity for REM sleep is normally low. Approximately 85% of patients with narcolepsy will have a positive MSLT. HLA haplotyping is useful for ruling out narcolepsy in cases of excessive daytime sleepiness attributed to obstructive sleep apnea or other causes.

**IMAGING STUDIES**

Brainstem MRI abnormalities have been described, but imaging is rarely useful.

**SPECIAL TESTS**

None
Narcolepsy

Management

 GENERAL MEASURES
 Narcolepsy is a lifelong condition that requires treatment with stimulant medication(s) plus self-management of sleep. The latter includes (a) regular, rational periods of bed rest and prevention of sleep deprivation; and (b) planned naps of limited duration (20–30 minutes), especially before activity requiring alertness, such as driving. Shift work should be avoided.

 SURGICAL MEASURES
 None.

 SYMPTOMATIC TREATMENT
 EDS can be controlled with a wake-promoting or stimulant medication (modafinil, 200–400 mg/d or methylphenidate 10–40 mg/d) plus planned naps lasting 20 to 40 minutes. Cataplexy can be temporarily suppressed by imipramine 25 mg (or other tricyclic antidepressant drug) taken q4h PRN or a selective serotonin reuptake inhibitor (SSRI)-type antidepressant taken daily. The latter may also control sleep paralysis and hypnagogic hallucinations.

 ADJUNCTIVE TREATMENT
 Insomnia can occur not infrequently in narcolepsy and may be treated with triazolam with an increase in total sleep time.

 ADMISSION/DISCHARGE CRITERIA
 Hospital admission is almost never required.

 Medications

 DRUG(S) OF CHOICE
 For treatment of EDS:
 • Methylphenidate (Ritalin), 10–20 mg taken 1–2 times a day up to a maximum of 100 mg/d.
 • Modafinil (Provigil) 200 mg taken 1–2 times a day. It is quite expensive. Modafinil has been shown to stimulate the release of hypocretins in cells present in the anterior hypothalamus.
 • Amphetamine (dextro- and mixed dextro- and levosomers) not to exceed 100 mg/d
 • Methamphetamine up to 80 mg/d
 • Pemoline up to 150 mg/d
 For occasional cataplexy:
 • Imipramine 25 mg q4h PRN or other tricyclic antidepressant. 
 • For cataplexy, sleep paralysis, or hypnagogic hallucinations that occur several times a week or more often, zaleplon (Celexa) 20 mg/d or other SSRI agents may be useful.

 Contraindications
 Amphetamines are relatively contraindicated for patients with a previous history of chemical dependency.

 Precautions
 Sympathomimetic adverse effects of amphetamine stimulants include anxiety, tachycardia, palpitations, anorexia, headache, insomnia, and tremor. Patients should be monitored for the development of tolerance and drug dependency, although this is rare in patients without a prior history of chemical dependency. Pemoline has been associated with the risk of acute hepatic failure and manufacturers now recommend that serum transaminases be monitored every 2 weeks during therapy. Modafinil has been associated with adverse side effects of headache, nausea, and nervousness.

 ALTERNATIVE DRUGS
 Gamma hydroxybutyrate (GHB), an investigational agent, has been helpful for cataplexy during the day for some patients.

 Follow-Up

 PATIENT MONITORING
 Regular patient visits several times a year.

 EXPECTED COURSE AND PROGNOSIS
 The severity of narcolepsy may seem to worsen or improve from time to time, but neither complete remission nor relentless progression is known to occur. Symptoms remain lifelong.

 PATIENT EDUCATION/ORGANIZATIONS

 Miscellaneous

 SYNONYMS
 Narcolepsy-cataplexy syndrome

 ICD-9-CM: 347 Narcolepsy

 SEE ALSO: N/A

 REFERENCES

 Author(s): Charles P. Pollak, MD; Joanne Lynn, MD
Neurofibromatosis

**Basics**

**DESCRIPTION**

Neurofibromatosis type 1 (NF-1) is a progressive genetic disease with extreme variability, even within families. NF-1 can be difficult to diagnose in infants, because the appearance of many signs and symptoms is age dependent. The National Institutes of Health (NIH) criteria require that two or more of the following be present: (a) six or more café-au-lait macules greater than 5 mm in diameter in prepubescent individuals or greater than 15 mm in diameter after puberty, (b) two or more neurofibromas of any type (cutaneous, subcutaneous, or plexiform) or one plexiform neurofibroma, (c) freckling in the axilla or groin, (d) a tumor of the optic pathway, (e) two or more Lisch nodules (iris hamartomas), (f) a distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the cortex of the long bones (with or without pseudarthrosis), (g) a first-degree relative (parent, sibling, or child) with NF-1 by the above criteria.

Neurofibromatosis type 2 (NF-2) is an uncommon genetic disorder of tumors affecting the CNS. The diagnostic criteria include individuals with bilateral vestibular schwannomas (VS) or a family history of NF-2 in a first-degree relative plus any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities.

Most nerve sheath tumors associated with NF-2 are schwannomas and not neurofibromas. The average age of onset of symptoms is 18 to 24 years.

**ETIOLOGY**

- Both NF-1 and NF-2 are autosomal-dominant diseases, with nearly complete penetrance. Half of cases occur from new mutations.
- The NF-1 gene is on the long arm of chromosome 17. This gene is a tumor suppressor gene that encodes a peptide neurofibromin. Multiple mechanisms cause mutations of this gene, most of which inactivate neurofibromin.
- The NF-2 gene is on chromosome 22 and encodes the protein merlin.

**RISK FACTORS**

N/A

**PREGNANCY**

- Healthy women with NF-1 usually have normal pregnancies. Growth of neurofibromas has been reported during pregnancy. Most complications occur from preexisting problems such as pelvic neurofibromas or existing seizures.
- It is not known if NF-2 worsens during pregnancy.

**ASSOCIATED CONDITIONS**

N/A

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

**NF-1**

- Familial café-au-lait spots
- Schwannomatosis
- Nevoid syndrome
- Proteus syndrome
- Watson syndrome

**NF-2**

- Neurofibromatosis type 1
- Schwannomatosis
- Multiple meningiomas

**SIGNS AND SYMPTOMS**

**NF-1**

Pain or weakness can develop from tumor compression of nerves. Associated features include macrocephaly, scoliosis, learning disabilities, seizures, and unidentified bright objects (UBOs) in the basal ganglia, thalamus, cerebellum, and brainstem. UBOs are well-circumscribed, hyperintense lesions without mass effect. Their clinical and pathologic significance is unclear. Rarely, individuals can develop malignant peripheral nerve sheath tumors, pheochromocytomas, juvenile chronic myeloid leukemia, precocious puberty, or renal artery stenosis.

**NF-2**

- Focal weakness or sensory loss
- Neuropathic pain
- Balance disorder
- Headaches
- Bowel/bladder changes
- Hearing loss/tinnitus
- Visual impairment
- Skin tumors

**LABORATORY PROCEDURES**

Presymptomatic and prenatal diagnostic testing is available.

**IMAGING STUDIES**

**NF-1**

Imaging should be based on the clinical exam. MRI of the head with thin cuts through the internal auditory canals with and without contrast enhancement should be performed to evaluate for VS. Spinal MRI should be performed to evaluate for tumors.

**NF-2**

NF-2 is progressive, and new tumors can develop at any time. Neurologic exams and hearing evaluations should be performed at least annually and when new symptoms occur.
Neurofibromatosis

Management

GENERAL MEASURES
• There is no specific treatment or cure for NF-1. Referral to a NF clinic or multidisciplinary treatment team including pediatricians, neurologists, ophthalmologists, surgeons, radiologists, and oncologists should be considered. Seizures can be treated with typical antiseizure medication. Optic pathway tumors should be followed with imaging and ophthalmologic exams. They may require treatment with chemotherapy and less commonly radiation.
• There is no cure or specific treatment for NF-2.

SURGICAL MEASURES
NF-1
Painful or disfiguring neurofibromas can be surgically removed. Plexiform neurofibromas are difficult to completely resect. Dumbbell tumors of spinal nerve roots are difficult to manage. Nerve root and spinal cord compression can occur and surgical removal of the tumors or spinal decompression may be necessary. Patients with spinal dysplasia should be referred to an orthopedic surgeon who is familiar with NF-1. Scoliosis may require spine fusion.

NF-2
The timing of surgical treatment of VS is critical to preserve hearing and facial nerve function.

SYMPTOMATIC TREATMENT
Pain and itching frequently occur from neurofibromas. The pain can be severe and may require nonsteroidal antiinflammatory drugs (NSAIDs), opiates, or antiseizure medication such as gabapentin.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
N/A

Medications

DRUG(S) OF CHOICE
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Neurologic exams should be performed at least yearly, as NF-1 is progressive and new manifestations can occur at any time. This exam should always include blood pressure monitoring because of the rare possibility of renal artery stenosis or pheochromocytoma. When optic pathway tumors occur, it is in childhood. Therefore, children should have a yearly exam by an ophthalmologist. NF-2 patients should have annual neurologic exams, cranial MRI, and hearing evaluations.

EXPECTED COURSE AND PROGNOSIS
• NF-1 is progressive and unpredictable. Patients with more severe disease have increased mortality, but it is difficult to make generalizations because of the extreme variability of the disease.
• The clinical course of NF-2 is variable and dependent on tumor burden. Within families, there is a tendency to similar clinical course. The disease is progressive.

PATIENT EDUCATION
• Genetic counseling should be offered. Because of the progressive nature and unpredictability of the disease many patients benefit from support groups.
• First-degree relatives of patients with NF-2 should be screened for NF2. If patients with NF-2 should be referred to an audiologist upon diagnosis. Hearing aids, lip reading skills, and sign language may be helpful. Patients with vestibular tumors should be instructed on problems they may develop with balance, including underwater disorientation. Genetic counseling should also be offered. Many patients benefit from support groups.

Miscellaneous

SYNONYMS
NF-1
von Recklinghausen's disease
NF-2
Central, bilateral vestibular, or bilateral acoustic neurofibromatosis

ICD-9-CM: 237.71 Neurofibromatosis type 1; 23772 Neurofibromatosis type 2

SEE ALSO: N/A

REFERENCES

Author(s): Laura Krietemeyer, MD
Neuroleptic Malignant Syndrome

**Basics**

**DESCRIPTION**

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening reaction that occurs in patients who are treated with antipsychotic agents (neuroleptics). It appears that the cause of NMS is dopamine blockade, which would explain why this disorder has also been associated with drugs such as: Amoxapine (an antidepressant), Antiemetics such as prochlorperazine (Compazine), promethazine (Phenergan), and metoclopramide (Reglan).

**EPIDEMIOLOGY**

**Incidence/Prevalence**

- Estimated incidence of NMS ranges from 0.02% to 3.2% of patients treated with neuroleptics.
- Reasons for this variability include:
  - Diverse patient populations
  - Different thresholds for diagnosing the disorder
  - Variations in treatment practices
- Incidence of NMS is decreasing due to increased awareness, early detection and treatment, and efforts at prevention.

**Race**

African Americans may be at higher risk because they have a higher proportion of alleles that code for reduced CYP2D6 enzymatic activity (genetic polymorphisms exist in most of the CYPs).

**Age**

All ages are affected, although NMS most commonly occurs in adults ages 20 to 50.

**Sex**

NMS is more commonly seen in men, but this may be attributed to the fact that men are medicated more frequently and more aggressively with neuroleptics than women.

**ETIOLOGY**

- There is still a fair amount of controversy over the etiology of NMS.
  - Dopamine D2 receptor antagonists are associated with this disorder, and it is assumed that NMS is caused by dopamine receptor blockade.
  - Studies show that dopamine blockade could lead to hypothalamic dysfunction resulting in:
    - Hyperthermia
    - Labile blood pressure
    - Tachycardia
  - Dopamine blockade in the striatum can cause:
    - Tremor
    - Rigidity
    - Rhabdomyolysis (due to prolonged muscular hypertonicity)

**RISK FACTORS**

- Dehydration
- History of prior episodes of NMS
- High doses of neuroleptics
- Intramuscular administration of neuroleptics
- Rapid rate of neuroleptic loading
- Catatonia
- Iron deficiency
- Use of other medications (especially lithium) in conjunction with neuroleptics
- Prolonged use of seclusion/restraints
- Electrolyte disturbances
- Presence of an organic dysfunction
- Presence of an mood disorder

**PREGNANCY**

**N/A**

**ASSOCIATED CONDITIONS**

**N/A**

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Catatonia
- Serotonin syndrome
- Heat exhaustion and heat stroke
- Malignant hyperthermia
- Delirium-secondary to anticholinergic toxicity
- Withdrawal of antiparkinsonian agents in a patient with Parkinson's disease
- Thyrotoxicosis
- CNS infections
- Drug toxicity: amphetamines, phencyclidine (PCP), cocaine
- Intermittent acute porphyria
- Pheochromocytoma
- Tetany
- Prolonged use of seclusion/restraints
- Intermittent acute porphyria
- Rhabdomyolysis
- Malignant hyperthermia
- Heat exhaustion and heat stroke
- Delirium-secondary to anticholinergic toxicity
- Thyrotoxicosis
- CNS infections
- Drug toxicity: amphetamines, phencyclidine (PCP), cocaine
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- CNS infections
- Drug toxicity: amphetamines, phencyclidine (PCP), cocaine
- Intermittent acute porphyria
- Pheochromocytoma
- Tetany
- Prolonged use of seclusion/restraints
- Intermittent acute porphyria
- Rhabdomyolysis

**SIGNS AND SYMPTOMS**

- Hyperthermia
- Generalized rigidity (lead pipe)
- Autonomic instability
- Mental status changes
- Profuse diaphoresis

**DIAGNOSTIC CRITERIA for Neuroleptic Malignant Syndrome**

- Recent treatment with neuroleptics (within 1 day before onset)
- Hyperthermia (temperature above 38°C)
- Muscle rigidity
- Exclusion of systemic or neuropsychiatric illness
- And at least three of the following:
  - Change in mental status
  - Change in blood pressure
  - Creatinine phosphokinase (CPK) elevation or myoglobinuria

**LABORATORY PROCEDURES**

- CPK
- CBC
- Electrolytes, including calcium and magnesium
- Renal and hepatic function tests
- Urinalysis, including urine myoglobin

**SPECIAL TESTS**

- Lumbar puncture to rule out CNS infection

**Management**

**GENERAL MEASURES**

- The most critical intervention is to discontinue all neuroleptic agents immediately.
- The discontinuation of other medications such as lithium or antihistaminic agents should be considered.

**SURGICAL MEASURES**

**N/A**

**SYMPTOMATIC TREATMENT**

- IV fluids to correct dehydration, hypotension, and electrolyte imbalance
- A cooling blanket and antipyretics to reduce the temperature
- If rhabdomyolysis occurs, it is important to hydrate patients and alkalinize the urine to prevent renal failure
- Aspiration precautions
- Maintain good nutrition, as this may minimize rhabdomyolysis

**ADJUNCTIVE TREATMENT**

- Dialysis may be necessary, if renal failure develops.
- ECT (electroconvulsive therapy) has been found to be effective both in treating NMS and the underlying psychiatric condition.
Neuroleptic Malignant Syndrome

ADMISSION/DISCHARGE CRITERIA
• Most patients suspected of having NMS should be treated (at least initially) in the medical intensive care unit.
• Patients may be transferred to a medical or psychiatric inpatient unit if their vital signs are stable, their hydration status and electrolyte imbalance are correct, and there is no evidence of renal failure or cardiorespiratory compromise.

ALTERNATIVE DRUGS
• There are controversial data on the use of benzodiazepines and barbiturates for NMS.
• Nifedipine may be used in hypertension.
• Subcutaneous heparin should be used to prevent pulmonary embolism or deep vein thrombosis.
• Iron deficiency anemia may aggravate NMS. Therefore, iron supplements should be prescribed for patients who are deficient.

Medications

DRUGS OF CHOICE
• In most cases pharmacologic management is instituted if the course of the syndrome fails to improve with supportive measures alone.
• Dopamine agonist agents are the drugs of choice, and some studies have shown that they may decrease mortality and shorten the course of NMS.
• Bromocriptine (Parlodel): a dopamine agonist (usually the starting dose is 2.5 mg PO tid).
• Dantrolene (Dantrium): a muscle relaxant and is specifically recommended for severe hyperthermia. It may be given IV or PO.
• Sinemet

Follow-Up

PATIENT MONITORING
Patients with NMS should be off neuroleptics for 2 weeks following resolution of the syndrome. Vital signs and CPK levels need to be monitored.

EXPECTED COURSE AND PROGNOSIS
• The clinical course of NMS usually lasts 2 to 14 days, although in the case of long-acting depot antipsychotic agents it may be prolonged up to 30 days.
• Mortality rate is 10% to 20% from complications listed above. In the absence of these complications the prognosis for full recovery is good.
• Patients who develop NMS are more likely to have a recurrence upon reintroduction of neuroleptic agents. To minimize the risk of a recurrence, several measures may be helpful:
  — Try a neuroleptic from a different chemical class and with a lower D2 affinity, such as an atypical antipsychotic, (risperidone, olanzapine, quetiapine).
  — Clozapine is currently recommended for patients who need an antipsychotic and have a history of NMS (but the risk for agranulocytosis needs close monitoring with this agent). In addition, clozapine has also been associated with NMS (but less frequently).
  — Consider alternative treatments with lithium, valproate, carbamazepine, or ECT.
  — If an antipsychotic agent is necessary, use the lowest effective dose and increase the dose slowly.
  — Obtain informed consent from the patient and family and discuss at length risks, benefits, and side effects of treatment. In addition, closely monitor vital signs and CPK levels.

PATIENT EDUCATION
Every patient who has had NMS should be told that he or she is at risk for recurrence if challenged with any dopamine-blocking agent.

REFERENCES

Author(S): Radu Saveanu, MD
**Neuronal Ceroid Lipofuscinoses**

**Basics**

**DESCRIPTION**
- Neuronal ceroid lipofuscinoses (NCLs) Group of neurodegenerative disorders characterized by progressive dementia, visual loss, epilepsy and intralysosomal accumulation of a membrane-bound fluorescent lipopigment in neurons and other cells. Although this abnormal lipopigment is widely distributed in the skin, muscle, peripheral nerve, and viscera, signs and symptoms are confined to the central nervous system.
- There are four major subtypes: infantile (NCL1 or Santavuori-Haltia type), late infantile (NCL2 or Jansky-Bielschowsky type), juvenile (NCL3 or Batten type), and an adult recessive form (NCL4 or Kufs type). A dozen atypical variant forms, including Finnish late infantile variant (NCL5), have been described.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- The NCLs are the most common group of neurodegenerative disorders in children.

**Race**
- NCL2 and NCL3 are the most prevalent subtypes in the United States and Europe. NCL1 and NCL5 are particularly frequent in Finland.

**Age**
- See Signs and Symptoms

**Sex**
- Because of autosomal recessive inheritance, there are equal numbers of male and female cases.

**ETIOLOGY**

**Y Genetics**
- Autosomal recessive mode of inheritance except for a rare adult-onset variant that is autosomal dominant. Gene identification has been accomplished for NCL1, NCL2, NCL3, and NCL5. Prenatal diagnosis is available for most subtypes.

**RISK FACTORS**
- N/A

**PREGNANCY**
- N/A

**ASSOCIATED CONDITIONS**
- N/A

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- The NCLs are easily distinguished from other known inherited metabolic neurodegenerative diseases based on physical examination, funduscopic evaluation, and clinical course. It is most important to distinguish between the different forms of the NCLs because they share many clinical features. It also is important to confirm the diagnosis to rule out other neurodegenerative disorders of unknown etiology.

**SIGNS AND SYMPTOMS**
- Classified according to age of onset, clinical features, ultratrasstructural morphology, and genetic analysis.
  - NCL1: dramatic onset of psychomotor deterioration, seizures and blindness during the first year of life. The most common ocular abnormality is optic atrophy; retinal abnormalities have been reported.
  - NCL2: onset between 2 and 5 years of age, with psychomotor deterioration and intractable seizures. Blindness associated with optic atrophy or retinitis pigmentosa. Vegetative state ensues after symptoms have been present for about 1 year.
  - NCL3: onset between 5 and 15 years of age, with either gradual visual loss resulting in blindness within 3-5 years and/or behavioral symptoms. There is prominent macular degeneration, optic atrophy, or retinitis pigmentosa. Some time after the onset of the visual disturbance, motor dysfunction (apraxia and ataxia), seizures, and slow dementia are noted.
  - NCL4: average onset at 30 years, with a steadily progressive dementia and seizures that ultimately be come refractory. Vision usually is not affected.

**LABORATORY PROCEDURES**
- See Special Tests

**IMAGING STUDIES**
- Neuroimaging may reveal atrophy. SPECIAL TESTS
- Diagnosis is suspected based on physical examination, which must include a funduscopic evaluation, and clinical course. EEG, electoretinogram, visual evoked potentials, and somatosensory evoked potentials may add supportive evidence. Confirmation is made by histologic identification of characteristic ultrastructural abnormalities noted on skin or conjunctival biopsy and/or genetic analysis when available.
- Histologic inclusions:
  - NCL1: granular osmiophilic deposits
  - NCL2: curvilinear inclusion bodies
  - NCL3: fingerprint inclusions
  - NCL4: curvilinear inclusion bodies, fingerprint inclusions, granular osmiophilic deposits
**Neuronal Ceroid Lipofuscinoses**

**Management**

**GENERAL MEASURES**
- Patients and their families require emotional support.

**SURGICAL MEASURES**
- N/A

**SYMPTOMATIC TREATMENT**
- Correction of associated visual refractive errors
- "Valproate and clonazepam for seizure control
- Psychotropic drugs for treatment of behavior problems

**ADJUNCTIVE TREATMENT**
- Braille training and visual impairment education

**ADMISSION/DISCHARGE CRITERIA**
- Patients usually are admitted for evaluation and treatment of the complications of their disease.

**DRUGS OF CHOICE**
- No medications are available to reverse the symptoms of these disorders. Antioxidants may temporarily improve mentation.

**ALTERNATIVE DRUGS**
- N/A

**Patient Monitoring**
- Patient follow-up is guided by the predicted course and potential complications of the particular disease.

**Expected Course and Prognosis**
- NCL1: rapid and severe neuronal devastation. Usually fatal before the end of the first decade.
- NCL2: rapidly progressive. Usually fatal before the end of the first decade.
- NCL3: may remain ambulatory and able to attend school until the late teens, although 25% of patients die in their teens after a more rapidly deteriorating course with prominent seizures.
- NCL4: slow progression. Duration of illness 20-30 years.

**Patient Education**
- Batten Disease Support and Research Association, 2600 Parsons Avenue, Columbus, OH 43207. Phone: 800-448-4570.
- National, Batten Disease Registry, 1050 Forest Hill Road, Staten Island, NY 10314-6399. Phone: 800-952-9628.

**Miscellaneous**

**Synonyms**
- N/A

**ICD-9-CM:** 272.7 Ceroid storage disease

**See Also:** N/A

**References**

**Author(s):** Eveline C. Traeger, MD
Neuropathy, Diabetic

Basics

DESCRIPTION
• Diabetes mellitus (DM) is the most frequent cause of peripheral neuropathy in the developed world. The most common peripheral neuropathic syndrome associated with diabetes is diabetic polyneuropathy, an insidiously progressive, length-dependent peripheral neuropathy. Patients with diabetic polyneuropathy may exhibit distal sensory loss and dyesthesias, autonomic dysfunction, and distal weakness. Morbidity related to diabetic polyneuropathy is significant and includes neuropathic pain, sensory loss leading to limb infections and amputations, and reduced proprioception with unsteady walking and falls.

EPIEMIOLOGY
• DM is an increasingly common disorder affecting nearly 7% of the US population. Late complications, which include retinopathy, nephropathy, and peripheral neuropathy, are more common with prolonged and severe hyperglycemia.
• More than half of diabetics eventually develop clinically evident peripheral neuropathy. At the time of diagnosis, 5% of diabetics have clinically overt peripheral neuropathy. Fifty percent have overt peripheral neuropathic findings within 10 years of diagnosis.

ETIOLOGY
• Diabetic polyneuropathy results from chronic hyperglycemia, but the precise pathophysiology has not been established. Microangiopathy and metabolic abnormalities are the two major proposed causes. Endoneurial microvascular changes with basement membrane thickening and pericyte degeneration progress to vessel and nerve ischemic injury. Proposed metabolic abnormalities include accumulation of advanced glycosylation products leading to smooth muscle proliferation and capillary attherosclerosis. Accumulation of polyol constituents, such as sorbitol and fructose, ultimately may lead to nerve demyelination and axonal injury. Oxidative stress with excessive free radical production may lead to lipid peroxidation of nerve membranes. Circulating nerve growth factors are also reduced, suggesting a role in pathogenesis.

RISK FACTORS
• Diagnosis of DM with chronically poor glycemic control is the most important risk factor for the development of diabetic polyneuropathy. Older diabetic patients and men are at greater risk. The risk for developing diabetic polyneuropathy can be significantly reduced with a regimen of strict glycemic control. Once axonal injury becomes well established, there are no known effective interventions for reversing diabetic polyneuropathy.

PREGNANCY
• Pregnant women who develop gestational diabetes are not at increased risk for developing diabetic polyneuropathy, unless their hyperglycemia persists beyond 6 weeks postpartum.

ASSOCIATED CONDITIONS
• Several other peripheral neuropathic syndromes occur in diabetics and are distinct from, and often coexist with, diabetic polyneuropathy.
• Cranial neuropathies related to diabetes include oculomotor, abducens, and trochlear neuropathies presenting with subacute external ophthalmoplegia, frequently preceded by pain. The most common is diabetic oculomotor neuropathy, which presents with ocular or hernial pain, ptosis, and diplopia. Sparing of pupil constrictor function may help to differentiate diabetic from compressive causes of oculomotor neuropathy, but pupillary function may be spared initially in compressive lesions. The prognosis is favorable in these patients with functional recovery occurring over 1-3 months.
• Peripheral neuropathies related to diabetes include compressive mononeuropathies: Diabetics have increased susceptibility to compression neuropathies, including median neuropathies at the wrists (carpal tunnel syndrome), ulnar neuropathies at the elbows, peroneal neuropathies at the fibular heads, and lateral femoral cutaneous neuropathies (meralgia paresthetica).

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Differential diagnosis includes peripheral neuropathy due to peripheral neurotoxins, uremia, nutritional deficiency, hypothyroidism, and paraproteinemia, along with hereditary, idiopathic sensory, and chronic immunemediated peripheral neuropathies.
• Central clinical diagnosis of diabetic polyneuropathy can be made in patients with DM and a history of prolonged hyperglycemia. Diagnosis of DM requires a random serum glucose measurement >200 mg/dL, fasting plasma glucose >126 mg/dL, or plasma glucose >200 mg/dL during a 2-hour oral glucose tolerance test. In this setting, a diagnosis of diabetic polyneuropathy is supported by findings of a distal, symmetric, peripheral neuropathy in the absence of other causes of polyneuropathy.

SIGNS AND SYMPTOMS
• The initial symptoms of diabetic polyneuropathy are related to dysfunction of the longest sensory nerve fibers with early impairment of small-fiber sensory function. This may present as tingling or burning paraesthesias in the toes and distal feet with abnormal pain and temperature sensation. Achilles tendon reflexes and vibratory sensation in the toes are often reduced early.
• Hand numbness and sensory loss may develop later as a consequence of the progression of length-dependent neuropathy or from compressive median or ulnar neuropathies. As diabetic polyneuropathy progresses, abnormal sensation may be perceived on the anterior abdomen due to distal involvement of thoracic nerves.
• Autonomic neuropathy may produce postural hypotension with an increased and invariant pulse and reduced sweating in the distal limbs. Gastrointestinal manifestations include delayed gastric emptying, gastroparesis, postprandial sweating, and nocturnal diarrhea. Genitourinary manifestations include bladder atony with difficulty initiating micturition, incomplete bladder emptying, and postvoid dribbling. Most men are aware of erectile impotence, although ejaculation initially is unaffected.
• Large-fiber sensory deficits develop later, with distal proprioceptive loss and sensory ataxia. Patients may complain of gait unsteadiness, with difficulty walking in a dark environment or loss of balance with eyes closed. Romberg’s sign is often present. Neurogenic foot arthropathy (Charcot joint) may develop at the instep.
• Distal weakness with reduced strength and bulk for great toe extension, foot dorsiflexion, and intrinsic hand musculature may develop with advanced disease.
LABORATORY PROCEDURES
- Electrodiagnostic studies: Nerve conduction studies may demonstrate reduced conduction velocity and amplitudes of sensory nerve action potentials and of compound muscle action potentials in a length-dependent fashion. Needle electromyography may demonstrate denervation and reinnervation in distal muscles with more advanced disease. Electrodiagnostic studies are particularly useful when a sperm is used compression neuropathy is being considered.
- Quantitative sensory testing: Quantitative sensory testing demonstrates increased vibratory, touch pressure, and thermal sensory thresholds.
- Autonomic studies are utilized to assess autonomic function. Heart rate variability to deep breathing (R-R interval testing) may demonstrate loss of the normal sinus arrhythmia with slow deep breathing at six times per minute.
- Nerve biopsy is not normally indicated to evaluate diabetic polyneuropathy.

IMAGING STUDIES
N/A

SPECIAL TESTS
See above

Management

- Strict glycemic control can prevent or slow progression of diabetic polyneuropathy. Meticulous foot care is essential to prevent the development of foot infections, which are difficult to treat and may lead to amputation.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
- Symptomatic treatment of neuropathic foot pain is frequently required; see Medications.

ADJUNCTIVE TREATMENT
- Podiatric referral for foot hygiene, including nail care and callus removal, should be promoted. Physical therapy may be indicated for patients with sensory ataxia.

ADMISSION/DISCHARGE CRITERIA
- Hospital admission is not generally required.

Medications

**DRUG(S) OF CHOICE**
- Neuropathic pain involving the distal extremities may require treatment. For mild symptoms, ibuprofen 400 mg twice a day may be given in the setting of normal renal function.
- For more severe and continuous neuropathic pain, tricyclic antidepressant agents such as amitriptyline beginning at a low dosage of 10–25 mg at bedtime may be effective over 10 days. If pain relief is inadequate, the dosage may be increased slowly to 100–150 mg at bedtime. Sedation is a prominent side effect of amitriptyline and may be desirable in patients with insomnia related to neuropathic pain. Desipramine and nortriptyline offer less sedation. Tricyclic agents should be used with great caution in patients with heart disease or prostatism.

**Contraindications**
- Known hypersensitivity, glaucoma, serious cardiac conduction delays, benign prostatic hypertrophy

**Precautions**
N/A

**ALTERNATIVE DRUGS**
- Selected anticonvulsants (gabapentin, carbamazepine, phenytoin) are helpful in neuropathic pain.

Follow-Up

**PATIENT MONITORING**
- Glycemic control should be closely monitored by the primary physician or endocrinologist. Neuropologic reexamination at long intervals can document sensory, motor, and autonomic function.

**EXPECTED COURSE AND PROGNOSIS**
- Progression of polyneuropathy occurs with chronic hyperglycemia and is not inevitable if glycemia is well controlled.

**PATIENT EDUCATION**
- Exercise, weight loss in obesity, appropriate diet, optimal foot care, and compliance with insulin and/or oral hypoglycemic medications are important for best outcomes.
- National Diabetes Information Clearinghouse, 1 Information Way, Bethesda, MD 20892-3560. Website: ndic@info.niddk.nih.gov

AUTHOR(S): Vern C. Juel, MD
Neuropathy, Hereditary

Basics

DESCRIPTION
• Hereditary neuropathies probably account for a majority of the cases referred to large neuromuscular centers. Most common sensory motor hereditary neuropathies fall under the category of Charcot-Marie-Tooth (CMT) neuropathy or disease, which encompasses disorders resulting from different genetic defects involving either the ensheathing Schwann cell or the nerve cell itself. Other less common hereditary neuropathies include sensory and autonomic neuropathies, familial amyloid polyneuropathy, disorders of lipid metabolism, ataxia with neuropathy syndromes, and rare miscellaneous conditions. The subclassification of different categories of CMT is done according to the principal pathology (demyelinating [CMT1, CMT3, CMT4] or axonal [CMT2]), mode of inheritance (autosomal dominant, autosomal recessive, X linked), age at onset (infancy, childhood, adulthood), and the specific gene mutation. CMT1, the most common form, refers to an autosomal dominant demyelinating form (sporadic in 20%). CMT2 refers to an autosomal dominant or recessive axonal form. CMT3 begins in infancy and is associated with severe hypomyelination, inherited in an autosomal recessive or dominant form, CMT4 subgroup includes cases resembling CMT1 or CMT3 phenotype but is inherited only in an autosomal recessive fashion. Although this classification offers some practical considerations, it is far from complete or accurate in considering the variability in phenotype (axonal vs. demyelinating) that could result from different mutations in the same gene. An expected influence of molecular genetics on clinical neurology is now resulting in the currently evolving classification of CMT neuropathies.

EPIDEMIOLOGY
• Estimates suggest a prevalence rate of 1 in 2,500, but exact numbers are difficult to ascertain because of the heterogeneity of the syndromes. Duplication of CMT1A locus is the most prevalent mutation found in CMT1. Female carriers for the X-linked form of CMT caused by connexin 32 (Cx32) mutations have mild signs, but 10% of patients have obvious changes on examination with mild functional impairment.

ETIOLOGY
• It is now well established that mutations in myelin-making Schwann cells, particularly in CMT1, have a profound influence on their axonal counterpart. This results in alterations in the cytoskeletal components and impaired axonal transport leading to preferential distal axonal atrophy and degeneration giving rise to a clinical presentation of a length-dependent axonal neuropathy. In CMT2, the primary axonal form, mutations affecting components of axonal cytoskeleton, their regulators, and axonal transport motors result in primary axonal pathology.

Genetics
• New mutations responsible for different forms of CMT are being discovered at a rapid pace (recent information available at https://molgen.vuw.ac.nz/ac.be/CMT mutations/). Most common CMT mutations are as follows:
  - CMT1A has 1.5-Mb duplication at chromosome 17p11.2-12 encompassing the peripheral myelin protein 22 (PMP22) gene in the majority; others have point mutations.
  - Deletion of the same gene causes the reciprocal disorder hereditary neuropathy with pressure paresthesias (HNPP).
  - CMT1B has point mutations and small deletions in the peripheral myelin protein zero (PO) on chromosome 18p22.3.
  - CMT1C has point mutations in LITAF/SIMPLE, a putative protein degradation gene on chromosome 16p13.1-p12.3.
  - CMTX has point mutations, small deletions, or insertions in the Cx32 gene encoding a gap junction protein on chromosome Xq13.1.
  - CMT2A has point mutation in KIF1B (kinesin family member for axoplasmic motor) gene on chromosome 1p35-p36.
  - CMT2B has point mutations in RAB7 (member of RAS oncogene) gene on chromosome 3q27.
  - CMT2C has point mutations in NEFL (neuromuscular protein light chain) gene on chromosome 8p21.
  - CMT2D has point mutations, small deletions, or insertions in GDAP1 (ganglioside-induced differentiation-associated protein 1) gene on chromosome 19q13.
  - CMT2E has point mutations, small deletions, or insertions in MTMR2 (myotubularin-related protein 2) gene on chromosome 14q22.
  - CMT2F has point mutations in EGR2 (early growth response 2) gene on chromosome 8p21.1.
  - CMT4B has point mutations, small insertions, or deletions in MTHFR (methylenyltetrahydrofolate reductase) gene on chromosome 1q42.
  - CMT4C has point mutations in EGR2 (early growth response 2) gene on chromosome 10q21.1-12.1.
  - CMT4F has point mutations and deletions in PRX (periaxin) gene on chromosome 19g13-19.

RISK FACTORS
N/A

PREGNANCY
• The rate of obstetric complications in CMT patients is in accordance with that of the normal population. Exacerbation of CMT (increasing weakness) was reported as a temporary worsening (35%) or persistent disability (65%) during at least one pregnancy in one third of patients.

ASSOCIATED CONDITIONS
• Essential tremor is present in one third of CMT1 cases but is less common in CMT2 cases. Palpable nerve enlargement is seen in 50% of CMT1 cases. Pes cavus and hammertoes are common (not invariable). Associated deafness has been reported in rare families with demyelinating phenotype.

Diagnosis

DIFFERENTIAL DIAGNOSIS
• In sporadic cases or when a reliable family history is unavailable, a broad differential of peripheral neuropathy with an insidious onset and slowly progressive course, as in toxic metabolic and deficiency states, should be ruled out.

SIGNS AND SYMPTOMS
• CMT1: type IA (70%), IB (20%), IC (10%)
  - Most common form of hereditary motor and sensory neuropathy manifesting in the first or second decade with distal muscle weakness and atrophy, more prominent in the lower than upper extremities. Latter occurs in about two thirds of cases.
  - Loss of distal muscle stretch reflexes (majority anarthritic throughout).
  - Early age at onset of motor impairment is predictive of a more severe course.
  - Sensory complaints are minimal, usually not modality specific. Decreased vibration with preservation of position sense is common.
  - CMT2: incidence is about half that of CMT1. For types A, B, and D, onset is in the first or second decade (maybe later). Findings on neurologic examination are similar to CMT1. CMT2C may have an onset in infancy or later, with associated vocal cord paralysis and respiratory muscle weakness from diaphragm, intercostal and laryngeal involvement, and minimal sensory loss.
  - CMT3 (Dejerine-Sottas syndrome [DDS]): should be considered a severe phenotypic variant of CMT1. Onset is in infancy or early childhood and includes cases with hypotonia at birth with delayed motor milestones, Generalized limb and trunk weakness with prominent large-fiber sensory loss resulting in ataxia and palpable peripheral nerves is common. Muscle stretch reflexes are absent. Skeletal abnormalities, including kyphoscoliosis, pes cavus, and hammertoes, may be prominent. Cases with recessive inheritance and severe hypomyelination at infancy are now being classified as CMT4 to include EGR2 and PRX gene defects.
### Laboratory Procedures

#### Electrodiagnosis
- **CMT1**: uniform slowing (by 25% or more of normal, <40 m/s in arms and <30 m/s in legs)
- **CMT2**: motor normal or mildly slow (not demyelinating range); sensory nerve action potentials reduced or absent
- **CMT3**: uniform slowing (<20 m/s in arms, <10 m/s in legs)
- **HNPP**: focal slowing of conduction velocities and loss in amplitude in relation to compression; may have features of mild generalized demyelinating sensory motor neuropathy
- **CMTX**: uniform slowing with loss of compound muscle action potentials

#### Pathology
- **CMT1**: loss of myelinated nerve fibers; many thinly myelinated fibers; prominent onion bulbs
- **CMT2**: loss of myelinated nerve fibers; axonal atrophy; clusters of regenerating fibers
- **CMT3**: severe loss of myelinated nerve fibers; many thinly myelinated fibers; prominent onion bulbs
- **HNPP**: loss of myelinated nerve fibers; occasionally clustered thinly myelinated fibers; tomaculi (focal sausage like myelin thickening)
- **CMTX**: loss of myelinated nerve fibers; axonal atrophy; regeneration-associated onion bulbs

### Imaging Studies
- White matter abnormalities in brains are seen rarely in patients with X-linked CMT and HNPP.
- In CMTX cases, nonenhancing and symmetric white matter abnormalities were transient, corresponding to acute transient ataxia, dysarthria, and weakness.

#### Special Tests
- Genetic testing is commercially available for some CMT subclasses. The mode of inheritance, age at onset, and clinical features with electrophysiology should guide the clinician in selecting a candidate gene defect for testing.

### Medications

#### Drugs of Choice
- There currently is no medical therapy to reverse or slow down the disease process.

#### Contraindications
- N/A

#### Precautions
- Drugs with neurotoxic side effects, such as cancer chemotherapeutic agents, and particularly those with well-known neurotoxicity, such as vincristine, paclitaxel (Taxol), or doxorubicin (Adriamycin), can result in severe and rapid progression of CMT neuropathy. Patients should be monitored closely while taking such medications if possible, switched to less toxic alternatives.

### Management

#### General Measures
- Many patients benefit from ankle-foot orthoses. Appliances may be useful for patients with hand weakness. Patients with DDS phenotype may require knee-ankle-foot orthosis. Patients should be tested to ensure an early diagnosis of possible superimposed diabetes, thyroid dysfunction, or vitamin B₁₂ deficiency.

#### Surgical Measures
- Corrective surgical procedures for foot deformities may help selected patients, depending on their needs.

#### Symptomatic Treatment
- A significant number of patients with CMT neuropathies have pain. When neuropathic pain is present, as in the case of idiopathic painful neuropathies, the pain must be treated aggressively with anticonvulsants, tricyclic antidepressants, or antiarrhythmic agents. A monotherapy approach is desirable, but combination therapy might be beneficial in failed cases. Cramping pain can be treated with quinine sulfate.

### Adjunctive Treatment
- N/A

### Admission/Discharge Criteria
- N/A

### ICD-9-CM
- 356.0 Hereditary peripheral neuropathy

### Synonyms
- Hereditary motor and sensory neuropathies (HMSN, 1975 classification; type I synonymous with CMT1; type II with CMT2 also called neuronal form of peroneal muscular atrophy; type III refers to DDS)

### Expected Course and Prognosis
- CMT neuropathies usually have an insidious-onset, slowly progressive course with age. Patients with a recent history of notable worsening of their disease should be evaluated for the possibility of superimposed autoimmune neuropathies or metabolic disorders.

### Patient Education
- [Charcot-Marie-Tooth Association](http://www.charcot-marie-tooth.org)
- [The Neuropathy Association](http://www.neuropathy.org)

### References

**Author(s):** Zarife Sahenk, MD, PhD
Neuropathy, Peripheral

Basics

DESCRIPTION

• Acquired or hereditary disorder of multiple peripheral nerves, with primary injury to sensory and/or motor axons, myelin sheaths, and/or neurons; occasional autonomic involvement. Mononeuropathies are beyond the scope of this chapter.

ETIOLOGY

Age

• Occurs at all ages.

Risk Factors

• Any genetic predisposition or associated condition listed elsewhere

DESCRIPTION

Neuropathy, Peripheral

— Defective DNA repair (Cockayne’s syndrome, ataxia telangiectasia)

— Familial amyloid polyneuropathy

— Hereditary sensory and autonomic neuropathies (HSAN)

— Hereditary sensory neuropathies (HSN)

— Leukodystrophies (metachromatic, globoid cell/Krabbe’s), lipoprotein disorders (HDL deficiency/Tangier, atabelliproteinemia), lysosomal enzyme deficiency (Fabry disease)

— Peroxisomal disorders (X-linked adrenomyeloneuropathy, Refsum’s),

— Porphyrias (acute intermittent, variegate, others)

— Miscellaneous: giant axonal neuropathy, myotonic dystrophy, spinocerebellar degenerations, Friedreich’s ataxia

RISK FACTORS

• When confronted with suspected polyneuropathy, the goal is to determine the predominant pathologic process (axon loss vs. demyelination) and likely cause, if possible, to guide specific treatment. An orderly approach is as follows:

—Consider whether polyneuropathy is truly present. Although most patients with polyneuropathy report foot numbness and tingling—usually progressing insidiously from the toes to the balls of feet, then more proximally over plantar and dorsal pedal surfaces—this is not absolutely diagnostic.

—When confronted with suspected polyneuropathy, the goal is to determine the predominant pathologic process (axon loss vs. demyelination) and likely cause, if possible, to guide specific treatment. An orderly approach is as follows:

• Consider whether polyneuropathy is truly present. Although most patients with polyneuropathy report foot numbness and tingling—usually progressing insidiously from the toes to the balls of feet, then more proximally over plantar and dorsal pedal surfaces—this is not absolutely diagnostic.

• Occasional patients with CNS disorders (e.g., multiple sclerosis) report “pseudo-neuropathic” distal symptoms but show upper motor neuron (UMN) signs such as hyperreflexia and Babinski signs not observed in polyneuropathy.
Consider the time course (acute over days in AIDP and some toxic neuropathies; subacute over several months in some inflammatory and vasculitic neuropathies; or chronic over many months to many years in mononeuronal polyneuropathies). Often, polyneuropathies in childhood have a hereditary or inflammatory basis.

Consider predisposing medical conditions (e.g., diabetes, family history [e.g., amyloidosis, HMSN], habits [see above], and occupational exposures [e.g., painters and lead; smelters and arsenic, plastics, and acrylamide; farmers and organophosphate]).

Consider the anatomic distribution. At least three fourths of polyneuropathies have a "fiber-length-dependent" pattern, commonly known as "stocking glove." Sensory and motor involvement is symmetric, legs > arms and distal > proximal. Predominant pathology is axon loss, mimicked by some chronic inflammatory demyelinating polyneuropathies (CIDP) or congenital mononeuropathy multiplex. Other polyneuropathies show a proximal > distal pattern, usually symmetric, such as many demyelinating polyneuropathies (AIDP/GBS, some CIDP). Uncommon polyneuropathies show an asymmetric or "multifocal" pattern, such as mononeuropathy multiplex (random lesions, usually vasculitic nerve infarcts, rarely inflammatory or infiltrative). Other multifocal polyneuropathies include MMN and HNPP.

Known as "tomaoculcus neuropathy.

Consider whether paresthesias are present and whether sensory symptoms are predominant.

Positive sensory symptoms (e.g., tingling, burning, "lancinating pain, cutaneous hypersensitivity), are "best" sensations from abnormality and - generally indicate the p, I neuropathy is acquired (e.g., alcoholism). Most acquired axonal polyneuropathies are predominantly sensory or sensory = motor symptomatically, whereas many acquired demyelinating (e.g., AIDP, CIDP, MMN) and most hereditary polyneuropathies (e.g., HMSN I and HMSN II) are axon predominant. The particular quality of the neuropatic pain is not helpful in etiologic diagnosis, beyond the nonspecific but commonplace burning quality of selective small-fiber sensory polyneuropathies. Certain neuropathies are often painful (e.g., alcohol, amyloid, arsenic, cryptogenic, diabetic, neoplastic, porphyric, vasculitic, uremic). Most patients with hereditary polyneuropathies report "negative" symptoms of numbness and weakness without paresthesias (e.g., HMSN); however, many of these patients report nociceptive pain due to tissue stress.

Consider whether deep tendon reflexes are reduced out of proportion to muscle weakness, especially proximal areflexia with distal weakness and numbness. When present, consider demyelinating polyneuropathy (AIDP, CIDP, HMSN I).

Consider other investigative physical findings. Palpably enlarged nerves in HMSN I, amyloid, leprosy, occasionally CIDP. Autonomic signs, such as orthostatic hypotension, sweating abnormalities, cold extremities, dry eyes and mouth, bowel and bladder dysfunction, and erectile dysfunction, may be seen together or individually in AIDP, porphyria, amyloidosis, and uremia. Other physical findings, including skin changes, are beyond the scope here.

Determine if there is selective fiber-type involvement, which, if present, is etiologically suggestive. Most polyneuropathies are "mixed" in that there is involvement of large sensory neurons and their axons (proprioception, vibration, two-point discrimination), small sensory neurons and their axons (perception of heat and cold, non-specific nociception), motor neurons and axons, and to variable degrees autonomic nerves (postganglionic sympathetic efferents supply arms and legs). Important differential diagnosis of fiber-selective neuropathies includes the following:

- Large sensory neurons and axons (sensory ataxia): paraneoplastic (SCLC), Sjogren's, idiopathic, toxic (excess B6 >200 mg daily for many months), cis-platinum, docetaxel, vincristine, and vitamin deficiency states (B12 and E).
- Small sensory neurons and axons (often painful): cryptogenic sensory neuropathy of elderly, diabetes, vasculitis, amyloid, arsenic, Fabry, HIV
- Motorneurons and axons: motor neuron diseases, HMSN II, demyelinating (MMN, AIDP, CIDP), porphyria, lead, dapsone, imipramine
- Autonomic: diabetes, amyloid, AIDP, HIV, vincristine, paclitaxel (Tarot), amiodarone, porphyria, HSAN, idiopathic and paraneoplastic pandyautonomias

SIGNS AND SYMPTOMS

- Numbness (subjective "deadness," loss of vibration, joint position sense)
- Tingling (paresthesias)
- Burning, jabbing (dysesthesias)
- Lancinating pain
- Heat, cold, and/or touch intolerance
- Gait ataxia
- Pseudo-athetosis
- Muscle weakness and fatigability
- Muscle atrophy, sometimes with deformities (e.g., pes cavus)
- Cramping
- Fasciculations
- Myokymia (quivering muscles under skin)
- Hyperhidrosis and anhidrosis
- Sicca complex (dry eyes and mouth)
- Orthostasis
- Sphincter and erectile dysfunction
- Cranial nerve symptoms

LABORATORY PROCEDURES

- A clinically directed approach to laboratory testing of unknown polyneuropathy is more revealing and cost effective than a "shotgun" approach. Rational laboratory testing follows logically from knowing whether the polyneuropathy is acute or subacute/chronic, symmetric or multifocal, predominantly axonal or demyelinating, and fiber-type specific or mixed sensory and motor. Such knowledge requires a detail-oriented history and neurologic examination, followed by a problem-focused nerve conduction and EMG study designed and performed by a physician well-trained in clinical neurophysiology and neuro muscular diagnosis.
- Among identifiable polyneuropathies, the most likely cause- usually is a known or clinically discernible condition, predisposing genetic disorder, or toxic-metabolic state (e.g., metabolic, medication toxicity, alcoholism, illicit drugs, occupational, environmental). About half of unknown polyneuropathies, especially chronic, predominantly axonal polyneuropathies, remain "cryptogenic" after thorough workup, which stands to reason as laboratory tests seek harmful factors extrinsic to nerves, although intracellular causes that Cannot be assayed play a role. Commercial "diagnostic panels" for polyneuropathy seldom justify their expense in clinical practice, without clinically driven selection of particular laboratory assays. Until evidence-based and consensus guidelines for polyneuropathy testing are available, the following stepwise testing approach is offered for consideration:
  - Primary tests (all patients; need not be repeated if normal within 3-6 months): EMG and nerve conduction studies (NCS). CBC with differential, complete metabolic profile (CMP), fasting blood sugar (FBS), TSH, US, RPR, vitamin B12, ANA, rheumatoid factor (RF), serum immunoelectrophoresis (SIEP), UIEP (urine immunoelectrophoresis; note: serum protein electrophoresis [SPEP] may miss a small monoclonal band or a monoclonal present in some cases).
  - Secondary tests (often, specific clinical suspicion and/or abnormality above): glucose tolerance test, HgbA1c, methyImalonic acid (especially elderly with serum B12 low normal), vitamins B1 and E, y-glutamyl transferase (GGT), hepatitis B and C, thyroxine, FTA-ABS, ANA profile (including ds-DNA, SS-A, SS-B), complement (C3, C4, CH50), Lyme titer, HIV, lead and mercury (if motor), arsenic and thallium (if sensory). Chest x-ray film in many for malignancy.
Neuropathy, Peripheral

**Management**

**GENERAL MEASURES**
- Rational, pattern-recognition, cost-effective approach to diagnostic testing. If unexpected progression occurs during follow-up (clinically, NCS, QST), reopen and widen progression occurs during follow-up
- Low threshold for consulting neuromuscular diseases specialized neurologist regarding unexplained polyneuropathy, particularly if progressive in a young patient.
- Treatment of cause—i.e., known—influenza may limit progression or improve neuropathy (e.g., tight glucose control in diabetes, abstinence in alcoholic neuropathy, replete vitamin B12 or thyroid if deficient, eliminate neurotoxic exposure).
- Effective immunotherapy for treatable, proven immune-mediated neuropathy.
- Vigorous treatment for neuropathic pain and secondary nociceptive pains.
- Monitor cognitive and psychosocial function pending or during treatment.
- Referral or evaluation of secondary nociceptive pain (joints, ligaments): chronic myofascial pain may respond to selective cyclooxygenase 2 (COX2) inhibitors. Associated with very high protein (>125-150 mg/dL). Serologic abnormalities in Lyme polyradiculoneuropathy and neurosphyliasis.

**IMAGING STUDIES**
- Chest x-ray film (possibly followed by chest CT or other malignancy workup depending on results and clinical suspicion): Tumor, radiculopathy
- MRI and CT of spinal cord, occasionally brain: occasionally helps to exclude CNS causes of "pseudo-neuropathic" limb paresthesias and weakness; gadolinium may show root enhancement in demyelinating, infectious, and autoimmune polyradiculoneuropathies or in carcinomatus meningitis
- MRI of brachial or lumbar sacralplexus, with gadolinium: very occasional yield for compressive, inflammatory, hypertrophic, infiltrating lesions
- Skeletal survey: paraprotein evaluation for marrow abnormality (plasmacytoma)

**SPECIAL TESTS**
- Nerve conductions and EMG: essential test to characterize polyneuropathy as likely predominantly axonal or demyelinating, acuteness, and severity.
- Sensory nerve biopsy (usually sural nerve; occasionally superficial peroneal sensory fascicle with peroneus tertius muscle): occasionally performed. Best candidate when suspect autoimmune vasculitis (sometimes biopsy peroneus tertius muscle); amyloid; mononuclear cells or edema (inflammation); active myelin breakdown.
- CSF: albuminocytologic dissociation in demyelinating polyneuropathies (few or no WBC, elevated protein), such as AIDP and CIDP. HIV-related AIDP has lymphocytic pleocytosis (>50 WBC). CIDP may be associated with very high protein (>125-150 mg/dL). Serologic abnormalities in Lyme polyradiculoneuropathy and neurosphyliasis.

- Quantitative sensory testing (QST): measure cold and heat perception, and cold and heat pain, detection thresholds. Quite valuable for small-fiber neuropathy and longitudinal follow-up, pending or during treatment.
- Autonomic testing: quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test (TST), tilt table (orthostasis), Schimper's (sicca).
- Cautiously nerve punch biopsy: verify small-fiber dying-back neuropathy. Specialized technique, with limited availability in few neuromuscular centers.
- Other biopsies: minor salivary gland (Sjogren's), rectal mucosa/fat pad (amyloid).

**SURGICAL MEASURES**
- Nerve biopsy: selective, recognizing possible persisting pain at biopsy site.
- Other biopsies: skin, minor salivary gland, abdominal fat pad, rectal mucosa, marrow.
- Conservative approach to surgery of incidental spinal stenoses, unless severe.

**SYMPTOMATIC TREATMENT**
- Pain management: Neuropathic pain may respond to empirically applied single agents or combinations of low-dose tricyclics, antiepileptic drugs (gabapentin, topiramate, carbamazepine, others), topical analgesics (lidocaine creme or patch, capsaicin), mexiletine, clonidine, opioids (selected). Nociceptive pain may respond to nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors. Associated with very high protein (serum). Refractoriness to conventional immunotherapies.
- Discourage megadoses of "alternative medications, particularly those taken regularly.
- Limit vitamin B6 to <5 mg/day in polyneuropathy (avoid in sensory polyneuropathy).
- Protect limbs with loss of protective sensation from physical and thermal trauma.
- Excellent professional foot and nail care, in appropriate cases (e.g., diabetic).
- Effective pedal arch supports; special shoes as needed (e.g., HMSN).
- Ankle-foot orthoses for footdrop; high shoes for ankle instability.
- Ambulation aids appropriate to sensory ataxia and/or weakness (cane, ideally four-prong; walker, including wheeled walker; wheelchair; electric scooter).
- For severe hypermobility, bed cradle over feet to prevent blanket contact.
- Reassures patients with "cryptogenic" sensory/sensorimotor neuropathy and elderly patients with "cryptogenic" painful small-fiber neuropathy—after adequate diagnostic evaluation—that recent literature supports usually good prognosis for indolent progression. Follow for unexpected change.
- Medical professionalism. Commitment to ongoing care. Sensitivity to patient's inner experience of disease. Goal is to support capability for a full life.
Neuropathy, Peripheral

ADJUNCTIVE TREATMENT

• Depression: judicious antidepressants; counseling (individual and family), support groups, psychiatrist or psychologist; exercise (important)
• Physical therapy: strengthening, flexibility, endurance; range-of-motion
• Occupational therapy: upper extremity adaptive aids; thickened utensil handles; custom splints; work-hardening occupational assessment
• Durable goods: ankle-foot orthoses, cane, walker, wheelchair, scooter

ADMISSION/DISCHARGE CRITERIA

• AIDP: initial monitored setting (telemetry, q shift forced vital capacity until trend clear
• Elective intravenous immunoglobulin (IVIG) and PLEX (selected cases)
• Immunosuppression complications

Follow-Up

PATIENT MONITORING

• Variable, depending on cause

EXPECTED COURSE AND PROGNOSIS

• Variable, depending on cause

PATIENT EDUCATION

• Charcot-Marie-Tooth Association (CMTA), 2700 Chestnut Street, Chester, PA 19013-4867. Phone: 800-606-CMTA, website: www.charcot-marie-tooth.org
• Guillain-Barre Syndrome Foundation International (GBSFI), P.O. Box 262, Wynnewood, PA 19096. Phone: 610-667-7036, website: www.guillain-barre.org
• Muscular Dystrophy Association-USA (MDA; support and advocacy for 43 neuromuscular diseases, including CMT and Friedreich’s ataxia). National Headquarters, 3300 East Sunrise Drive, Tucson, AZ 85718. Phone: 800-572-1717, website: www.mdausa.org
• The Neuropathy Association (public, nonprofit organization established by people with neuropathy and their families or friends to help those who suffer from disorders that affect the peripheral nerves), 60 East 42nd Street, New York, NY 10165-0999. Phone: 212-692-0662, website: www.neuropathy.org

ALTERNATIVE DRUGS

• a4Lipoic acid (omega-3)

Medications

DRUG(S) OF CHOICE

• AIDP/GBS: PLEX and IVIG equivalent efficacy; avoid corticosteroids
• CIDP: corticosteroids, PLEX, IVIG, azathioprine, cyclosporine
• Connective tissue syndromes: treat primary condition, vasculitis if present
• Deficiency states: replete deficient vitamins, nutritional factors
• Familial amyloid polyneuropathy: liver transplantation
• MMN: IVIG, cyclophosphamide; rituximab
• Osteodystrophic myeloma and POEMS syndrome: radiation and/or surgery
• Paraproteinemias (including MGUS): PLEX, IVIG, immunosuppression
• Vasculitis: corticosteroids, cytotoxic agents

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ALTERNATIVE DRUGS

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Neuropathy, Vasculitic

DESCRIPTION

- Vasculitis is a term that covers a diverse group of disorders in which inflammatory changes destroy blood vessel walls, resulting in ischemia and thrombosis. Inflammatory changes typically result from dysfunctional immunologic mechanisms, but they also occur as a direct consequence of infections. Peripheral nerve damage occurs when inflammation affects the vas a nervorum supplying individual nerves. This most commonly is part of a systemic illness, although peripheral neuropathy may be the sole manifestation of vasculitis. The vasculitides are commonly distinguished by their organ system involvement and the size of the blood vessels pathologically affected.

EPIDEMIOLOGY

Incidence

- The exact incidence of vasculitic neuropathy is unknown. In polyarteritis nodosa, which is considered the most common systemic necrotizing vasculitis, approximately 60% of individuals have peripheral nerve involvement, equating to roughly 5 cases per million people.

Age

- More common at older ages (mean age of onset 60 years)

Sex/Gender

- There is no clear sex or racial predominance.

ETIOLOGY

- Autoimmune disease is the presumed pathologic mechanism, although this remains largely unproven. An inciting antigen is thought to trigger a cascade involving humoral or cellular responses, resulting in leukocyte adherence to the endothelial surface of blood vessel walls. Inflammatory changes then damage the endothelial surface, and the blood vessel may undergo necrosis. The immunologic hypothesis stems from the fact that vasculitides occur with connective tissue diseases, malignancies, and hyper-sensitivity drug reactions, or in association with infections including syphilis, Lyme disease, rickettsia, human immunodeficiency virus, cytomegalovirus, and Cryptococcus.

RISK FACTORS

- Vasculitis occurs in the setting of connective tissue disease, drugs, infections, and malignancy.

PREGNANCY

- There is no known relationship with pregnancy.

ASSOCIATED CONDITIONS

- Peripheral nerve vasculitis is often part of a wider systemic illness. Other organ manifestations that may occur with peripheral nerve involvement include coronary artery disease (Kawasaki disease), necrotizing glomerulonephritis (Wegener's granulomatous, microscopic polyangiitis), respiratory tract inflammation and eosinophilia (Churg-Strauss), skin disorders (HP, cryoglobulinemia, leukocytoclastic vasculitis), arthropathies (rheumatoid arthritis), and polymyalgia rheumatica (temporal arteritis).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes diabetic mononeuropathy multiplex, and infectious or carcino-matous causes of polyradiculopathy. Autoimmune conditions, such as multifocal acquired demyelinating sensory and motor neuropathy, may also mimic vasculitic mononeuropathy multiplex. Guillain-Barré syndrome should be considered in cases with more acute onset and symmetric neural involvement. Other conditions with a clinical presentation resembling vasculitic neuropathy include Sjögren's-related sensory neuronopathy, amyloidosis neuropathy, sarcoidosis, and toxic neuropathies related to heavy metal exposure (e.g., arsenic, thallium).

SIGNS AND SYMPTOMS

- Vasculitic neuropathy typically presents as asymmetric weakness and sensory loss in the distribution of multiple individual nerves. Clinical involvement most commonly occurs in the peroneal and ulnar distributions. Symptoms occur acutely or subacutely, and progress in a stepwise pattern to involve one nerve after another. Pain and dysesthesia are common (30%-80%), usually noted at the onset of peripheral nerve damage. Sensory loss and weakness conform to individual peripheral nerves and typically are apparent on neurologic examination. Constitutional symptoms of fever, myalgia/arthritis, and weight loss are common, and their presence, along with skin, lung, kidney, or joint involvement, should help point to a systemic illness. Besides mononeuritis multiplex, other clinical presentations may occur, including a rapidly progressive, arthritic paralytic resembling Guillain-Barré syndrome, and a slowly progressive, symmetric, distal sensorimotor polyneuropathy. Gradual overlapping involvement of multiple individual peripheral nerves may lead to the appearance of a symmetric or generalized sensorimotor polyneuropathy.

LABORATORY PROCEDURES

- Laboratory studies, including complete blood cell count, electrocardiogram, sedimentation rate, coagulation panel, serum chemistries, % liver function tests, urinalysis, serum protein electrophoresis, rheumatoid factor, antinuclear antibody, extractable nuclear antigen antibodies, serum complements, and cryoglobulins, help to identify more widespread systemic disease. Additional testing, aimed at identifying a vasculitis-related illness, include HIV, Lyme titer, syphilis serologies, serum angiotensin-converting enzymes, chest x-ray film, cytoplasmic (c) ANCA (Wegener's granulomatous), and perinuclear (p) ANCA (Churg-Strauss, microvascular polyangiitis). Cerebrospinal fluid analysis is of limited utility.

IMAGING STUDIES

- There are no specific imaging abnormalities.

SPECIAL TESTS

- Nerve conduction studies reveal a multifocal sensorimotor axonopathy with reduced amplitude compound motor and sensory nerve action potentials. Sensory changes tend to be more prominent, and the lower extremities are affected more than the upper extremities. Distal latencies and conduction velocities typically are normal. A few reports describe primarily demyelinating features and motor conduction block, which may be apparent if testing is performed within 1 week of symptom onset. Subclinical abnormalities in asymptomatic nerves may help with diagnosis in difficult cases.

- Needle electromyography (EMG) typically demonstrates active denervation (fibrillations, positive sharp waves) and decreased recruitment patterns most severely affecting the distributions of individual peripheral nerves where weakness is present. Nerve biopsy provides pathologic confirmation of vasculitic neuropathy. The sural, superficial peroneal, or superficial radial nerves are most commonly biopsied. Biopsy features of vasculitis include lymphocytic inflammatory cell infiltration within the blood vessel wall, endothelial cell destruction, fibrinoid necrosis, intimal hyperplasia, vascular sclerosis, and perivascular inflammation. Simultaneous muscle biopsy, looking for inflammatory changes in blood vessels supplying small nerve twigs entering muscle, may increase the diagnostic yield compared to nerve biopsy alone. Overall, the need for diagnostic confirmation by muscle or nerve biopsy is greatest in cases of isolated peripheral nerve vasculitis when there is often no evidence of systemic involvement; it has the least value in cases where systemic disease is obvious.
Management

GENERAL MEASURES

• The four basic principles of vasculitic neuropathy management are (i) removal of the inciting antigen (drug reaction, infections, malignancy); (ii) immunosuppressive therapy, (iii) treatment of vasculitis, and (iv) supportive/adjunctive care.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

• Neuropathic pain is common. Effective medications include tricyclic antidepressants (amitriptyline, nortriptyline); antiepileptic medications (gabapentin, phenytoin [Dilantin], carbamazepine [Tegretol]); me adulte; topical creams (capsaicin, lidocaine); transdermal medications (lidocaine patch, fentanyl patch); and scheduled opioid therapy (methadone). Trials of these various medications can be managed through routine clinic visits, but recalcitrant pain may require management by a pain specialist.

ADJUNCTIVE TREATMENT

• Physical and occupational therapy assist in maintenance of strength, flexibility, and functional ability in the setting of neurologic impairment from vasculitic neuropathy. Ankle-foot orthoses may be required for footdrop, and splints may be required to stabilize and protect weakened extremities. Once the underlying vasculitis is under control, aggressive physical therapy may be required to hasten strength recovery.

ADMISSION/DISCHARGE CRITERIA

• Hospital admission is not commonly required, unless the neuropathy is particularly severe and rapidly progressive.

Medications

DRUG(S) OF CHOICE

• Immunosuppression: In vasculitic neuropathy associated with systemic necrotizing vasculitis, a combination of prednisone (1.5 mg/kg daily) and a cytotoxic agent (cyclophosphamide 2 mg/kg PO daily, or 500-600 mg/m² IV pulse every 4 weeks) is recommended. Mesna can be administered intravenously with pulse IV cyclophosphamide to reduce the risk of hemorrhagic cystitis. If clinical improvement is noted, prednisone is then tapered by 5-10 mg every 2-4 weeks. The cytotoxic agent usually is discontinued after 6-12 months. In cases where there is no clinical response, alternative cytotoxic medications, including azathioprine, methotrexate, or cyclosporine, may be considered. Prednisone alone may be sufficient if the neuropathy is slowly progressive, if there is no systemic involvement, or in the setting of temporal arteritis or hypersensitivity reaction. High-dose steroid induction with methyl prednisone (15 mg/kg qd for 3-5 days) may be necessary if the neuropathy is severe or rapidly progressing.

• Vaso-occlusion: Antiplatelet therapy with aspirin (81-325 mg daily) may help reduce thromboxane-induced vasoconstriction and platelet activation that is not covered by glucocorticoid administration. Calcium channel blockers may also be helpful.

Contraindications

• Prednisone should be used under supervision in poorly controlled diabetes mellitus or hypertension. Cyclophosphamide may impair renal or liver function and may lead to bone marrow suppression or opportunistic infections. Both prednisone and cyclophosphamide should be used cautiously during pregnancy.

Precautions

• Side effects of long-term prednisone use include weight gain, glucose intolerance, osteoporosis, cataracts, hypertension, acne, and myopathy. Cyclophosphamide may cause hemorrhagic cystitis, bladder and hematologic malignancies, gastrointestinal symptoms, and alopecia.

ALTERNATIVE DRUGS

• Both intravenous immunoglobulin and plasmapheresis have been considered as possible therapies, but no reports demonstrate specific improvement in vasculitic neuropathies.

Follow-up

PATIENT MONITORING

• Patients should be seen frequently when there is active vasculitis and when immunosuppressive therapy is initiated. Follow-up should focus on clinical change, adjustment of medications, and monitoring of adverse effects. Blood testing for patients on cyclophosphamide should include a monthly complete blood count, electrolytes, liver function tests, and urinalysis. Patients on prednisone should be monitored for symptoms of diabetes. Dietary consultation and TB skin testing may be considered before initiating prednisone therapy.

EXPECTED COURSE AND PROGNOSIS

• There are no long-term, prospective studies specific to vasculitic neuropathy. However, 25%-50% of patients with systemic vasculitis fail to respond to therapy or may relapse during treatment. In addition, 40% experience drug-related side effects and up to 85% experience disease-related morbidity primarily involving other organ systems. As in most neuropathies associated with significant axonal damage, clinical stabilization and improvement can be expected, although recovery often is protracted and incomplete.

PATIENT EDUCATION

• There are no specific therapies, activities, or dietary restrictions related to vasculitis. Nutritional therapists may instruct patients regarding appropriate dietary changes while taking prednisone. Information about peripheral nerve vasculitis is available from the following:

Miscellaneous

SYNONYMS

• Peripheral nerve vasculitis
• Mononeuritis multiplex

ICD-9-CM: 447.6Vasculitis; 354.5 Mononeuritis multiplex

SEE ALSO: N/A

REFERENCES


Author(s): Patrick M. Grogan, MD; Jonathon S. Katz, MD

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Nonepileptic Seizures

**Basics**

**DESCRIPTION**
- Nonepileptic seizures (pseudoseizures) are spells of paroxysmal behavior that resemble epileptic seizures without electroencephalographic evidence of abnormal brain electrical activity during the event. They are most often characterized by convulsive activity but also may present with periods of stiffening, unresponsiveness, staring, or a variety of abnormal behaviors. Almost any type of abnormal behavior may be called a seizure and present for evaluation. Nonepileptic seizures usually are not stereo-typed (vary from occurrence to occurrence) and remain refractory to antiepileptic drugs (AEDs). Unlike epileptic seizures, which almost always are <2 minutes in duration, nonepileptic seizures may go on for many minutes or even hours, frequently waxing and waning.
- Usually all previous evaluations have been normal, including EEGs, neuroimaging (MRI, CT head), and neurologic examination. The best diagnostic data come from a well-performed EEG during an episode of pseudo seizure activity that shows a normal background and no electrographic seizure activity.

**EPIDEMIOLOGY**

*Incidence/Prevalence*
- The overall incidence is unknown, but approximately 25%-30% of patients who are monitored at a tertiary epilepsy center are diagnosed with pseudoseizures.

*Age*
- Usually presents in adulthood

*Race*
- No apparent predisposition for race

*Sex*
- From 50%-80% of patients are women. (Note: Gates study quotes 80% female, but other studies reported equal male and female [Gulick TA, Spinks IP, King DW, Pseudoseizures: ictal phenomena. Neurology 1982;32:24–30].)

**ETIOLOGY**
- The etiology of nonepileptic seizures is not well understood. Most nonepileptic seizures are believed to be conversion symptoms and result from psychological factors. The cause of conversion symptoms in general is controversial. One hypothesis is that conversion symptoms represent an expression of an unconscious psychological need or conflict that has been repressed. Another hypothesis is that conversion symptoms are an unconscious means for patients to obtain secondary gain in the form of support or services.

**Genetics**
- There are no genetic studies.

**RISK FACTORS**
- Patients with lower levels of education are at higher risk. In addition, patients with a number of psychiatric diagnoses, including dissociative identity disorder, hypochondriasis, and somatization disorder, are at greater risk. Victims of physical, sexual, or emotional abuse are at significantly increased risk. Some patients with nonepileptic seizures also have true epilepsy (10%-34%), so epilepsy may be a risk factor. Note that because psychiatric diagnoses are common in the epilepsy population, just the presence of psychopathology may not help in the diagnosis.

**PREGNANCY**
- There is no association with pregnancy.

**ASSOCIATED CONDITIONS**
- Dissociative disorder, somatization disorder, hypochondriasis, conversion disorder, history of physical or sexual abuse

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Epilepsy including frontal lobe epilepsy (which may be very hard to detect with EEG)
- Syncope
- Malingering
- Nonepileptic myoclonus
- Sleep disorders, including narcolepsy and cataplexy, periodic limb movements, night terrors
- Paroxysmal movement disorders
- Panic disorder

**SIGNS AND SYMPTOMS**
- The manifestations may be extremely varied but usually involve some shaking or unresponsiveness. Symptoms occur often but certainly not always during times of stress. Features that may suggest pseudoseizures rather than true seizures include gradual onset, waxing and waning of symptoms, a long duration, conspicuous absence of postictal confusion, crying during the spell, out-of-phase clonic movements of the limbs, and suggestibility.

**LABORATORY PROCEDURES**
- CBC, chemistries, AED levels

**IMAGING STUDIES**
- MRI is the preferred form of neuroimaging. As with epilepsy patients, it is important to rule out a structural pathology in this population.

**SPECIAL TESTS**
- EEG is indicated; if EEG is normal and an episode is not captured, prolonged EEG recording may be needed. Inpatient video-EEG is the preferred test. This test lasts from 1 to several days as needed. Outpatient ambulatory EEG may be adequate but is prone to artifact that is confusing. Use of suggestion may needed at the time of the EEG to assist patients in having one of their typical spells. Patients with pseudoseizures commonly will respond to suggestion 'during recording, whereas patients with epilepsy will rarely have a seizure with suggestion.
- If syncope is suspected, Hotter ECG monitoring may be indicated, as may be cardiod noninvasive testing and neuroimaging (MRI usually is preferable to CT). If disorders of sleep or arousal are suspected, a polysomnogram or multiple sleep latency test may be indicated.
Nonepileptic Seizures

Management

GENERAL MEASURES

• Presenting the patient and his/her family with the diagnosis is the first step to management. It may be the most difficult step. This must be done in a nonconfrontational style. The patient or family may not initially accept the diagnosis. If the patient and/or family are alienated, they may go to other physicians and be treated for the wrong diagnosis or have to repeat the previous evaluations. The neurologist should follow-up with the patient, and AEDs (if any) should be gradually tapered off on an outpatient basis as long as there is no evidence that the patient also has epileptic seizures. Most patients are not aware that the events are psychologically mediated. Patients should not be viewed as "crazy" but rather as having inappropriate reaction to some unconscious conflict. They need to be referred to a psychiatrist or psychologist. Treatment by the psychologist/social worker/psychiatrist may include insight-oriented psychotherapy, behavioral therapy, family therapy, hypnosis, and drug therapy.

SURGICAL MEASURES

N/A

SYMPTOMATIC TREATMENT

• Psychotherapy, including psychodynamic therapy, behavioral therapy, family therapy, and hypnosis

ADJUNCTIVE TREATMENT

• Some patients require antidepressant medications during their outpatient treatment.

ADMISSION/DISCHARGE CRITERIA

• In-patient video-EEG monitoring is warranted in patients for whom the diagnosis of pseudoseizures is suspected but not proven. Inpatient monitoring is also indicated if the patient is suspected of having both epileptic and nonepileptic seizures. Sometimes it is important to know which type of seizures (if there is more than one type) is epileptic and which is not. The patient should be discharged when the diagnosis is no longer in doubt.

Medications

DRUG(S) OF CHOICE

• There are no recommended medications, but antidepressants and/or anxiolytics are often used. Patients may often be taking multiple AEDs prior to diagnosis; such polypharmacy should be reduced to a minimum.

Contraindications

N/A

Precautions

N/A

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

• The patient ideally should be followed by both mental health professionals and a neurologist initially. Taper of AEDs is best handled by the neurologist, if necessary. As the patient improves, the follow-up with neurology can be gradually extended and then terminated when both parties are comfortable.

EXPECTED COURSE AND PROGNOSIS

• Prognosis is better when the diagnosis is made and treatment is commenced closer to the start of the pseudoseizures. A small but significant percentage of patients will improve after learning that the seizures are not epileptic. The rest will need a multidisciplinary approach that may take many months of therapy.

PATIENT EDUCATION

• The only reading materials widely available are books and journal articles, some of which are listed below. There is no organization that acts as an advocate for these patients.

Miscellaneous

SYNONYMS

• Hysterical pseudoseizures
• Pseudoepileptic seizures
• Hysteroepilepsy
• Psychogenic seizures

ICD-9-CM: 300.11 Conversion; 300.14 Dissociative identity disorder; 300.81 Somatization disorder (Briquet's syndrome); 300.70 Somatoform disorder; 301.51 Factitious disorder with physical symptoms

SEE ALSO: N/A

REFERENCES


Author(s): J. Layne Moore, MD
Opsoclonus

DESCRIPTION

Opsoclonus affects both eyes and consists of back-to-back saccades (rapid eye movements) in the horizontal, vertical, and torsional planes. It can be continuous, or intermittent, and represents the most dramatic acquired eye movement disorder when the saccades are of large amplitude. The descriptive term saccadomania has been used to describe its striking manifestations. Opsoclonus, however, can also be of very small amplitude, and may require careful observation of the eyes for detection. Other neurologic signs such as ataxia, myoclonus, and an encephalopathic state are commonly associated with opsoclonus.

EPIDEMIOLOGY

In incidence/Prevalence

Opsoclonus is a relatively rare disorder.

Race

Opsoclonus shows no ethnic preference. Age

Age at presentation depends on the etiology and ranges from infancy to old age.

Sex

Opsoclonus shows no gender preference.

ETIOLOGY

- Opsoclonus has multiple etiologies but in a considerable number of cases the underlying disease process remains undetermined. It is most commonly seen in the context of cancer, and as a parainfectious disorder. In both circumstances the pathophysiology is presumed to be autoimmune with antibodies damaging neurons involved in ocular motor control. Pathologically, damage to pontine structures, possibly including saccade-suppressing omnipause neurons, has been described. Loss of inhibitory input to cerebellar nuclei has also been theorized to produce opsoclonus.

- Opsoclonus occurring in infants and young children is associated with neural crest tumors (neuroblastoma, ganglioneuroma) in more than 50% of the cases. However, only 2% to 3% of children with these tumors develop opsoclonus. Of these patients, 62% also have myoclonus and ataxia. In adults the most common cancers causing opsoclonus as a paraneoplastic syndrome include small cell lung and breast cancers. Numerous other neoplasms have also been implicated (ovarian, bladder, renal, thyroid, pancreatic, transitional cell carcinomas, malignant melanoma, and T-cell lymphoma). It has been estimated that 20% of all adult opsoclonus cases are of paraneoplastic origin.

- Opsoclonus as a parainfectious disorder may be preceded by a viral prodrome, usually on the order of a few days. Coccidiod, parainfluenza, Epstein-Barr virus, and enterovirus are most commonly implicated. Other infections include AIDS, salmonellosis, psittacosis, syphilis, Lyme, and rickettsial diseases.

- Among the rarer etiologies of opsoclonus are the following:
  - Drug toxicity: phenytoin, amitriptyline, lithium, cocaine, diazepam
  - Inborn errors of metabolism: biotin responsive carboxylase deficiency,
  - Toxic metabolic states: hyperosmolar nonketotic coma, hyperphosphatemia, thallium, organophosphates, toluene, strychnine, chlorodecone
  - Demyelinating disorders: multiple sclerosis, acute disseminated encephalomyelitis

RISK FACTORS

N/A

PREGNANCY

N/A

ASSOCIATED CONDITIONS

N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Ocular flutter also consists of back-to-back saccadic oscillations of both eyes. In contrast to opsoclonus, however, ocular flutter occurs only intermittently, and the oscillations are restricted to the horizontal plane. Etiologies of both disorders overlap and they likely represent a pathophysiologic continuum. However, several disease processes have been reported to cause only ocular flutter. These include cyclosporine toxicity, malaria, and carbohydrate-deficient glycoprotein syndrome type 1a.

SIGNS AND SYMPTOMS

Onset of opsoclonus is usually subacute. Visual complaints are nonspecific and range from mild, involuntary blurring to frank oscillopsia (the visual illusion of movement of stationary objects). Myoclonus, dysarthria, and variable degrees of truncal and appendicular ataxia often coexist, and patients may complain of vertigo and nausea. Encephalopathic states are more commonly associated with paraneoplastic opsoclonus and may be severe. Opsoclonus can be elicited by fixation and gaze shifting and persists during sleep. The frequency of oscillations ranges from 6 to 15 Hz, very small amplitude opsoclonus may be detectable only during direct ophthalmoscopy.

LABORATORY PROCEDURES

- Obtain urine catecholamines and homovanillic acid in suspected neuroblastoma, and anti-Ri (breast, ovarian cancer) and anti-Hu autoantibodies (small cell lung cancer, neuroblastoma) in suspected paraneoplastic opsoclonus. Note that the presence of these autoantibodies indicates a very high likelihood of cancer, even if the oncologic workup is negative. Repeat testing after several months is mandatory, as delays between the emergence of opsoclonus and tumor detection of up to 1 year have been reported. Even in the absence of autoantibodies, a workup for cancer is required in all adults presenting with opsoclonus.

- Antiviral antibodies and other screens for infectious disorders are indicated when an underlying infectious process is suspected. The sensitivity for detecting a viral CNS infection can be increased by performing polymerase chain reaction (PCR) on the cerebrospinal fluid.

IMAGING STUDIES

MRI of the brain is unrevealing in the majority of cases. Imaging studies of the lungs, breasts, abdomen, and pelvis are elements of the oncologic workup. Octreotide scanning is a sensitive screen for the detection of neural crest tumors.
General Measures

- New-onset opsoclonus warrants hospital admission, particularly if other symptoms such as ataxia, myoclonus, and encephalopathy coexist.
- The multitude of etiologies requires diagnostic and therapeutic approaches tailored to each patient. In paraneoplastic opsoclonus two main management strategies need to be applied: treatment of the underlying malignancy and suppression of the immune response against nervous system targets. In adults, the latter is usually attempted with corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange, or immunoadsorption, with the latter being preferred by some. In select cases, several immunomodulatory measures may need to be tried sequentially before a treatment response is achieved.
- Children with neuroblastoma-related opsoclonus respond acutely to adrenocorticotropic hormone (ACTH) or prednisone. Early treatment success, however, needs to be followed up with long immunosuppressant measures (see below), as untreated patients often show a progressive course of developmental and behavioral abnormalities.
- Postinfectious opsoclonus generally has a benign, but sometimes protracted, course. Corticosteroids are commonly applied in this situation. However, concern about, potentiating an underlying infection, particularly in children, may make IVIG a better choice. In view of the high rate of spontaneous improvement and unpredictable disease course, it has not been possible to define the value of immunomodulatory treatment in this situation.

Surgical Measures

N/A

Symptomatic Treatment

Aside from immunomodulatory therapies, benzodiazepines, Myoline, gabapentin, and thiamine have been tried in the symptomatic treatment of opsoclonus and myoclonus. Unfortunately, no well-designed treatment trials exist to guide the clinician.

Adjuvant Treatment

N/A

Admission/Discharge Criteria

N/A

Medications

Drug(s) of Choice

N/A

Alternative Drugs

N/A

Follow-Up

Patient Monitoring

N/A

Expected Course and Prognosis

- Opsoclonus that is not related to neoplastic disease has a much more favorable prognosis than the paraneoplastic variant. Postinfectious opsoclonus, nonetheless, may require weeks or months to resolve and relapses can occur. Complete recovery is common, but mild deficits, such as truncal ataxia, may remain.
- Children with neural crest tumors show a high initial response rate to ACTH or prednisone, but ongoing immunosuppression is often required. A significant proportion of children show signs of permanent CNS injury and of a possibly progressive encephalopathy presenting with expressive language disturbances, attentional deficits, irritability, and delayed motor and cognitive development. Intercurrent illnesses may precipitate recurrences of ataxia and myoclonus. Such patients require long-term treatment with prednisone or other immunosuppressants (methotrexate).
- The least favorable prognosis is encountered in adults with paraneoplastic opsoclonus; especially when an encephalopathic state coexists. Immunoadsorption, and other immune therapies do not show consistent benefit and even responders may be left with permanent cerebellar dysfunction such as truncal ataxia. Occasionally, however, patients may show resolution of opsoclonus after successful tumor removal, and rare patients have improved spontaneously without cancer treatment. Compared to other adult paraneoplastic syndromes, opsoclonus appears to have somewhat more favorable prognosis.

Patient Education

N/A

SYNONYMS

- Opsoclonus-myoclonus syndrome (OMS)
- Opsoclonus-myoclonus-ataxia syndrome
- Opsoclonus myoclonus atactic encephalopathy (OMAE), dancing eyes and dancing feet (childhood opsoclonus, myoclonus), saccadomania.

ICD-9-CM: 379.39 Irregular eye movements not elsewhere classified

See Also: N/A

References


Author(s): Bernd F. Remler, MD
Optic Neuritis

Basics

DESCRIPTION
Optic neuritis refers to inflammation of the optic nerve with variable demyelination. Optic neuritis may be acute, chronic, or subclinical. Acute optic neuritis is most common and is characterized by sudden, usually unilateral vision loss, which progresses over hours to days. The central visual disturbance may be mild or severe. Many patients notice color desaturation and difficulty seeing in dim illumination. Ninety percent of patients have mild to moderate pain in or around the eye, usually worse with eye movement.

EPIDEMIOLOGY
Incidence
Approximately 6 per 100,000. Peak incidence is in the third and fourth decades.

Sex
The female to male ratio is approximately 2:1.

ETIOLOGY
Optic neuritis occurs as the initial symptom of MS in 35% to 62% and is likely a forme fruste of MS in its isolated form.

Causes of Optic Neuritis Other Than MS
- Viral and parainfectious causes—adenovirus, Coxsackie, cytomegalovirus, HIV, hepatitis A, Epstein-Barr virus, measles, mumps, rubella, varicella zoster, herpes zoster
- Postvaccination
- Syphilis
- Lyme disease
- Tuberculosis
- Mycobacterium pneumoniae
- Sarcoïdosis
- Vasculitides (systemic lupus erythematosus, Wegener’s)
- Autoimmune
- Sinus infection
- Bee venom
- Toxoplasmosis
- Cat scratch disease

RISK FACTORS
Patients with known MS are at significant risk of optic neuritis.

PREGNANCY
Little is known concerning the relationship between pregnancy and optic neuritis. In patients with MS, there is a diminished risk of new exacerbations including optic neuritis, especially during the third trimester.

ASSOCIATED CONDITIONS
In patients presenting with isolated optic neuritis, the risk of developing MS is approximately 30% after 5 to 7 years. In long-term follow-up studies (up to 30 years), 75% of women and 34% of men developed clinically definite MS.

Diagnosis

DIFFERENTIAL DIAGNOSIS
Numerous infectious or inflammatory disorders other than demyelinating disease may cause optic neuritis. Acute optic neuritis can usually be distinguished from other conditions on clinical grounds. History is usually suggestive with compressive optic neuropathy from intracranial tumors, anterior ischemic optic neuropathy, sinus disease, and radiation-induced optic neuropathy. Patients presenting with bilateral anterior optic neuritis should be evaluated for papillodema. Leber’s hereditary optic neuropathy (LHON), a mitochondria disorder usually causing bilateral central visual loss, may mimic optic neuritis, especially in young men in early stages before the fellow eye is involved.

Optic Neuropathies and Ophthalmic Conditions Mimicking Optic Neuritis
- Neuro-retinitis
- Big blind spot syndrome
- Leber’s hereditary optic neuropathy
- Diabetic papillitis
- Ischemic optic neuropathy
- Central retinal vein occlusion
- Venous stasis retinopathy
- Optic disc drusen
- Central serous retinopathy
- Carcinomatous meningitis.
- Infiltrating neoplasm (lymphoma)
- Radiation-induced optic neuropathy
- Paraneoplastic disorder

SIGNS AND SYMPTOMS
- The diagnosis is clinicial one. Examination should confirm optic nerve dysfunction. Central acuity is usually reduced, but 10% of patients have preserved central vision of at least 20/20. Patients who retain normal or near-normal acuity often have reduced color vision and contrast sensitivity out of proportion to central visual disturbance.
- Virtually all patients with unilateral optic neuritis have a relative afferent pupillary defect (RAPD or Marcus Gunn pupil) in the affected eye. A RAPD may be demonstrated objectively by the swinging flashlight test, or subjectively by asking the patient to compare brightness of a light source in the affected and unaffected eyes.
- Central visual field loss (central scotoma) is the hallmark of optic neuritis, accounting for over 90% of the visual field defects. However, virtually any visual field defect can occur, including cecocentral, paracentral, arcuate, hemianoptic, peripheral constriction, and diffuse suppression. The optic disc may appear normal in retrobulbar optic neuritis (approximately two thirds of patients), inspiring the adage “the patient sees nothing and the physician sees nothing.” In anterior optic neuritis (or papillitis), the disc may be swollen. Hemorrhage at the disc margin occurs in less than 6% of patients.
- The optic disc may become pale weeks after the initial episode. Transient reversible neurologic dysfunction in response to exercise or exposure to heat is referred to as Uhthoff’s symptom (after the German ophthalmologist). Uhthoff’s symptom should raise suspicion of, but is not pathognomonic for, MS.

LABORATORY PROCEDURES
Blood Work
The following tests should be considered:
- CBC/differential, thyroid function: tests, vitamin B12 and folate levels, RPR, ANA, RF, anti-SSA, anti-SSB, p & c ANCA, HIV, serum and/or CSF angiotensin-converting enzyme level, Lyme titer, immunofixation, CSF studies including IgG index and synthesis rate, oligodendral bands, cryptococcal antigen, AFB smear and culture, cytology, and hypercoagulable studies in selected patients (including anticardiolipin antibodies, protein C & S, antithrombin III, activated protein C resistance, factor V Leiden, plasma viscosity, homocysteine, fibrinogen).

IMAGING STUDIES
Lesions in the optic nerve may be difficult to detect with conventional MRI. Gadolinium enhancement on MRI is demonstrated in the optic nerves of the majority of patients with acute optic neuritis with newer techniques of fat suppression. In most patients, enhancement is no longer observed 1 month after the onset of optic neuritis and correlates with recovery of visual acuity and improvement of visual evoked potential (VEP) amplitudes. Abnormalities on MRI in the periventricular area or other white matter areas are seen in 30% to 70% of patients with isolated optic neuritis and in 90% to 98% of patients with clinically definite MS. The presence of lesions on MRI is a strong predictor of the risk of developing clinically definite MS. Cranial MRI should be considered in an attempt to establish a diagnosis, facilitate counseling of the individual regarding risk of MS, and to guide decisions for treatment.

SPECIAL TESTS Visual Field Testing
Confrontational visual field techniques may be used for screening, but are insensitive compared to Goldmann perimeter or automated threshold perimeter.
Optic Neuritis

Neurophysiologic Studies
Visual evoked potentials (VEPs) record electrical activity of the occipital lobe in response to visual stimuli. Optic neuritis typically causes prolongation of the latency and decreased amplitude of the P100 the first large positive peak occurring approximately 100 msec after stimulus. Pattern reversal stimulus presentation yields more reproducible results. However, flash VEP can be used to confirm visual pathway integrity when the P100 is not seen with pattern VEPs. Abnormalities of the VEP indicate dysfunction at any point along the visual pathways from the retina to the striate cortex, and are not pathognomonic for demyelinating optic neuropathy. Other disorders can cause VEP disturbance (e.g., compressive lesions, congenital optic nerve anomalies, glaucoma, hereditary and toxic optic neuropathy, and papillodema).

GENERAL MEASURES
The disparity of visual functioning between the two eyes is often sufficient to provoke headache and ocular discomfort. Analgesic agents should be used as necessary. Patching the involved eye for a few days may be helpful if the interocular visual functioning is highly disparate.

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
There are currently no approved therapies for the symptomatic complaints associated with optic neuritis. In those who experience Uhthoff's phenomenon, high temperatures should be avoided. Ingestion of ice-cold liquids or the use of cooling devices may also be helpful.

ADJUNCTIVE TREATMENT
Format evaluation by an ophthalmologist is suggested to maximize visual function with refractive techniques and to exclude potentially treatable ophthalmic conditions.

ADMISSION/DISCHARGE CRITERIA
Patients with optic neuritis can be treated in the hospital or at home. Diabetes mellitus and uncontrolled hypertension are comorbidities that may warrant hospitalization.

Follow-Up

PATIENT MONITORING
Patients should be reexamined after steroid therapy to exclude a further decline in visual function.

Medications

DRUG(S) OF CHOICE
- Corticosteroids have long been the cornerstone of therapy for optic neuritis despite conflicting studies of effectiveness.
- In most patients, 1,000 mg/day of methylprednisolone may be administered as a single daily intravenous infusion for 3 to 5 days, followed by tapering dose, of oral prednisone (starting at 100 mg for 4 days and then tapering by 10 mg every other day) over 2 to 4 weeks.
- Oral prednisone, at least in conventional doses of 1 mg/kg/d, is contraindicated as the sole treatment, although some practitioners are exploring the use of higher doses (2-5 mg/kg/d or more).

Contraindications
In patients with a suspected infectious etiology, corticosteroids should be withheld until appropriate antibiotic therapy is instituted.

Precautions
Common adverse events related to high-dose corticosteroid treatment include gastric irritation, insomnia, euphoria, depression, and occasionally psychosis, tachycardia, hypertension, hypokalemia, hyperglycemia, increased appetite and fluid retention. Pretreatment with an H2 blocker for GI prophylaxis and potassium supplementation should be considered. A single morning dose of corticosteroids may reduce the risk of insomnia. Blood pressure, potassium, and glucose levels should be monitored. Those with diabetes or hypertension require more careful monitoring that often includes the use of sliding-scale insulin. Mild tranquilizers are effective for insomnia.

ALTERNATIVE DRUGS
While controlled studies are lacking, some consider treating steroid refractory visual loss with either intravenous immunoglobulin (IVIG) or plasma exchange.

EXPECTED COURSE AND PROGNOSIS
The natural course of acute optic neuritis is variable. Visual deficits typically worsen over a few days to 2 weeks. Most patients then recover rapidly, achieving most of their improvement by 5 weeks. Some continue to recover for up to a year. The mean visual acuity 12 months after the onset is 20/15. Fewer than 10% have visual acuity less than 20/40 at 1 year. Despite recovery of vision to “near normal,” most patients remain aware of residual visual dysfunction due to deficits in contrast sensitivity, color vision, and depth perception.

PATIENT EDUCATION
See: Multiple Sclerosis.

Miscellaneous

SYNONYMS
Inflammatory optic neuropathy
Retrobulbar optic neuritis
Optic papillitis

ICD-9-CM: 377.3 Optic neuritis; 377.30 Optic neuritis, unspecified; 377.31 Optic papillitis; 377.32 Retrobulbar neuritis

SEE ALSO: N/A

REFERENCES

Author(s): Elliot M. Frohman, MD, PhD
Orthostatic Hypotension

**DESCRIPTION**
Clinically, it is important to recognize mild degrees of autonomic failure that present as orthostatic intolerance (OI), postural tachycardia syndrome (POTS) or syncope. Orthostatic hypotension (OH) is a dominant feature of severe autonomic failure. For example, autonomic neuropathy in amyloidosis or diabetes is widespread, progressive, and hallmarks an unfavorable prognosis. OI is defined as (a) symptoms triggered by standing and relieved in supine position, (b) heart rate increase >30 bpm or >120 bpm, and (c) blood pressure is normal or increased. Orthostatic hypotension is defined as (a) blood pressure fall >20/10 mm Hg for 3 minutes, (b) with or without symptoms of cerebral hypoperfusion, and (c) loss of heart rate increase indicates severe autonomic failure. Neurogenic syncope is triggered by reflex mechanism and may occur with both conditions.

**EPIDEMIOLOGY**

**incidence/Prevalence**
In the U.S., 500,000 patients have orthostatic intolerance.

**Race**
N/A

**Age**
Orthostatic intolerance may affect all ages. Orthostatic hypotension is more common in the middle aged and the elderly.

**Sex**
Female > male; multiple system atrophy (MSA) male > female.

**ETIOLOGY**

**Genetics**
Unknown, except for familial dysautonomia [Riley-Day syndrome in Ashkenazi Jews on chromosome 9 (q31)].

**RISK FACTORS**
Falls, injury.

**PREGNANCY**
- OI—generally improvement during pregnancy
- OH—determined by primary diagnosis

**ASSOCIATED CONDITIONS**
- Orthostatic intolerance
  - Small fiber neuropathy
  - Vascular pooling/deconditioning/prolonged bed rest/weightlessness
  - Hypovolemia
  - α-receptor supersensitivity
  - Brainstem dysregulation, Arnold-Chian malformation
- Orthostatic hypotension
- Primary autonomic failure

**SIGNS AND SYMPTOMS**
- Light-headedness
- Dizziness
- Blurred vision
- Fatigue
- Nausea
- Gastrointestinal symptoms
- Palpitations
- Shortness of breath, hyperventilation, dyspnea
- Headache
- Memory loss (OH in elderly)

**DIFFERENTIAL DIAGNOSIS**
- Non-neurogenic orthostatic intolerance
  - Anxiety
  - Cardiogenic syncope
  - Tachyarrhythmias/bradycardia
  - Seizures, pseudoseizures
  - Porphyria
  - Pheochromocytoma
  - Anemia
- Non-neurogenic orthostatic
  - Cardiac impairment (myocardial infarction, myocarditis)
  - Impaired cardiac filling/output (e.g., aortic stenosis, Câtdiorrlyppathy, heart failure)
  - Nephrogenic (nephropathy, hemodialysis)
  - Blood/plasma loss—hemorrhage, burns, sepsis
  - Fluid/electrolyte loss—vomiting, diarrhea, fluid loss
  - Increased intracranial pressure
  - Drug-induced—centrally acting agents that reduce sympathetic activity (clonidine, methyldopa, reserpine, barbiturates, anesthetics)
  - Peripheral-dopamine-,6-hydroxylase deficiency
  - POTS-dopamine-,6-hydroxylase deficiency

**LABORATORY PROCEDURES**
- ECG normal; Hotter monitoring shows episodes of sinus tachycardia.
- Standing plasma catecholamines are increased in some OI patients, but reduced in OH.
- Reduced ACTH and 6/3-endorphin can distinguish OH due to MSA vs. PAF (normal).
- Reduced growth hormone and melatonin in dopamine-6-hydroxylase deficiency.

**IMAGING STUDIES**
- OI—MRI typically normal; Arnold-Chian malformation, cervical stenosis (rare)
- OH—MSA—T2-weighted images show putamen hypointensity, olivo-ponto-cerebellar atrophy. Positron emission tomography shows reduced reuptake of F-dopa in MSA.

**DIAGNOSIS**

**SPECIAL TESTS**
- Tilt table testing is done at 60 to 80 degrees for 5 to 45 minutes without medications. OI shows sinus tachycardia (>100 bpm) for at least 5 minutes with normal or increased blood pressure. POTS is severe form of OI with orthostatic heart rate >120 bpm. OH shows sustained blood pressure drop >20/10 mm Hg, for 3 minutes. Loss of heart rate increment indicates severe autonomic failure. Isosorotrine/nitroprusside infusions are used for evaluation of syncope.
- Heart rate variation to deep breathing and bradycardia/sinus tachycardia ratio during Valsalva maneuver is typically reduced.
- Quantitative sudomotor axon reflex test (QSART) stimulation of postganglionic sudomotor fibers using iontophoresis of 10% acetylcholine chloride. QSART may be normal in 0I but is typically reduced with OH due to peripheral neuropathy.
- Thermoregulatory sweat test—body is covered by allantin powder and temperature is raised by 1°C.

**THERAPY**
- Treatment of orthostatic hypotension includes a combination of volume expansion, pressor agents, and supportive measures.

**GENERAL MEASURES**
- Treatment of orthostatic hypotension includes a combination of volume expansion, pressor agents, and supportive measures.

**SURGICAL MEASURES**
- Tumor removal
- Brainstem decompression in Arnold-Chian malformation
Orthostatic Hypotension

**Symptomatic Treatment**
- Liberaize fluid and salt intake.
- Review all medications to determine if any that might be contributing to orthostasis may be discontinued, especially diuretics, antihypertensive agents, antianginal agents, and antidepressants.
- Have patient move from supine to sitting and standing positions in gradual stages.
- Head-up tilt bed—elevation of bed to 20-degree angle activates the renin angiotensin-aldosterone system and decreases nocturnal diuresis.
- Elastic body garments (custom-fitted stockings with graded pressure, abdominal binder inflatable, or Easy-wraps)

**Adjuvant Treatment**

**ADMISSION/DISCHARGE CRITERIA**
Frequent loss of consciousness (L 0.0/ADMISSION/DISCHARGE CRITERIA

**DRUGS**

**Carvedilol, ProAmatine—CHF**

**Sodium Chloride (Salt Tablets): 50 mEq or 1, 200 mg PO tid**

**Fludrocortisone 250 mg (2 cups)**
- Caffeine 250 mg (2 cups) in the morning and 1 cup with meals (postprandial hypotension)
- Pindolol(Visken) 2.5-5.0 mg bid to tid
- Orthostatic hypotension: ephedrine sulfate 12.5-25 mg, PO tid

**SIDE EFFECTS:**
- Hypertension; may increase urinary Nab loss.

**Orthostatic Intolerance**
- Knowing precise diagnosis is important for prognosis.
- Diabetic neuropathy—increased risk for death/arrhythmias
- MSA survival 5 years from diagnosis
- PAF survival >10 years

**Expected course and prognosis**
- Good prognosis-majority of patients improve over time.

**Orthostatic Hypotension**
- Monitor supine hypertension, peripheral edema, and congestive heart failure.

**Contraindications**
- Symptomatic treatment: ephedrine sulfate 0.2-0.8 mg bid to tid
- 3- to 6-lb weight gain is desirable—supine exercise (leg lifting, weight bearing, marching, bending forward, abdominal contraction); supine exercise (leg lifting, weight pressing), swimming; relaxation. Avoid overheating and straining maneuvers. Schedule activities for the afternoon since the symptoms are typically worse in the morning.

**Diet**
- High sodium and 2-2.5 L of fluids; small, more frequent, low-carbohydrate meals.

**Follow-Up**

**PATIENT MONITORING**
- If no improvement of symptoms, repeat tilt study on medications. Monitor supine hypertension (24-hour BP monitoring might be useful).

**PATIENT EDUCATION**
- Countermaneuvers (squatting, leg crossing, toe touching, marching, bending forward, abdominal contraction); supine exercise (leg lifting, weight pressing), swimming; relaxation. Avoid overheating and straining maneuvers. Schedule activities for the afternoon since the symptoms are typically worse in the morning.

**Diet**
- High sodium and 2-2.5 L of fluids; small, more frequent, low-carbohydrate meals.

**Organizations**
- The National Dysautonomia Research Foundation, contact person: Linda J. Smith (Email: ndfrf@ndfrf.org, phone: 715-594-3140; fax: 715-594-3140; website: http://www.ndfrf.org)

**REFERENCES**
Paraneoplastic Neurologic Syndromes

**Basics**

**DESCRIPTION**

Paraneoplastic neurologic syndromes are disorders of the nervous system pathogenetically related to an underlying systemic malignancy, but not due to direct tumor invasion or other indirect effects of cancer.

**ETIOLOGY**

Reflects the sex distribution of the underlying cancer.

- **Age**
  - Most patients are older than 40. Paraneoplastic opsoclonus-myoclonus (POM) may occur in very young children and infants with neuroblastoma.

- **Sex**
  - Reflects the sex distribution of the underlying cancer.
  - No known racial or ethnic predisposition.

- **Race**
  - Most patients are older than 40. Paraneoplastic opsoclonus-myoclonus (POM) may occur in very young children and infants with neuroblastoma.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

**PCD/POD/PEM**

- Primary or metastatic tumor of the cerebellum
- Toxic/metabolic disorders causing ataxia
  - (5-FU, ARA-C, anticovulvulant medications, lithium, alcohol, vitamin B12 or B1 deficiency, heavy metal poisoning, Wilson's disease, etc.)
- Brainstem or cerebellar infarct/hemorrhage
- Infection (bacterial, fungal, or parasitic abscess, encephalitis, PML)
- Demyelinating disease
- Heritable ataxias
- Toxic or metabolic encephalopathy (diabetic hyperosmolar nonketotic coma, lithium, thalidomide, amitriptyline overdose, tolune, strychnine)
- Hydrocephalus
- Brain metastases
- Cerebral vasculitis
- Multiple cerebrals infarcts
- PNS
  - Acute or chronic inflammatory demyelinating polyradiculoneuropathy (AIDP/CIDP)
  - Monogonal gangliopathy associated polyneuropathy
  - Diabetic polyneuropathy
  - Vasculitic neuropathy (particulary Sjogren's syndrome)
  - B12 deficiency
  - Toxic neuropathies (vitamin B6 overdose, heavy metal poisoning, thalidomide)
  - Idiopathic subacute sensory neuropathy

**SIGNS AND SYMPTOMS**

**PCD**

- Subacute, progressive cerebellar dysfunction (may be asymmetrical)
- Gait and limb ataxia
- Dysarthria
- Dysphasia
- Diplopia/nystagmus/osclesis
- Vertigo

**ETIOLOGY**

- The etiology is unknown, although an inflammatory, immune-mediated mechanism is suspected. Specific serum and CSF onco-neuronal antibodies are detectable in a large percentage of patients. While these antibodies do not appear to be pathogenic, their presence confirms the diagnosis of paraneoplastic disease. Moreover, they are useful markers to prompt search for underlying malignancy, which is occult at the time of neurologic diagnosis in over 50% of patients. Many of these antibodies share specificity to antigens expressed by cells of the CNS and antigens expressed by systemic tumors. These syndromes may result from intrathelial synthesis of some as yet undiscovered antineuronal antibody or from cell-mediated immunity directed against the underlying cancer. The absence of serum or CSF onco-neuronal antibodies does not exclude the diagnosis of paraneoplastic disease.

- A specific area of the nervous system is targeted in each of these syndromes. In patients with paraneoplastic cerebellar degeneration (POD), the focus of the injury is the cerebellar Purkinje cells. In POM, the pathology is most commonly limited to the brainstem and cerebellum. Patients with paraneoplastic encephalomyelitis/paraneoplastic sensory neuropathy (PEM/PSN) suffer symptoms related to injury to the limbic structure, cerebellum, and dorsal root ganglia. There is a good deal of clinical overlap between these syndromes.

**RISK FACTORS**

N/A

**PREGNANCY**

There is no known association between paraneoplastic disorders and pregnancy.

**ASSOCIATED CONDITIONS**

Systemic malignancy

**LABORATORY PROCEDURES**

- **Blood work**
  - A subset of patients may have serum antibodtis that react with CNS cell antigens and sometimes the underlying tumor. -PCD: Anti-Yo or APCA; anti-Hu or ANNA-1; Anti-Ri or ANNA-2
  - POM: A subset of adult patients will have circulating serum and CSF antibodies to neural antigens. When opsoclonus occurs as a component of PCD, APCA (anti-Yo) and ANNA-1 (Anti-Hu) antibodies have been noted. ANNA-2 (anti-Ri) antibodies have been found in some female patients with POM and breast or pelvic cancers.
  - PEM/PSN: anti-Hu or ANNA-1

- While not pathogenic, these antibodies point to the causal malignancy. Anti-Yo (APCA) is associated with breast, ovarian, and uterine cancer. Anti-Hu (ANNA-1) is associated with small cell cancers and Anti-Ri (ANNA-2) is seen in association with breast cancer. These antibodies are specific but not sensitive. A patient may harbor a paraneoplastic nervous system disease but be seronegative for antibodies.

- Testing for all three of the above-mentioned antibodies inappropriate in an adult patient with opsoclonus-myoclonus, an otherwise unexplained diffuse encephalopathy or a severe, predominantly sensory polyneuropathy.

- **PEM/PSN**: Serologic testing to rule out underlying infection (CBC and differential, ESR, and blood cultures if febrile), toxic/metabolic disorders (sodium, calcium, magnesium, liver and renal function tests), and vasculitis (ESR, ANA, RF, ENA, and ANCA) should be performed. Serum and urine immunoelectrophoresis, fasting glucose, serum B12 level, and urine heavy metals may also be appropriate.
**Paraneoplastic Neurologic Syndromes**

**IMAGING STUDIES**

- Neuroimaging is important to rule out alternative causes. Early in the evolution of PCD, POM, and PEM, CT and MRI of the head may be normal. After several months, marked diffuse cerebellar atrophy is usually noted in PCD. Nonspecific areas of abnormal T2 signal abnormalities have been described in some patients with POM and PEM. After several months, brainstem, cerebral, and cerebellar atrophy is often noted.
- An aggressive search for an underlying malignancy should be undertaken. This may include total body CT, mammogram, liver function tests, bone scan, or other tests deemed appropriate by the oncologist. Some have advocated an exploratory laparotomy in patients with APCA (Anti-Yo), if pelvic imaging and mammography are negative, to search for an occult tumor. Pediatric patients should have testing to detect a thoracic or abdominal neuroblastoma. In patients seropositive for ANNA-1 (Anti-Hu), bronchoscopy is indicated even if chest CT or MRI is normal.

**SPECIAL TESTS**

- Lumbar puncture after neuroimaging has excluded a mass, CSF should be examined to exclude hemorrhage and infection. Approximately 50% of patients with PCD, POM, and PEM PSN will have nonspecific inflammatory changes of CSF including a modest increase in protein, CSF lymphocytic pleocytosis, increased IgG index, and the presence of oligoclonal bands.
- PEM/PSN
  - Electroencephalography may demonstrate diffuse or symmetric cerebral slowing and focal or multifocal epileptiform activity.
  - Nerve conduction studies typically show reduced sensory and motor amplitudes and F wave deficit.
  - EMG may show evidence of muscle denervation.

**Follow-Up**

- If malignancies are not found on initial evaluation, periodic reevaluations for malignancy should be conducted.

**MANAGEMENT**

**GENERAL MEASURES**

Supportive care is paramount to avoid secondary complications like aspiration pneumonia, decubiti, urinary tract infection, deep venous thrombosis, and injury from falls.

**SURGICAL MEASURES** 

N/A

**SYMPTOMATIC TREATMENT**

Physical therapy may assist with gait and avoidance of joint contractures.

**ADJUNCTIVE TREATMENT**

- Admission or discharge criteria
  - Admission may be required for hydration and evaluation for oncologic workup and exclusion of other neurologic disorders.

**Medications**

Unfortunately, there is no specific therapy for these disorders. There are reports of spontaneous remission or improvement with treatment of the underlying cancer. Treatment with thiamine and clonazepam has produced neurologic improvement in anecdotal cases of POM. Pediatric POM associated with neuroblastoma often responds to treatment with corticosteroids, although most patients will be left with residual neurologic deficits. Immunosuppressant medications, intravenous immunoglobulin (IVIG), and plasmapheresis are often tried without significant improvement, although there have been occasional reports of response.

**ALTERNATIVE DRUGS N/A**

**ADMISSION/DisCHARGE CRITERIA**

Effect on host defenses to cancer. Although patients may die from progression of their underlying cancers, many die from complications of their neurologic disease.

**PATIENT EDUCATION**

N/A

**SYNONYMS**

PCD: Anti-Yo syndrome
- POM: "Dancing eyes and dancing feet," infantile polymyoclonia
- PEM: Anti-Hu syndrome, paraneoplastic limbic encephalitis
- PSN: Anti-Hu syndrome, subacute sensory neuropathy

**ICD-9-CM:** PCD/PSN: 334.4 Cerebellar ataxia in diseases classified elsewhere: neoplastic disease (140.0-239.9); POM: 333.2 Myasthenia; PEM: 323.8 Other causes of encephalitis; PSN: 357.7 Polyneuropathy in malignant disease

**REFERENCES**


**Author(s):** Julie E. Hammack, MD
Parkinson's Disease

DESCRIPTION

Parkinson's disease (PD) is a common, progressive neurodegenerative disorder of the extrapyramidal system. PD has a classic pathology, the eosinophilic, cytoplasmic intraneuronal inclusion bodies known as Lewy bodies, which appear in the substantia nigra, locus ceruleus, nucleus basalis of Meynert, and dorsal motor nucleus of the vagus. PD is characterized by a slowly progressive movement disorder with tremor, rigidity, bradykinesia, and gait disorders. It responds to therapies that alter dopaminergic and cholinergic neurotransmission.

EPIDEMIOLOGY

Incidence/Prevalence
PD is a common disorder of the elderly affecting 1-3/1,000 adults in the U.S. It is the second most common neurodegenerative disorder in the U.S. after Alzheimer's disease. Incidence may approach 5 to 20 new cases per 100,000 annually (U.S.).

Race
Highest prevalence in East Indian > Caucasian > African American > Chinese.

Age
The prevalence increases with age, averaging 1% or greater after the age of 65.

Sex
Males are slightly more frequently affected than females.

ETIOLOGY

The cause of PD is unknown. The two most likely contributing factors are genetics and environmental or endogenous toxins.

Genetics
Twin studies have shown that young-adult PD (onset typically before age 40) has a high concordance rate among monozygotic twins. The typical older adult-onset PD in twins had a concordance rate that was similar between monozygotic and dizygotic twins. The risk of developing PD is approximately two to three times above average when a first-degree relative is affected. Rare cases of familial PD are scattered throughout the world, but examination of the gene affected in familial PD (coding for the protein α-synuclein) has not shown similar mutations in the sporadic form of PD. Another gene product, referred to as parkin, has also been associated with a hereditary, early adult onset form of PD.

Environment
The greatest risk factor for developing PD is advanced age. Rural residence with exposure to well water and herbicide and pesticide preparations is an additional risk factor, as is exposure to industrial chemicals, especially metals (manganese, iron, and steel alloys).

RISK FACTORS
See above

PREGNANCY

N/A

ASSOCIATED CONDITIONS

N/A

DIFFERENTIAL DIAGNOSIS

• Essential or familial tremor (10 times higher prevalence than PD and commonly misdiagnosed as PD)
• Diffuse Lewy body disease (DLBD)
• Drug-induced parkinsonism (e.g., antipsychotics, antiemetics, and other dopamine blocking agents)
• Multiple system atrophy (MSA)
• Progressive supranuclear palsy (PSP)
• Vascular parkinsonism
• Posttraumatic parkinsonism
• Wilson's disease
• Frontotemporal dementia with parkinsonism
• Alzheimer's with extrapyramidal features (possibly a DLBD variant)
• Creutzfeldt-Jakob disease

SIGNS AND SYMPTOMS

Primary Motor Symptoms
The early cardinal signs and symptoms of idiopathic PD (tremor, rigidity, and bradykinesia) are essentially always asymmetric at onset, progressing slowly (months to years) to involve the contralateral side. The initial symptoms develop insidiously over months to years. Patients may be undiagnosed or misdiagnosed for months (or years) until an experienced clinician performs a careful history and neurologic examination. The classic tetrad of PD includes:

• Tremor at rest
• Rigidity (with cog-wheeling)
• Bradykinesia (masked facies, decreased blink rate, decreased spontaneous arm swing while walking, slowness in initiating and maintaining movements, slow shuffling gait)
• Postural instability (late manifestation)

Diagnosis is made from the patient's clinical history, two of three cardinal signs (rest tremor, rigidity, bradykinesia) on exam, and exclusion of secondary causes of parkinsonism.
Parkinson's Disease

Other Signs and Symptoms

- **Cognitive dysfunction**
  - Bradyphrenia, a slowing of response time
  - Visuospatial disturbances (typically in late PD)

- **Ocular dysfunction**
  - Limitations of upgaze, but not downgaze
  - Saccadic eye movements with pursuit
  - Persistent eye blinking when the forehead is repeatedly tapped (glabellar reflex or Myerson's sign)

- **Speech and swallowing disturbances**
  - Monotonous, hypophonia
  - Palilalia (repetition of the first syllable)
  - Pooling of saliva with drooling
  - Dysphagia (late in disease)

- **Musculoskeletal abnormalities**
  - Dystonias (fixed postures of hands or feet)
  - Muscle cramping
  - Kyphoscoliosis

- **Autonomic disturbances**
  - Constipation
  - Urinary frequency, urgency, and, rarely, incontinence

- **Sleep disturbances**
  - Sleep fragmentation
  - REM sleep behavior disorder

- Symptoms more characteristic of DLBD
  - Dramatic fluctuations in motor function and mentation
  - Syncope like spells
  - Visual hallucinations (sometimes prior to dopaminergic medication)
  - Exquisite sensitivity to conventional neuroleptics

LABORATORY PROCEDURES

There are no specific blood tests to diagnose PD, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism:

- Serum vitamin B12 level
- Thyroid function tests
- Serum ceruloplasmin
- 24-hour urine copper excretion

IMAGING STUDIES

There is no evidence to suggest that structural imaging studies (CT, MR) can assist in the diagnosis of PD. MRI scans reveal evidence of other causes of parkinsonism such as vascular insults, mass lesions, calcium or iron deposition in the striatum, atrophy in the posterior fossa, and cortical atrophy by patterns suggestive of other neurodegenerative illnesses.

SPECIAL TESTS

A therapeutic trial of Sinemet, a combination of carbidopa and levodopa, doses of up to 600-800 mg of levodopa equivalents in 24 hours, is sometimes considered diagnostic of true idiopathic PD when the patient responds with dramatic symptomatic improvement (see Management, below).

Management

GENERAL MEASURES

See Medications, below.

SURGICAL MEASURES

Stereotactically placed deep brain stimulation (DBS) electrodes for the management of PD are FDA approved. This procedure can be performed bilaterally with few long-term side effects. Electrodes have been placed in either the globus pallidum or subthalamic nucleus with significant improvement in PD symptoms. Ablative pallidotomy is used less now due to side effects.

SYMPTOMATIC TREATMENT

See Medications, below.

ADJUNCTIVE TREATMENT

See Medications, below.

ADMISSION/DISCHARGE CRITERIA

PD is usually managed in an outpatient setting. Rarely, concomitant illnesses (e.g., pneumonia, UTI) can lead to an acute exacerbation of PD symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility. Psychosis in the setting of idiopathic PD with excessive dopaminergic medication may precipitate hospitalization and/or institutionalization.
Parkinson’s Disease

Medications

**DRUG(S) OF CHOICE**

- Levodopa therapy
  - Carbidopa/Levodopa (C/L) (brand name Sinemet, multiple generic formulations) is the preparation that provides the standard of care for people with idiopathic PD. While its use is controversial as a first-line agent due to predictable development of motor fluctuations after prolonged exposure to levodopa, it is the most efficacious and biologically effective medication available.
  - Controlled-release form of C/L (Sinemet CR or C/L ER) is only 70% bioavailable on average compared to immediate release C/L, and thus there is a tendency to underdose patients when using this formulation.
  - The complications of levodopa therapy are common to all the dopaminergic agents and include confusion, hallucinations, gastrointestinal distress including nausea and vomiting, orthostatic hypotension, and others. The long-term motor complications associated with levodopa usage include dystonias (involuntary abnormal movements), dyskinesias (abnormal involuntary posturing), on/off symptoms in which medication quits working abruptly, and complicated combinations of all of the above. As the disease progresses, most patients require additional levodopa doses, with or without the use of adjunctive therapy, in order to avoid “off” periods, defined as a hypokinetic state associated with minimal or no pharmacologic benefit from their medications.

- COMT inhibitors
  - These molecules block residual breakdown of levodopa in the gut by inhibiting catechol-o-methyl transferase (COMT) activity, increasing the bioavailability and effective half-life of C/L. These agents appear to decrease off time in patients with motor fluctuations by approximately 20% to 30%, with some patients concurrently able to decrease their total daily levodopa intake by 20% to 30%. The most common side effects from these medications are the result of the increased dopaminergic tone induced by the increased bioavailability of levodopa, including onset or exacerbation of nausea, dyskinesias, and/or hallucinations. Other side effects include urine discoloration and diarrhea.
  - Tolcapone (Tasmar, 100-200 mg bd) had the adverse side effect of lethal hepatic damage in several patients worldwide, resulting in a black-box warning on the PDR insert. There is an absolute requirement for liver function monitoring every 2 weeks for the first year, followed by every 4 weeks for 6 months after that, and then every 8 weeks indefinitely when using this medication. This medication should be prescribed only by specialists familiar with its use and contraindications.
  - Entacapone (Comtan, 200 mg with every dose of C/L) has not shown any evidence of hepatic toxicity. A new combination pill incorporating carbidopa/levodopa/entacapone—Stalevo—will be newly introduced worldwide in the summer of 2003.

- Dopamine agonists
  - Dopamine agonists (DA) routinely used since the 1970s as adjunctive therapy to supplement C/L- when daily levodopa doses approached or exceeded 600 mg/d. While dopamine agonists, especially the two newer derivatives, are purported as ideal initial treatment for PD, the incidence of adverse events, especially confusion, hallucinations, and orthostatic hypotension increase dramatically as the patient ages. Other potential side effects include nausea, sleepiness (including possibly sleep attacks), and peripheral edema. The frequency of these side effects in clinical practice depends largely on individual patient differences, including age, premorbid conditions (especially dementia), concomitant medications, etc.
  - Bromocriptine (Parlodel, 15-40 mg/d) and pergolide (Permax, 0.75-3.0 mg/d) are ergot derivatives that are useful as adjunctive therapy. In general, patients placed on adjunctive DA therapy experience 20% to 30% improvement in their overall daily mobility, and some patients concurrently decrease their total daily dose of C/L by 20% to 30%. Due to cost and side effect profile, bromocriptine is rarely, if ever, used.
  - Ropinerole (Requip 9-24 mg/d) and pramipexole (Mirapex, 1.5-4.5 mg/d) are newer, non-ergot derivatives. They were released late in the 1990s with dual indications as monotherapy agents in patients newly diagnosed with PD and as adjunctive agents for patients currently on levodopa therapy;
• Trihexyphenidyl (Artane) 6-15 mg/dand; benztropine (Cogentin) 1.5-6 mg/d are anticholinergic agents commonly used in the early treatment of PD. Both have a slightly greater propensity for treating the symptom of tremor. The risk of cognitive effects in the elderly as well as multiple other anticholinergic side effects in all populations limits their usefulness.

• Amanitadine (Symmetrel) 200-400 mg/d is an antinfluenza agent that works through a variety of different mechanisms, including decreasing dopamine reuptake, glutamatergic blockade, and possibly mild anticholinergic effects. It also may be especially useful for the treatment of tremor. Recent data suggest that amantadine at 300-400 mg/d may significantly alleviate the dyskinesias in patients with associated motor fluctuations.

• Selegiline (Eldepryl) 5-10 mg/d is a selective MAO-B inhibitor that delays or decreases the breakdown of dopamine in the brain, resulting in a mild symptomatic benefit. Initial studies suggested that it may be neuroprotective; however, follow-up analysis of the data has failed to show any statistically significant evidence of neuroprotection. Its use in the elderly as well as prolonged use greater than 5 to 10 years is controversial.

• Atypical antipsychotics
  —Atypical antipsychotics are used to treat the symptoms of drug-induced hallucinations in PD. These medications are normally given in dosages representing a fraction of that used for patients with schizophrenia.

  —Clozapine (Clozaril) 12.5-25 mg/d is the prototypic aticantipsychotic. Its"use is "compli cated"he rare; but lifethreatening"potential side effect of agranulocytosis; Weekly/CBC is required during the first 6 months of therapy; followed by every 2 weeks there after.

  —Olamipine (Sertraline) 25-100 mg/d is the first; other atypical antipsychotics currently on the market that; like clozapine; shows no use-dependent extrapyramidal side effects.

• Waters C. Diagnosis and management of Parkinson's disease, 2nd ed. Laddo, OK: Professional Communications, 1999.

SELENGILINE (Eldepryl) 5-10 mg/d is a selective MAO-B inhibitor that delays or decreases the breakdown of dopamine in the brain, resulting in a mild symptomatic benefit. Initial studies suggested that it may be neuroprotective; however, follow-up analysis of the data has failed to show any statistically significant evidence of neuroprotection. Its use in the elderly as well as prolonged use greater than 5 to 10 years is controversial.

ALTERNATIVE PFGB
In patients with dementia, cholinesterase-inhibiting medications may be used.
 Pituitary Apoplexy

Basics

DESCRIPTION

Pituitary apoplexy is characterized by a hemorrhage, infarction, necrosis, or a hemmorhagic infarction of a pituitary tumor (mostly adenoma), which usually presents suddenly. This is accompanied by expanding space-occupying sellar lesion, which compresses the sellar and/or para- or suprasellar anatomic structures. Subclinical or silent courses may occur. Histologic findings include hemorrhaged pituitary adenoma tissue, occasionally infarctions, necrosis, cysts, or calcifications. There may be infiltration of adjacent structures (e.g., sphenoid sinus, cavernous sinus, hypothalamus, chiasm).

Epidemiology

Incidence

General incidence of pituitary adenomas is about 10/1,000,000/year. Incidence of all types of pituitary apoplexy is about 10% to 15% (range: 0.6% to 27.7%) of all pituitary adenomas. Incidence of pituitary apoplexy is higher in males (male > female).

Sex

Male > female.

Etiology

- Spontaneous
- External causes (see Risk Factors, below)
- Pathophysiological and pathoanatomic aspects: hemorrhage and necrosis are frequently the result of increased intratumoral pressure, edema, and pathologic alterations of the microarchitecture of the tumor vessels, which are supported by the regular vascularization of the pituitary originating from branches of the internal carotid artery (meningohypophyseal trunk, superior and inferior hypophyseal arteries)

Risk Factors

- (Minor) trauma
- Pregnancy (e.g., Sheehan syndrome
- Cerebral angiography
- Endocrine stimulation tests
- Radiation therapy
- Dopamine agonist therapy
- Estrogen therapy
- Anticoagulation therapy (also due to dialysis or cardiac/vascular surgery)
- Increased abdominal pressure (also during surgery)
- Chronic coughing and sneezing
- Postoperative tumor remnants in case of incomplete resection

Associated Conditions

Pituitary adenoma, sella tumors, and other space-occupying lesions, empty sella, (subarachnoid) hemorrhage, ischemia, necrosis, vascular insults

Pregnancy

Sheehan syndrome is the occurrence of pituitary apoplexy during or after pregnancy.

Diagnosis

Differential Diagnosis

- Subarachnoid hemorrhage (caused by ruptured aneurysm or AV malformation
- Cavernous-sinus thrombosis
- Venous sinus thrombosis
- Meningitis
- Hemorrhage of another (unknown) intrasellar or intracranial mass lesion
- Acute optic neuritis
- Migraine with aura

Signs and Symptoms

- Usually acute symptoms
- Sudden headache
- Meningism
- Visual disturbances/amnesia
- Impaired consciousness
- Nausea/vomiting
- Oculomotoric palsies/cranial nerve defects (nerves III, IV, V, VI)
- Hemiapresis
- Diabetes insipidus
- Signs of (partial or pan-) hypopituitarism
- Signs of anterior lobe hormonal excess (e.g., acromegaly, Cushing's disease)
- Hypothalamic dysregulation (temperature imbalance, disturbance of water/electrolyte balance)
- (Extremely rare) unexpected death

Laboratory Procedures

- Electrolytes
- Urinary concentration
- Osmolarity of serum and urine
- Serum prolactin Level
- Anterior pituitary hormone concentrations (basal)
- Anterior pituitary hormone function tests

Imaging Studies

- Head CT (axial and coronal projection) and/or MRI confirms pituitary apoplexy. Additionally, angiography or helical CT angiography to exclude vascular malformations may be required. MRI and CT scan can also identify subclinical or silent lesions (cysts, hemorrhages, necrosis, etc.).

Special Tests

- Lumbar CSF puncture (usually bloody or xanthochromic) should be avoided (possible risk of transtentorial brain herniation)
- Doppler ultrasound examination in case of extended subarachnoid hemorrhage (diagnosis/treatment control for vasospasm)
- Ophthalmologic examination (visual fields,

Management

General Measures

Most important measurements: endocrinologic and general stabilization
- Corticosteroids (initially minimum 200 mg hydrocortisone)
- In case of diabetes insipidus: DDAVP (desmopressin)
- Balance of electrolytes
- If necessary: intensive care treatment/artificial respiratory treatment/brain edema treatment (e.g., mannitol)

Surgical Measures

Treatment of choice in case of progressive visual disturbances or neurologic deficits, if the patient is in stable condition (e.g., endocrinologic or anesthesiologic parameters)
- (Usually) transsphenoidal surgery with removal of tumor and hematoma (decompression of chiasm)
- (Rarely) craniotomy necessary
- In case of extended subarachnoid hemorrhage, hydro-/hematocraLus or coma, supplemental ventricular drainage

Symptomatic Treatment

Appropriate pain medication may be given for headache.
Medications

**DRUG(S) OF CHOICE**

- Endocrinologic substitution with hydrocortisone, T₄, testosterone/estrogens, possibly growth hormone and DDAVP are necessary depending to the individual deficits.
- Hormonal substitution (mentioned above)

**CONTRAINdications**

- No specific contraindications unless specific hypersensitivity reactions are present.

**Precautions**

- Avoid sudden withdrawal of any of these medications, which are substituted for naturally occurring hormones. Adrenal insufficiency may be precipitated by sudden steroid withdrawal.

**ALTERNATIVE DRUGS**

N/A

Follow-up

**PATIENT MONITORING**

- Regular endocrinologic controls (basal and function tests) for adaption of hormonal substitution. In case of functioning tumors, control of the specific tumor hormones.
- Regular ophthalmologic examinations (visual fields, visual acuity)
- Regular MRI controls (mandatory in non-functioning tumors, in endocrine active tumors depending on the endocrinologic parameters)

**EXPECTED COURSE AND PROGNOSIS**

- Usually recovery following a critical clinical course in the acute cases, if hormonal replacement and surgery have been done in time. Lethal courses are rare. In the subclinical or silent cases, the prognosis is generally favorable.

**PATIENT EDUCATION**

- Information and management of the follow-up examinations listed above.
- Information about the need for endocrine substitution (especially hydrocortisone) in case of stress and emergency situations (e.g., accident, infections, surgery, different diseases, etc.)

**MISCELLANEOUS**

**SYNONYMS**

- Pituitary hemorrhage
- Pituitary necrosis
- Hemorrhagic pituitary adenoma

**ICD-9-CM**

253.2 Pituitary necrosis postpartum

**SEE ALSO**

- Pituitary adenoma
- Subarachnoid hemorrhage

**REFERENCES**


Author(s): Manfred Lange, MD
Plexopathy, Brachial

ASSOCIATED CONDITIONS
- Autoimmune diseases: systemic lupus erythematosus, giant cell arteritis, polyarteritis nodosa, inflammatory bowel disease
- Infectious diseases: HIV infection, CMV infection, Coxsackie-virus infection, parvovirus, Mycoplasm pneumonia, bacterial pneumonia, typhoid, syphilis
- Postimmunization: tetanus toxoid, immune sera, diphtheria, swine flu, hepatitis B vaccination
- Neoplasia: Hodgkin's disease, neuroblastoma, postirradiation
- Hereditary neuropathies: hereditary neuropathy with liability to pressure palsies (HNPP)

DIFFERENTIAL DIAGNOSIS
- Palomelitis
- Entrapment neuropathy
- Cervical root syndromes
- Vertebrolysis
- Rotator cuff injuries
- Subacromial bursitis

SIGNS AND SYMPTOMS
- The onset of brachial neuritis is often dramatic, with acute pain in the shoulder radiating into the neck and into the arm to the level of the elbow. The arm is often held flexed at the elbow and adducted at the shoulder. The pain may be constant for several weeks and may be intermittently painful for long periods. After several weeks, weakness develops, in the limb and the distribution varies depending on what portion or portions of the plexus is involved. Lesions that involve the entire plexus affect muscles innervated by C5 through T1, and often the arm hangs limp at the patient's side. Sensory loss involves almost the entire arm.

LABORATORY PROCEDURES
- EMG is very helpful in making the diagnosis and defining the degree of plexus injury. Denervation changes in muscles innervated by two cervical roots and involving at least two peripheral nerves point to the plexus as the site of the lesion. By definition, the lesion must be distal to the roots. Examination of the cervical paraspinal muscles by EMG is normal. Traumatic lesions may cause both plexus lesions as well as cervical nerve root lesions if the root is avulsed. Occasionally neoplastic lesions may also affect the plexus as well as the cervical roots.

IMAGING STUDIES
- Plain x-rays of the chest and neck are often very helpful. A lesion at the pulmonary apex with erosion of the first or second rib may be the cause of a lower plexus lesion. Similarly the presence of a cervical rib or elongated C7 transverse process may explain thoracic outlet syndrome symptoms. MRI and CT with contrast are also helpful in finding mass lesions compressing or infiltrating the plexus.

SPECIAL TESTS
- N/A
**Plexopathy, Brachial**

**Management**

**GENERAL MEASURES**
Management is largely supportive with efforts focused on pain control and passive and active range of motion exercises for the limb. Corticosteroids do not alter the course of the disease but may be helpful in the acute stage with pain not relieved by narcotics. Prednisone 60 mg/d for a few days with a rapid taper may be useful.

**SURGICAL MEASURES**
Surgery may occasionally be needed to define the lesion's full extent. Intraoperative electrical monitoring of evoked responses may help determine motor root damage. Occasional nerve grafting along with tendon transfers may allow return of function for some patients.

**SYMPTOMATIC MANAGEMENT**
Extensive physiotherapy is often needed for many months to maintain range of motion and avoid a frozen shoulder syndrome.

**ADJUNCTIVE TREATMENT**
N/A

**ADMISSION/DISCHARGE CRITERIA**
N/A

**Medications**

**DRUG(S) OF CHOICE**
Narcotics are often used for pain control in the acute stages.

**Contraindications**
Known hypersensitivity to narcotic drugs.

**Precautions**
The clearance of various narcotic agents or their metabolites may be decreased in patients with hepatic or renal dysfunction.

**ALTERNATIVE DRUGS**
N/A

**Follow-Up**

**PATIENT MONITORING**
Regular visits to ensure full range of motion in the joints are recommended.

**EXPECTED COURSE AND PROGNOSIS**
About one third of nontraumatic plexus injuries return to normal function in 1 year. Seventy-five percent have full recovery at 2 years and almost all by 4 years. Upper brachial plexus lesions recover more quickly. Weakness in the diaphragm and serratus anterior are associated with persistent weakness.

**PATIENT EDUCATION**
N/A

**Miscellaneous**

**SYNONYMS**
Parsonage-Turner syndrome
Brachial neuritis
Neuralgic amyotrophy
Brachial plexus neuropathy

**ICD-9-CM:** 723.4 Brachial neuritis NOS

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** J. Ned Pruitt II, MD
Lesions involving the lumbosacral plexus produce symptoms of weakness, numbness, and pain in the affected lower extremity. Neoplastic infiltration and radiation necrosis are common etiologies and can usually be distinguished based on clinical, radiographic, and electrodagnostic differences.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
Lumbosacral plexopathies are less common than brachial plexopathies, in part because the lumbosacral plexus is less likely to be involved in trauma.

**Race**
No demonstrated ethnic predominance.

**Age**
Many etiologies for lumbosacral plexopathy occur in older individuals.

**Sex**
Lumbosacral plexopathies due to cancer infiltration are more common in women. Radiation-induced lumbosacral plexopathy occurs in women, but is also seen in young men after treatment for testicular cancer.

**ETIOLOGY**

- Neoplastic infiltration is a relatively common cause of lumbosacral plexopathy and produces symptoms by mass effect. This can occur by direct extension from pelvic tumors or due to distant metastasis.
- Radiation treatment for pelvic tumors produces a delayed plexopathy, with symptom onset occurring 3 to 5 years after treatment, although the range is broad and may occur from 3 months to 30 years after radiotherapy. The mechanism is not clear, although vascular injury appears to play an important role, as obliterated blood vessels have been found on histologic studies. Radiation plexopathies become more likely with a higher total dose given (3,000-6,000 cGy), increased size of the individual treatment fractions, a higher frequency of treatments, and increased radiation field size.
- A hemorrhage into the retroperitoneum can involve the lumbar plexus, which is formed in the psosas muscle. The hemorrhage can also extend to involve the sacral plexus. The cause is usually heparin therapy, and roughly 5% of patients on intravenous heparin may develop a spontaneous hemorrhage into the psosas muscle. Patients with hemophilia and disseminated intravascular coagulopathy (DIC) are also at increased risk.

**RISK FACTORS**

- Pelvic tumors, radiation treatment, diabetes, complicated childbirth, heparin therapy, and trauma.

**PREGNANCY**

**Delivery**
Can result in a lumbar plexopathy. The incidence of obstetrics-related nerve injuries is estimated to occur between 1/2,600 and 1/6,400 of all deliveries.

**ASSOCIATED CONDITIONS**

Cancer, whether local in the pelvis (colorectal, uterine, cervical, ovarian, prostate and testicular cancers) or from distant sites (breast and thyroid carcinoma, sarcoma, and lymphoma), and diabetes are the major associated diseases.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Lumbosacral radiculopathy, including cauda equina syndrome; this can be difficult to distinguish clinically and often requires neuroradiologic and EMG studies.
- Sciatic neuropathy—strength of the gluteus medius (thigh abduction) and gluteus maximus (hip extension) are important to assess in this differential. If these muscles are weak, the lesion must be above the sciatic nerve at least as proximal as the plexus or nerve root level.
- Polyneuropathy is a diagnostic consideration in patients who have received chemotherapeutic agents, especially since polyneuropathies affect the lower extremities to a greater degree. To distinguish from plexopathy it is important to look for evidence of polyneuropathy involving the upper extremities.

**SIGNS AND SYMPTOMS**

In general, lumbosacral plexopathy presents with weakness, sensory loss, paresthesias, pain, loss of reflexes, and atrophy in the affected lower extremity. Many of the etiologies mentioned above may result in bilateral lumbosacral plexopathies resulting in signs and symptoms in both legs. Preferential involvement of the sacral plexus results in more prominent weakness below the knee, and involvement of the gluteus medius and maximus, with a diminished Achilles reflex. Preferential involvement of the lumbosacral plexus results primarily in weakness of proximal muscles, such as the quadriceps and thigh adductors and patellar reflex loss.

- Patients with cancer infiltration present with back and leg pain in at least 75% of cases. Leg edema and a rectal mass are found in some patients. Bowel and bladder involvement can be seen uncommonly.
- As opposed to neoplastic infiltration, radiation plexopathy presents with paresthesias and indolent leg weakness. Pain may eventually occur, but is less common and not as severe as in cancer infiltration.
- Patients with retroperitoneal hemorrhage due to heparin therapy present with acute-onset low back pain, leg pain, leg weakness, and paresthesias. The lumbar plexus is involved to a greater degree in retroperitoneal hemorrhage.
- In diabetic amyotrophy, intense pain begins in the anterior thigh, and inguinal region. Over the following weeks, the patient has progressive weakness, primarily in the distribution of the lumbar plexus, although the more distal sacral plexus innervated muscles may also be involved. The opposite leg may be involved to a milder degree. Some patients have a significant degree of weight loss.
- Neuropathy from the lumbosacral plexus presents similarly to diabetic amyotrophy with severe pain and preferential involvement of the lumbar plexus.
**LABORATORY PROCEDURES**

Blood work: an urgent CBC and PT/PTT are important when a lumbosacral plexopathy is suspected due to retroperitoneal hemorrhage from heparin therapy.

**IMAGING STUDIES**

MRI with gadolinium is the best test for identifying neoplastic infiltration of the lumbosacral plexus and is more sensitive than CT, although CT can often identify cancer infiltration. A CT of the pelvis should urgently be performed if a patient is suspected of having a retroperitoneal hemorrhage due to heparin therapy. A radio-nucleotide bone scan may show abnormal uptake in the pelvic, sacrum, and lumbosacral vertebrae in cases of lumbosacral metastasis.

**SPECIAL TESTS**

Electrodiagnostic Studies

EMG is useful to confirm the diagnosis of lumbosacral plexopathy and to distinguish between neoplastic and radiation etiologies. By nerve conduction study, low-amplitude compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) are found. The low-amplitude SNAPs distinguish the lesion from a radiculopathy, in which the SNAPs are normal. Needle electrode examination reveals widespread active and chronic denervation involving muscles innervated by the lumbosacral plexus, including the proximal gluteus medius and maximus muscles. The finding of spontaneous, semirhythmic bursts of potentials, called myokymic discharges, is a most useful finding that makes radiation plexopathy a more likely cause than neoplastic infiltration (seen in roughly two thirds of patients with radiation-induced lumbosacral plexopathy).

**ADJUNCTIVE TREATMENT**

If a neoplasm is identified, chemotherapy, radiation therapy, and other treatments are indicated. Patients with retroperitoneal hemorrhage may require blood transfusion and correction of the bleeding disorder.

**ADMISSION/DISCHARGE CRITERIA**

N/A

**Medications**

**DRUG(S) OF CHOICE**

No specific therapy. Pain management includes nonsteroidal antiinflammatory drugs, tricyclic antidepressants, and narcotic medications.

**Contraindications**

N/A

**Precautions**

N/A

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

N/A

**EXPECTED COURSE AND PROGNOSIS**

Prognosis varies widely depending on the etiology. Patients with retroperitoneal hemorrhage, diabetic amyotrophy, neuralgic amyotrophy of the lumbosacral plexus, and postobstetrical plexopathy tend to improve over time. While patients with diabetic amyotrophy have a good recovery, only 40% make a full functional recovery. Patients with radiation plexopathies usually have slow progression of symptoms, although some patients have spontaneously improved. Neoplastic infiltration is typically associated with a poor prognosis, although early treatment results in a better outcome. Of study of 30 patients with neoplastic infiltration of the lumbosacral plexus showed that 86% had died 3 ½ years after the onset of symptoms.

Due to the wide variety of disorders that can cause lumbosacral plexopathy, the patient can be referred to support groups for the underlying disease (e.g., cancer, diabetes, etc.).

**REFERENCES**


**SYNONYMS**

None

**ICD-9-CM:** 353.1 Lumbosacral plexopathy

**SEE ALSO:** N/A

**AUTHOR(S):** Brad Cole, MD
6,349 confirmed paralytic polio cases were reported seen due to live attenuated virus vaccine. In 1998, Incidence/Prevalence

Today the disease has already been eradicated from Africa. In the U.S. and other countries where the wild virus has been eradicated, paralytic polio is still seen due to live attenuated virus vaccine. In 1998, 6,349 confirmed paralytic polio cases were reported worldwide, and 2,289 of these were due to wild virus. Age

Any age can be affected; however, in 50% of cases children under the age of 3 are affected. Sex

No sex difference is present. Season

The disease is most frequent in summer and fall (July through September).

ETIOLOGY

Poliovirus is a single-stranded RNA enterovirus belonging to the Picornaviridae family. It has three serologically distinct types (polio 1, 2, and 3). Polio spreads through food or drink contaminated by feces. Also flies can passively transfer the virus from feces to food. Risk Factors

• Several factors increase the likelihood of paralytic form of the disease:
  • Tonsillectomy
  • Intramuscular injections
  • Immune deficiency
  • Hypogammaglobulinemia
  • Pregnancy
  • Exercise
  • Adult age (>18 years)

PREGNANCY

Pregnancy is associated with increased risk of paralytic disease.

ASSOCIATED CONDITIONS

• Vaccine-associated paralytic polio
• Postpolio syndrome

Diagnosis

DIFFERENTIAL DIAGNOSIS

• Acute causes of peripheral neuropathy
• Guillain-Barré syndrome
• Acute intermittent porphyria
• Lyme disease
• Diphtheria
• Transverse myelitis
• Heavy metal poisoning
• Acute spinal cord compressive lesions
• Other viral infections (Coxsackie virus, echovirus)

SIGNS AND SYMPTOMS

• The incubation period varies between 5 and 35 days, and oral and fecal shedding of the virus starts within 24 hours of the exposure.
• About 90% polio infections are asymptomatic. Minor illness (abortive polio): 5% to 10% of infected people develop nonspecific influenza-like syndrome characterized by fever, malaise, anorexia, headache, sore throat, and myalgia. Symptoms last 2 to 3 days.
• Nonparalytic poliomyelitis (aseptic meningitis): in about 1% of patients 7 to 10 days after the minor illness, aseptic meningitis is characterized by fever, headache, neck stiffness, and back pain develops. Symptoms resolve completely in most patients.
• Paralytic poliomyelitis: 1% of people infected develop the paralytic form of the disease. Paralysis develops 2 to 5 days after abortive polio when patient starts to recover. Symptoms start with fever, headache, and muscle pain. Asymmetrical weakness develops over several hours to days, affects legs more than arms. Neurologic examination reveals neck stiffness, decreased or absent deep tendon reflexes, and flaccid paralysis. A single muscle or roupsof muscles of one or more extremities can be involved. While monoparesis is common in children, quadriplegia is more frequent in adults. Sensory examination is normal. Dysautonomia (cardiac arrhythmias, blood pressure instability, bladder and bowel dysfunction) can be seen. Involvement of cervical or thoracic cord may lead to intercostal and diaphragmatic weakness. Bulbar involvement is seen in 10% to 15% of cases. Symptoms include dysphagia, dysphonia, facial paralysis, diplopia, stridor, and respiratory weakness. Death may result from respiratory insufficiency and autonomic disturbances. Long-term sequelae include weakness, atrophy of limb; and growth failure especially in young children.

LABORATORY PROCEDURES

Blood Work

• Routine blood tests are normal except for lymphocytic pleocytosis.
• CSF examination: typically pleocytosis with increased protein is seen. Cell count does not usually exceed 500 cells/mm³; initially polymorphonuclear leukocytes shifting to lymphocytic predominance after 72 hours. Protein content increases up to 200 mg/dL in the first few weeks. Virus isolation from CSF is rare.
• Virus can be isolated from feces and throat swabs 2 weeks before paralysis and several weeks after the onset of symptoms.
• A fourfold or greater increase in neutralizing antibody titers between acute phase and convalescent (3 to 6 weeks later) serology is diagnostic.

Imaging Studies

Hyperintense signal of the ventral horns of the spinal cord has been demonstrated on spinal MR in patients with poliomylitis. These findings are nonspecific but may be helpful to differentiate acute lower motor neuron syndromes from Gullain-Barré syndrome.

Special Tests

Electrodiagnost Studies

Nerve conduction velocities are usually normal; compound muscle action potentials may have low amplitudes. Needle EMG shows a reduced number of voluntary motor unit potentials; and fibrillation potentials appear at about 3 weeks. As improvement occurs, giant motor units indicating reinnervation appear.

Management

General Measures

Intensive care with respiratory support may be lifesaving. When forced vital capacity decreases below 12 mL/kg (less than 1 to 15 L for adults) or significant subjective dyspnea appears, intubation and mechanical ventilation should be considered. Cardiac function should be monitored. Bulbar functions should be followed and aspirations precautions observed.

Surgical Measures

There are no surgical procedures for the acute illness. For chronic phase correction of scoliosis; tendon lengthening and transfers are examples of rehabilitative surgeries. As improvement may continue up to 2 years, surgical procedures should be postponed until this time.
Symptomatic Treatment

Bed rest, analgesics, and hot wet packs relieve the muscle pain during acute illness.

Adjunctive Treatment

In the acute phase, respiratory exercises, hot packs to relieve pain, and passive exercises to prevent contractures should be performed. Active exercises and occupational therapy can be started at the subacute phase.

Admission/Discharge Criteria

For acute paralytic disease, hospitalization and bed rest are mandatory.

Medications

DRUG(S) OF CHOICE

There are two kinds of polio vaccine, both providing immunity against three types of poliovirus.

- Inactivated polio vaccine (IPV) (Salk) — Administered subcutaneously — Provides only serum humoral immunity; therefore, cannot prevent the multiplication of virus in gastrointestinal system and shedding in stool — Safe for immunizing people with immune system problems

Contraindications

Does not cause vaccine-associated polio.

Contraindicated in children allergic to neomycin, streptomycin, or polymyxin B.

- Oral polio vaccine (OPV) (Sabin)
  - Live attenuated vaccine
  - Easy to administer
  - In addition to serum humoral immunity, provides secretory immunity in mucous membranes; therefore, limits the multiplication of virus in gastrointestinal system and prevents person-to-person transmission. Therefore, preferred in areas where the wild virus is still present.
  - Carries vaccine-associated polio paralysis risk 1 in 2.4 million doses, more common with the first dose.

Contraindications

Contraindicated in children with immunodeficiency, hypogammaglobulinemia, leukemia, lymphoma, malignancy, and lowered resistance due to corticosteroid treatment, chemotherapy, or radiation and close contacts of such patients.

Precautions

Four doses of polio vaccine are enough to protect from polio. Committee on Infectious Diseases of the American Academy of Pediatrics recommends OPV for routine immunization. OPV is administered at ages 2, 4, and 15 months and 4 to 6 years. An additional dose can be administered at 6 months of age in areas with high risk of disease. Immunization programs in countries where polio has been eradicated may employ combined immunization schedules with both OPV and IPV. The Centers for Disease Control and Prevention recommends first and second doses as IPV in the U.S. This decreases the risk of vaccine associated poliomyelitis by 50% to 75% and provides the advantages of both vaccines.

For people traveling to areas where polio is common: if vaccinated previously, they should receive an additional dose of the vaccine they previously had. If they have not been previously vaccinated, they should be immunized with IPV. People younger than 18 years of age who have not been vaccinated in infancy can get two doses of OPV separated by 2 months and a third dose 6 to 12 months later. People over 18 years of age should not be given OPV as the risk of paralysis with OPV is higher in adults.

Follow-Up

PATIENT MONITORING

Patients in the convalescent phase of poliomyelitis may require physical therapy, bracing, and other orthoses.

EXPECTED COURSE AND PROGNOSIS

- Recovery from polio infection is complete except paralytic disease.
- CNS involvement determines the outcome of paralytic poliomyelitis. Ten percent of paralytic cases die due to respiratory and bulbar involvement. In bulbar poliomyelitis cases, mortality goes up to 60%. Fifty percent of cases recover completely. The rest are left with neurologic sequelae.
- Paralysis is evident by 2 to 3 days of onset of symptoms. Improvement begins in weeks and plateaus by 6 months.
- Postpolio syndrome: in a group of patients, two to three decades after the paralysis, slowly progressive weakness and atrophy of previously affected or unaffected muscles may develop. This condition is called postpolio syndrome. Fatigue and pain accompany the picture. This is an extremely slowly progressive condition and the patients should be reassured about this.

Patient Education

Polio is a rare disease now and is already eradicated from a large part of the world. However, there is a risk of spread of polio by travelers in areas where polio still exists. Improvement of hygiene and sanitation, and immunization are important to prevent and eradicate polio infections. Immunization programs should be continued until the disease is eradicated all over the world even in areas free of polio.


References


Author(s): Ersih Tan, MD
Polymyositis

**DESCRIPTION**

Polymyositis (PM) is an idiopathic inflammatory myopathy. The syndrome is characterized by primary inflammation of skeletal muscle with myofiber necrosis; other organs may be involved. The history, pattern of weakness, and muscle pathology distinguish polymyositis from the other idiopathic inflammatory myopathies (dermatomyositis and inclusion body myositis).

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Most studies have grouped polymyositis and dermatomyositis (DM) together. The annual incidence ranges from 0.1 to 0.93 per 100,000 population.

**Race**

The incidence among white Americans is 0.32 per 100,000 population. The incidence among black Americans is 0.77 per 100,000.

**Sex**

Females have PM more frequently in all age groups.

**Genetics**

PM is associated with human leukocyte antigen (HLA) DR3 in 48% of white patients and also with HLA-B7 and HLA-DR6 in black patients.

**RISK FACTORS**

None identified.

**PREGNANCY**

PM is a rare event in pregnancy. Perinatal mortality approaches 60% in the few cases (less than two dozen) reported.

**ASSOCIATED CONDITIONS**

- Autoimmune conditions: Crohn's disease, Hashimoto's disease, primary Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, and mixed connective tissue disease.
- Malignancy: many authors report an increased association (0%-28%) between PM and malignancy, though the evidence is less strong than that between DM and malignancy.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

- Inflammatory myopathies
  - Dermatomyositis
    - Inclusion body myositis (especially previously diagnosed PM unresponsive to corticosteroids)
  - Toxin-induced inflammatory myopathies
    - Pencillamine
    - Zidovudine
    - Procainamide
    - Remote effect of ciguatera poisoning
- Sarcoïd myopathy
- Infections
  - Bacterial (tropical pyomyositis)
  - Staphylococcus aureus
  - Straphylococcus
- Paracitic
- Cysticerisosis
- Teoeplasmosis
- Sporadic hibb lydil muscular dystrophy
- Metabolic myopathy Endocrinopathy
- Progressive muscular atrophy (neurogenic muscular atrophy)

**SIGNS AND SYMPTOMS**

- Insidious onset of weakness of proximal greater than distal muscles
- Usually symmetric, occasionally asymmetric or focal on presentation
- Neck flexor weakness
- Muscle pain/tenderness may occur
- Dysphagia
- Arthritis in 25% to 65% of PM patients
- Cardiac abnormalities: bundle branch block, atrioventricular conduction defects, atrial dysrhythmias
- Dyspnea, suggesting diaphragm involvement, interstitial lung disease, or aspiration

**LABORATORY PROCEDURES**

**Serum Studies**

- Muscle enzymes (elevated up to 50-fold) - creatine kinase. Aldolase, glutamic oxaloacetic transaminase (SGOT) may be elevated in the serum.
- Erythrocyte sedimentation rate (ESR) normal in more than half of patients, and no useful in diagnosis, determining treatment efficacy, or prognosis.
- Antibodies - patterns of antibody production may provide additional support for clinical diagnosis of some inflammatory muscle diseases but are usually not clinically useful. Antibodies against Mi-2 and Mas antigens are associated with relatively mild muscle disease. Anticytoplasmic antibodies against translational components (antisynthetase and anti-SRP, or signal recognition particle antibodies) are associated with severe muscle and systemic illness. The anti-Jo1 antibody is associated with interstitial lung disease.

**IMAGING STUDIES**

MRI detects muscle and subcutaneous edema and inflammation, but is rarely helpful in making the diagnosis. Use of MRI may be no better than clinical exam, is expensive, and has been limited to research.

**SPECIAL TESTS**

- EMG/NCS - sensory action potentials, late responses (F-waves and H-reflexes), conduction velocities, and repetitive nerve stimulation, are normal. The compound muscle action potential (CMAP) is normal in latency and amplitude early in disease; the CMAP amplitude may decrease with disease progression, reflecting loss of myofibers. Needle EMG studies demonstrate increased insertional activity (>500 msec), increased spontaneous activity (fibrillations, occasional complex repetitive discharges, and, rarely, myotonic discharges), and reduced amplitude and duration of voluntary motor unit action potentials (MUAPs). Voluntary MUAPs are often polyphasic with increased recruitment patterns. Chronic PM may demonstrate long duration motor unit action potentials.
- Muscle biopsy is the preferred diagnostic test for PM. Histologic features include myofiber size variation, regeneration, necrosis, an increase in connective tissue, an increase in central nuclei, and inflammation.

Inflammation is perivascular, perimysial, and endomysial. Endomyosal inflammation consists primarily of activated CD8+ cells, macrophages, very few natural killer cells, and few or no B cells. CD8+ cells focally invade non-necrotic muscle fibers.

**Management**

**GENERAL MEASURES**

Once PM is suspected, the main focus should be to exclude alternative causes of myopathic weakness and treat the disease;
Polymyositis

Medications

DRUG(S) OF CHOICE

Prednisone (at least 1 mg/kg/d, typically 60-80 mg) is administered in a single oral daily dose for 3 to 4 weeks, followed by a slow taper over 10 weeks to 1 mg/kg on alternate days. In severe cases, intravenous methylprednisolone 1 g qd or pod for five to six doses can be used to initiate therapy. If prednisone demonstrates efficacy, the dose may be reduced by 5 or 10 mg every 3 to 4 weeks until the least necessary dose is determined. If prednisone is ineffective, another immunosuppressive medication may be initiated and prednisone more rapidly tapered.

Contraindications

Corticosteroids are contraindicated in patients with a known hypersensitivity to any of the corticosteroids. Corticosteroids should not be used in persons with peptic ulcer (except life-threatening situations). An apparent association of corticosteroids and left ventricular free-wall rupture after recent myocardial infarction (MI) has been suggested, and corticosteroids should be used with extreme caution in patients with recent MI.

PRECAUTIONS

- Corticosteroids may reduce resistance to and aid in bacterial, viral, or fungal infections and mask clinical signs of infection. Corticosteroids can reactivate tuberculosis, and chemophylaxis is used in patients with a history of active tuberculosis undergoing prolonged steroid treatment. Patients should be instructed to notify any surgeon, anesthesiologist, or dentist if a surgical procedure is required and they have recently (within 12 months) been on glucocorticoids.
- Anaphylactoid reactions are seen in some patients given parenteral glucocorticoids, and may represent hypersensitivity to paraben preservatives.
- Corticosteroids should be used with caution in persons with diverticulitis, non-specific ulcerative colitis, cirsitis, hypothyroidism (who may demonstrate an exaggerated response to the drugs), hypertension, psychosis, and congestive heart failure.
- Prolonged use of corticosteroids may cause adenocortical insufficiency (in supraphysiologic doses), and muscle wasting, pain, or weakness (“steroid myopathy”).
- Corticosteroid use is associated with hyperglycemia and hypokalemia.

ALTERNATIVE DRUGS

Considered if prednisone is ineffective or if relief for steroid complications is sought. Consider azathioprine 2 to 3 mg/kg daily orally for approximately 4 to 6 months. If azathioprine is ineffective, consider methotrexate 15 to 25 mg/week orally.

Follow-Up

PATIENT MONITORING

- Recommendations about following creatine kinase vary, depending on the author. Clinical examination is the best measure of progress and treatment efficacy.
- Patients on steroids should have weight, blood pressure, serum glucose, and potassium, and eyes (for cataract formation) monitored every 1 to 2 months.
- Consider supplementation patients on methotrexate (a folate acid analog inhibiting dihydrofolate reductase) with folate 5 mg once weekly after the methotrexate dose.

EXPECTED COURSE AND PROGNOSIS

The prognosis in PM without malignancy is relatively favorable, but may require lifelong treatment. Five-year survival rates range from 70% to 93%. Poor prognostic features include older age, malignancy, interstitial lung disease, cardiac disease, respiratory muscle weakness, dysphagia, acute onset, fever, presence of Jo-1 or SRF antibodies, and a delay in, or inadequate, treatment.

Patients who will be on long-term corticosteroids should be told of potential complications such as electrolyte disturbances, osteoporosis, peptic ulcer, weight gain, bruising, insomnia, hypoglycemia, and cataract formation. Such potential complications form the basis for monitoring (see above) and consideration for treatment with potassium and calcium supplementation, a no added-salt diet, antacids, and exercise program. Physical therapy should also be considered early in the disease to prevent atrophy and preserve muscle function. The Myositis Association of America serves as a source of information for patients as well as patient advocate and support group. Myositis Association of America, Inc. (MAA), 755 Cantrell Avenue, Suite C, Harrisonburg, VA 22801. Phone: 540-433-7688, fax: 540-432-0206, email: maa@myositis.org, website: http://www.myositis.org.
Porphyria

DESCRIPTION

Porphyria is an autosomal-dominant condition with highly variable expression. It results from a relative deficiency of porphobilinogen deaminase (known as uroporphyrinogen I) of the heme biosynthesis pathway. Acute intermittent porphyria is the most common porphyria associated with neurologic manifestations and is classified as a hepatic porphyria due to the overproduction and accumulation of porphyrin precursors in the liver.

EPIDEMIOLOGY

Incidence
Porphyria has an incidence of approximately 1 in 50,000. It is much more common in Sweden with an incidence of approximately 1 in 1,000.

Age/Sex
Manifestations usually occur in adult women. Attacks of acute intermittent porphyria are rare before puberty.

ETIOLOGY

The deficiency of porphobilinogen deaminase results in higher levels of aminolevulinic acid and porphobilinogen in both the blood and urine during attacks. How accumulation of these metabolites contributes to the clinical symptoms is not well understood.

Genetics
Many deletions and point mutation in the porphobilinogen-deaminase gene on chromosome 11 have been described.

RISK FACTORS

Many drugs and hormones may precipitate attacks. Drugs that are contraindicated are typically inducers of the P-450 system and include barbiturates, carbamazepine, ergots, synthetic estrogens and progesterones, griseofulvin, valproate, and sulfonamide antibiotics. Attacks in women are often in the luteal phase of their menstrual cycle.

PREGNANCY

As many as 75% of patients experience an exacerbation of porphyria during pregnancy with some series showing up to 20% mortality. During an attack there is a high risk for spontaneous abortions. There are no known effects on the fetus; although there is passive transfer of porphyrins through the placenta.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute abdominal pain associated with common conditions such as appendicitis, ectopic pregnancy, or subacute bacterial peritonitis
- Paralytic ileus
- Guillain-Barré syndrome
- Arsenic poisoning
- Thallium poisoning

SIGNS AND SYMPTOMS

Attacks of acute intermittent porphyria manifest themselves as acute attacks of abdominal pain, which is poorly localized and may be associated with abdominal cramping and nausea and vomiting. Neuropsychiatric manifestations also can occur, ranging from restlessness and agitation to delirium with psychosis. Two to 3 days after the onset of abdominal pain the patients often develop a predominantly motor axonal neuropathy. Weakness, develops rapidly and is predominantly proximal, although the extensors of the fingers and wrists seem to be usually affected. Reflexes are diminished but are not usually lost in the early course of the illness, unlike in acute demyelinating neuropathies such as Guillain-Barré syndrome. An autonomic neuropathy is frequently encountered and may result in unexplained arrhythmias and wide fluctuations in blood pressure. Rarely seizures may occur.

LABORATORY PROCEDURES

Porphyria is easily diagnosed once the disease is suspected. During an acute attack high levels of porphobilinogen and alanine are present in the blood. Definite diagnosis depends on demonstrating a porphobilinogen deficiency in erythrocytes. Nerve conduction studies and electromyography confirm the axonal nature of the neuropathy and help distinguish it from an acute demyelinating neuropathy or rhabdomyolysis.

IMAGING STUDIES

N/A

SPECIAL TESTS

N/A

MANAGEMENT

GENERAL MEASURES

Long-term management focuses on avoiding precipitating factors and recognizing the possibility of acute intermittent porphyria in the setting of an acute attack of abdominal pain.

SURGICAL MEASURES

N/A

SYMPTOMATIC MANAGEMENT

Specific treatment of an acute porphyric attack involves intravenous administration of glucose or heme. Both agents inhibit the heme biosynthetic pathway. Glucose is given in doses of 300 g per day and heme in the form of hematin albumin, or heme arginate at doses of 3 to 4 mg per day for 4 days. Narcotics can be used safely to treat the abdominal pain, and phenothiazines are safe for the treatment of nausea and vomiting. Seizures may be difficult to treat since many of the typical anticonvulsants are contraindicated. Benzodiazepines can be used safely.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

N/A
Medications

**DRUG(S) OF CHOICE**

No medications are available to prevent acute attacks. Avoidance of contraindicated drugs is recommended.

**Contraindications**

Barbiturates, carbamazepine, ergots, danazol, estrogens and progesterones, griseofulvin, valproate, sulfonamide antibiotics, meprobamate, phenytoin

**Precautions**

N/A

**ALTERNATIVE DRUGS**

N/A

Follow-Up

**PATIENT MONITORING**

The acute axonal neuropathy may also affect cranial nerves, causing bulbar weakness and increasing the risk for aspiration. Respiratory weakness can also occur due to involvement of the phrenic and intercostal nerves.

**EXPECTED COURSE AND PROGNOSIS**

The recoveries from the attacks of acute abdominal pain are often quite rapid. Recovery of strength is dependent on the degree of axonal injury.

**PATIENT EDUCATION**

Patients should be aware of potential precipitating medications and wear a medical identification bracelet. Family members of patients identified as having porphyria should also be screened for the genetic defect.

Miscellaneous

**SYNONYMS**

Acute intermittent porphyria

**ICD-9-CM:** 277.1 Dis porphyrin metabolism

**SEE ALSO:** N/A

**REFERENCES**


**Author(s):** J. Ned Pruitt II, MD
Primary Lateral Sclerosis

**DESCRIPTION**

Primary lateral sclerosis (PLS) is a clinical term applied to a disorder that in life remains restricted to the corticospinal tracts (CSTs) and is proven only at autopsy. The definition of PLS mandates the exclusion of other likely causes of progressive spastic paraparesis (PSP) such as demyelinating disease, hereditary conditions, structural disorders, malformations, and infection of the CNS.

**EPIDEMIOLOGY**

Incidence/Prevalence

PLS is a rare disorder, and as a result the incidence and prevalence have not been established. There is no known predilection for race, age, or sex.

**ETIOLOGY**

PLS is a neurodegenerative disorder with predominant degeneration of the upper motor neurons. Autopsy studies demonstrate loss of large pyramidal Betz cells in layer V with secondary degeneration of the pyramidal tract. There is no known genetic predisposition.

**RISK FACTORS**

There is a paraneoplastic association of PLS with cancer of the lung and breast and lymphoma; however, a discrete autoantibody has not been isolated.

**PREGNANCY**

There is no association with pregnancy.

**ASSOCIATED CONDITIONS**

PSL may be a forme fruste of amyotrophic lateral sclerosis (ALS).

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**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis includes primarily progressive spinal multiple sclerosis (MS), hereditary spastic paraplegia (HSP), cervical spondylotic myelopathy (CSM), tumors of the foramen magnum, syringomyelia, spinal arteriovenous malformations, human T lymphotrophic virus and HIV infections, and stroke.

**SIGNS AND SYMPTOMS**

Spasticity in PLS results from the underlying upper motor neuron (UMN) lesion and the disinhibition of velocity-dependent increase in muscle tone during passive stretch. The associated positive clinical signs of this disinhibition are hyperreflexia, Babinski signs, and painful extensor and flexor spasms. The negative signs of spasticity are UMN weakness, fatigability, and incoordination.

**LABORATORY PROCEDURES**

Electromyography and nerve conduction studies (EMG-NCS) should be performed in all patients for the possibility of ALS because fibrillation, positive sharp waves, and widespread fasciculation should not be seen in PLS.

**IMAGING STUDIES**

MRI of the brain and cord excludes structural disorders of the CNS, and in conjunction with sensory evoked responses (SERB) of the arms and legs, auditory evoked responses (AERs), and visual evoked responses (VERs), and lumbar CSF analysis excludes MS and chronic infection.

**SPECIAL TESTS**

Transcranial magnetic stimulation (TMS) complements EMG-NCS because it quantitates central conduction time, which should be reduced in isolated disease of the CST.

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**Management**

**GENERAL MEASURES**

The goal of treatment is to prevent or reduce the undesirable consequences of spasticity that include decreased mobility, disabling pain, contractures, dependency for activities of daily living (ADL) sexual dysfunction, and sleep disturbances. Untreated, these consequences lead to low self-esteem and mood disorders. The management of spasticity should ideally be based on ongoing clinical assessment leading to an appropriate therapeutic plan.

**SURGICAL MEASURES**

Selective dorsal rhizotomy (SDR) can be performed in selected patients who do not benefit from other measures to manage spasticity. Physiologically, this procedure reduces spasticity by removing the stimulating afferent input of muscle stretch receptors on motor neurons. However, SDR invariably leaves the patient with some undesirable sensory deficits.

**SYMPTOMATIC TREATMENT**

Physiotherapy should be prescribed to prevent contractures, improve overall active function, and provide comfort, but it is rarely sufficient therapy alone. Occupational therapy is needed periodically to optimize ability to perform ADLs.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

Admission is not generally required except for management of complications such as aspiration pneumonia.
DRUG(S) OF CHOICE

Oral antispasticity agents should be tried in all patients. Baclofen, a γ-aminobutyric acid analogue, is the drug of choice for the treatment of spasticity associated with PLSS. It is given in doses of 10 to 40 mg PO tid to qid (and often higher doses, although the PDR recommended limit is 100 mg per day). It penetrates the blood-brain barrier poorly; thus to obtain significant therapeutic benefit, high doses need to be taken that may induce unacceptable weakness, lethargy, somnolence, and other side effects.

Contraindications
Known hypersensitivity to baclofen.

Precautions
Oral antispasticity agents may cause increased weakness, sedation, and nausea. These agents should be started at low doses and titrated up gradually.

ALTERNATIVE DRUGS

- Alternative oral agents for spasticity include tizanidine, diazepam, clonidine, dantrolene, and cyproheptadine.
- Botulinum toxin can be injected into affected muscles in selected individuals with focal severe spasticity, but there may be bruising, focal weakness, flu-like symptoms, and antibody development with chronic use.
- Baclofen can be delivered intrathecally via a surgically implanted programmable pump with the advantage of easier penetration of the drug into the CNS and higher drug levels. However, the disadvantages include an operative procedure and potential malfunction of the pump system.

PATIENT MONITORING

A thorough clinical assessment is crucial in formulating a local management program that requires a multidisciplinary approach. The Ashworth Scale is an objective bedside rating system of spasticity that can be easily applied to patients with PLSS, both in initial assessment and in determining treatment benefit.

EXPECTED COURSE AND PROGNOSIS

The course is usually slowly progressive, leading to a bed-bound state over decades. Oropharyngeal involvement may predispose to aspiration pneumonia.

PATIENT EDUCATION

- Spastic Paraplegia Foundation, P.O. Box 1208, Forston, GA 31808. Phone: 978-256-2673, email: info@sp-foundation.org, website: [http://www.sp-foundation.org](http://www.sp-foundation.org).
- Primary Lateral Sclerosis Newsletter, 101 Pinta Court, Los Gatos, CA 95032, 73112. 611@compuserve.com.

REFERENCES


Author(s): David S. Younger, MD
Progressive Multifocal leukoencephalopathy

DESCRIPTION
Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the CNS secondary to activation of latent JC virus, usually occurring in immunoincompetent individuals.

EPIDEMIOLOGY

Incidence/Prevalence
PML is a rare disease in the general population. It occurs most commonly in HIV-infected patients, and occurs in approximately 5% of that population. The age-adjusted death rate increased from 0.2 per million persons before 1984 to 3.3 per million persons in 1994, attributable to HIV. During the 16-year period from 1979 through 1994 3,694 PML deaths were reported.

Race
No study has demonstrated an ethnic predominance.

Age
Range 5 to 84 years.

Sex
Males > females.

ETIOLOGY
It is estimated that 70% to 80% of the adult population harbors latent JC virus (a human polyomavirus). An immunocompromised state secondary most commonly to HIV, lymphoproliferative disorders, and iatrogenic immune suppression allows reactivation of the JC virus in oligodendrocytes. PML has been described in immunocompetent individuals.

Genetics
PML appears to be sporadic and genetic factors are not identified.

RISK FACTORS
Immunocompromised state.

PREGNANCY
Little is known about any relationship of PML to pregnancy.

ASSOCIATED CONDITIONS
PML has been described in association with AIDS, chronic neoplastic disease, Hodgkin’s disease, lymphoma, myeloproliferative diseases, tuberculosis, sarcoidosis, and multiple immunosuppressive drugs.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- HIV demyelination
- Multiple sclerosis
- Hypertensive leukoencephalopathy
- Vasculitis
- Lymphoma
- Toxoplasmosis
- Gliona
- Central pontine myelinolysis
- Radiation-related leukoencephalopathy
- Stroke
- Acute disseminated encephalomyelitis
- CMV

SIGNS AND SYMPTOMS
Patients present with focal neurologic deficit including hemiparesis, visual loss, aphasia, ataxia, dysarthria, sensory changes, and cognitive impairment. Headache, seizures, and extrapyramidal syndromes are more rare.

LABORATORY

PROCEDURES Blood Work
There are no specific blood tests to diagnose PML, but the following tests should be considered to rule out other possible etiologies: ESR, CBC, coagulation profile, HIV, RPR, vitamin B₁₂, BUN, creatinine, Na, ammonia level, and toxoplasmosis titer.

IMAGING STUDIES
- CT demonstrates hypodense lesions in the white matter. These lesions are commonly seen in the frontal and parieto-occipital regions, but may occur in any white matter distribution including the posterior fossa. Scattered lesions may enlarge and become confluent. These lesions are usually bilateral, but may be unilateral.
- MRI is much more sensitive in evaluating white matter involvement. MRI often shows T2 hyperintense lesions in the periventricular and subcortical white matter. Lesions are often seen to progress from focal to extensive and confluent areas of T2 hyperintensity. Contrast enhancement is typically absent.
- MR spectroscopy can be used to further evaluate PML, and MR magnetization transfer can help in distinguishing PML from HIV encephalitis.

SPECIAL TESTS
CSF cell count, glucose, and protein are usually normal. Polymerase chain reaction (PCR) for JC virus DNA is specific but not sensitive for PML and should be done to aid in diagnosis. Cytology, cell count, glucose, protein, Gram stain, bacterial culture, fungal culture, AFB, VDRL, and viral screen should be done to rule out other possible causes of white matter lesions. Biopsy remains the standard for diagnosis demonstrating characteristic histopathology; however, clinical and radiographic evidence accompanied by positive PCR for JC virus DNA suffices in most situations.

MANAGEMENT

GENERAL MEASURES
PML, with few exceptions, is the result of iatrogenic immunosuppression should be determined if unknown as part of the initial evaluation. Iatrogenic immunosuppressive agents should be discontinued when plausible. When PML is the initial presenting feature of HIV infection (-5%), patients should be offered optimal antiretroviral therapy (HAART). Antiviral therapy directed at the JC virus is of proven benefit. Cytosine arabinose has been the most commonly used agent, but in a controlled trial in HIV+ patients was ineffective. Other agents under investigation include Cidofovir and interferon.

SURGICAL MEASURES
There are no surgical procedures for the treatment of PML.

SYMPTOMATIC TREATMENT
- Antiseizure medication should be initiated when seizures occur.
- Pain may be present as part of a central pain syndrome and should be treated appropriately. Tricyclic antidepressants and selective serotonin reuptake inhibitor antidepressants, gabapentin, and narcotics may be of benefit.
- Spasticity may occur and can be treated with baclofen or tizanidine.

ADJUNCTIVE TREATMENT
- Physical therapy and occupational therapy may be of benefit when hemiparesis or paralysis occur.
- Intrathecal cytarabine and interferon alpha are of proven benefit.

ADMISSION/DISCHARGE CRITERIA
Patients should be admitted for initial evaluation, treatment, and stabilization, if rapidly progressive neurologic deficits, fever, or recurrent seizures occur. If a neoplasm or acute infection is strongly suspected, admission for diagnostic evaluation including possible brain biopsy may be necessary. Inpatient rehabilitation should be considered at discharge when deficits dictate.
Progressive Multifocal leukoencephalopathy

Medications

**DRUG(S) OF CHOICE**
No specific anti-JC viral treatment is known to be effective. Treatment of the underlying immune disorder may help.

**ALTERNATIVE DRUGS**
N/A

Follow-Up

**PATIENT MONITORING**
Patient should be followed every 4 to 6 weeks to observe progression.

**EXPECTED COURSE AND PROGNOSIS**
Most patients die within 9 months of diagnosis. Spontaneous remission have been reported to occur in as much as 8% of the HIV population. When the underlying cause of immunosuppression can be reversed, survival is improved.

Patient Education

N/A

Miscellaneous

**SYNONYMS**
N/A

ICD-9-CM: 046.3 Progressive multifocal leukoencephalopathy

SEE ALSO: N/A

REFERENCES


Author(s): Stephen J. Gomez, MD; Paul L. Moots, MD
Progressive Supranuclear Palsy

DESCRIPTION
Progressive supranuclear palsy (PSP) is one of the Parkinson's plus syndromes. Despite clinical similarities, however, the basic neuropathologic processes are significantly different from idiopathic Parkinson's disease (IPD). Clinically, PSP is regarded as one of the akinetic-rigid syndromes. Pathologically, however, it falls more in the class of tauopathies, which include, but are not limited to, Alzheimer's disease, frontotemporal dementias including Pick's disease, corticobasal ganglionic degeneration (CBGD), and Others. Characterized by early gait disturbance, bradykinesia, rigidity, and occasionally tremor, it is most commonly misdiagnosed as PD early in its onset. Relentlessly progressive, PSP usually leads to significant motor and cognitive decline in 5 to 7 years, resulting in institutionalization and death.

Like many of the Parkinson's plus syndromes, PSP shares the clinical characteristic of being poorly responsive or totally unresponsive to dopaminergic stimulation.

Classical Pathologic Changes in Progressive Supranuclear Palsy
- Prominent neurofibrillary tangles (NFTs) in subcortical regions as well as cortex, including hippocampus
- Granulovacuolar degeneration in:
  - Basal ganglia
  - Brainstem, especially the red nucleus, locus ceruleus, and superior olivary nucleus
  - Cerebellum

EPIDEMIOLOGY
Incidence/Prevalence
Incidence rates of PSP have been estimated at 0.3 to 1.1 new cases per year per 100,000 individuals. Prevalence rates in the United Kingdom may approach 6 to 7 cases per 100,000 population. PSP represents approximately 3% to 5% of all cases of parkinsonism, while idiopathic PD represents at least 85%.

Race
No known ethnic predilection. Age
The median age of diagnosis is mid- to late 50s to early 60s, slightly earlier than idiopathic PD.

Sex
Some authors suggest a male/female ratio of 2:1, while other studies have found no gender differences.

ETIOLOGY
The cause of PSP is unknown. The possibility of infection has been raised due to similarities between PSP and postencephalitic parkinsonism. Rare cases of autosomal-dominant, familial clusterings have been reported, but the gene has not been identified yet. Recent evidence suggests that homozygous carriers of the A30P genotype with mutations of the tau gene may be at increased risk of developing PSP.

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSES
- Corticobasal ganglionic degeneration
- Diffuse Lewy body disease
- Drug-induced parkinsonism (e.g., antipsychotics, antemetics, and other dopamine blocking agents)
- Multiple system atrophy (MSA)
  - Shy-Drager syndrome (SDS) — PD plus autonomic insufficiency
  - Striato-nigral degeneration (SND) — PD plus levodopa unresponsiveness
- Olivopontocerebellar atrophy (OPCA) — PD plus ataxia
- Vascular parkinsonism
- Postencephalitic parkinsonism
- Posttraumatic parkinsonism
- Wilson's disease
- Frontotemporal dementia with parkinsonism
- Alzheimer's with extrapyramidal features (probably a DLBD variant)

SPECIAL TESTS
N/A

SIGNS AND SYMPTOMS
The earliest symptoms of PSP include frequent falling with profound postural instability (usually affecting >95% of patients at time of diagnosis), usually accompanied by bilateral bradykinesia, i.e., masked facies, pauciarity of spontaneous limb movement, slowness and shuffling of the gait. On exam, patients occasionally have a resting tremor, but may have complicating postural and intention tremors. The distribution of increased resistance to passive manipulation is predominantly axial, affecting neck and trunk movements more than the limbs. This pattern is the opposite of that seen in IPD. Tremor and rigidity are also typically more symmetric at onset in PSP, differentiating it from the largely asymmetric onset of signs and symptoms in IPD. The classic neuro-ophthalmologic features of PSP include loss of voluntary vertical gaze, followed by loss of voluntary horizontal gaze. This "supranuclear" ophthalmoplegia can be overcome by doll's-eyes maneuvers, confirming the intact nature of the brainstem nuclei and their connections. Patients may have a neck dystonia with retrocollis and eyelid retraction, resulting in a prominent "staring" appearance. Other neuro-ophthalmologic hallmarks include gaze insensitivity, loss of optokinetic nystagmus (first in vertical, then in horizontal planes), and square wave jerks with oculograde fixation. Other frequent symptoms include dysarthria, dysphagia, disinnhibiton, and frontal lobe symptoms such as perseveration, grasping, apathy, and/or depression.

LABORATORY PROCEDURES
Blood Work
There are no specific blood tests to diagnose PSP, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism: serum vitamin B12 level, thyroid function tests, serum ceruloplasmin, 24-hour urine copper excretion.

IMAGING STUDIES
Functional neuroimaging using PET and SPECT scanning with markers for neuronal activity (fluorodeoxyglucose), dopaminergic terminals (beta-CIT, DTBZ, and others) and dopamine receptors (IBZD) may distinguish PSP from idiopathic PD, but does not distinguish from other Parkinson's plus syndromes. These methods are not being widely implemented. There is no evidence to suggest that structural imaging studies (CT, MRI) can assist in the diagnosis of PSP. MRI may reveal evidence of other causes of parkinsonism such as vascular insults, mass lesions, calcium or iron deposition in the striatum, atrophy in the posterior fossa suggestive of multiple system atrophies, and cortical atrophy patterns suggestive of other dementing illnesses.

IMAGING STUDIES
SPECIAL TESTS
N/A
Progressive Supranuclear Palsy

**Management**

**GENERAL MEASURES**

There is no effective treatment for PSP. Management is aimed at alleviating the consequences of the motor and cognitive changes associated with PSP.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

The primary symptom of gait instability may be overcome by the use of four-wheel walkers, although the predominant tendency of patients with PSP to fall backward usually limits the effective duration of this intervention. Patients with dysarthria or dysphagia may benefit from speech pathology intervention. Percutaneous endoscopic gastrostomy (PEG) may be performed to provide life-sustaining nutrition. Exposure keratitis may be prevented by frequent administration of artificial tears.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

PSP is usually managed in an outpatient setting. Rarely, concomitant illnesses, especially aspiration pneumonia, can lead to an acute exacerbation of PSP symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility. Symptoms of psychosis may precipitate hospitalization and/or institutionalization.

**Medications**

**DRUG(S) OF CHOICE**

Rarely, patients with PSP will transiently respond to carbidopa/levodopa (C/L) therapy at the beginning of the disease process. This response is usually minimal and short-lived. Antidepressants, especially amitriptyline and trazodone have helped ameliorate some of the symptoms of rigidity, bradykinesia, and gait disturbance. Botulinum toxin injections have been useful for severe dystonias.

Contraindications

Individuals with a history of cardiac arrhythmias or orthostatic hypotension may have adverse effects when prescribed tricyclic antidepressants.

Precautions

The use of high doses of carbidopa/levodopa and other dopaminergic therapies may be associated with confusion, hallucinations, and agitation, especially in individuals with advanced symptoms of PSP.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

PSP is a relentlessly progressive illness, typically leading to death within 6 to 10 years. Patients are monitored in the outpatient setting, usually at 4 to 6 month intervals. Judicious use of antidepressant medications and timely discussion of PEG tube placement are recommended to assist patients and their families prepare for future decline.

**EXPECTED COURSE AND PROGNOSIS**

Due to its progressive nature, the symptoms of PSP always worsen with time. Death usually occurs as a consequence of pulmonary embolism or aspiration pneumonia.

**PATIENT EDUCATION**

The severe gait instability in PSP prevents the use of ambulatory exercise, although stretching and strengthening exercises in a sitting position may be useful. Aqua therapy with close supervision may help forestall some of the immobility issues associated with this illness. Speech therapy is useful for speech and swallowing disturbances. National organizations provide information to patients and their families.

**SYNONYMS**

Steele-Richardson-Olszewski syndrome

**ICD-9-CM:**

333.0 Progressive supranuclear palsy; Other disorders of the basal ganglia

**SEE ALSO:**

MULTIPLE SYSTEM ATROPHY,

PARKINSON'S DISEASE,

DIFFUSE LEWY BODY DISEASE

**REFERENCES**


**Author(s):** Lawrence W. Elmer, MD, PhD
Pseudotumor Cerebri

DESCRIPTION
Pseudotumor cerebri (PTC) is a condition that mainly affects obese women and is associated with significant morbidity due to increased intracranial pressure (ICP). Headaches, transient visual obscurations (TVOs), and progressive visual loss are the most common presenting symptoms. The elevated ICP is transmitted through the optic nerve sheaths to the optic discs, causing papilledema, which is generally considered a medical emergency. CT scan demonstrates no evidence of a mass lesion, while lumbar puncture reveals an elevated opening CSF pressure. This process unchecked can lead to irreversible blindness.

EPIDEMIOLOGY
Incidence/Prevalence
- Obese women of childbearing age are most commonly affected.
- Incidence in the general population (1:100,000): In women age 20-44, >10% over ideal body weight (13:100,000)
- In men age 20-44, 20% over ideal body weight (19.3:100,000)
- In men age 20-44, 20% over ideal body weight (1.5:100,000)

Race
No known association with race. Sex
Female/male ratio of 8:1 in the adult population.
Age
Peak incidence is in the third decade, but can occur from infancy to old age.

ETIOLOGY
The etiology remains elusive; however, the leading theory proposes low conductance to CSF outflow at the arachnoid villi leading to increased CSF volume and increased ICP. The majority of cases are idiopathic; but resistance to CSF egress may be secondary to venous occlusive disease, meningeal carcinomatosis or other infiltrative processes. A variety of medications including tetracycline, doxycycline, minocycline, fluoroquinolones, nalidixic acid, exogenous growth hormone, birth control pills and hyperthyroidism, hypoparathyroidism, and secondary causes. PTC has also been associated with steroid withdrawal, Addison's disease, hypothyroidism, and increased ICP. The majority of cases are idiopathic; but resistance to CSF egress may be secondary to venous occlusive disease, meningeal carcinomatosis or other infiltrative processes. A variety of medications including tetracycline, doxycycline, minocycline, fluoroquinolones, nalidixic acid, exogenous growth hormone, birth control pills and hyperthyroidism, hypoparathyroidism, and meningioma, and menstrual irregularities and pregnancy, betraying a possible underlying endocrine etiology.

Genetics
No known genetic syndrome.

PREGNANCY
No evidence of an increased risk of PTC onset or exacerbation during pregnancy.

ASSOCIATED CONDITIONS
- Obesity/recent weight gain
- Empty sella syndrome
- Systemic lupus erythematosus
- Behcet's disease

Diagnosis
DIFFERENTIAL DIAGNOSIS
The diagnosis of idiopathic PTC is largely one of exclusion. Therefore, it is necessary to rule out other causes of papilledema and increased ICP as well as secondary PTC. Focal neurologic signs other than cranial nerve VI palsy should suggest a diagnosis other than PTC.
- Intracranial mass lesion with obstructive hydrocephalus
- Pseudopapilledema (i.e., optic disc drusen)
- Meningitis (i.e., bacterial, viral, neurophilis)
- Venous sinus thrombosis
- Medication related (e.g., tetracycline, growth hormone therapy)
- Endocrine related (e.g., systemic lupus erythematosus, acromegaly)

SIGNS AND SYMPTOMS
- Headache (most frequent symptom)
  - Generally holocranial or retrobulbar — Relatively constant, "aching" or "throbbing" quality, variable intensity — May be associated with nausea or light-headedness
- Transient visual obscurations
  - Bilateral or unilateral, dimming, or loss of vision lasting for 2 to 3 seconds
  - Secondary to optic disc swelling
- Visual loss (optic disc related)
  - Causes of permanent loss of vision: compressive optic nerve damage, optic disc infarction, choroidal folds, and subretinal hemorrhage
  - Visual field loss
  - Enlarged blind spot and generalized constriction are most common.
  - Nasal step, arcuate defects, and cecocentral scotomas may also be encountered.
  - Relative afferent pupillary defect with asymmetric optic nerve involvement
- Bilateral optic disc swelling secondary to increased ICP (i.e., papilledema) is generally noted; patients with unilateral optic disc swelling or no optic disc edema are rare.
- Diplopia, secondary to cranial nerve VI palsy, which may be unilateral or bilateral — Photopsia (seeing "sparkles" or "flashes")

LABORATORY PROCEDURES
Blood work is generally unnecessary in the typical idiopathic PTC patient. In an atypical patient (e.g., thin male) or in a patient with uncharacteristic symptoms or signs (e.g., arthralgias, malar rash, tetanic muscle spasms, cranial nerve III palsy), other laboratory tests may prove diagnostic for secondary forms of PTC: VDRL, FT-ABS, antinuclear antibody, anti-dsDNA, or serum Ca²⁺ determinations.

IMAGING STUDIES
CT and MRI are the main imaging techniques used in PTC. Normal to small-sized ventricles are seen with no evidence of mass lesion. Up to 70% of PTC patients have evidence of an empty sella. Clear differentiation between the optic nerve and sheath, with an enlarged, elongated subarachnoid space, and flattening of the posterior aspect of the globe may also be seen. MRI is better than CT to rule out infiltrative diseases and venous sinus thrombosis.

SPECIAL TESTS
- Lumbar puncture (LP) is necessary to obtain the opening pressure and to rule out infection or inflammation. Opening pressures greater than 200 mm H₂O are considered elevated. Falsely low pressures may occur when the LP requires multiple attempts with reinsertion and redirection of the needle. LP under radiologic guidance should be considered in obese patients, especially when normal landmarks cannot be palpated. CSF analysis should include cell counts, differential, cytology, protein and glucose levels, Gram stain, and routine cultures and sensitivities. These are all within normal limits in idiopathic PTC.
- Visual acuity testing, pupillary responses, slit lamp and dilated funduscopy evaluation, and visual fields are necessary to assess baseline visual function. Stereoscopic optic disc photographs taken on initial evaluation can be used to monitor disease progression. Fluorescein angiography of the fundus may help to differentiate optic disc drusen (i.e., pseudopapilledema) from true papilledema.
Pseudotumor Cerebri

Management

GENERAL MEASURES
Weight loss is the most effective treatment for PTC and may reduce the need for medications or surgery. Suspect exogenous agents should be discontinued. Lumbar puncture initially done for diagnostic purposes may also be therapeutic.

SURGICAL MEASURES
Surgical intervention is necessary to control intractable headaches and to preserve visual function when weight loss and medical therapies are not successful. Serial lumbar puncture can be used to lower ICP; however, the effects are often temporary, and repeat procedures may be poorly tolerated. The main surgical considerations for PTC are lumboperitoneal shunting (LPS) and optic nerve sheath fenestration (ONSF). In a retrospective study of 30 PTC patients who underwent LP shunting, headache improved in 82%, papilledema resolved completely or nearly completely in 96%, and visual acuity or field improved in 68% of patients. Unfortunately, reoperation is the general rule, most commonly due to shunt malfunction. In the previously mentioned PTC study, the mean follow-up duration was 34.9 months and the mean shunt revision rate was 4.2 per patient. In ONSF, multiple incisions are made in the anterior dural covering of the optic nerve. ONSF is useful to decompress the optic nerve in cases with severe papilledema. It is less likely to relieve high ICP in the long run; however, it does reduce the risk of visual loss with recurrent elevation of ICP. In this regard, ONSF is also helpful in cases of PTC with recurrent LPS failure to prevent them from “picking off” vision each time. Gastric bypass surgery may be indicated to improve weight loss in morbidly obese patients.

SYMPTOMATIC TREATMENT
Symptomatic treatment includes judicious use of analgesics for relief of headache.

ADJUNCTIVE TREATMENT
Weight loss is an important component of treatment and may require consultation with a diettian.

ADMISSION/DISCHARGE CRITERIA
Hospital admission may be indicated (a) for radiologic-guided lumbar puncture and initiation of medical therapy, OR (b) for urgent surgical intervention to preserve vision.

Medications

DRUG(S) OF CHOICE
Carbonic anhydrase inhibitors are the mainstay of medical therapy for PTC, and work by reducing CSF production. Neptazane 50 mg bid to qid and acetazolamide 250 mg bid to 500 mg qid are generally well tolerated.

Contraindications
Carbonic anhydrase inhibitors should not be used in patients with sulfa allergy. They have a relative contraindication during pregnancy (class B) and should definitely not be used during the first 4 months’ gestation.

Precautions
Common adverse effects at higher doses include tingling and numbness in the fingers and toes, fatigue, nausea, and metallic taste, K+ wasting. Aplastic anemia is a rare idiosyncratic reaction.

ALTERNATIVE DRUGS
Furosemide in doses of 20 mg bid to 40 mg qid is also effective; however, it is important to monitor serum potassium. Corticosteroids are a controversial alternative that are most useful in patients with an underlying inflammatory condition such as systemic lupus. Prolonged corticosteroid use may be counterproductive by leading to further weight gain and fluid retention. Octreotide, a somatostatin analog has been found in several small case series to lower intracranial pressure, relieve headache, reduce papilledema, and improve vision in PTC patients, although the mechanism of action is unknown. Octreotide is an option in patients with sulfa allergy.

Follow-Up

PATIENT MONITORING
The goal of treatment is to eradicate intolerable headaches and to preserve visual function. It is necessary to monitor the degree of papilledema and formal visual field testing over time. Papilledema may not resolve completely with appropriate treatment and may not recur significantly with ICP once it becomes chronic in nature. Optic disc appearance alone is not adequate to assess for recurrent elevation in ICP; subjective symptoms and visual field progression may be more reliable.

EXPECTED COURSE AND PROGNOSIS
PTC appears to be a self-limited disease. Once the condition is controlled on medication for 6 months to a year, attempts to wean off the medication should be made periodically, especially when weight loss has been achieved. Systemic hypertension is a risk factor for increased visual loss.

PATIENT EDUCATION
Patients should be educated that PTC is self-limited, but that visual loss secondary to the disease may be permanent or progressive.

Miscellaneous

SYNONYMS
Idiopathic intracranial hypertension

ICD-9-CM: 348.2 Pseudotumor cerebri; 377.01 Papilledema
SEE ALSO: N/A

REFERENCES

Author(s): James A. McHale, MD; Steven E. Katz, MD
Rabies

Basics

DESCRIPTION

Rabies ("rage" or "madness" in Latin) is a viral infection that causes rapidly progressive and almost always fatal encephalomyelitis. It is transmitted to humans primarily through close contact with saliva (bites, scratches, licks on broken skin and mucous membranes) of infected animals (dog, bat, raccoon, fox, skunk), rarely through laboratory exposure, inhalation (caves that harbor bats), and iatrogenic (corneal transplant) tissue exposure.

EPIDEMIOLOGY

Incidence/Prevalence

Rabies causes more than 40,000 deaths each year worldwide, primarily in Asia, Africa, and Latin America. About 10 million people receive postexposure prophylaxis each year. In the U.S., 33 cases were reported between 1980 to 1996.

Race

No race difference was reported.

Age

Although rabies can occur at any age, about half of the cases reported occur in children.

Sex

No sex difference was present.

RISK FACTORS

The risk of an unimmunized person to develop rabies after a bite of a rabid animal is 5% to 15%. Modifying factors include the site and the severity of bite and the virus concentration of saliva. Bites on the head and face result in the highest incidence of disease with the shortest incubation period.

PREGNANCY

Transplacental transmission of rabies has rarely been reported, and the possibility of transmission through lactation has not been excluded. Postexposure prophylaxis of pregnant women has been reported as safe in several case reports.

ASSOCIATED CONDITIONS

None

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Other causes of viral encephalitis
  - Herpes simplex virus encephalitis — Arbovirus encephalitis
- Nonviral causes of encephalitis
  - Mycoplasma pneumonia
  - Legionnaire disease
  - Central nervous system toxoplasmosis
  - Guillain-Barré syndrome (GBS) (paralytic or dumb rabies cases)
- Poliomyelitis
- Tetanus
- Allergic encephalitis due to nerve tissue-derived rabies vaccine
- Acute hepatic porphyria with neuropsychiatric disturbances
- Alcohol withdrawal (delirium tremens)

IMAGING STUDIES

Routine blood work is nonspecific except leukocytosis. CSF examination is normal until late in the disease.

LABORATORY PROCEDURES

- Antibody detection in the serum and CSF: serum antibodies may not be present until several days after the onset of symptoms. Rapid fluorescent focus inhibition test measures the neutralizing antibodies, while indirect immunofluorescence assay detects antibody reactive to rabies antigen in infected cell cultures.
- Virus isolation from saliva, nuchal skin, CSF, oral or nasal mucosa, brain
- Antigen detection by direct immunofluorescence from nuchal skin biopsy, corneal, and salivary impressions
- Detection of viral RNA in saliva
Rabies Management

GENERAL MEASURES
Rabies is almost always fatal after the onset of symptoms. Pulmonary and cardiac functions should be monitored. Dysautonomia, seizures, and increased intracranial pressure should be managed aggressively. Sedation with barbiturates, benzodiazepines, and phenothiazines may be necessary.

SURGICAL MEASURES
There is no surgical procedure for rabies. Brain biopsy for diagnosis is debatable because of the risks of the procedure and the inaccessibility of tissues with greatest involvement. If done, eosinophilic viral inclusions (Negri bodies) will be seen.

SYMPTOMATIC TREATMENT

Prophylaxis
- Preexposure prophylaxis
  - Should be applied to high-risk individuals (veterinarians, certain laboratory workers, animal control workers, travelers to countries where rabies is endemic). Cell or tissue culture vaccines [human diploid cell vaccine (HDCV), purified duck embryo vaccine, purified chick embryo cell vaccine] should be used if possible. Vaccine should be administered IM or ID in the deltoid area on days 0, 7, and 21 or 28 (according to package instructions). Two to 3 weeks after the last injection, the antibody titer should be checked and if inadequate, a booster dose should be given. Follow-up of the antibody titer every 6 months for persons who work with live rabies virus and every year for those under continuous risk (veterinarians, travelers to endemic areas) is recommended.
- Postexposure prophylaxis
  - Local wound cleaning
    - The wounds or scratches should be washed with water and soap or detergent immediately followed by ethanol, tincture, or aqueous iodine. Deep wounds should be irrigated by syringe and these solutions applied by cotton-tipped applicators. An antibacterial agent can be applied to prevent secondary infections. Provide tetanus prophylaxis.
    - Do not suture the wound. If suturing is unavoidable, do it after immune globulin infiltration.
- Vaccination
  - Five doses of cell or tissue culture vaccine, 1 mL each is enough. First dose should be given as soon as possible, subsequent doses on days 3, 7, 14, and 28 after the first dose. (WHO recommends a sixth dose on day 90.)
  - Vaccine should be given IM in the deltoid muscle in adults and anterior thigh in infants.
- Postexposure prophylaxis for those previously immunized: two doses of vaccine on days 0 and 3 IM in the deltoid area should be given. Human rabies immune globulin (HRIG) is contraindicated.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
All suspected cases should be followed in the intensive care units.

DRUG(S) OF CHOICE
- HRIG
  - Infiltrate 20 IU/kg HRIG in the tissues around the wound. As much HRIG as anatomically possible should be given to the wound and rest intramuscularly to the anterior thigh. HRIG should be given as early as possible, but can be given up to 8 days after the first dose of the vaccine. Doses given in and after the 8th day will compromise patient’s response to vaccine.

Contraindications
N/A

Precautions
Never draw HRIG with the same syringe with the vaccine and do not administer in the same site.

ALTERNATIVE DRUGS
N/A

WEBSITES
World Health Organization: http://www.who.int/emc/diseases/zoo
Centers for Disease Control and Prevention: http://www.cdc.gov/ncidod/dvrd/rabies

ICD-9-CM: 071 Rabies

SEE ALSO: N/A

REFERENCES

Author(s): Sevim Erdem, MD
Cervical radiculopathy (CR) refers to dysfunction of a cervical nerve root, usually due to compression and usually caused by degenerative spine disease or acute disc herniation. Typical clinical picture includes neck and arm pain with or without alterations in strength, sensation, and reflexes.

**Epidemiology**

**Incidence/Prevalence**

Annual incidence rate 83.2/100,000 population.

**Age**

For CR due to herniation of the nucleus pulposus (HNP), incidence highest at ages 50 to 54, mean age 47. CR in older patients more often due to cervical spondylosis and spinal stenosis with root compression due to osteophytes rather than disc material, or to both. Approximation: 50% of compressive CR affects the C7 root, 30% C6, 10% C5, and 10% C8. Isolated T1 radiculopathy is rare.

**Sex**

Male predominance.

**Etiology**

Degenerative spine disease (spondylosis) has two elements: degenerative disc disease (DDD) and degenerative joint disease (DJD). Primarily due to aging; superimposed macro- or micro trauma may aggravate the process. DDD predisposes to HNP (“soft disc”). DJD causes osteophytic narrowing of the neural foramina (“hard disc”). Either process may cause compressive radiculopathy. More advanced spondylosis may also lead to spinal stenosis and cord compression.

**Risk Factors**

The only major risk factor is trauma.

**Pregnancy**

N/A

**Associated Conditions**

Osteoarthritis

**Description**

Osteoarthritis (OA) is a chronic condition affecting the joints, characterized by the breakdown of cartilage and the development of bone spurs. It occurs most frequently in the hands, knees, hips, and spine. OA can lead to pain, stiffness, and physical limitations.

**Diagnosis**

**Differential Diagnosis**

- Peripheral neuropathy
- Cervical or lumbar disc herniation
- Spinal stenosis
- Degenerative disc disease
- Osteoarthritis
- Spondylolisthesis
- Fracture
- Infection
- Tumor
- Cervical spondylosis
- Cervical facet arthropathy
- Cervical radiculopathy

**Signs and Symptoms**

- Patients can experience pain in the neck, arm, or hand.
- Sensory disturbances such as numbness or tingling may be present in the affected area.
- Motor weakness or muscle atrophy may occur.
- Increased pain with neck extension or tilting to the symptomatic side.
- Pain on leaning or putting the ipsilateral ear to the shoulder.
- Radiating pain with coughing or sneezing.

**Laboratory Procedures**

None helpful.

**Imaging Studies**

Plain cervical spine films with obliques to assess for osteoarthritic changes and osteophytes. MRI to assess for disc herniation and evidence of root compression. Abnormalities on MRI common in asymptomatic individuals. CT myelogram is the most sensitive test.

**Special Tests**

EMG and MRI are complementary studies. Each has about 55% to 70% sensitivity; studies agree in about 55% to 70% sensitivity. Studies agree in about 55% to 70% sensitivity. Studies agree in about 55% to 70% sensitivity.

Radiating pain with neck extended and tilted slightly to the symptomatic side suggests CR; brief breath holding in this position sometimes elicits radial paresthesias. Axial compression (Spurling’s maneuver) adds little. Light digital compression of the external jugular veins until the face is flushed sometimes elicits radial symptoms: unilateral shoulder, arm, pectoral or periscapular pain, or radiating paresthesias into the arm or hand (Naffziger sign), a highly specific but insensitive finding.

**Findings**

- Findings that suggest a lesion at a given level as follows:
  - C5—pain only in neck and shoulder, no pain below elbow, depressed biceps and brachioradialis reflexes, weakness of spinati or deltoid
  - C6—weakness of deltoid or biceps, paresthesias limited to the thumb, sensory loss over thumb only, depressed biceps and brachioradialis reflexes
  - C7—presence of scapular/intercostal pain, pain involving the posterior upper arm, pain involving the medial upper arm, paresthesias limited to index and middle fingers, whole hand paresthesias, depressed triceps reflex, weakness of triceps, sensory loss involving middle finger
  - C8—presence of scapular/intercostal pain, pain involving the medial upper arm, depressed triceps reflex, paresthesias limited to ring and small fingers, weakness of hand, intrinsics, sensory loss involving small finger
  - T1—disproportionate weakness of abductor pollicis brevis (APB)

**Laboratory Procedures**

None helpful.
Radiculopathy, Cervical

**Management**

**GENERAL MEASURES**
- Treatment relies on three approaches: mechanical, medicinal, and surgical. Nerve roots lying in the foramen normally enjoy freedom of movement through a small range. The size of the intervertebral foramen and the lateral recess changes dynamically with neck movement. When neck is extended or tilted or turned ipsilaterally, foramen IS narrower; with flexion or contraversive movement, foramen is wider. When caliber of foramen or lateral recess is narrowed because of osteophyte or HNP, neck movement may cause microtrauma, which induces inflammation and edema. With HNP, intradiscal inflammatory mediators may spill onto the root, exacerbating the process. Maintains of treatment is to reduce neck movement and increase the size of the foramen.
- Soft cervical collar is usually helpful. For compressive CR, collar should be worn "backward," with high side posterior, to maintain neck in slight flexion and open foramina. Hard collars cannot be turned around in this fashion and are not as useful for a radiculopathy syndrome. Soft collar should be worn at night if tolerated; if not, use cervical pillow. Prolonged use of collar may weaken neck muscles.
- Cervical traction for 15 to 30 minutes tid often very helpful—distracts spine, opens foramina, gives involved root respite. Over-the-door home traction unit adequate; referral to a physical therapist unnecessary. Start with low weight (5-8 lb), advance as tolerated to 12-15 lb. Too rapid weight increase may cause neck or jaw soreness, and limit compliance. Best for patient to face door with neck slightly flexed; combination of flexion and distraction more effective in opening the foramen. However, it is difficult to do anything but stare at the door during treatment, and if facing away from the door appears equally efficacious for the individual patient, it is permissible and may improve compliance.

**SURGICAL MEASURES**
Consider referral to a spine surgeon in patients with medical research council (MRC) strength of grade 4/5 or worse in any muscle, evidence of myelopathy, or excruciating pain unresponsive to conservative treatment. In a population-based study, 26% required surgery. Newer surgical techniques are much less invasive.

**SYMPTOMATIC TREATMENT**
Modality physical therapy, or local heat or ice, may provide some relief of axial pain component, but the effects seldom persist much beyond the individual treatment session. Cervical ROM exercises are of no benefit and possibly harmful.

**ADJUNCTIVE TREATMENT**
Cervical epidural steroids, acupuncture used rarely; spinal manipulation imprudent.

**ADMISSION/DISCHARGE CRITERIA**
Hospital admission not required for medically treated patients.

**Medications**

**DRUG(S) OF CHOICE**
Nonsteroidal antiinflammatory drugs (NSAIDs) may decrease radicular inflammatory component and relieve pain. Other analgesics are often necessary, including occasional narcotics. When neurologic deficit is moderate (MRC grade 4+/5 in the most involved muscles), a course of oral steroids is reasonable, e.g., predni lone 60-100 mg/day for 7 to 10 days, tapering over the next 7 to 10 days. Caution about short-term steroid side effects.

**Intensive conservative therapy usually continued for 3 to 6 weeks.**

**Contraindications**
Known hypersensitivity for medications.

**Precautions**
Standard precautions for the drug employed.

**ALTERNATIVE DRUGS**
Muscle relaxants add little; side effects of sedation and depression.

**Follow-Up**

**PATIENT MONITORING**
Follow especially strength and reflexes of involved segment; worsening strength or loss of reflex may prompt more aggressive treatment.

**EXPECTED COURSE AND PROGNOSIS**
The typical patient is significantly improved by 2 to 3 months. Generally favorable long-term prognosis; 90% have minimal to no symptoms on prolonged follow-up. When due to HNP, CR has a tendency to recur: 31% have previous history of CR, 32% have recurrence during follow-up.

**PATIENT EDUCATION**
Neck owner's manual (Krames 800-333-3032).

**SYNONYMS**
N/A

**ICD-9-CM:**
721.0 Cervical spondylosis; 722.0 Cervical disc herniation; 722.4 Cervical disc degeneration; 723.1 Cervicalgia; 723.4 Cervical HNP; 722.6 Degenerative disc disease, NOS; 722.9 Cervical disc disorder, other; 723.3 Cervicobrachial pain; 847.0 Cervical strain; 353.2 Cervical root lesion, NEC

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** William W. Campbell, MD, MSHA

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Radiculopathy, Lumbosacral

**Basics**

**DESCRIPTION**

Lumbosacral radiculopathy (LSR) refers to dysfunction of a lumbar or sacral nerve root often presenting as low back pain with radiating leg pain/paresthesias with or without neurologic deficits of weakness, sensory disturbance, and reduced or absent reflexes.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Multiple studies of incidence and prevalence show disparate numbers but the cumulative lifetime prevalence for low back pain may range from 14% to 65%. Providing an accurate number for LSR is even more difficult but may be around 12% of patients, with low back pain having symptoms that may indicate radiculopathy.

- Majority of herniated discs occur at L4-5 and L5-S1 (>90%), much less frequently at L3-4, and rarely at L1-2 and L2-3.
- Male to female ratio 1.5:1 in one series of surgically proven cases.
- The incidence of degenerative disc disease (DDD) is highest in the fourth and fifth decades, whereas compression from degenerative joint disease (DJD) is at an older age.

**ETIOLOGY**

LSR is most commonly caused by extrinsic processes such as compression by disc material (DDD) or bone/synovium/ligaments (DJD) and infrequently by intrinsic processes such as infiltration from tumor or infection.

**Genetics**

N/A

**RISK FACTORS**

Trauma is a major risk factor; other possible risk factors include cigarette smoking, greater number of hours spent in a motor vehicle, and occupations requiring lifting while twisting the body. Advancing age is a risk factor for DJD.

**PREGNANCY**

N/A

**ASSOCIATED CONDITIONS**

Osteoarthritis

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Tumor
  - Primary, metastatic, carcinomatous meningitis
  - Infection
    - Herpes zoster, Lyme, HIV, CMV
  - Osteomyelitis (Staphylococcus aureus most common, TB)
  - Epidural abscess (S. aureus)
  - Diabetic polyradiculopathy
  - Paraneoplastic polyradiculopathy
  - Non-neuropathic mimickers
  - Facet arthropathy
  - Discitis
  - Referred pain from abdominal and pelvic organs, aorta

**SIGNS AND SYMPTOMS**

Features favoring LSR over other etiologies of back pain with radiating leg pain:

- Age over 30
- Acute/subacute back pain, recurrent back pain with radiating symptoms down one or both legs
- Past history of cervical or lumbosacral radiculopathy
- Paresthesias or pain in posterior leg, lateral aspect and sole of foot or lateral leg and top of foot
- Radiating pain with cough, sneeze, or bowel movement
- Positive root compression signs
  - Straight leg raise (Lasegue's sign). With the patient supine, the affected leg is raised by the ankle until pain is elicited. Reproducing the pain or paresthesias under 60 degrees is a positive sign of root compression.
  - Crossed straight leg raise. With the patient supine, the asymptomatic leg is lifted. A positive root compression sign is elicited if there is reproduction of pain or paresthesias in the symptomatic leg on lifting the asymptomatic leg. More specific but less sensitive than the straight leg raise.
  - Femoral stretch test (reverse straight leg raise). With the patient prone, the hip of the symptomatic leg is maximally extended. Reproducing the symptoms is a positive test; most useful in upper level herniated discs (L2, L3, L4).
- Myotomal weakness
- Dermatomal sensory loss
- Decreased reflexes
  - Bowel or bladder dysfunction (polyradiculopathy/cauda equina syndrome from canal stenosis)
  - No systemic illness
  - Findings that suggest a lesion at a given level as follows:
    - High lumbar (L1-3)—sensory signs (altered sensation) in the inguinal region, anterior thigh, and medial aspect of knee. May have weakness in illoposas (hip flexion), quadriceps (knee extension), and thigh adductors.
    - Cremasteric reflex (L2) and patellar reflex (L3) may be depressed. Positive femoral stretch test.
    - L4—sensory signs over the knee and medial leg, may have weakness in the quadriceps and tibialis anterior (foot dorsiflexion and inversion). Patellar reflex may be depressed.
    - L5—sensory signs over the lateral leg, dorsomedial foot, and large toe. May have weakness in gluteus muscles (hip extension, hip abduction), tensor fascia latae (abduction and internal rotation of thigh), hamstring muscles (knee flexion), tibialis posterior (plantar flexion and inversion of foot), tibialis anterior, peroneal (foot plantar flexion and eversion), extensor hallucis longus (extension of great toe and foot dorsiflexion). No reflex changes.
    - S1—sensory signs over the little toe, lateral foot, and sole of foot. May have weakness in the gluteus maximus (hip extension), hamstring muscles, gastrocnemius (foot plantar flexion), flexor hallucis longus (foot plantar and great toe flexion), and flexor digitorum longus (plantar flexion of the foot and toes except for great toe). Achilles reflex may be depressed.
    - S2—sensory abnormalities involving the perianal region, buttocks, posterior thigh, and calf. May have bowel or bladder disturbance. Anal reflex may be absent.

**LABORATORY PROCEDURES**

N/A

**IMAGING STUDIES**

- MRI is the imaging procedure of choice in suspected LSR. It has the benefits of imaging in the sagittal view, giving excellent soft tissue resolution, and does not involve radiation. Contraindicated for patients with implanted magnetic sensitive devices, difficult to perform on patients with claustrophobia or obesity.
- CT has a lower sensitivity, but acceptable if there is a need, such as in patients unable to undergo MRI or when more bony detail required. Using intrathecal contrast (CT myelogram) increases the sensitivity, but makes it an invasive procedure with potential for the same adverse reactions as a conventional myelography.
Radiculopathy, Lumbosacral

• Myelography has a role in some selected cases such as in patients with metallic fixation in place or are morbidly obese. It is capable of evaluating patients in a full weight-bearing position. It has the advantage over CT of imaging in the sagittal plain and better evaluates the cauda equina. Myelography is an invasive procedure and can result in headache, nausea/vomiting, seizures, arachnoiditis, infection, and allergic reaction to the contrast.

• Plain lumbosacral spine films are generally not helpful except in the setting of acute trauma, suspected infection, or malignancy, and then is often only the starting point of the evaluation.

• Of note, there is a high incidence of lumbosacral abnormalities on neuroimaging in asymptomatic individuals. CT and MRI potentially demonstrate abnormalities in 36% and 30%, respectively, of asymptomatic individuals. Therefore, imaging should be done only when clinically indicated, for example, if the patient is a surgical candidate.

SPECIAL TESTS
EMG is complementary to MRI and has the advantage of providing information about nerve function, severity of the lesion, and the prognosis for recovery. Should be done between 3 weeks and 6 months for the highest yield.

GENERAL MEASURES
Conservative treatments shown to have potential benefit outweighing potential harm include certain medications, gradual return to normal activities, patient education, and low-stress aerobic exercise. Treatment options with weak or equivocal evidence of benefit include manipulation, self-application of heat or ice, epidural steroid injections, wearing a corset, and bed rest of 2 to 4 days.

SURGICAL MEASURES
Referral to surgeon if pain is severe or neurologic deficit persists after 1 month of conservative treatment. May need to refer earlier for suspicion of cauda equina syndrome, infection, malignancy, recent trauma, or severe weakness.

SYMPTOMATIC TREATMENT
See General Measures, above.

ADJUNCTIVE TREATMENT See General Measures, above.

ADMISSION/DISCHARGE CRITERIA
Not required unless rapidly progressing neurologic deficits, as might be seen in cauda equina syndrome.

Medications

DRUG(S) OF CHOICE
• Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, naproxen, or from the newer class of nonsteroids, the cyclooxygenase-2 (COX-2) inhibitors like celecoxib and rofecoxib.
• Acetaminophen

Contraindications
Previous hypersensitivity reaction to NSAIDs, history of asthma, and nasal polyps. Also, celecoxib should not be given to patients who have a history of allergic reactions to sulphonamides.

Precautions
Use with caution if there is a history of renal, hepatic, or hematologic disease. May cause gastrointestinal distress (much less common with the COX-2 inhibitors; however, these are currently more expensive).

ALTERNATIVE DRUGS
• Narcotics—rarely indicated, especially in chronic pain, helpful for a brief period during acute symptoms.
• Muscle relaxants—short course may be helpful, limited due to sedation and depression.

Miscellaneous

SYNONYMS
Sciatica; herniated nucleus pulposus (HNP)

ICD-9-CM: 722.32 Lumbar/lumbosacral disc degeneration; 953.2 Lumbar root injury; 953.3 Sacral root injury; 722.10 Lumbar/lumbosacral disc displacement; 722.2 Intervertebral disc (with neuritis, radiculitis, sciatica, or other pain)

REFERENCES

Author(s): Kristen C. Barner MD, William W Campbell, MD, MSHA
Reflex Sympathetic Dystrophy

DESCRIPTION
Reflex sympathetic dystrophy (RSD) usually involves a limb, and combines extreme pain, hyperalgesia and other sensory abnormalities, vasomotor and sweating disturbances, motor disturbances such as spasm, dystonia or loss of mobility, and, later in the course, trophic changes involving hair, nails, skin, and thinning of bone. RSD commonly develops after limb trauma, without involving hair, nails, skin, and thinning of bone. The pain arises from three sources: peripheral, central, and abnormal sympathetic-somatosensory coupling.

ETIOLOGY
Incidence/Prevalence
The incidence of RSD remains uncertain. Although upper extremity RSD is more commonly reported, a large pain center usually finds cases equally distributed between the upper and lower extremities. RSD occurs with fractures of the radius in 1% to 16% of cases and 15% to 25% after major hemispheric stroke. There is no age, race, or sex predilection.

Etiology
The exact etiology of RSD is unknown. Useful clinical observations include (a) local and neurogenic inflammation in the limb, (b) a-adrenergic sensitivity at the nociceptor and dorsal root ganglion levels, (c) architectural reorganization of the dorsal horn, and (d) changes in thalamic and anterior cingulate function.

RISK FACTORS
Phenobarbital and isoniazid are drugs associated with the production of RSD, refractory to any standard treatment until the offending agent is removed. Immobilization is the most common major risk factor, followed by trauma or operation, fracture, nerve injury (defining type 2), and stroke with significant paresis. Prior occurrence of RSD increases the probability of the disorder's recurrence, or occurrence in another limb.

PREGNANCY
Pregnancy has been associated with pelvis and lower extremity RSD.

ASSOCIATED CONDITIONS
Any disease associated with a small fiber neuropathy, such as diabetes and collagen-vascular disorders.

DIFFERENTIAL DIAGNOSIS
RSD is usually a complication of tissue injury rather than a primary disorder. All of the conditions that could mimic RSD could also underlie RSD, and should be considered. Such diseases include vascular disorders such as deep venous thrombosis, arterial occlusion, and stenosis; inflammatory disorders such as cellulitis and osteomyelitis; anterior compartment syndrome; and occult stress fracture.

SIGNS AND SYMPTOMS
• The diagnosis is established on clinical grounds, based on four symptom groups: sensory abnormalities (spontaneous pain, allodynia, reduced sensation); motor abnormalities (spasm, dystonia, reduced range of motion); autonomic abnormalities (vasomotor, sudomotor, and interstitial fluid disturbances); and trophic changes in hair, skin, nails, and bone. The presence of symptoms in all four groups—definite RSD; three groups—high probability of RSD; two groups—possible RSD; and one group—probably not RSD.
• The syndrome is divided into three stages: early (weeks–6 months) when the limb is dry and warm, middle (3 months–years) when the limb becomes wet and cool, and late (6 months–years). Atrophy sets in while pain and autonomic signs wane. Autonomic symptoms include swelling, temperature changes, erythematous or cyanotic color, and sweating asymmetry. Motor disturbances include severe spasm, various dystonias, postural and action tremors, and progressively limited range of motion. Sensory symptoms include hypesthesia, paresthesia, and severe allodynia. Pain increases when the limb is dependent and with activity, and in severe cases, even with passive range of motion. Trophic changes occur later in the course of the disease, including periarticular osteoporosis, glossy skin, nail and hair growth abnormalities, and contractures.

LABORATORY PROCEDURES
Diffusely increased technetium pyrophosphate uptake by bone scan occurs in RSD, especially in the lower limb, and this study can also exclude a focal inflammatory or infectious process. Autonomic testing of the affected limbs can also be useful to diagnose RSD.

IMAGING STUDIES
Comparative x-ray examinations of the limbs can demonstrate diffuse or local bone demineralization, and exclude a stress fracture. MRI of the limb can show deep tissue swelling and exclude other structural processes.

SPECIAL TESTS
Increased resting sweat output on the affected side is very specific for the diagnosis of RSD. Skin temperature measurements are useful to predict response to a sympathetic block.

MANAGEMENT

GENERAL MEASURES
Management is most successful when carried out early, in the first 5 months of the disorder. Since presentations are quite diverse, management must be tailored to the main obstacles preventing return to normal function. A rehabilitation program with training and education at its core is the cornerstone of successful management. The program should include psychological intervention to address pacing strategies, coping issues, and approaches to chronic pain. Physical therapy and occupational therapy can address physical and postural issues.

SURGICAL MEASURES
Spinal cord and deep brain stimulation can be of benefit in selected patients.

SYMPTOMATIC TREATMENT
Transcutaneous electrical nerve stimulation (TENS) units and nerve stimulation may be of benefit in selected patients. Lumbar sympathetic blocks as well as stellate ganglion blocks, though never proven effective, are still widely used for relief of pain in RSD. The greatest benefit is derived when they are used in the context of a pain management program.

ADJUNCTIVE TREATMENT
Acupuncture can be of benefit in selected cases.

ADMISSION DISCHARGE CRITERIA
N/A
Medications

**DRUGS OF CHOICE**
- **Corticosteroids:** A short trial of prednisone 60 mg for 5 to 7 days is often helpful and should be extended to 3 to 4 weeks if effective. It is most effective for early disease of the lower extremity. Patients with systemic fungal infections, allergy to glucocorticoids, and recent live virus vaccination should not be placed on chronic steroids.
- **Tricyclic antidepressants:** Most of the tricyclic antidepressants have some impact on RSD pain. Typically a nonseminating tricyclic is administered during the day such as imipramine or desipramine (in the elderly), with a sedating tricyclic agent such as amitriptyline or nortriptyline at night to aid sleep. The total tricyclic dosage usually begins at 20 to 30 mg and becomes maximally effective between 75 and 150 mg. Patients should not receive these medications if they have cardiac conduction defects (especially prolonged QT interval) or active suicidal ideation. Patients with tachy- or bradycardia, conduction block, Q-T interval prolongation, hypertension or hypotension, agitation, disorientation, hallucinations, dystonia, seizures, decreased secretions, urinary retention, mydriasis, and hyperthermia should be treated with caution.
- **Selective serotonin reuptake inhibitors:** Generally not used to treat pain directly, with the possible exception of venlafaxine, but can be very helpful in high doses to manage concomitant depression. May be used in double the usual dose to treat depression, to achieve the desired pain control.
- **Antiepileptic agents:** Nearly all agents have been tried, with intermittent success. Gabapentin, carbamazepine, topiramate, Gabitril, clonazepam, keppra, oxcarbazepine, and mexiletine have been beneficial in individual patients. Drugs should be started at the lowest available dose and advanced slowly. The only contraindication is allergy to the drug. All these agents can be associated with various types of cognitive deficits, tremors, ataxia, and other neurologic side effects.
- **Nonsteroidal antiinflammatory drugs:** Marginally helpful. When combined with other agents they can produce some added pain relief. They are seldom helpful in isolation. Maximal doses are usually necessary and the antiinflammatory precautions are always imperative.

Adrenergic agents: Clonidine decreases adrenergic transmission by activating presynaptic α2 receptors. A dosage of 0.1-0.3 mg bid may be effective; higher doses may be needed for improved control. Clonidine can be particularly effective when applied as a patch over an area of scar suspected to harbor an underlying neuroma. Side effects include dry mouth, nausea, dizziness, impotence, nightmares, anxiety, and depression. Phenoxybenzamine, another adrenergic agent, blocks both α1- and α2-adrenergic receptors, producing systemic sympathetic blockade through the oral route. Dosage must be advanced until the patient experiences mild symptoms of orthostasis (light-headedness), usually about 80 to 220 mg per day. This drug is most often effective when sympathetic blocks have produced pain relief. It can be used to prolong the effect of sympathetic blocks.
- **Calcitonin:** The only other agent with significant activity in the literature. It is typically administered in high doses intravenously. It is also available as an intranasal formulation.
- **Antispastic agents:** Baclofen, methocarbamol, tizanidine, Artane, and Sinemet can all be helpful for particular movement disturbances.

**ALTERNATIVE DRUGS**
- **Medications**
  - **International Research Foundation for RSD/CRPS:** www.rsdfoundation.usf.edu
  - **International RSD Foundation:**
  - **RSD Syndrome of America:** www.rsds.org

**Follow-Up**

**PATIENT MONITORING**

Once patients are taught self-management and are on a stable drug regimen (which may take approximately 6 months), they may continue regular follow-up with their primary care physician, with support from the pain specialist as needed.

**EXPECTED COURSE AND PROGNOSIS**

Patients with RSD may develop complications including infection (cellulitis), ulcers, chronic edema, dystonia, atrophy of muscles in the affected area, and deep venous thrombosis (if immobile). The longer the symptoms and duration of RSD, the poorer the prognosis.

**PATIENT EDUCATION**

Proper education for the patient and caregiver is essential. Continued passivity on the part of the patient and shopping for health professionals can prove extremely detrimental to long-term control of RSD symptoms. Web-based information sources:
- **International RSD Foundation:** www.rsdinfo.com
- **RSD Syndrome of America:** www.rsds.org
- **International Research Foundation for RSD/CRPS:** www.rsdfoundation.usf.edu

**SYNONYMS**

Complex regional pain syndromes (CRPS) type 1 or type 2

**ICD-9-CM:** 337.20 RSD; 337.22 RSD lower limb; 337.21 RSD upper limb

**REFERENCES**


**Author(s):** Thomas Chelimsky, MD
# Refsum's Disease

## Basics

**DESCRIPTION**

Sigvald Refsum initially described Refsum's disease in 1945. It is caused by defective metabolism of phytanic acid with subsequent accumulation. This can lead to impairment of function of a wide variety of bodily systems.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Refsum's disease is very rare. Exact incidence and prevalence rates are unknown but United Kingdom figures suggest a prevalence rate of 1/1,000,000. There may be a number of patients particularly with retinitis pigmentosa who are undiagnosed.

**Race**

The disease may be slightly more common in Scandinavian races and other racial groups with Nordic or Viking ancestry.

**Age**

The onset of symptoms is usually in late childhood.

**Sex**

Males and females are equally affected.

**ETIOLOGY**

Inheritance is autosomal recessive. The defective genes (PAHX) are on chromosome 10. Point mutations and deletions have been described. The single enzymatic deficiency in Refsum's disease affects phytanoyl CoA hydroxylase, which normally catalyzes the second step in the breakdown of phytanic to pristanic acid. This results in accumulation of phytanic acid with elevated levels in blood and other tissues including fat and neurons. The mechanism of phytanic acid toxicity is unclear.

**RISK FACTORS**

N/A

**PREGNANCY**

Pregnancy may be associated with acute and subacute presentations.

**ASSOCIATED CONDITIONS**

N/A

## Diagnosis

**DIFFERENTIAL DIAGNOSIS**

Phytanic acid accumulates in other conditions including Zellweger disease, neonatal adrenoleukodystrophy, infantile Refsum's, and rhizomelic chondrodysplasia punctata. However, these conditions have a different phenotype. Other enzymatic defects in the metabolic pathway of phytanic acid have also been described. Patients with a deficiency of a-methylacyl-CoA racemase have a Refsum's phenotype, but in that condition pristanate levels are also elevated, whereas in classical Refsum's the pristanate to phytanate ratio is <0.0001. Friedreich's ataxia, mitochondrial disease, other hereditary neuropathies, and vitamin E deficiency can usually be differentiated on clinical grounds.

**SIGNS AND SYMPTOMS**

The cardinal neurologic manifestations include a demyelinating neuropathy, pes cavus, sensorineural deafness, cerebellar ataxia, anosmia, and cranial nerve involvement. There may be marked nerve hypertrophy. Night blindness secondary to retinitis pigmentosa (RP) is common. RP and anosmia occur most frequently. Cardiac involvement may cause premature death usually secondary to arrhythmias. The skin is thickened and dry, and epiphyseal dysplasia and syndactyly may lead to a characteristic shortening of the fourth toe, which can be diagnostically useful. However, this latter feature is present in only 30% of patients.

**LABORATORY PROCEDURES**

Nerve conduction studies show evidence of a demyelinating neuropathy. CSF protein levels are often elevated. Plasma levels of phytanic acid are consistently elevated (normal range <194nmol/L) sometimes >800 µmol/L. Nerve biopsy is no longer particularly useful, but onion bulb formation and targetoid inclusions have been described.

**IMAGING STUDIES**

N/A

**SPECIAL TESTS**

N/A

## Management

**GENERAL MEASURES**

Phytanic acid is almost exclusively of exogenous origin, and dietary restriction reduces plasma and tissue levels. Fish, beef, lamb, and dairy products should be avoided. Poultry, pork, fruit, and vegetables are freely allowed. The diet should contain enough calories to prevent weight loss and consequent mobilization of phytanic acid from fat. Dietary treatment needs to be lifelong.

**SURGICAL MEASURES**

Cataract surgery and orthopedic correction of foot deformities may be necessary in some patients.

**SYMPTOMATIC TREATMENT**

N/A

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

N/A

**IMAGING STUDIES**

N/A

**SPECIAL TESTS**

N/A
Refsum's Disease

Medications

**DRUG(S) OF CHOICE**

N/A

**ALTERNATIVE DRUGS**

N/A

Follow-Up

**PATIENT MONITORING**

Patient should be assessed at regular intervals by a neurologist. Ophthalmologic, audiologic, and dietary advice is often helpful.

**EXPECTED COURSE AND PROGNOSIS**

The neurologic, cardiac, and dermatologic sequelae usually can be reversed to some extent by lowering plasma phytanic acid levels. The visual and hearing deficits and anosmia are less responsive to treatment. Pregnancy, rapid weight loss, and fever may be associated with rapid deterioration. Life expectancy is not significantly reduced.

**PATIENT EDUCATION**

Dietary surveillance needs to be lifelong. There is a Refsum's clinic at the Chelsea and Westminster Hospital, London, UK (phone: 0-044-2082372730).

Miscellaneous

**SYNONYMS**

Heredoataxia hemeralopica polyneuritiformis
Heredopathia atactica polyneuritiformis
HMSN IV.

**ICD-9-CM:** 356.3 Refsum's disease

**SEE ALSO:** PEROXISOMAL DISORDERS

**REFERENCES**


**Author(s):** Adrian J. Wills, MD
Restless Leg Syndrome

DESCRIPTION

Restless leg syndrome (RLS) is a disorder characterized by uncomfortable sensations in the calves or feet and, rarely, the upper extremities. The sensations are variously described as painful, tingling, crawling, or “pins and needles.” Typically, the sensations begin late in the evening around bedtime and may present as insomnia. However, patients may be awakened by the sensations or they may occur earlier in the day and may interfere with sedentary work or driving. The uncomfortable sensation is immediately quenched by movement of the extremity but frequently returns when movement ceases.

EPIDEMIOLOGY

Incidence/Prevalence

RLS is thought to affect 2% to 5% of the population. There appears to be no racial preference. Age Although the syndrome tends to appear in middle age, symptoms are frequently present for many years prior to presentation.

Sex

Men and women are affected equally.

ETIOLOGY

Etiology is unknown. RLS occurs as an idiopathic form without evidence of any other disease process and as secondary or symptomatic disease in association with several other medical conditions. Some researchers theorize that some of the manifestations of RLS result from disinhibition of descending inhibitory spinal pathways. In addition, the response of many patients to dopaminergic medications suggests that there may be a dysregulation of dopaminergic pathways in the brainstem or spinal cord.

Genetics

Approximately 50% of patients with RLS describe relatives with similar symptoms, suggesting a genetic factor, although the high prevalence of this condition in the general population may make this simply a chance happening. In contrast, families have been described with multiple members clearly affected in a pattern suggestive of autosomal-dominant inheritance. A French-Canadian family was reported with apparent autosomal-recessive mode of inheritance and several candidate locations on chromosome 12.

RISK FACTORS

No known risk factors.

PREGNANCY

Symptoms of RLS have been reported in 10% to 20% of pregnant women and usually resolve after delivery.

ASSOCIATED CONDITIONS

In addition to pregnancy, RLS has also been shown to be associated with iron deficiency with or without anemia and chronic renal failure (especially patients on dialysis). There also appears to be a higher frequency in patients with Parkinson's disease, peripheral neuropathy, and radiculopathy. Tricyclic antidepressants as well as fluoxetine, caffeine, and verapamil have all been demonstrated to increase symptoms of RLS. Other conditions with less well-established associations include:

- Magnesium deficiency
- Folate deficiency
- Rheumatoid arthritis
- Diabetes

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Nocturnal leg cramps: tend to have an abrupt onset at night and may awaken the patient from sleep. They are painful, tend to be located in the calf or foot, and are accompanied by visible and palpable muscle cramps.
- Fibromyalgia: symptoms tend to occur throughout the day, are not improved by movement, and usually involve more widespread areas of the body (neck, shoulders, and hips).
- Radiculopathy
- Neuropathy/claudication
- Akathisia (neuroleptic induced): this syndrome of restlessness with a compulsion to move is seen most commonly with phenothiazine use or in association with Parkinson's disease. In contrast to RLS, the sensory features are less and are more likely to affect the entire body as opposed to the extremities. Symptoms are less prominent at night, and consequently there is less sleep disturbance.
- Small-fiber polyneuropathies: in contrast to RLS, small-fiber polyneuropathies are usually associated with distal sensory loss or abnormal reflexes.
- Painful legs and moving toes syndrome: usually described as aching pain in the feet or toes associated with involuntary writhing movements. The movements are not increased during the evening and night and therefore are not associated with a sleep disturbance.
- Vesper's curse: this is the sudden awakening from sleep with painful calf cramps and fasciculations, frequently with the urge to move. An increase in right atrial filling pressures with subsequent increase in paraspinal venous volume associated with lumbar stenosis has been cited as the cause.

SPECIAL TESTS

- Although 80% to 90% of patients with RLS have frequent periodic limb movements (PLMs) during sleep, polysomnography is of little diagnostic value because of the frequency of PLMs in patients without RLS. Thus the diagnosis of RLS is clinical, based on the presence of dysesthesias of the limbs with the desire to move the extremity, motor restlessness, and worsening of the symptoms at rest or at night.
- NCV/EMG should be considered if there is any evidence of distal sensory loss or diminution of reflexes.

LABORATORY PROCEDURES

CBC, electrolytes, BUN and creatinine, vitamin B12, folate, iron, and ferritin.

IMAGING STUDIES

None

SIGNS AND SYMPTOMS

Diagnostic criteria put forth by the International Restless Legs Syndrome Study Group in 1995 include:

- Desire to move the extremities in association with unpleasant sensations in the calves or feet (and occasionally the upper extremities). These unpleasant sensations are variable and described as a deep burning, tingling, cramping, achling, or itching.
- Motor restlessness: people with RLS feel a compelling urge to move a limb but do have some choice of which type of movement to perform. The spectrum of movements includes walking, pacing, rocking, shaking, stretching, etc.
- Symptoms are worse at rest with partial and temporary relief with movement, but recur as soon as the patient stops moving and rests.
- Symptoms are worse in the evening or at night, worsening to a peak around midnight and then improving in the morning. These movements may prevent or fragment sleep.
- Although the syndrome is chronic, there is tremendous fluctuation in the intensity of symptoms. Patients may go weeks or months without symptoms followed by nightly occurrences. There is some evidence that stress may play a role as symptoms tend to be more severe at the end of the work week.
Management

GENERAL MEASURES
The mainstay of treatment is the use of various medications that reduce the uncomfortable symptoms of RLS (see below). There is some evidence that daily vigorous exercise may improve the symptoms of RLS. Also, reduction or the elimination of caffeine may be of benefit.

SURGICAL MEASURES
None

SYMPTOMATIC TREATMENT
• Avoid tobacco products, alcohol, antinausea medications, neuroleptics.
• Avoid sleep deprivation.
• Some patients find a massage or stretching helpful before sleep.
• Hot baths or cold or hot compresses to the limbs.

ADJUNCTIVE TREATMENT
None

ADMISSION/DISCHARGE CRITERIA
N/A

Medications

DRUG(S) OF CHOICE
• Levodopa/carbidopa: historically, levodopa/ carbidopa has been the treatment of choice for RLS. The starting dose is 100 mg levodopa and 25 mg carbidopa. Most patients can be controlled with doses of 200 mg of levodopa. Unfortunately, two major problems can occur with this drug. First, many patients will suffer a recurrence of symptoms during the night. In this setting, a second dose can be taken or consideration given to using a sustained release form of L-dopa. However, this preparation tends to be less efficacious. A second problem that may occur with L-dopa, particularly when a second dose is taken, is the onset of paresthesias and restlessness during the day. In this setting, a prolonged trial of a benzodiazepine (clonazepam) may be beneficial. Tardive dyskinesia, a possible long-term side effect of L-dopa, does not usually appear in patients with RLS. However, tolerance to the beneficial effects of the drug also may develop.
• Dopamine agonists: if levodopa/carbidopa becomes ineffective, changing to a dopamine agonist such as pergolide (0.05 mg at bedtime with increase by 0.1 mg every third day) or bromocriptine (2.5 or 5 mg at bedtime) may prove effective. It appears that the daytime occurrence of RLS symptoms is less with the dopamine agonists.
• Other agents that have proven to be effective in the treatment of RLS include the anticonvulsants gabapentin and carbamazepine. Of these, gabapentin has probably been most effective in doses of 300 to 1,000 mg at bedtime.

Contraindications
• Hypersensitivity to levodopa/carbidopa products
• History of melanoma, undiagnosed skin lesions
• Narrow-angle glaucoma
• Nonselective MAO inhibitors

Precautions
There is a 10% incidence of orthostatic hypotension with use of the dopamine agonists.

ALTERNATIVE DRUGS
Benzodiazepines, and specifically clonazepam (0.5 to 2 mg at bedtime), have been shown to be effective at reducing the symptoms of RLS and improving subjective sleep quality, but the major drawback to these drugs is daytime sedation, particularly in the elderly. Finally, opioids (propxyphene 65 mg, hydrocodone 5 mg, codeine 30 mg) have long been recognized to reduce the symptoms of RLS and improve sleep quality, but the risks of these medications need to be considered.

Follow-Up

PATIENT MONITORING
Polysomnography is of little use in RLS. Therefore, clinical assessment with questioning both the patient and bed partner about the quality of sleep as well as the presence of daytime sleepiness is indicated on a regular basis.

EXPECTED COURSE AND PROGNOSIS
In general the prognosis is good. However, RLS is a lifelong condition, although the intensity of symptoms tends to fluctuate greatly.

PATIENT EDUCATION
Because of the relatively high prevalence of this disorder, numerous support groups are available, such as WEMOVE, website: www.wemove.org.

Miscellaneous

SYNONYMS
None

ICD-9-CM: 333.99 Extrapyramidal disease NEC

SEE ALSO: N/A

REFERENCES

Author(s): Jeffrey Weiland, MD
Rhabdomyolysis

**DESCRIPTION**
Rhabdomyolysis is the acute lysis of skeletal muscle. This often causes the release of myoglobin into the circulation and then into the urine, resulting in myoglobinuria.

**EPIDEMIOLOGY**
Incidence/Prevalence
Because of the many causes of rhabdomyolysis, the exact incidence is unknown.

**ETIOLOGY**
Many hereditary and acquired diseases may cause rhabdomyolysis, but the most frequent cause is crush injuries. Malignant hyperthermia is a rare cause of rhabdomyolysis associated with certain types of inhaled anesthetics. Although traumatic injury is the most frequent cause of a single episode of rhabdomyolysis, many toxins, drugs, infections, and metabolic derangements may induce the syndrome.

**Genetics**
The main hereditary disorders that cause rhabdomyolysis are due to inborn errors of metabolism affecting carbohydrate and lipid metabolism within the muscle. The glycolytic defects include deficiencies in muscle phosphohexose isomerase (McArdle's disease), phosphorylase b kinase, phosphofructokinase, phosphoglycerate mutase, phosphoglycerate kinase, and lactate dehydrogenase. Lipid metabolism defects may also cause recurrent rhabdomyolysis, with the most common being carnitine palmitoyltransferase deficiency. Defects in long, medium, and short chain fatty acids oxidation may also cause recurrent rhabdomyolysis. More recently, rhabdomyolysis with mitochondrial and respiratory chain disorders have been described. Other biochemical defects can cause recurrent episodes including deficiencies of glucose-6-phosphate dehydrogenase and myoadenylate deaminase. Dystrophinopathies such as Duchenne's muscular dystrophy and Becker's muscular dystrophy are sometimes associated with rhabdomyolysis.

**RISK FACTORS**
Hereditary causes of rhabdomyolysis are often precipitated by brief, intense exercise or fasting. Malignant hyperthermia is precipitated by the inhaled anesthetic halothane. Traumatic crush injury may damage the muscle directly, but may also cause ischemia to the muscle, resulting in muscle infarctions. Extreme muscle exertion, even in well-conditioned individuals, may cause rhabdomyolysis. Drugs associated with rhabdomyolysis include alcohol, cocaine, heroin, phenycyclidine, amphetamines, phenylpropanolamine, and toluene. Lipid-lowering agents, especially in combination with fibrates, may cause rhabdomyolysis. Snake and insect venoms often cause rhabdomyolysis. Rapid withdrawal of dopaminergic agents may induce a neuroleptic malignant syndrome with rhabdomyolysis.

**PREGNANCY**
Pregnant women with carnitine palmitoyltransferase deficiency or myophosphorylase deficiency may benefit from intravenous glucose at the time of delivery.

**ASSOCIATED CONDITIONS**
- Acute renal failure
- Renal tubular acidosis
- Hyperkalemia
- Hypocalcemia
- Compartment syndromes

**DIFFERENTIAL DIAGNOSIS**
Other causes of pigmenturia such as hematuria, hemoglobinuria and porphyria. A history of recurrent pigmenturia suggests an inborn error in metabolism.

**SIGNS AND SYMPTOMS**
Rhabdomyolysis that causes myoglobinuria often causes severe myalgias and muscle swelling. Often the patient is unable or unwilling to move due to the severe myalgias. Nausea and vomiting are often present. If an injury has occurred to a well-localized area, a compartment syndrome may develop, causing further damage to the muscle secondary to ischemic as the internal pressures within the muscle compartment rise. Compartment syndrome may lead to arterial and nerve compression with near irreversible damage to the limb. A drop in urine output is a warning of impending renal failure. With rhabdomyolysis, large releases of potassium from the muscle may cause cardiac arrhythmias. Disseminated intravascular coagulation is a rare complication.

**LABORATORY PROCEDURES**
Pigmenturia is present when concentrations of urine myoglobin are greater than 100 µg/mL. Serum levels of creatine kinase (CK) peak within the first 2 days after the onset of the illness. Hyperkalemia and hyperphosphatemia with hypocalcemia are often present.

**IMAGING STUDIES**
N/A

**SPECIAL TESTS**
If the history suggests recurrent episodes of rhabdomyolysis, a muscle biopsy with routine histochemistry and quantitation of enzymes associated with rhabdomyolysis should be done. This can be done after the acute episode has resolved.
**Management**

**GENERAL MEASURES**

The patient should be put to bed rest during the acute phase. The major complications of rhabdomyolysis include renal failure, hyperkalemia, and hypocalcemia. Renal failure can often be prevented with fluid replacement to avoid hypotension and intravenous mannitol or furosemide to maintain urine output. Alkalization of the urine with intravenous sodium bicarbonate promotes the excretion of myoglobin. Hemodialysis is needed if urine output fails despite these efforts. Hyperkalemia needs to be managed with electrocardiogram monitoring and intravenous glucose and insulin.

**SURGICAL MANAGEMENT**

Compartment syndrome requires emergent fasciotomy to prevent further ischemia to the muscle and nerve injury.

**SYMPTOMATIC TREATMENT**

Myalgias often respond to intravenous fluid replacement, but narcotic analgesics may be helpful.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

Patients should be admitted for observation and monitoring of renal function until the severity of the episode is determined.

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**Medications**

**DRUG(S) OF CHOICE**

N/A

**ALTERNATIVE DRUGS**

N/A

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**Follow-Up**

**PATIENT MONITORING**

Maintenance of urine output and management of hyperkalemia are key features for the first several days after the onset of the illness.

**EXPECTED COURSE AND PROGNOSIS**

Most patients recover fully with no lasting effects on their muscle strength if renal failure is avoided. Patients with inborn errors of metabolism or a dystrophinopathy may develop muscle weakness late in life due to recurrent muscle injury.

**PATIENT EDUCATION**

Precipitating factors need to be avoided.

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**Miscellaneous**

**SYNONYMS**

Myoglobinuria

**ICD-9-CM:** 791.3 Myoglobinuria

**SEE ALSO:** N/A

**REFERENCES**


**Author(s):** J. Ned Pruitt II, MD
Rheumatoid Arthritis, Neurologic Complications

**Basics**

**DESCRIPTION**
Rheumatoid arthritis (RA) is a chronic multisystem immune complex disease. Extraarticular manifestations occur in 10% to 20% of patients. Neurologic complications usually occur in patients with moderate to severe RA and can involve the CNS and PNS, including the spine. Chronic synovitis of the spine typically occurs in the cervical region, with damage to the atlantoaxial complex. Complications affecting the PNS are frequent, with carpal tunnel syndrome (CTS; compression neuropathy of the median nerve) being most common.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
RA affects 1% to 2% of the population. Cervical spine involvement occurs in 30% to 50% of all RA patients. CTS occurs in 20% to 65% of RA patients. Vasculitis is noted in 5% to 15% of all patients. CTS occurs in 20% to 65% of RA patients. CNS vasculitis and RA nodules are uncommon.

**Race**
All races and ethnic groups are affected. Age
Onset is usually between 35 and 50 years of age, but can occur at any age.

**Sex**
There is a female predilection, accounting for 75% of cases of RA.

**ETIOLOGY**
RA is mediated by interaction of autoantibodies, such as rheumatoid factor (IgM or IgG class), with circulating immunoglobulins. The immune complexes are composed of IgG combined with IgM or IgG anti-IgG antibodies. Deposition of the immune complexes into the joints and soft tissues induces activation of complement and other inflammatory pathways. Atlantoaxial subluxation (AAS) results from rheumatoid synovial tissue-inflamed synovial sacs and can affect the median, ulnar, and posterior tibial nerves.

**Genetics**
There can be a genetic predisposition for RA; first-degree relatives of seropositive patients are four times more likely to develop RA than controls.

**RISK FACTORS**
AA is more likely in patients with RA of 10 years' duration or longer, seropositivity, erosive and deforming peripheral joint disease, and male gender. Compression neuropathies correlate with the severity of local synovitis. Vasculitis is more likely to occur in patients with long-standing RA; the incidence is higher in males.

**PREGNANCY**
A hormonal role is suspected in disease expression, because there is an increased risk of RA in nulliparous women and a possible protective effect in women who use oral contraceptives.

**ASSOCIATED CONDITIONS**
There is a higher incidence of vasculitic complications in RA patients with Felty's syndrome (i.e., RA, splenomegaly, neutropenia, anemia, and thrombocytopenia).

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
The differential diagnosis is broad and includes other causes of myelopathy, cervical subluxation disorders, CNS and PNS vasculitis, entrapment neuropathies, and peripheral neuropathy. RA must be distinguished from degenerative osteoarthritis and from deforming inflammatory arthritis associated with other connective tissue disorders.

**SIGNS AND SYMPTOMS**

**Spine Involvement**
In most cases AAS is asymptomatic, despite the radiologic appearance. Cord and nerve compression is more likely to occur if there is an atlanto-dens interval of greater than 9 mm. Compression of the second spinal nerve roots often causes localized neck pain with radiation to the occiput and scalp. Early signs of cervical radiculopathy are numbness and paresthesias in the glove-stocking distribution. Later signs of progression to cord compromise include myelopathy, lower motor neuron injury at the level of compression, and gait difficulty. Lhermitte's sign (sudden tingling paresthesias that radiate down the spine after cervical flexion) can occur at any stage. Intrudal spinal nodules can cause nerve root compression, spinal stenosis, and cord compression.

**CNS Involvement**
Intraparenchymal rheumatoid nodules can cause encephalopathy, seizures, and obtundation. Cerebral vasculitis can present with seizures, stroke syndromes, encephalopathy, cranial neuropathies, ataxia, and hemorrhage (intracerebral or subarachnoid).

**PNS Involvement**
CTS typically presents with night numbness, paresthesias, and pain in the thumb, index, and middle fingers of the affected hand. In severe cases, atrophy of the thenar muscles may be present, along with thumb weakness, and retrograde pain up the forearm. Tinel's sign is often positive—reproduction of symptoms elicited by percussion of the median nerve on the volar aspect of the wrist. Phalen's sign may also be present—flexion of the wrist for at least 1 minute, eliciting numbness, tingling, or pain in the median nerve distribution. Tarsal tunnel syndrome presents as paresthesias, pain, and burning in the toes and soles of the feet. Weakness and atrophy of the intrinsic toe muscles may occur.

Other PNS manifestations of RA include mild and severe forms of sensorimotor polyneuropathy, as well as a mononeuritis multiplex.

**LABORATORY PROCEDURES**
Serologic testing for rheumatoid factor and other autoantibodies is necessary.

**IMAGING STUDIES**
- To evaluate spinal involvement, lateral radiographs of the cervical spine (flexion and extension views) are required to demonstrate subluxation. Lateral AAS can be demonstrated on open-mouthed, anteroposterior views. MRI can further evaluate bony spinal degeneration and screen for spinal cord compression. MRI is also indicated for patients with suspected basilar invagination for whom standard radiographs are inconclusive. A dynamic flexion-extension MRI may be able to reveal subtle instability patterns (e.g., atlantoaxial instability) of the spinal column.
- MRI (with or without MR angiography) can be helpful for the diagnosis of CNS vasculitis.

**SPECIAL TESTS**
Somatosensory evoked potentials can evaluate the functional integrity of central sensory pathways. Disease processes affecting the cervical spinal cord may produce prolongation of wave and intacneve latencies recorded along these pathways. EMG and sensory nerve conduction studies are the most accurate method to diagnose compression neuropathies and peripheral neuropathies. Surat nerve biopsies can be helpful if the diagnosis of vasculitis is unclear.
Rheumatoid Arthritis, Neurologic Complications

Management

GENERAL MEASURES
• For patients with AAS, surgical intervention with SURGICAL MEASURES
• For patients with cervical spine disease, neck GENERAL MEASURES
• Surgical release of compression neuropathy may
• Rheumatoid vasculitis is a potentially life-threatening problem that requires high-dose corticosteroids in combination with a cytotoxic drug such as oral cyclophosphamide or methotrexate.

SURGICAL MEASURES
• For patients with AAS, surgical intervention with C1-2 arthrodesis stabilizes the atlantoaxial complex and usually eliminates occipital pain. The indications for surgery include basilar invagination, neurologic abnormality with spinal instability, intractable neck and head pain, vertebral artery compromise, and asymptomatic spinal cord compression on MRI.
• Surgical release of compression neuropathy may be indicated when there is a significant motor or sensory abnormality and evidence of denervation on neurophysiologic testing.

SYMPTOMATIC TREATMENT
Soft cervical collars can stabilize the spine and reduce neck pain in patients with severe AAS. Local corticosteroid injections and splints may be of benefit for compression neuropathies.

ADJUNCTIVE TREATMENT
Simple neck traction may be helpful in patients with severe AAS. Physical and occupational therapy should be considered for patients with myelopathy, peripheral neuropathy, and other forms of weakness.

ADMISSION/DISCHARGE CRITERIA
Admission is uncommon except in cases of acute neurologic deterioration, where the diagnosis is indeterminate or therapeutic intervention is necessary. Patients with CNS or PNS vasculitis are the most likely subgroup to require admission, usually for weakness, seizures, encephalopathy, gait dysfunction, or other acute complications.

Medications

DRUG(S) OF CHOICE
Pharmacotherapy of neurologic manifestations of RA consists of a combination of corticosteroids and a cytotoxic agent, such as oral cyclophosphamide or methotrexate. The corticosteroid is started at 60 to 100 mg per day and then tapered over several weeks. Monotherapy with one of the cytotoxic agents is then continued for long-term maintenance therapy. The efficacy of other immunosuppressive therapies such as plasmapheresis and intravenous immunoglobulin (IVIG) is unknown.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
RA patients who should be screened for AAS with radiographic evaluation include those with posterior skull and/or neck pain and stiffness, and patients with long-standing erosive RA in whom radiographs have not been done within the previous 2 or 3 years. Serial neurologic examinations and appropriate follow-up testing (e.g., MRI of the brain or spine, EMG, and nerve conduction testing) is necessary.

EXPECTED COURSE AND PROGNOSIS
The best course of management is to prevent significant morbidity in RA. Aggressive immunosuppressant therapy reduces the neurologic complications of RA. The overall 5-year mortality rate of RA patients with radiographic evidence of cervical subluxation (with or without neurologic symptoms) is similar to that of severe RA patients without cervical involvement. The risk of developing upper cervical spinal cord compression secondary to anterior AAS is increased by male sex, anterior subluxation >9 mm, and coexistent atlantoaxial impaction. There is a higher incidence of fatality with basilar invagination. The prognosis of rheumatoid vasculitis is poor. Independent variables that best predict mortality include cutaneous vasculitis, multifocal neuropathy, and depressed C4 level.

PATIENT EDUCATION
• National Institute of Arthritis and Musculoskeletal Disorders: www.niams.nih.gov
• Arthritis Foundation Home Page: www.arthritis.org

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SYNONYMS
N/A

ICD-9-CM: 714.0 Rheumatoid arthritis; 354.0 Carpal tunnel syndrome; 336.9 Myelopathy—spinal cord; 454.1 Vasculitis—cerebral; 447.6 Vasculitis—disseminated

SEE ALSO: VASCULITIS, MYELOPATHY, PERIPHERAL NEUROPATHY

REFERENCES

Author(s): Doruk Erkan, MD; Stephen A. Paget, MD; Herbert B. Newton, MD
**Basics**

**DESCRIPTION**
Sarcoidosis is a chronic disorder of unknown etiology characterized by multisystem dissemination of noncaseating granulomas. Approximately one third of patients with involvement of the CNS have no other known systemic involvement. Sarcoidosis can affect all parts of the nervous system including the brain, spinal cord, and peripheral nerves, as well as muscle.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
Worldwide incidence ranges from 1 to 64 per 100,000. The disorder is thought to be more frequent in the southeastern part of the United States.

**Race**
There appears to be significantly more involvement of African Americans, with a tenfold increase compared to Caucasians in the southeastern part of the United States.

**Age**
Occurs in all ages.

**Sex**
A slight preponderance is reported in females.

**ETIOLOGY**
The cause of this disorder is unknown. Abnormalities of immune regulation in the genetically susceptible individual induced by an as yet unidentified environmental agent is the prevailing hypothesis.

**Genetics**
A genetic basis for this disease is speculated, but no specific gene has been identified.

**RISK FACTORS**
There are no known risk factors for this disorder. However, for reasons that are unclear, the disorder favors the nonsmoker.

**PREGNANCY**
Specific information regarding pregnancy is tacking. Anecdotal reports of remissions as well as flare-ups during pregnancy have been reported.

**ASSOCIATED CONDITIONS**
None. However, patients with sarcoidosis can have increased susceptibility to mycobacterial infections.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
Neurologic dysfunction in sarcoidosis is due to granulomas that act as space-occupying lesions. The granulomas themselves are non-toxic and do not usually elicit any inflammatory response in the adjoining brain. Entities to be considered include infectious disorders such as cryptococcosis, histoplasmosis, coccidioidomycosis, tuberculosis, syphilis, and Lyme disease; inflammatory disorders including vasculitis and berylliosis; and malignancies such as meningial carcinomatosis, primary lymphoma of the CNS, metastatic disease, and gliomatosis cerebri.

**SIGNs AND SYMPTOMS**
In the CNS sarcoidosis affects the basal meninges and the area around the third ventricle, including the thalamus, hypothalamus, and hypophysis. Patients may present with features of meningitis. Multiple cranial nerve palsies are common, especially unilateral or bilateral Bell’s palsy. Recent seventh nerve palsy of the lower motor neuron type, especially when bilateral, should suggest sarcoidosis. Optic neuritis occurs, especially in the form of papillitis. Hypothalamic and hypophysial involvements are especially common, and can manifest as the syndrome of inappropriate secretion of vasopressin or diabetes insipidus. Almost half of patients with CNS sarcoidosis develop hyperprolactinemia with secondary galactorrhea in either sex. When involved, the spinal cord is usually enlarged with evidence of an intramedullary mass and resultant compressive myelopathy and its clinical manifestations. Rarely, sarcoidosis can affect the peripheral nervous system in isolation. The symptoms of peripheral nerve involvement are due to the space-occupying nature of the granulomas that result in expansion of the nerves and sometimes compression. Muscle involvement in systemic sarcoidosis is common. Often, the muscle can be a useful site for biopsy for demonstration of the sarcoid granuloma.

**LABORATORY PROCEDURES**
Since meningeal involvement is common, CSF evaluation is particularly helpful. CSF pressure is usually normal. Fluid is colorless unless associated with elevated spinal fluid protein, which causes xanthochromia. Moderate to severe pleocytosis is common, causing some concern of an infectious process. Total WBC counts can be around 100/mm³. Most cells are mononuclear and of the T-cell type, mostly of the CD4 phenotype. Sore B cells are evident as well. Increased production of intrathecal IgG is common with abnormally elevated IgG index and the presence of oligoclonal bands. Measurement of a angiotensin-converting enzyme (ACE) levels in the CSF is of limited value since this enzyme can be transported from serum into CSF across an intact blood–brain barrier. Accordingly when serum ACE levels are elevated, CSF levels may go up as well, although there may not be any evidence of CNS involvement by other studies. Conversely, CSF ACE levels can be normal in patients with isolated spinal cord or brain sarcoid granulomas. In every patient with suspected sarcoidosis of the CNS, evaluation should be done to identify multisystemic involvement. This may include measurement of serum ACE levels, liver enzyme levels, bronchoalveolar lavage with phenotyping of the washed cells, and liver or lung biopsy or biopsy of enlarged lymph nodes.

**IMAGING STUDIES**
Granulomatous involvement of the meninges and parenchyma of the brain and spinal cord can be readily detected by MRI. Detection can be improved with the use of gadolinium, which can show enhancement of the meninges affected by the sarcoid granuloma as well as parenchymal lesions with disruption of the blood-brain barrier. CT of the brain does not have any role in diagnosis of this disorder because of low sensitivity to detect sarcoid lesions.

**SPECIAL TESTS**
There are no special tests for diagnosis of sarcoidosis of the CNS. In the absence of systemic sarcoidosis, biopsy is the only method of diagnosis. In a third of patients with CNS, sarcoidosis such methods may be necessary.
Sarcoidosis, Neurologic Complications

GENERAL MEASURES
The focus of treatment is corticosteroid therapy as well as supportive measures necessary and appropriate to the mode of presentation. Accordingly, encephalopathic patients may require correction of electrolyte imbalance if the problem was related to alteration of electrolytes secondary to diabetes insipidus or syndrome of inappropriate antidiuretic hormone (SIADH). A patient presenting with seventh nerve paresis may require attention to prevent exposure keratitis. Patients with myelopathy may require attention to bowel and bladder function and emergent treatment with steroids to treat compressive myelopathy.

SURGICAL MEASURES
Surgery is not necessary for diagnosis unless the clinical presentation is confusing and the sarcoidosis is confined to the nervous system. In such instances biopsy of the lesion or basal meninges may be necessary to make the diagnosis. When the granuloma is located in the spinal cord, often masquerading as a tumor, excision of the Lesion may be necessary.

SYMPTOMATIC TREATMENT
None specific for neurosarcoidosis.

ADJUNCTIVE TREATMENT
Adjunctive therapy to reduce steroid complications is necessary. Diphosphonate therapy to reduce loss of bone mass, H2 Mockers for prevention of peptic acid disease, and when appropriate, use of trimethoprim with sulfa for chemoprophylaxis against Pneumocystis cannni should be considered.

ADMISSION/DISCHARGE CRITERIA
Admission is necessitated by clinical status of the patient, often dictated by the nature of involvement, such as altered mental status from encephalopathy, spinal cord involvement with paresis, etc.

DRUGS OF CHOICE
Corticosteroids are the mainstay of treatment of sarcoidosis, and neurosarcoidosis is no exception. Acutely, patients may be treated with intravenous steroids for disorders that require immediate resolution, such as optic neuritis, transverse myelitis, encephalopathy secondary to diabetes insipidus, or SIADH. Methylprednisolone is administered in doses of 500 to 1,000 mg in D5/0. 45 N saline daily for 3 to 5 days. Oral prednisone may be necessary in severe cases and is used in doses of 1 mg/kg daily or every other day, best administered, as a single oral dose in the morning. There are no good controlled studies that have examined the dose, route of administration, or duration of treatment necessary for neurosarcoidosis. The duration of treatment can vary from 3 to 18 months, depending on the response and steroid dependence exhibited by these patients.

Contraindications
Corticosteroids are contraindicated in cases of known hypersensitivity or allergy. Steroids should be used with caution in patients with hypertension, diabetes, or known history of gastroduodenal ulceration. However, these conditions are not absolute contraindications for treatment with glucocorticoids since additional therapeutic measures can be instituted to permit their use.

Precautions
Corticosteroid treatment can be associated with glucose intolerance and steroid-induced diabetes. In rare individuals, aseptic necrosis of the femur can occur with need for surgical replacement of the femoral head with prosthesis. Daily treatment for prolonged periods can result in adrenal insufficiency, which can be minimized with alternate day regimen.

ALTERNATIVE DRUGS
A number of drugs have been used as adjunctive therapy with steroids to reduce the granuloma load and to reduce the doses of steroids required. These include methotrexate, cyclosporine, cyclophosphamide and, less often, indomethacin, chloroquine, allopurinol, and levarminole. There are no good studies that have documented the usefulness of any of these agents.

PATIENT MONITORING
Patients should be monitored for corticosteroid-induced complications as well as response to treatment. Cushingoid side effects can be minimized by reduction of oral salt intake. Patients should be instructed on a low-carbohydrate diet to minimize weight gain as well as glucose intolerance. ACE levels are often not elevated, and therefore seldom helpful in monitoring treatment. The best guide to effective treatment is the clinical response of the individual patient. Imaging with gadolinium-enhanced MRI can be helpful.

EXPECTED COURSE AND PROGNOSIS
Excellent resolution of the symptoms can be expected in the short term with corticosteroid therapy. Patients with extensive basal meningeal disease, endocrinopathy, or spinal cord granulomas often require more chronic therapy. With long-term therapy prognosis for complete resolution is often excellent.

PATIENT EDUCATION
Patients on chronic steroid therapy should be instructed to maintain a 1-g sodium and 1,500- to 2,000-calorie low-carbohydrate diet to minimize weight gain and cushingoid side effects.

SYNONYMS
Hutchinson’s disease
Boeck’s disease
Uveoparotid fever
Heerfordt’s disease

ICD-9-CM: 135 Sarcoidosis; additional codes may apply according to areas of involvement such as meningitis (322.9), encephalitis (323.9), transverse myelitis (323.9), cranial neuropathy (facial paresis 351.8, ocular paresis 378.52, 378.53, and 378.54), optic neuritis/papillitis (377.3), endocrinopathy, myopathy (359.9), neuropathy (355.9).

SEE ALSO: N/A

REFERENCES
Kottil W. Rammohan, MD
Obstruction of the airway causes apnea or partial or complete upper airway obstruction during sleep. In addition, the growing body of evidence that untreated OSA has serious long-term cardiovascular effects, OSA also has public health ramifications, largely due to its effects on driving and workplace performance.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

OSA is estimated to affect 2% of women and 4% of men over the age of 50. The prevalence is somewhat lower in younger populations, though it has been reported to affect even very young children, largely due to congenital upper airway abnormalities. At least one series suggests that a significant minority of OSA occurs in patients without the “typical” body habitus.

**Race**

OSA has no well-established racial predilection.

**ETIOLOGY**

- Partial or complete upper airway obstruction during sleep is the crucial event in the genesis of OSA. The physiologic decrease in pharyngeal muscle tone seen in all sleeping persons is a major contributor, though this effect alone is generally inadequate to cause symptomatic obstruction. Sedative drugs and alcohol accentuate the decrease in muscle tone and can worsen the occlusion. Most patients also have anatomic upper airway narrowing, usually related to the pharyngeal infolding of fat seen in obesity. Retrognathia, macroglossia, and abnormally large tonsils, soft palate or uvula are other abnormalities that are sometimes seen. Additionally, posterior movement of the tongue in the supine sleeper narrows the airway further.

- Obstruction of the airway causes apnea or hypopnea in the face of repeated respiratory efforts, oxyhemoglobin desaturation, and ultimately, arousal. Arousal then increases muscle tone in the upper airway, relieving the obstruction. Arousal is usually partial, and may occur more than a hundred times per hour, leading to fragmented sleep.

**DESCRIPTION**

Obstructive sleep apnea (OSA) is a severely underdiagnosed disorder characterized by intermittent nocturnal upper airway occlusion. This occlusion causes loud, irregular snoring, hemoglobin desaturation, and recurrent arousals from sleep. In addition to its impact on patient well-being, there is a growing body of evidence that untreated OSA has serious long-term cardiovascular effects. OSA also has public health ramifications, largely due to its effects on driving and workplace performance.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of OSA includes simple snoring, central sleep apnea, narcolepsy, insufficient sleep, idiopathic CNS hypersomnia, periodic limb movement disorder, psychiatric disorders, and alcohol or sedative drug use.

**SIGNS AND SYMPTOMS**

Loud, irregular snoring and daytime hypersomnolence are the hallmarks of OSA. Patients commonly awaken in the morning unrefreshed, and often describe falling asleep during quiet activities, such as reading, watching TV, or driving. A history from the patient’s bed partner is crucial, and often reveals witnessed episodes of apnea during sleep. Other symptoms include nocturnal choking, sore throat, morning headache, difficulty concentrating, memory impairment, irritability, and depression.

**LABORATORY PROCEDURES**

A thyroid-stimulating hormone (TSH) level should be measured to assess for hypothyroidism; CBC may reveal polycythemia if nocturnal desaturations are significant.

**IMAGING STUDIES**

Radiologic studies are generally not useful in USA.

**SPECIAL TESTS**

- Polysomnography (PSG) performed in a sleep lab is the test of choice for diagnosing OSA. PSG consists of EEG, electrocogulation, EMG, electrocardiography, pulse oximetry, nasal and oral airflow measurements, and measurement of chest and abdominal wall movement, all done during a night of sleep. PSG in a patient with obstructive sleep apnea typically demonstrates repeated apneas and hypopneas with EGG-documented arousal and varying degrees of oxyhemoglobin desaturation.

- The number of apneas and hypopneas per hour of sleep is referred to as the respiratory disturbance index (RDI); an RDI of greater than 5 is usually considered abnormal.

- The high cost of polysomnography has given rise to various portable monitors for home diagnosis of OSA; however, none of these monitors have been well validated, and they should still be considered experimental.
Sleep Apnea

Management

GENERAL MEASURES

• CPAP is the primary nonsurgical treatment for OSA. CPAP acts as a pneumatic splint for the upper airway, preventing obstruction during sleep, and is quite effective in most cases. It can be delivered either via nasal mask or full-face mask, and is titrated to a normal RDI during polysomnography. Compliance data are mixed, although adherence to therapy tends to be greater in those with more severe OSA.

• Mandibular advancement devices are oral appliances custom fit to the patient’s mouth, and designed to direct the mandible anteriorly, preventing obstruction at the level of the hypopharynx. Though well tolerated, these devices are not as effective as CPAP, and are only useful in those with mild-moderate OSA.

SURGICAL MEASURES

• Uvulopalatopharyngoplasty (UPPP) is the most commonly performed surgical procedure for OSA. It consists of removal of the uvula, posterior soft palate, and redundant peripharyngeal tissue. Long-term cure rates with this procedure are less than 50%, and many patients ultimately require CPAP or repeat surgery. UPPP is probably most effective in those with mild OSA.

• More invasive base-of-tongue and mandibular advancement procedures can be effective in carefully selected patients; these procedures require an experienced ENT surgeon and carry a higher risk of complications.

• Tracheostomy is curative for OSA, but is reserved for patients with very severe OSA who are noncompliant or unresponsive to maximal CPAP.

SYMPTOMATIC TREATMENT

There is no symptomatic treatment for OSA other than those listed above.

ADJUNCTIVE TREATMENT

Weight loss can decrease the severity of OSA, and can occasionally be curative, but is usually difficult to maintain. Avoidance of the supine sleeping position can also be helpful, and the use of alcohol and sedative medications should be limited if possible.

ADMISSION/DISCHARGE CRITERIA

N/A

Medications

DRUG(S) OF CHOICE

Although a number of medications have been used to treat OSA in the past, none are effective, and pharmacotherapy is not currently indicated for this disorder.

ALTERNATIVE DRUGS

N/A

Follow-Up

PATIENT MONITORING

Periodic reassessment of the patient’s sleep quality by interview is important to assure sustained response to therapy. If symptoms such as daytime hypersomnolence or snoring recur, repeat PSG is sometimes needed to titrate CPAP or evaluate the need for further therapy.

EXPECTED COURSE AND PROGNOSIS

The prognosis for treated USA is generally good. While surgery or significant weight loss can sometimes lead to a permanent cure, OSA usually requires lifelong therapy.

PATIENT EDUCATION

• Patients should be advised that weight gain could decrease the effectiveness of most therapies for OSA

• For those patients using CPAP, an experienced respiratory therapist is an invaluable educational resource, and can often provide advice regarding the technical aspects of CPAP use that the physician cannot.

• There is an extensive body of information on USA available via the Internet, including professional societies, nonprofit organizations, and support groups. Links to many of these groups can be found at www.sleepapnea.org.

REFERENCES


• George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax 2001;56(7):508-512.


Author(s): LeRoy Essig, MD

Follow-Up

N/A

SYNONYMS

None

ICD-9-CM: 780.51 Insomnia with sleep apnea; 780.53 Hypersomnia with sleep apnea; 780.57 Other unspecified sleep apnea

SEE ALSO: N/A

ADMISSION/DISCHARGE CRITERIA

N/A
Sphingolipidoses

**DESCRIPTION Basics**

Degenerative storage disorders are caused by deficiency of an enzyme that is required for the conversion of a ceramide to a sphingosine. The lipids that accumulate in tissues and organs of affected individuals are from the normal turnover of cells and cell components. Differences in properties of the accumulating substances as well as the type of tissue in which a particular lipid component is rapidly turning over account for the diverse clinical manifestation of the disorders. There are ten diseases, most of which have variable phenotypes that correlate with the level of residual enzyme activity. Central or peripheral nervous system involvement is true of all except type 1 Gaucher and Niemann-Pick type B. The clinical features described in this chapter are for the most common phenotype with neurologic manifestations. Less common phenotypes that may be characterized by delayed onset during adolescence or adulthood and associated with variable neurologic and systemic manifestations are described in more extensive reviews.

**EPIDEMIOLOGY**

Tay-Sachs: Disease incidence of 1 in 4,000 Ashkenazi Jewish births. Among non-Jews, the disease incidence is 100 times less. Five geographic isolates do exist: Switzerland, Japan, the Pennsylvania Dutch group in Pennsylvania, French-Canadians in Quebec, and Cajuns in southern Louisiana.

Sandhoff: Incidence of 1 in 309,000 non-Jewish infants; 1 in 1,000,000 Jewish births. Several populations have an increased incidence: Creole population in Argentina, Metis Indians in northern Saskatchewan, Lebanese-Canadians, as well as in Lebanon.

Fabry: Estimated incidence of 1 in 40,000. Niemann-Pick type A: Panethic but with an increased incidence in Ashkenazi Jews of 1 in 40,000. Niemann-Pick type C: Panethic, but with an increased incidence in Spanish-Americans in southern Colorado.

Niemann-Pick type D: All patients share a common ancestry in Nova Scotia. Incidence is 100 times less. Five geographic isolates do exist: Switzerland, Japan, the Pennsylvania Dutch group in Pennsylvania, French-Canadians in Quebec, and Cajuns in southern Louisiana.

**ASSOCIATED CONDITIONS**

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

The sphingolipidoses must be differentiated from other inherited neurodegenerative diseases.

**SIGNS AND SYMPTOMS**

- **GM, gangliosidosis (Tay-Sachs) and Sandhoff:** Onset at 3 to 5 months with exaggerated startle response to sound and decreased visual attentiveness. By 6 to 10 months of age, there is progressive weakness and loss of previously attained milestones. Thereafter progression is rapid. A cherry red spot is present in almost all patients. Seizures usually develop by the end of the first year. Macrocephaly from reactive cerebral giosis is common.
- **GM, gangliosidosis:** Onset of developmental arrest before 6 months of age followed by progressive CNS deterioration. Fifty percent of patients have a cherry red spot. Hepatosplenomegaly is almost always present. Skeletal dysplasia seen. Patients become vegetative with generalized spasticity, contractures and generalized seizures.

- **Fabry disease:** Onset in preteen and adolescent boys. Two pain syndromes are described:
  - Episodic painful, burning sensations in the hands and feet, which may last minutes to several days (Fabry crises)
  - Constant discomfort of burning paresthesias in the hands and feet. Progressive CNS damage, such as transient ischemic attacks and cerebral hemorrhage, from multifocal small vessel involvement. Reddish-purple angiokeratoma on the skin, which may be limited to the umbilical and scrotal areas. Hypohidrosis and characteristic corneal and lenticular opacities.

  Progressive cardiac and renal disease.

- **Niemann-Pick type A:** Onset prior to 6 months of age with psychomotor retardation. A cherry red spot is present in 50% of patients. Progressive spasticity, rigidity, and vegetative state. Hepatosplenomegaly, foam cells in bone marrow.

- **Niemann-Pick type C:** History of neonatal jaundice. Presents in late childhood with inattention/school difficulties progressing to dementia. Down gaze, ophthalmoplegia, ataxia, dystonia, dysarthria, and dysphagia are common. Seizures do occur. Some patients have hepatosplenomegaly.

- **Niemann-Pick type D:** Similar to Niemann-Pick type C but with a slower neurodegenerative course. All patients share a common ancestry in Nova Scotia.

- **Gaucher disease type 2:** Onset from infancy to 6 months of age with progressive CNS damage including marked mental retardation, seizures, hypertoncity with hyperactive reflexes, cranial nerve involvement with strabismus, facial weakness, and dysphagia. Hepatosplenomegaly and bone lesions.

- **Farber lipogranulomatosis:** Onset from infancy to 4 months of age. Swollen, painful joints with subcutaneous nodules over affected joints and pressure points. Apathy, swallowing, and feeding difficulties due to laryngeal involvement. Lower motor neuron involvement, which manifests as hypotonia and muscular atrophy. Psychomotor development variable from severe involvement to normal intelligence. Some patients exhibit hepatomegaly.

- **Krabbe or globoid cell leukodystrophy:** Onset 3 to 6 months of age with psychomotor delay, tonic seizures, progressive motor impairment with hypertonicity. Deafness and blindness are common. Peripheral neuropathy detected. CSF protein increased. Clinical symptoms restricted to nervous system.

- **Metachromatic leukodystrophy (MLD):** Late infantile form with onset at age 1 to 2 years, with progressive ataxia, hypotonia, and diminished deep tendon reflexes. Progressive optic atrophy and spastic quadriaparesis. Slowing of conduction velocities of peripheral nerve. CSF protein increased.
LABORATORY PROCEDURES
See Special Tests, below.

IMAGING STUDIES
Neuroimaging studies may reveal nonspecific changes such as atrophy.

SPECIAL TESTS
Diagnosis is made by enzymatic assay of the specific enzyme in leukocytes, skin fibroblasts, and in some cases, serum.
- GM1: hexosaminidase A deficiency
- Sandhoff: hexosaminidase A and B deficiency
- GM2: β-galactosidase deficiency
- Fabry: α-galactosidase A (ceramide trihexosidase) deficiency
- Niemann-Pick type A: sphingomyelinase deficiency
- Niemann-Pick type C/D: defective cellular esterification of exogenously derived cholesterol
- Gaucher: glucocerebrosidase deficiency
- Farber: ceramidase deficiency
- Krabbe: galactocerebrosidase deficiency
- Metachromatic leukodystrophy: arylsulfatase A deficiency

MANAGEMENT

GENERAL MEASURES
N/A

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
- Carbamazepine or phenytoin, occasionally in combination with amitriptyline, is used to treat the painful neuropathy in patients with Fabry disease.
- Kidney transplant in patients with Fabry disease is successful in most cases.
- Joint replacement and splenectomy in patients with Gaucher type 1 may improve quality of life.
- Bone marrow transplant for treatment of Niemann-Pick type C and Gaucher type 3 may decrease visceral storage.

ADJUNCTIVE TREATMENT
The indication for physical therapy should be assessed on an individual basis.

ADMISSION/DISCHARGE CRITERIA
Patients are usually admitted for evaluation and treatment of the neurologic and respiratory complications of their disorder.

DRUGS OF CHOICE
Enzyme replacement therapy (ERT) with macrophage-targeted glucocerebrosidase (Ceredase) for patients with Gaucher type 1 and type 3 effectively reverses the systemic manifestations of the disease. ERT in patients with Gaucher type 3 can stabilize or slightly improve CNS disease. There are no specific treatments for the other disorders.

ALTERNATIVE DRUGS
N/A

PATIENT FOLLOW-UP
Patient follow-up is guided by the predicted course and potential complications of the disease.

EXPECTED COURSE AND PROGNOSIS
- GM2 and Sandhoff: vegetative state rapidly ensues with death by 2 to 4 years of age.
- GM1: death ensues a few years after onset of the disease.
- Fabry: death usually occurs from renal failure, cardiovascular involvement, or cerebrovascular disease. Average age at death is 41 years.
- Niemann-Pick type A: death occurs by 2 to 3 years of age.
- Niemann-Pick type C: indolent downhill course with death in adolescence.
- Niemann-Pick type D: death in adolescence to more prolonged survival.
- Gaucher (infantile): death in infancy.
- Farber: death in late infancy or early childhood.
- Krabbe: death in infancy or early childhood.
- Metachromatic leukodystrophy: death 1 to 7 years after onset.

PATIENT EDUCATION
United Leukodystrophy Foundation, 2304 Highland Dr., Sycamore, IL 60178.
Phone: 800-728-5483.
National Tay-Sachs and Allied Diseases Association, 2001 Beacon St., Ste. 204, Brighton, MA 02135.
Phone: 800-96-NTSAD.
Phone: 800-925-8885.

SYNONYMS
N/A

ICD-9-CM: 272.7 Sphingolipidosis (Fabry, Niemann-Pick, Gaucher); 272.8 Farber lipogranulomatosis; 330.1 Gangliosidosis (Tay-Sachs, Krabbe, MLD)

SEE ALSO: N/A

REFERENCES

Author(s): Eveline C. Traeger, MD
Neoplastic epidural spinal cord compression (ESCC) is a common neuromuscular complication of systemic cancer that is associated with severe neurologic morbidity. ESCC develops after growth of metastatic deposits to the vertebral column (85% to 90% in the thoracic spine, with and without gadolinium contrast, is the rule out epidural abscess, discitis, and osteomyelitis. MRI of the involved region in 85% to 90% of cases. The most common primary tumors include cancers of the prostate, breast, kidney, and lung, as well as melanoma, myeloma, and lymphoma. In children, ESCC can arise from sarcoma, neuroblastoma, and lymphoma. ESCC develops most often in the thoracic spine (70%), but is also noted in the lumbar spine (20%) and cervical spine (10%). Approximately 90% of ESCC occurs in patients with an established diagnosis of cancer. In 10% of cases, ESCC is the first manifestation of the malignancy. After the onset of back pain, neurologic deterioration can occur quickly in patients with ESCC.

**Clinical Presentation**

- **Back pain** is a common symptom with an annual incidence of 5% and a lifetime prevalence of 60% to 90% in the general population. Most back pain is benign and self-limited; in cancer patients, the presenting symptoms of ESCC are mild at first, then progressively worse. The initial symptom is usually pain (95%), which can develop anywhere, but usually in the thoracic spine. The pain is regional and often associated with a radicular component (e.g., down an arm, around the ribs). Several weeks after the onset of pain other symptoms develop, including extremity weakness (75%; usually the legs), autonomic dysfunction (60%; urinary retention, urinary and/or bowel incontinence), sensory alterations (50%) of the lower extremities such as ascending numbness and paresthesias, and gait disturbance.
- **The general physical examination often reveals** localized pain to percussion over the involved vertebral bodies (usually thoracic). The neurologic examination usually demonstrates leg weakness; early on, the weakness is mild and may involve only the iliopsoas and hamstring muscle groups. Later in the course a myelopathy develops, with upper motor neuron pattern weakness, spasticity, Babinski’s sign, and exaggerated reflexes. ESCC of the lumbar region affects the cauda equina and produces a lower motor neuron syndrome (hypotonia, areflexia, muscle atrophy, fasciculations). Sensory loss is mild initially, with distal decrements to vibration and proprioception; with advanced disease, a level develops below the ESCC, characterized by loss of light touch and pinprick sensation.

**Laboratory Procedures**

Patients with a history of fever require a white blood cell count, blood cultures, and sedimentation rate to rule out epidural abscess, discitis, and osteomyelitis.

**Imaging Studies**

Spine x-rays can identify an abnormality of the involved region in 85% to 90% of cases. The most common lesions are vertebral body erosion and collapse, subluxation, and pedicle erosion. MRI of the spine, with and without gadolinium contrast, is the most sensitive imaging test (> 90%). Axial, coronal, and midsagittal enhanced images should be obtained. MRI can easily demonstrate epidural or paravertebral masses and any associated ESCC. The degree of cord displacement is clearly revealed, along with cord damage, as shown by high signal within the parenchyma. Nonmalignant lesions are clearly delineated (e.g., herniated disc, degenerative spine disease). CT and myelography are not as sensitive as MRI and are not required if MRI is available.

**Special Tests**

N/A
Spinal Cord, Neoplastic Cord Compression

Management

GENERAL MEASURES
Should include symptomatic treatment and consultation by radiation oncology and neurosurgery for treatment evaluation. ESCC is a medical emergency and requires rapid treatment.

SURGICAL MEASURES
Surgical intervention is appropriate for carefully selected patients with ESCC. It should be considered for patients with acute deterioration of neurologic function at presentation, if there is progressive neurologic dysfunction during radiotherapy (RT), an unknown primary tumor, evidence for spinal instability, bone involvement with ESCC, and if the involved tumor is known to be radiosensitive (e.g., renal). The anterior surgical approach is preferred (i.e., vertebral body resection) in most patients, since it removes the bulk of the tumor and directly decompresses the spinal cord. Spinal stability is better following the anterior approach than the posterior approach (i.e., laminectomy).

SYMPTOMATIC TREATMENT
Consists of high-dose intravenous dexamethasone and pain control. Pain is often severe and may need treatment before imaging can be performed. Definitive treatment (surgery and/or RT) should begin within 24 hours after the initiation of dexamethasone.

ADJUNCTIVE TREATMENT
• Conventional RT is the mainstay of treatment of ESCC in most patients. The recommended dose is 30 Gy in 10 daily fractions over 2 weeks. The radiation port should include two vertebral bodies above and below the region of compression. RT is also usually necessary after surgical decompression of ESCC. Many patients improve during RT (30% to 50%/o with increase in leg strength and/or ambulation).
• Chemotherapy has a limited role in most patients with ESCC. In some cases, it can be used as adjunctive therapy in addition to surgical resection or RT. Chemotherapy should be considered first-line treatment for ESCC only from Hodgkin's lymphoma, germ cell tumors, or neuroblastoma, which are very chemosensitive tumors and respond rapidly.

ADMISSION/DISCHARGE CRITERIA
Admission is for initial diagnosis and treatment of ESCC. Readmission may occur for patients with recurrent or progressive spinal disease.

Medications

DRUG(S) OF CHOICE
Intravenous dexamethasone is always necessary as initial treatment of ESCC, to reduce edema and swelling of the spinal cord. Recommended initial dosing consists of a load of 20 to 100 mg, followed by maintenance doses of 2 to 24 mg q6h. Dexamethasone often improves pain and neurologic function. Narcotic analgesics are usually necessary for adequate amelioration of pain.

Contraindications
Patients on chemotherapy must meet appropriate hematologic parameters before proceeding with the next cycle; WBC >2.0, hemoglobin >10.0, and platelets >100,000.

Precautions
All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Patients are followed with assessment of neurologic function and spinal MRI every 3 to 6 months.

EXPECTED COURSE AND PROGNOSIS
• ESCC is a severe complication of cancer that requires emergent treatment. In ESCC patients who are ambulatory at the start of treatment, 80% remain so after therapy; only 45% of paraparetic patients and 510 to 10% of paraplegic patients are ambulatory after treatment. Nonambulatory patients have reduced survival due to medical complications such as pneumonia, decubitus ulcers, urinary infections, and septic episodes.
• The most important factor for improved prognosis is preservation of gait and neurologic function at the onset of treatment. Factors related to poor prognosis include very rapid onset of compression and neurologic deficit, duration of paraplegia of greater than 24 hours, and presence of autonomic dysfunction at the time of diagnosis.

PATIENT EDUCATION
University of Washington-ESCC: www.stat.washington.edu/TAURUS/LS2.3.2.html
Patient/Family Resources: uasom-dl.slis.ua.edu/patientinfo/orthopedics/back/spinal-cord-compression
University of Michigan-ESCC: www.cancer.med.umich.edu/learn/bonespinalcord.htm

Miscellaneous

SYNONYMS
Epidural spinal cord compression, metastatic spinal cord compression

ICD-9-CM: 198.4 Secondary malignant neoplasm of other parts of CNS; 336.3 Myelopathy-other diseases classified elsewhere; 336.9 Unspecified disease of the spinal cord

SEE ALSO: N/A

REFERENCES

Author(s): Herbert B. Newton, MD
Spinal Cord Syndromes, Acute

**DESCRIPTION**

Acute spinal cord syndromes are neurologic emergencies and may result in permanent loss of function. Examples include complete or incomplete transection of the spinal cord from trauma, injury due to infarction, hemorrhage or disc herniation, and acute spinal cord injury secondary to hyperflexion or hyperextension of the spine in the elderly. Spinal cord compression due to tumor may present acutely. Acute spinal cord syndromes are important to recognize early because prognosis is directly related to the speed and accuracy of diagnosis and subsequent treatment.

**ETIOLOGY**

- Compression due to various mass lesions
- Ischemia due to atherosclerosis, embolic disease, hypercoagulable states or vasculitis
- Vascular (A/C)
- Infectious, idiopathic (A/C)
- E., deficiency (C)
- Radiation (C)
- Amyotrophic lateral sclerosis (C)
- Tumor (A/C), trauma (A), toxic-metabolic (A)
- Epidural abscess, electricity (A)
- Developmental, hereditary (C)
- Spondylosis (A/C)
- Paraneoplastic (C)
- Arachnoiditis (A/C)
- Syringomyelia (C)
- Myelitis (A), multiple sclerosis (A/C)
- Systemic disorders (A/C)

**SIGNS AND SYMPTOMS**

**Symptoms**

Patients may give "red flags" in the history that raise the suspicion of acute spinal cord dysfunction. Examples include numbness below a certain level, back pain, hesitancy or incontinence of bladder and bowel functions, and weakness in the lower extremities, especially in such activities as climbing stairs and walking.

**Signs**

Physical exam findings that raise suspicion and assist in the diagnosis of acute spinal cord syndrome include objective muscle weakness in upper and/or lower extremities, loss of reflexes in affected limbs, sensory level to pin and light touch, loss of vibration and position sense below a certain level, limited range of motion of the spine, change in gait, and loss of sphincter tone. Obvious signs of spasticity (hyperreflexia, clonus, increased tone) usually develop late, and cannot be depended on to make a diagnosis of an acute spinal cord syndrome.

**LABORATORY PROCEDURES**

Laboratory studies are important especially if cancer is suspected and should include serum CBC, calcium, and PSA; serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are helpful for a suspected gammapathy.

**DIFFERENTIAL DIAGNOSIS**

Diagnosis must be made early through a combination of accurate history, directed physical and neurologic exam, and imaging studies. The differential diagnosis to consider when collecting the history and physical exam data can be lengthy, but the mnemonic VIBRATED SPASMS (adapted from Wagner and Jagoda, 1997) is helpful for both acute (A) and chronic (C) spinal cord syndromes:

- Vascular (A/C)
- Infectious, idiopathic (A/C)
- E., deficiency (C)
- Radiation (C)
- Amyotrophic lateral sclerosis (C)
- Tumor (A/C), trauma (A), toxic-metabolic (A)
- Epidural abscess, electricity (A)
- Developmental, hereditary (C)
- Spondylosis (A/C)
- Paraneoplastic (C)
- Arachnoiditis (A/C)
- Syringomyelia (C)
- Myelitis (A), multiple sclerosis (A/C)
- Systemic disorders (A/C)

**IMAGING STUDIES**

The most helpful imaging study is MRI, which noninvasively images spinal cord tumors, disc protrusions, epidural abscess and hematoma, and intrinsic cord lesions. In patients with epidural metastases plain x-ray films show bony abnormalities approximately 80% of the time. Myelography is usually reserved for cases where more precise imaging of nerve root elements is needed, or where MRI cannot be used (e.g., patients with pacemakers, etc.).

**SPECIAL TESTS**

Special tests may include bone scan if cancer is suspected. Lumbar puncture is usually not helpful in acute spinal cord dysfunction, but may be very useful in chronic syndromes. Lumbar puncture usually shows a lymphocytic pleocytosis in patients with transverse myelitis, aiding in diagnosis.

**GENERAL MEASURES**

- Management depends on etiology. An etiology of tumor is treated with radiation therapy if the tumor is radiosensitive and with decompression if it is not. Blood dyscrasias are treated with coagulation factor replacement or platelet transfusions. Patients at bed rest require prophylactic anticoagulation to reduce the risk of venous thrombosis or pulmonary embolism.
- Medications may be required for acute pain management and spasticity. Careful attention to bladder function is important. Patients frequently require an indwelling catheter due to acute urinary retention. Bowel function is also frequently impaired, and may require laxatives, enemas, and monitoring.

**SURGICAL MEASURES**

Epidural spinal cord compression due to hematoma is treated with surgical decompression as soon as possible. Epidural abscesses or infections are treated with surgical drainage and IV antibiotics as appropriate. Occasionally acute disc herniations require decompression. Surgical instability of the spine requires stabilization.

**SYMPTOMATIC TREATMENT**

As above.

**ADJUNCTIVE TREATMENT**

As above. ADMISSION/DISCHARGE

**CRITERIA**

Suspicion of spinal cord dysfunction is reason for the immediate admission of the patient. Following treatment, discharge to a rehabilitation facility is common.
Medications

**DRUG(S) OF CHOICE**
The common use of high-dose IV methylprednisolone in acute spinal cord injury is now controversial. Antibiotics are used in cases of infection or abscess and cancers are treated appropriately with chemotherapy. Deep venous thrombosis prophylaxis should be instituted in all appropriate patients. Medications for pain management, bowel function, and relief of anxiety are all useful.

**Contraindications**
Known acute hypersensitivity to medications.

**Precautions**
Glucose monitoring if corticosteroids are used in spinal cord injury especially for diabetics.

**ALTERNATIVE DRUGS**
N/A

Follow-Up

**PATIENT MONITORING**
Careful follow-up of these patients is indicated and depends on the diagnosis. For example, a patient whose tumor was the cause of spinal cord compression is at risk for other metastases at other locations.

**EXPECTED COURSE AND PROGNOSIS**
This depends on the etiology and severity of neurologic injury. In general, patients with milder deficits, shorter time to decompression of cord compression, younger age, and better general medical status have a better prognosis.

**PATIENT EDUCATION**
Patients should understand the nature of spinal cord injury, the relationship between their clinical symptoms and the cord injury, the nature of treatments and rehabilitation, and options for care. In rehabilitation they should become acquainted with assistive devices, bowel and bladder regimens, vocational opportunities, etc.

Miscellaneous

**SYNONYMS**
N/A

ICD-9-CM: 336.9 Spinal cord compression

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** Lawrence P. Levitt, MD; Stacy Statler, PA-C
**Spinal Cord Syndromes, Chronic**

### Basics

**DESCRIPTION**
Chronic spinal cord syndromes are common, particularly in the elderly. They are characterized by progressive spasticity, gait disorders, paresthesias, and bowel and bladder dysfunction. Chronic spinal cord syndromes are recognized by a basic understanding of spinal cord anatomy combined with how a careful history, examination, and laboratory studies fit with various disease processes that affect the cord. A basic understanding of primary motor and sensory tracts is necessary. Thus, for example, amyotrophic lateral sclerosis (ALS) affects motor tracts but spares sensation. Combined system disease due to vitamin B12 deficiency affects both the posterior and lateral tracts producing characteristic symptoms and signs.

**Epidemiology**
Incidence/Prevalence
Precise incidence is not known.

**Etiology**
See Risk Factors.

**Risk Factors**
Include cervical spinal degeneration, HIV infection (AIDS myelopathy), malnutrition (B12 deficiency), cervical spondylosis (causing myelopathy), trauma (causing syringomyelia), toxin exposure, systemic infection (epidural abscess), radiation (myelopathy), and multiple sclerosis (MS). There are various familial syndromes of chronic spinal cord disease (familial spastic paraparesis, spinocerebellar degenerations, adrenomyeloneuropathy, etc.).

**Pregnancy**
N/A

**Associated Conditions**
Include underlying cancer, cervical spondylosis, vasculitis, systemic infections, toxins (e.g., nitrous oxide, which may precipitate a syndrome related to subacute combined degeneration).

### Diagnosis

**Differential Diagnosis**
As with acute syndromes, diagnosis depends on combining accurate history, physical and neurologic examinations, and imaging studies. The mnemonic VIBRATED SPASMS (adapted from Wagner and Jagoda, 1997) is useful (see Spinal Cord Syndromes, Acute).

**Signs and Symptoms**

**Symptoms**
Paresthesias (numbness, tingling) in limbs and trunk; limb weakness; change in urine or bowel function (either more or less frequent); incontinence; back pain; and root distribution pain, which may encircle the trunk. Patients usually complain most of a progressive gait disorder characterized by leg stiffness, with urgency of urination and constipation. In patients with cervical spine disease, weakness, dysesthetic sensation, and stiffness may be noticed in the hands. Neck or back pain may be present. Symptoms suggesting cranial nerve injury (diplopia, dysarthria, facial numbness, or weakness) are absent.

**Signs**
Loss of pin sensation below a certain level; "sweat" level; weakness in upper or lower extremities or both sparing the face; increased muscle tone; tenderness over the spine; hyperreflexia; up-going toes; absent abdominal reflexes; loss of anal sphincter tone; and distended bladder. Often patients have a stiff-legged gait and may hyperextend their knees. If there is cervical root injury, a combination of wasting and reflex loss in the arms (due to cervical root injury) and spasticity in the legs may occur. This must be differentiated from ALS, in which there are no sensory signs, but upper and lower motor neuron signs are present. In suspected familial syndromes, search for high arches (present in some spinocerebellar syndromes) and consider examining family members who might be affected subclinically.

**Laboratory Procedures**
B12 level in suspected combined systems disease; CSF examination for MS: pleocytosis, elevated protein, oligoclonal bands; pleocytosis in myelitis; elevated protein in arachnoiditis. In familial syndromes, more specialized tests may be useful (for example, very long chain fatty acids in adrenomyeloneuropathy).

**Imaging Studies**
MRI of spinal cord and brain in MS; MRI of the spinal cord for syrinx, epidural, subdural or intramedullary tumor, infarcts, and for evidence of myelitis and arteriovenous malformations (AVMs). X-rays show bony abnormalities in developmental and hereditary disorders and in atlantoaxial dislocations.

**Special Tests**
Rarely spinal cord angiography may be necessary for dural AV fistulas or spinal cord AVMs. This study should be performed in specialized centers due to risk of permanent spinal cord injury.

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Spinal Cord Syndromes, Chronic

**Management**

**GENERAL MEASURES**

Measures that are applicable to all patients with chronic spinal cord conditions include provision of therapy aimed at stretching and strengthening the affected muscles; avoiding decubitus ulcers in severely affected patients; provision of adequate bowel and bladder care; and attention to issues of rehabilitation including assistive devices, wheelchairs, transfer aids, and other appropriate support.

**SURGICAL MEASURES**

Surgery may be used in cases where there is spinal cord compression and alternative therapies cannot be used. Particularly patients with relatively rapidly progressive syndromes should be considered for surgery early, as accrued spinal cord deficits may not improve even after decompression.

**SYMPTOMATIC TREATMENT**

Medications for spasticity are useful in this population. Baclofen (Lioresal) or tizanidine (Zanaflex) are commonly used to relieve this symptom. Side effects of Lioresal include fatigue and leg weakness, particularly at higher doses. Side effects of tizanidine include fatigue, hypotension, and occasionally altered liver function tests. Occasionally very spastic muscles may require treatment with botulinum toxin or implantation of an intrathecal pump for Lioresal infusion near the spinal cord.

**ADJUNCTIVE TREATMENT**

Consider deep vein thrombosis (DVT) prophylaxis as necessary.

**Medications,**

**DRUG(S) OF CHOICE**

Medical management of chronic spinal cord syndromes depends on the cause. In patients with MS, for example, intravenous steroids are often used to treat individual attacks. To prevent attacks and the progression of disease, subcutaneous or intramuscular immunomodulating therapies (b-IFN 1-a IM, fil-IFN 1-a SC, b-IFN 1-b, and glatiramer acetate) and in some cases chemotherapy such as mitoxantrone or methotrexate may be given. For spinal cord compression due to malignancy, decompression, radiation therapy, and/or chemotherapy are used depending on the type of cancer. For compression due to abscess, drainage is done and antibiotics are given. For spondylitic myelopathy, decompression may be performed. Vitamin B12-deficient patients need replacement, orally or IM. For ALS patients, consider riluzole. Unfortunately, some causes, such as radiation-induced myelopathy have no specific treatments.

**ALTERNATIVE DRUGS**

N/A

**Follow-Up**

**PATIENT MONITORING**

Depends on the diagnosis. For example, patients with MS often require routine or frequent follow-up visits.

**EXPECTED COURSE AND PROGNOSIS**

Depends on the etiology of the spinal cord syndrome.

**PATIENT EDUCATION**

Patients should be educated generally about the effect of chronic spinal cord injury on sensory and motor function, bowel and bladder activity, and gait. The specific cause and its prognosis should be discussed with the patients. If there are specific societies with information for the etiology, the patient should be made aware of these (for example, the ALS and MS societies).

**Miscellaneous**

**SYNONYMS**

Chronic myelopathy Chronic spastic paraparesis ICD-9-CM: 336.9 Myelopathy, unspecified

**SEE ALSO:** SPINAL CORD SYNDROMES, ACUTE; MULTIPLE SCLEROSIS; VITAMIN B12 DEFICIENCY; SPINAL CORD, NEOPLASTIC CORD COMPRESSION

**REFERENCES**


**Author(s):** Lawrence P. Levitt, MD; Stacy Statler, PA-C
**Spinal Cord Tumor, Astrocytoma**

**DESCRIPTION**

Spinal cord astrocytomas (SCAs) are intradural, intramedullary tumors that arise from the gray or white matter of the spinal cord and can affect patients of all ages. They occur most commonly in the cervical and upper thoracic region, but can develop anywhere in the cord. Although most SCAs are low grade, they are all very infiltrative and typically span four to six spinal cord segments at diagnosis.

**EPIDEMIOLOGY**

**Incidence/Prevalence**

Spinal cord tumors (SCTs) are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. SCAs comprise 6% to 8% of all primary SCTs, approximately 30% of all intramedullary SCTs, and only 3% to 4% of all CNS astrocytomas. They are more common in children, comprising 35% to 60% of all pediatric SCTs, and representing the most common type of intramedullary SCTs.

**Race**

All races and ethnic groups affected; Caucasians are affected more commonly than blacks, Latinos, and Asians.

**Age**

Typical presentation is between 25 and 40 years, but can occur at any age. A secondary peak occurs in the pediatric years.

**Sex**

Males have a higher incidence than females: 4:1.

**ETIOLOGY**

- The World Health Organization (WHO) classifies astrocytomas of the spinal cord similarly to those of the brain: pilocytic astrocytoma as grade I (50%), fibrillary astrocytoma as grade II (22%), anaplastic astrocytoma (AA); 20%) as grade III, and glioblastoma multiforme (GBM; 8%) as grade IV.
- SCAs are mainly low grade (i.e., grade I, II; LGA). High-grade tumors are less common. The tumors are derived from transformed astrocytes. Pathologic evaluation of LGA reveals mild to moderate cellularity without anaplasia or severe nuclear atypia, minimal mitotic activity and endothelial proliferation, no necrosis, and frequent staining for glial fibrillary acidic protein. High-grade tumors have high cellularity, cellular and nuclear atypia, moderate to high mitotic rate, endothelial proliferation, and necrosis (in GBM).
- Molecular genetic studies of LGA reveal frequent allelic deletions of chromosome 17p, often with loss or mutation of the tumor suppressor gene, p53. Amplification of oncogenes (e.g., MDM2, CDK2, p63) and deletion of tumor suppressors genes (e.g., p16, retinoblastoma) may be present in some tumors.
- **Genetics**
  - Astrocytomas of the spinal cord are usually sporadic tumors, but can occur in association with neurofibromatosis type 1 (NF-1).
- **RISK FACTORS**
  - Risk factors for spinal astrocytomas remain unclear, but may be similar to astrocytomas of the intracranial cavity. These include spinal radiation (>10 Gy), breast cancer, regional trauma, and NF-1.
- **PREGNANCY**
  - Pregnancy does not affect the clinical behavior of spinal astrocytomas.

**ASSOCIATED CONDITIONS**

**N/A**

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

Includes other intramedullary enhancing spinal masses such as ependymoma, metastasis, and abscess. Other disorders that can have a similar neurologic presentation are syringomyelia, multiple sclerosis, transverse myelitis, hemiated disc, amyotrophic lateral sclerosis, vitamin B12 deficiency, and atrophy of the upper extremities, due to destruction of anterior horn cells.

**LABORATORY PROCEDURES**

**N/A**

**IMAGING STUDIES**

MRIs, with and without gadolinium contrast, are the most critical diagnostic test; axial, coronal, and sagittal enhanced images should be obtained. MRI is more sensitive than CT for intramedullary spinal cord tumors. On T1 images, the tumor is typically hypointense or isointense compared to normal spinal cord and causes diffuse multisegmental enlargement. On T2 images it is hypointense. Spinal astrocytomas have mild to moderate enhancement after administration of gadolinium. Regions of cyst, peritumoral edema, and areas of hemorrhage may be noted. CT demonstrates a hypodense enlargement of the spinal cord with variable enhancement and edema. Hydrocephalus can be noted in a small percentage of patients.

**SPECIAL TESTS**

Intraoperative neurophysiologic monitoring with evoked potentials may be helpful during surgical resection to maximize tumor removal and minimize neurologic morbidity. Ultrasound may be helpful for the surgeon to accurately localize the tumor before myelotomy and removal.

**GENERAL MEASURES**

Include symptomatic treatment and physical therapy.

**SURGICAL MEASURES**

Surgical resection is required for biopsy of diagnostic tissue and maximal tumor removal, while minimizing surgical neurologic morbidity. Many low-grade SCAs can be completely resected with modern microneurosurgical techniques if a cleavage plane is discerned. Infiltrative low-grade tumors and most high-grade SCAs will allow only a subtotal resection. Ideal surgical candidates have intact or almost normal gait and neurologic function.
**Spinal Cord Tumor, Astrocytoma**

**SYMPTOMATIC TREATMENT**
Consists of corticosteroids to control symptoms of spinal cord edema and pain control caused by compression of the spinal meninges and other neurovascular structures.

**ADJUNCTIVE TREATMENT**
- Radiation therapy (RT) should be considered for all adult patients with an SCA, even those of low grade that have undergone an apparently complete resection. All patients with residual tumor or high-grade histology require involved field RT. The recommended doses are 50 to 55 Gy over 6 weeks using 180 to 200 cGy/d fractions. Children with completely resected pilocytic SCAs (WHO grade I) can be followed without RT. Patients with high-grade SCAs that disseminate to the neuraxis may benefit from palliative RT.
- Chemotherapy has a limited role in the treatment of SCAs. It should be considered for patients who cannot undergo surgical resection and for tumors that recur despite surgery and/or RT. Drugs to consider have only modest activity and are the same as those used for astrocytic tumors of the brain; they include nitrosoureas (BCNU, CCNU), PCV (procarbazine, CCNU, vincristine), etoposide, cyclophosphamide, carboplatin, and temozolomide. Intrathecal chemotherapy with methotrexate or cytarabine should be considered for patients with high-grade SCAs that develop leptomeningeal metastases.

**ADMISSION/DISCHARGE CRITERIA**
Admission is generally reserved for presurgical evaluation and biopsy/resection. Patients can be admitted with progressive spinal neurologic dysfunction from tumor growth or leptomeningeal dissemination. Intravenous dexamethasone may be helpful to reduce spinal cord edema and control pain; new treatment may be necessary (e.g., RT, chemotherapy).

### Follow-Up

**PATIENT MONITORING**
Patients are followed with serial MRI scans and assessment of neurologic function every 3 to 6 months.

**EXPECTED COURSE AND PROGNOSIS**
- The 5-year survival rate for patients with low-grade SCA after complete resection, with or without RT, is 70% to 80%. After incomplete removal plus RT the survival is lower, with a 5-year rate of 50% to 65%. The prognosis for patients with high-grade SCA is poor, with typical overall survival ranging from 6 to 12 months.
- Factors that improve the prognosis for survival are young age, low-grade histology, relatively intact neurologic function before and after surgery, and complete resection; factors that worsen the prognosis include high-grade histology, older age, significant neurologic dysfunction with poor performance status, and incomplete removal of tumor.

**PATIENT EDUCATION**

**DRUG(S) OF CHOICE**
Dexamethasone (2 to 8 mg/d) may be of benefit to reduce spinal cord edema and often improves pain; it may also relieve transient symptoms of pressure and swelling after RT. Narcotic analgesics may be necessary to control severe pain prior to surgery and/or RT.

**Contraindications**
None

**Precautions**
All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

**ALTERNATIVE DRUGS**
N/A

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**Medications**

**DRUG(S) OF CHOICE**
Dexamethasone (2 to 8 mg/d) may be of benefit to reduce spinal cord edema and often improves pain; it may also relieve transient symptoms of pressure and swelling after RT. Narcotic analgesics may be necessary to control severe pain prior to surgery and/or RT.

**Contraindications**
None

**Precautions**
All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

**Miscellaneous**

**SYNONYMS**
N/A

**ICD-9-CM**
- 192.2 Malignant neoplasm of spinal cord; 225.3 Benign neoplasm of spinal cord

**SEE ALSO**
N/A

**REFERENCES**

**Author(s):** Herbert B. Newton, MD

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Spinal Cord Tumor, Ependymoma

**Basics**

**DESCRIPTION**

Spinal cord ependymomas (SCEs) are intradural tumors that arise from the ependymal lining cells of the central canal of the spinal cord, affecting patients of all ages. They occur most often in the extramedullary portions of the lumbar spine (60%; cauda equina and filum terminate). In 40% of patients, the tumor is intramedullary and develops within the spinal cord parenchyma. The cervical and upper thoracic cords are the most common (65% to 70%) locations for intramedullary SCEs. Most SCEs are low grade, with less infiltrative capacity than astrocytic tumors. At diagnosis, most SCEs span one to two spinal cord segments.

**EPIEMIOLOGY**

**Incidence/Prevalence**

Spinal cord tumors (SCTs) are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. SCEs comprise 12% of all intramedullary SCTs, and 30% to 35% of all CNS ependymomas. They are less common in children, comprising 12% to 15% of all pediatric SCT.

**Race**

All races and ethnic groups affected; Caucasians are affected more commonly than blacks, Latinos, and Asians.

**Age**

Typical presentation is between 35 and 50 years, but can occur at any age; a secondary peak occurs in the pediatric years.

**Sex**

Males have a higher incidence than females: 2:1.

**ETIOLOGY**

- The World Health Organization (WHO) classifies ependymomas of the spinal cord similar to those of the brain. Myxopapillary tumors are classified as WHO grade I and are the most common type of SCEs to arise in the cauda equina and filum terminate. Typical ependymomas are classified as WHO grade II. Anaplastic or malignant ependymomas correspond to WHO grade III.
- SCEs are usually slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 3 to 5 years). The presentation varies with tumor location, rate of growth, and amount of edema and compression of regional neural structures. Tumors that arise in the lumbar region typically present with low-back pain, with or without sciatica, lower extremity sensory dysfunction (e.g., numbness, paresthesias), bowel, and bladder incontinence, and lower extremity weakness. Intramedullary SCEs have a different presentation, with milder, more diffuse back pain, sensory complaints that usually manifest as dysesthesias, and less severe lower extremity weakness and bowel and bladder dysfunction.
- The most common neurologic sign is mild lower extremity weakness. However, it is different between intramedullary and extramedullary SCEs. Intramedullary tumors develop weakness as a late sign and have an upper motor neuron pattern (i.e., spasticity, hyperactive reflexes, Babinski sign). Extramedullary tumors develop weakness earlier and have a lower motor neuron pattern (i.e., flaccidity, hypoactive or absent reflexes, flexor plantar responses). Other frequent signs include sensory loss, sphincter dysfunction, gait disturbance, and loss of abdominal reflexes.

**LABORATORY PROCEDURES**

CSF analysis and evaluation of cytology are diagnostic (in addition to cranial and/or spinal MRI) for those rare SCEs (high grade, myxopapillary) that disseminate to the leptomeninges.

**IMAGING STUDIES**

MRI, with and without gadolinium contrast, is the most critical diagnostic test; axial, coronal, and midsagittal enhanced images should be obtained. MRI is more sensitive than CT for intramedullary and extramedullary spinal cord tumors. On T1 images, the tumor is usually hypointense or isointense compared to normal spinal cord and causes a well-demarcated, multisegmental enlargement of the cord or a mass in the cauda equina. On T2 images the mass is hyperintense. SCEs have mild to moderate enhancement after administration of gadolinium. Regions of cyst occur frequently in intramedullary SCEs (50% to 55%; even cranial-caudal distribution). Peritumoral edema may be noted. CT demonstrates a hypodense enlargement of the spinal cord or a mass in the lumbar region with mild enhancement and edema.

**SPECIAL TESTS**

Intraoperative neurophysiologic monitoring with evoked potentials may be helpful during surgical resection to maximize tumor removal and minimize neurological morbidity. Ultrasound may be helpful for the surgeon to accurately localize the tumor before myelotomy and resection.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**

Includes other intramedullary and extra- medullary enhancing spinal masses such as astrocytoma, metastasis, and abscess. Other disorders that can have a similar neurologic presentation are syringomyelia, multiple sclerosis, transverse myelitis, herniated disk, and vitamin B12 deficiency.

**SIGNS AND SYMPTOMS**

- SCEs are usually slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 3 to 5 years). The presentation varies with tumor location, rate of growth, and amount of edema and compression of regional neural structures. Tumors that arise in the lumbar region typically present with low-back pain, with or without sciatica, lower extremity sensory dysfunction (e.g., numbness, paresthesias), bowel and bladder incontinence, and lower extremity weakness. Intramedullary SCEs have a different presentation, with milder, more diffuse back pain, sensory complaints that usually manifest as dysesthesias, and less severe lower extremity weakness and bowel and bladder dysfunction.

- The most common neurologic sign is mild lower extremity weakness. However, it is different between intramedullary and extramedullary SCEs. Intramedullary tumors develop weakness as a late sign and have an upper motor neuron pattern (i.e., spasticity, hyperactive reflexes, Babinski sign). Extramedullary tumors develop weakness earlier and have a lower motor neuron pattern (i.e., flaccidity, hypoactive or absent reflexes, flexor plantar responses). Other frequent signs include sensory loss, sphincter dysfunction, gait disturbance, and loss of abdominal reflexes.

- The World Health Organization (WHO) classifies ependymomas of the spinal cord similar to those of the brain. Myxopapillary tumors are classified as WHO grade I and are the most common type of SCEs to arise in the cauda equina and filum terminate. Typical ependymomas are classified as WHO grade II. Anaplastic or malignant ependymomas correspond to WHO grade III.
- SCEs are usually slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 3 to 5 years). The presentation varies with tumor location, rate of growth, and amount of edema and compression of regional neural structures. Tumors that arise in the lumbar region typically present with low-back pain, with or without sciatica, lower extremity sensory dysfunction (e.g., numbness, paresthesias), bowel and bladder incontinence, and lower extremity weakness. Intramedullary SCEs have a different presentation, with milder, more diffuse back pain, sensory complaints that usually manifest as dysesthesias, and less severe lower extremity weakness and bowel and bladder dysfunction.
Spinal Cord Tumor, Ependymoma

Management

GENERAL MEASURES
Include symptomatic treatment and physical therapy.

SURGICAL MEASURES
Surgical resection with gross-total removal is the treatment of choice for all SCEs. Even intramedullary tumors can be totally removed in most cases, since a clear cleavage plane is often present. Infiltrative low-grade and all high-grade intramedullary tumors will allow only a subtotal resection. Some myxopapillary SCEs of the lumbar region cannot be totally excised due to adherence to, or envelopment of, surrounding nerve roots and vascular structures. Ideal surgical candidates have intact or almost normal gait and neurologic function.

SYMPTOMATIC TREATMENT
Consists of corticosteroids to control symptoms of spinal cord edema and pain control caused by compression of nerve roots, spinal meninges, and other neurovascular structures.

ADJUNCTIVE TREATMENT
• Radiation therapy (RT) should not be considered for SCEs of low grade that have undergone a complete resection. Similarly, RT should be held in patients with extensive subtotal resection until evidence of tumor progression. All patients with high-grade histology require involved field RT. The recommended doses are 45 to 50 Gy over 6 weeks using 180 to 200 cGy/d fractions. Patients with high-grade tumors that disseminate to the neuraxis may benefit from palliative RT.
• Chemotherapy has a limited role in the treatment of SCEs. It should be considered for patients with incompletely resected tumors and tumors that progress despite RT. Drugs to consider only have modest activity and are the same as those used for ependymomas of the brain. They include PCV (procarbazine, CCNU, vincristine), etoposide, cyclophosphamide, cisplatin, carboplatin, and temozolomide.

ADMISSION/DISCHARGE CRITERIA
Admission is generally reserved for presurgical evaluation and resection. Patients can be admitted with progressive spinal neurologic dysfunction from tumor growth. Intravenous dexamethasone may be helpful to reduce spinal cord edema and control pain. New treatments may be necessary (e.g., RT, chemotherapy).

Medications

DRUG(S) OF CHOICE
Dexamethasone (2 to 8 mg/d) may be of benefit to reduce spinal cord edema and often improves pain; it may also relieve transient symptoms of pressure and swelling after surgery or RT; narcotic analgesics may be necessary to control severe pain prior to surgery and/or RT.

Contraindications
None

Precautions
All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
Patients are followed with serial MRI scans and assessment of neurologic function every 6 to 12 months. Patients on chemotherapy may require more frequent assessments.

EXPECTED COURSE AND PROGNOSIS
• The 5- and 10-year survival rates for patients with low-grade SCEs after complete resection (without RT) are 75% to 90% and 65% to 70%, respectively. After incomplete removal plus RT the survival is lower. The prognosis for patients with high-grade SCEs is poor, with typical overall survival ranging from 12 to 18 months.
• The most important prognostic factor is degree of surgical resection. Factors that improve the prognosis for survival and quality of life are complete surgical resection, relatively intact neurologic function before and after surgery, and typical low-grade histology. Factors that worsen the prognosis include incomplete removal of tumor, high-grade histology, significant neurologic dysfunction with poor performance status, and tumor location within the conus medullaris.

PATIENT EDUCATION
Spine and Nerve Center at MGH/Harvard: neurosurgery.mgh.harvard.edu/lnkspine.htm
University Southern California Neurosurgery: www.uscneurosurgery.com/glossaty/m/ menangioma.htm

Miscellaneous

SYNONYMS
N/A

ICD-9-CM: 192.2 Malignant neoplasm of spinal cord; 225.3 Benign neoplasm of spinal cord
SEE ALSO: N/A

REFERENCES
• Chang UK, Choe WJ, Chung SK, et al.
• Newton HB, Newton CL, Gatens C, et al.

Author(s): Herbert B. Newton, MD
Spinal Cord Tumor, Meningioma

Basics

DESCRIPTION
Spinal meningiomas are intradural, extramedullary tumors that arise from the meninges of the spinal neuraxis. They are slow-growing, encapsulated masses that can develop in any location that has continuity with the meninges. The distribution within the spine is as follows: thoracic (75% to 85%), cervical (15% to 20%), and lumbar (2% to 4%). 10% of spinal meningiomas can extend outside of the dura into the paraspinal soft tissues and bone.

EPIDEMIOLOGY
Incidence/Prevalence
Spinal cord tumors are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. Meningiomas comprise 20% to 25% of all primary spinal cord tumors in patients over 20 years of age and are extremely rare in children. The estimated incidence of spinal meningiomas is less than 0.18 to 0.23 cases per 100,000 people per year.

Race
All races and ethnic groups are equally affected.

Age
The typical presentation is between 45 to 65 years of age.

Sex
Females have a higher incidence than males: 4:1.

ETIOLOGY
- The World Health Organization (WHO) grades typical low-grade meningiomas (e.g., syncytial, transitional) as WHO grade I, intermediate tumors (e.g., atypical, clear cell) as WHO grade II, and malignant tumors (e.g., anaplastic) as WHO grade III. The vast majority of spinal meningiomas are WHO grade I.
- The cells of origin of meningiomas are transformed arachnoidal cap cells from the outer layer of the spinal arachnoid membrane. Typical meningiomas of the spine are low-grade and demonstrate uniform sheets of spindle-shaped cells, minimal cellular and nuclear atypia, whorl formation, psammoma bodies, and no evidence of mitotic activity or brain infiltration; higher-grade tumors reveal higher cellularity, more prominent nucleoli, high mitotic activity, necrosis, and tissue invasion.
- Molecular genetic studies reveal frequent deletions of chromosomes 22q and 1p. The NF2 gene (located at 22q12.3) is mutated in up to 60% of meningiomas, with dysfunction of the Merlin protein. The majority of meningiomas are positive for estrogen and progesterone receptors. Other receptors of importance include the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors, both of which stimulate secretion of vascular endothelial growth factor. The ras signaling pathway is activated via stimulation by EGF and PDGF.
- Genetics
  - Meningiomas of the spine are usually sporadic; in rare cases they can be familial.

RISK FACTORS
Risk factors for spinal meningiomas remain unclear, but may be similar to meningiomas of the intracranial cavity; these include spinal radiation (>10 Gy), breast cancer, regional trauma, and rare familial clusters.

PREGNANCY
In some women, pregnancy can accelerate the growth and increase the clinical symptoms of spinal meningiomas. This is rare compared to cranial meningiomas.

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
Includes other extraaxial enhancing spinal masses such as schwannoma, metastasis, and abscess. Other disorders that can have a similar neurologic presentation are syringomyelia, multiple sclerosis, transverse myelitis, herniated disc, and vitamin B12 deficiency.

SIGNS AND SYMPTOMS
- Meningiomas are slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 12 to 24 months). The presentation varies with tumor location, rate of growth, and amount of compression of nearby nerve roots and spinal cord. The most common early symptom is pain, which occurs in 42% to 50% of patients. With tumor enlargement pain becomes more prominent, affecting 65% to 85% of patients by the time of initial admission. The pain can be localized and/or radicular (i.e., down an extremity, around the thorax). Leg weakness occurs in 35% to 50% of patients, and is also progressive. Sensory abnormalities develop in 22% to 25% of patients and include paresthesias, numbness, or hot and cold sensations; disturbances of bowel and bladder function can arise in later stages.
- Common neurologic signs include motor weakness (usually of the legs) in 90% to 95% of patients, reflex asymmetry and spasticity of the lower extremities, sensory loss of the extremities (65% to 70%), and sphincter abnormalities (25%/o). Frank myelopathy can be noted in more advanced patients with spinal cord compression. Up to one third of patients are nonambulatory due to leg weakness and/or pain.

LABORATORY PROCEDURES
Although typically unnecessary with MRI, CSF evaluation usually demonstrates an elevated protein. The WBC is frequently normal; a mild pleocytosis may occur in some cases.

IMAGING STUDIES
MRI, with and without gadolinium contrast, is the most critical diagnostic test. Axial, coronal, and mid-sagittal enhanced images should be obtained. MRI is more sensitive than CT for tumors of the spinal column. On T1 images, the tumor is usually isointense to spinal cord, while on T2 images it is hypointense. Spinal meningiomas enhance densely after administration of gadolinium. MRI usually demonstrates a site of dural attachment or a dural tail. The displacement of nerve roots and/or the spinal cord is well delineated by MRI. Meningiomas can cause heterotrophic changes in bones of the spinal column, but less commonly than in the intracranial cavity.

SPECIAL TESTS
Angiography is performed in selected patients to assess vascular anatomy and collateral blood supply prior to surgery. It may also be useful as a prelude to presurgical embolization (to minimize intraoperative bleeding).

Management

GENERAL MEASURES
In certain patient cohorts, spinal meningiomas are followed conservatively after diagnosis, including those with poor health, elderly patients with small lesions or who are reluctant to proceed to surgery, and patients with small tumors that do not correlate with symptoms. Observation should include an enhanced MRI every 4 to 6 months to monitor for growth. Tumors may remain quiescent if they are stable during the initial observation period. Conservative approaches are unjustified in symptomatic patients and most young patients, especially if growth potential is demonstrated.
**SURGICAL MEASURES**

Surgical resection is the treatment of choice for most symptomatic patients. The surgical approach varies depending on the location of the tumor. Complete surgical extirpation is the goal whenever possible. Subtotal removal is recommended for tumors intimately associated with spinal nerves and/or vessels. After removal of the tumor, involved bone and dural attachments should also be resected with a wide margin. Dural defects should be repaired with grafts.

**SYMPTOMATIC TREATMENT**

Consists of corticosteroids to control symptoms of spinal cord compression and pain control due to irritation or compression of nerve roots and other neurovascular structures.

**ADJUNCTIVE TREATMENT**

- Patients do not require irradiation after complete surgical resection. Conventional external beam radiotherapy (RT) may be of benefit for those infrequent patients with large symptomatic tumors after subtotal removal, for recurrent or progressive tumors that cannot be approached surgically, and for those rare patients with malignant pathology (WHO grade III). It remains unclear whether or not RT provides a survival advantage for patients with spinal meningiomas after subtotal removal or at recurrence, since no clinical trial data have been published. Recommended RT doses are 50 to 55 Gy over 6 weeks, with 180 to 200 cGy per day fractions.
- Chemotherapy has a very limited role in the treatment of spinal meningiomas. It should be considered for patients who cannot undergo surgical resection and for tumors that recur despite surgery and/or RT. Drugs with modest activity in phase II trials against intracranial meningioma could be considered and include mifepristone (RU-486; antagonist to progesterone receptors) and hydroxyurea (induces apoptosis in meningioma cells). Chemotherapy usually induces tumor stabilization; shrinkage is uncommon.

**ADMISSION/DISCHARGE CRITERIA**

Admission is generally reserved for presurgical evaluation (including angiography in some patients) and surgical resection. Patients with severe spinal cord compression might benefit from admission for intravenous dexamethasone.

**MEDICATIONS**

**DRUG(S) OF CHOICE**

Dexamethasone (2—8 mg/d) may be of benefit to reduce edema and swelling for patients with spinal cord compression; it may also improve transient symptoms of pressure and swelling after RT; analgesics may be necessary prior to surgery and/or RT.

**Contraindications**

None

**Precautions**

All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

**ALTERNATIVE DRUGS**

N/A

**FOLLOW-UP**

**PATIENT MONITORING**

Patients are followed with serial MRI scans and assessment of neurologic function every 6 to 12 months.

**EXPECTED COURSE AND PROGNOSIS**

- The complete resection rate in most series is 85%/o to 95%, using preoperative MRI planning and modern microsurgical techniques. Approximately 90% of patients have functional improvement after surgery. Symptomatic patients with neurologic deficits can often improve dramatically after surgery releases pressure on nerve roots and the spinal cord. Tumor recurrence or progression occurs in 3.5% to 7%/o of patients after complete surgical resection.
- Factors that increase the probability for recurrence include incomplete removal of tumor and all dural attachments, invasion of bone, soft tumor consistency, extradural extension, and malignant histology.

**PATIENT EDUCATION**

Brain tumors: www.brain tumors.com
National Brain Tumor Foundation: www.abta.org
American Brain Tumor Association: www.abta.org
The Brain Tumor Society: www.tbts.org
Spine and Nerve Center at MGH/Harvard: neurosurgery.mgh.harvard.edu/intraspine.htm
University Southern California Neurosurgery: o

**SYNONYMS**

N/A

**ICD-9-CM:** 225.4 Benign neoplasm of spinal meninges

**SEE ALSO:** N/A

**REFERENCES**


Author(s): Herbert B. Newton, MD
Spinal Muscular Atrophy

DESCRIPTION

The spinal muscular atrophies (SMAs) are a group of inherited disorders characterized by lower motor neuron weakness and wasting that is usually symmetrical and slowly progressive. This distinguishes SMA from the progressive muscular atrophy variant of amyotrophic lateral sclerosis (ALS), which is more rapidly progressive and usually fatal. SMA may show a proximal distribution of muscle weakness as in the childhood recessive SMAs due to mutations in the SMN gene, or be distal, as is common in dominantly inherited, later-onset forms of SMA. Both upper and lower limb predominant forms of distal dominant SMA are described.

The childhood recessive forms of SMA due to mutations in the SMN gene are classified according to severity. Type I (previously known as Werdnig-Hoffmann disease) presents with severe neonatal hypotonia, implying that the loss of motor neurons occurs in utero. Infants may require resuscitation and artificial ventilation. Most children with this type of SMA show signs before 6 months of age. By definition they do not achieve the ability to sit unaided and generally succumb to respiratory failure before the age of 2, though patients can survive longer with modern assisted ventilation. Type II SMA (intermediate SMA) is defined by onset in infancy, but affected children achieve the ability to sit but not stand unaided. The long-term outcome is dictated by the degree of respiratory muscle involvement and associated kyphoscoliosis. Approximately 60% of children survive into their 20s. Type III SMA (previously known as Kugelberg-Welander disease) is the mildest form, and children in this group achieve the ability to walk unaided. Onset for the majority is in infancy but rare cases of adult onset, even into the 40s and 50s, have been described. Life expectancy is normal and the probability of remaining ambulant in the long term is related to the age of onset. If this occurs before the age of 3 years, only 20% of patients are still ambulant 40 years later compared with 60% of those with an age of onset after 3 years.

Incidence/Prevalence

Childhood-onset autosomal-recessive SMA is one of the commonest causes of neurologic disability in childhood and has an incidence of 1 in 10,000 live births. Epidemiologic data on other forms of SMA are lacking but together they are probably just as common.

Sex

Males and females are affected equally except for Kennedy’s disease (spinal bulbar muscular atrophy), which is an X-linked form of SMA.

ETOLOGY

Sporadic cases of SMA in adulthood are not uncommon but most clinically well-characterized forms of the disease are single gene disorders. Inactivating mutations in the survival motor neuron (SMN1) gene cause recessive proximal SMA of childhood. Disease severity correlates with the level of residual SMN protein derived from a neighboring gene (SMN2), which varies in copy number. SMN appears to function as a cofactor in ribonucleoprotein metabolism and mRNA splicing. It may have a hitherto unknown function in motor neurons. Another, much rarer, form of infantile SMA with diaphragmatic involvement is due to mutations in another putative RNA interacting protein called IGHMBP2. The X-linked form of bulbar SMA is due to polyglutamine expansion in the first exon of the androgen receptor gene. This leads to partial androgen insensitivity as well as SMA. None of the genes for dominantly inherited forms of SMA has yet been identified. However, spino-ocular SMA and distal lower limb SMA have both been linked to different regions of chromosome 12q, while upper limb predominant SMA has been linked to chromosome 7p.

RISK FACTORS

The SMAs are single-gene disorders with no known environmental influence on incidence or progression.

PREGNANCY

There have been occasional reports of women with mild proximal recessive SMA (type III) undergoing significant deterioration during pregnancy. Careful monitoring of respiratory function is advisable.

ASSOCIATED CONDITIONS

N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS

- Childhood recessive SMA: a large number of genetic syndromes lead to neonatal hypotonia, which may be confused with infantile SMA. Rare “SMA-mimic” syndromes occur including cerebellar hypoplasia with anterior horn cell involvement, SMA with congenital contractures, and metabolic disorders due to mitochondrial dysfunction. The key features that distinguish SMA are the normal intellect, sparing of the diaphragm and facial muscles, and the proximal distribution of weakness. The legs are weaker than the arms and are typically held in a “frog-like” posture. SMA with respiratory distress, due to mutations in IGHMBP2, presents with distal muscle weakness and prominent diaphragmatic involvement leading to evertation of abdominal contents into the thorax.

- Other forms of SMA: a detailed description of the many inherited forms of SMA is beyond the scope of this chapter. However, as a general diagnostic point, the appearance of anterior horn cell disease in a patient of any age generally raises fears of ALS. While pure lower motor neuron forms of ALS account for about 10% of cases, these are generally rapidly progressive and many patients ultimately develop upper motor neuron signs. Furthermore, ALS generally has an asymmetrical onset compared with SMA, which is almost always symmetrical. SMA is always a slowly progressive condition, and the majority of patients with later onset, dominantly inherited, SMA have a normal life span and often remain ambulant into old age. There is a degree of confusion among specialists about whether distal SMA should be classified as a pure form of motor neuropathy (the so-called spinal form of Charcot-Marie-Tooth disease) or as an anterior horn cell disease. The identification of the various genes for these disorders will ultimately resolve this argument.

- An important consideration in the differential diagnosis of SMA is multifocal motor neuropathy with conduction block. This presents as slowly progressive asymmetrical wasting and weakness, generally upper in the upper limbs. Nerve conduction studies can be used to demonstrate conduction block (i.e., a reduction in the compound muscle action potential when the nerve is stimulated proximally compared to more distally). This condition responds to treatment with intravenous immunoglobulin.
Spinal Muscular Atrophy

**SIGNS AND SYMPTOMS**
See above.

**LABORATORY PROCEDURES**

Creatine kinase levels may be normal or slightly elevated in different forms of SMA. Levels greater than 1000 IU should always raise the suspicion of a primary myopathy. Neurophysiology is mandatory in cases of suspected SMA at any age as (a) this provides the primary diagnostic confirmation of an anterior horn cell disease, (b) differentiates SMA from a myopathy or peripheral neuropathy, and (c) excludes treatable conduction block neuropathy. Muscle biopsy is often performed in difficult cases where electrophysiology cannot distinguish between a myopathy and denervating disorder.

**IMAGING STUDIES**

While MRI scanning of muscle is under investigation as a tool for distinguishing neurogenic muscle atrophy from primary myopathies, it is unlikely to replace neurophysiology as the primary diagnostic test.

**SPECIAL TESTS**

Direct genetic analysis is routinely available for mutations in the SMN gene and the trinucleotide expansion associated with Kennedy’s disease. For other rarer forms of SMA for which genes have not yet been identified, contact should be made directly with research laboratories undertaking linkage studies.

**MANAGEMENT**

**GENERAL MEASURES**

The prognosis for infantile SMA presenting with respiratory compromise in the first few months of life is very poor and early and sensitive discussion with the parents is required in deciding when to withdraw ventilation. All children with childhood forms of SMA should be assessed for respiratory compromise on a regular basis. Physiotherapy can limit recurrent infections. A careful assessment for the development of scoliosis is important, as this leads to preventable disability.

**SURGICAL MEASURES**

Patients who develop painful muscle contractures may benefit from orthopedic intervention. Patients with type II and III SMA may require spinal surgery for scoliosis.

**SYMPTOMATIC TREATMENT**

Noninvasive ventilation is increasingly being used in type II SMA and prolongs life. A multidisciplinary team in a specialist center is required to support patients on home ventilation.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

N/A

**MEDICATIONS**

**DRUG(S) OF CHOICE**

N/A

**ALTERNATIVE DRUGS**

N/A

**FOLLOW-UP**

As with other chronic neurologic disorders, SMA is best managed by a dedicated multi-disciplinary team (with physiotherapy, occupational therapy, dietetics, and respiratory care specialists) in a specialist setting. The clinical course of the different forms of SMA dictates the pattern of follow-up, but the childhood recessive forms generally require more medical supervision. The role of the neurologist in milder adult-onset forms is primarily diagnostic.

**EXPECTED COURSE AND PROGNOSIS**

Described above and dependent on the exact type of SMA.

**PATIENT EDUCATION**

A major issue is that patients are appropriately informed about the pattern of inheritance (dominant versus recessive) of their disorder so that they can make choices about family planning. Referral to a clinical geneticist is usually advisable. For recessive SMA due to mutations in the SMN gene, preimplantation genetic diagnosis is available in selected centers.

**SYNONYMS**

Kennedy’s disease (spinobulbar muscular atrophy)
Werdnig-Hoffmann disease
Kugelberg-Welander syndrome

**ICD-9-CM:** 335.10 Spinal muscular atrophy, unspecified; 335.0 Werdnig-Hoffmann disease; 335.11 Kugelberg-Welander disease

**REFERENCES**


**Author(s):** Kevin Talbot, MD, DPhil
Spinocerebellar Ataxias

Basics

DESCRIPTION
• The inherited spinocerebellar ataxias (SCAs) represent a group of neurodegenerative diseases characterized by clinical and genetic heterogeneity. This group of disorders encompasses the autosomal dominant cerebellar ataxias (ADCA) and autosomal recessive Friedrich's ataxia (ARFA); only the ADCA will be discussed here. Among the ADCA, new gene loci for mutations are being steadily identified; the corresponding clinical syndromes are labeled as SCA-1, SCA-2, SCA-3 (Machado-Joseph disease), etc. These genetically distinct disorders have overlapping clinical features that make them difficult to diagnose based on clinical features alone.

EPIDEMIOLOGY
Incidence
• 5 per 100,000

ETIOLOGY
• The genetic mutation in five of the ADCA syndromes has been shown to be expansion of an unstable stretch of CAG trinucleotide repeats within the coding region of the respective gene. In the normal population, the CAG repeats are stable; however, when expansion occurs, the number of CAG repeats reaches a threshold at which neurodegeneration occurs and clinical manifestations are evident. As a group, the trinucleotide repeat disorders have several common features that are clearly demonstrated in the SCA kindreds with the CAG repeat mutation.

— Anticipation: Clinically, it is the occurrence of symptoms at an earlier age along with a more severe disease phenotype or more rapid progression in successive generations. Underlying clinical anticipation is the observed increasing expansion of the trinucleotide repeat sequence in successive generations through parent-child transmissions, i.e., intergenerational instability or meiotic instability.

— Inverse correlation between age of onset and repeat number: As repeat number increases, age of onset becomes earlier. There is also a tendency for larger repeat numbers to be associated with more severe disease phenotypes.

— Parenteral transmission bias: In a majority of these disorders, intergenerational instability of the repeat is largest in transmission from a father to his offspring.

• The CAG trinucleotide encodes for the amino acid glutamine. Thus, a stretch of CAG repeats results in a polyglutamine tract within the final gene product, i.e., the translated protein. It is thought that this addition to the protein results in a “gain of function” or “change of function” that leads to premature neurodegeneration.

RISK FACTORS
• Family history of ataxia, movement disorder, or gait disturbance

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
• Other autosomal dominant neurodegenerative diseases:
  — Huntington’s disease; CAG repeat disease
  — Dentatorubropallidoluysian atrophy; CAG repeat disease
  — Gerstmann-Straussler-Scheinker disease (prion disease)
  — Creutzfeldt-Jakob disease, ataxic form (prion disease)

— Autosomal dominant ataxias:
  — Episodic ataxia type 1
  — Ataxia telangiectasia
  — Dentatorubropallidoluysian atrophy; CAG repeat disease

— Autosomal recessive ataxias:
  — Friedreich’s ataxia; GAA repeat expansion
  — Ataxia telangiectasia
  — Ataxia with vitamin E deficiency — Bassen-Kornzweig syndrome (abetalipoproteinemia)

SIGNS AND SYMPTOMS
• These disorders demonstrate wide clinical variability, with ataxia the predominant manifestation, in conjunction with other neurologic findings. Clinical variability is evident within a single kindred, between kindreds with the same genotype, and between kindreds with different genotypes. General features among these disorders include a wide range of onset age and anticipation.

— SCA-1: SCA-1 is characterized by constant features of gait and limb ataxia, dystarthria, and dysfunction of cranial nerves IX, X, and XII. The disorder will start with ataxia, usually gait ataxia being more severe than limb ataxia, and dystarthria. Pyramidal tract findings (spasticity, hyperreflexia, Babinski signs) and oculomotor findings (e.g., nystagmus, slow saccades, ophthalmoparesis) can be seen early. Only late in the disease course do the cranial nerve palsies occur, leading to dysphagia, recurrent pneumonia, and eventual death. Dystonic posturing or involuntary movements, such as choreoathetosis, also tend to appear late. Mental retardation has been seen only in juvenile-onset cases and tends to appear before any other neurologic manifestations. Anticipation is observed clinically and correlates with larger CAG expansions; Larger expansions occur through paternal transmissions.

— SCA-2: SCA-2 is characterized by cerebellar ataxia, dystarthria, slow saccades, and peripheral neuropathy. A common initial complaint is muscular cramps at rest. Pyramidal and extrapyramidal features, optic atrophy, and dementia are infrequent features. Anticipation is observed in all kindreds, with larger CAG expansions occurring with paternal transmission.

— SCA-3: Machado-Joseph disease: The label of Machado-Joseph disease (MJD) arose in the 1970s in reference to families who exhibited ADCA with wide clinical diversity. However, a disorder with similar phenotypic variability had been described among families of different geographic origin, including Caucasians, the Japanese, and African Americans. It was unclear if these latter families had MJD or another dominant spinocerebellar ataxic syndrome. Subsequent work showed that all of the kindreds had the same genetic mutation, an expansion of CAG trinucleotide repeats in the ataxin-3 gene on chromosome 14. Thus, MJD and SCA-3 are the same disease because they share the same underlying genetic defect. The disorder almost always begins with cerebellar ataxia manifested as an unsteadiness of gait, followed consistently by dystathria and ophthalmoparesis. Thereafter, a wide range of clinical features may be seen. In early-onset patients (i.e., mid-20s), pyramidal and extrapyramidal features, and facial and lingual fasciculations, are frequently present. In later-onset patients, peripheral neuropathy with weakness and atrophy is common. Anticipation has been observed clinically. • SCA-4: This ataxic syndrome is characterized by progressive ataxia, sensory axonal neuropathy, and normal eye movements. Less common features include an extensor plantar response and distal weakness.
**Spinocerebellar Ataxias**

**LABORATORY PROCEDURES**
- Vitamin E level
- Peripheral smear for acanthocytes
- Lipoprotein levels
- Immunoglobulin levels
- a-Fetoprotein

**IMAGING STUDIES**
- Brain MRI

**SPECIAL TESTS**
- DNA testing is commercially available for the trinucleotide repeat disorders.

**GENERAL MEASURES**
- Prevention of falls and aspiration pneumonia are of primary concern.

**SURGICAL MEASURES**
- Gastric tube placement should be considered when swallowing becomes impaired.

**SYMPTOMATIC TREATMENT**
- Clonazepam and valproate for associated myoclonus

**ADJUNCTIVE TREATMENT**
- Mobility aids for ataxia
- Physical therapy

**ADMISSION/DISCHARGE CRITERIA**
- N/A

**LABORATORY PROCEDURES**
- Vitamin E level
- Peripheral smear for acanthocytes
- Lipoprotein levels
- Immunoglobulin levels
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**ADJUNCTIVE TREATMENT**
- Mobility aids for ataxia
- Physical therapy

**ADMISSION/DISCHARGE CRITERIA**
- N/A

**Follow-Up**

**PATIENT MONITORING**
- Patients should be seen routinely for identification of potential complications, such as excessive falls and dysphagia.

**EXPECTED COURSE AND PROGNOSIS**
- All of the ADCAs are progressive disorders that typically shorten the individual’s lifespan; however, variability is the rule, not the exception, in these conditions.

**PATIENT EDUCATION**
- National Ataxia Foundation. Website: www.nafmr.net

**SYNONYMS**
- N/A

**ICD-9-CM:** 781.3 Ataxia; 334.2 Hereditary ataxia; 334.3 Cerebellar ataxia

**SEE ALSO:** FRIEDREICH'S ATAXIA

**REFERENCES**

**Author(s):** Paul G. Wasielewski, MD
**Stiff Person Syndrome**

**Basics**

**DESCRIPTION**

- Stiff person syndrome (SPS) is a rare disabling disorder of motor function characterized by muscle rigidity and spasms that involve the axial and limb musculature. Continuous contraction of agonist and antagonist muscles caused by involuntary motor unit firing at rest are the hallmark clinical and electrophysiologic signs of the disorder. Except for involuntary global stiffness, the remainder of the neurologic examination is normal.

**EPIDEMIOLOGY**

- **Incidence/Prevalence**
  - The prevalence has not been reported, but it is clear that SPS is rare.

- **Race**
  - There is no clear racial or ethnic predisposition.

- **Age**
  - The age of onset of symptoms is usually in the fifth decade of life but ranges from the third through the seventh decade. Cases in children are rarely reported.

- **Sex**
  - The disease may be more common in women than in men.

**ETIOLOGY**

- The etiology of SPS is unknown; however, it is believed to be a central nervous system (CNS) disorder. Approximately 10% of patients with SPS have seizures. Drugs that enhance CNS levels of y-aminobutyric acid (GABA), such as diazepam or valproic acid, improve patient symptoms. One theory proposes that patients with SPS have impaired cortical and spinal inhibitory GABA-nergic intraneurons. The proposed loss of this GABA-nergic input to motor neurons is thought to produce the tonic firing of motor neurons at rest and lead to their hyperactive excitation. Supportive of this theory is that up to 65% of patients with SPS have antibodies against glutamic acid decarboxylase (GAD), which is the rate-limiting enzyme for the synthesis of GABA at the GABA-nergic nerve terminals. The hypothesis is that the anti-GAD antibodies cause a functional impairment in the synthesis of GABA and therefore may play a pathogenic role in the disease. Anti-GAD antibodies have been isolated in both the serum and the CSF of patients with SPS.

- In a subgroup of patients, SPS is a paraneoplastic disease. In these patients, the stiffness is mostly in the proximal muscles and may predate the detection of the tumor. The most common tumor detected is breast cancer.

**ASSOCIATED CONDITIONS**

- There are clinical and laboratory associations with autoimmune diseases such as type 1 diabetes, pernicious anemia, thyroiditis, and epilepsy. The autoimmune pathogenesis of SPS is strongly supported by the presence of antibodies to glutamic acid decarboxylase (anti-GAD) or anti-islet cell antibodies (anti-ICA) in most patients. Common presence of other autoimmune diseases or autoantibodies in SPS patients and first-degree relatives.

**SPECIAL TESTS**

- EMG shows continuous activation of normal-appearing motor unit potentials in affected muscles despite attempts to relax.

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Diseases that should be differentiated from SPS include chronic tetanus, neuromyotonia, and various types of dystonia and extrapyramidal disease, all of which are easily excluded based on the neurologic examination.

**SIGNS AND SYMPTOMS**

- SPS is a disabling disorder that begins insidiously and progresses over months to years. Two sets of symptoms characterize the disease: stiffness and spasms. Patients first develop a sensation of progressive stiffness that involves the paraspinal musculature. This stiffness manifests over time as paraspinal hypertrophy and lumbar hyperlordosis. To the examiner, the patient's muscles may feel as firm as rocks. Over months the rigidity may extend to involve the extremities. If this occurs, it is not uncommon for the rigidity to be asymmetric. A few cases of extension to the facial musculature have been reported. Superimposed on this set of symptoms, patients experience painful muscle spasms that are triggered by emotional duress, unexpected noise, or tactile stimulation. Collectively these symptoms impair a patient's ability to ambulate effectively.

**LABORATORY PROCEDURES**

- The presence of anti-GAD, anti-ICA, and other autoantibodies helps to support the diagnosis of SPS in a patient with the appropriate clinical presentation but is not necessary for the diagnosis. These antibodies may be isolated from the serum and CSF.

**IMAGING STUDIES**

- CT and MRI of the brain and spinal cord are normal in patients with SPS. However, neuroimaging is suggested because it can exclude a demyelinating process that could result in some symptoms, such as spasticity, that can mimic SPS.

**Management**

**GENERAL MEASURES**

- Patients require a significant amount of counseling to educate them on the condition. Attention should be given to how the disorder affects their quality of life. If appropriate, psychological and social services should be offered to support patients as they cope with their disability.

**SURGICAL MEASURES**

- N/A

**SYMPTOMATIC TREATMENT**

- There is no cure for SPS, but a variety of medications are available to alleviate symptoms. On the basis of the proposed pathogenesis of the disorder, two types of therapy are rationally applied: (i) drugs that enhance CNS GABA-nergic activity, and (ii) immunomodulators.

**ADJUNCTIVE TREATMENT**

- Behavioral medicine and biofeedback may be helpful in managing the psychological factors that can aggravate symptoms.

**ADMISSION/DISCHARGE CRITERIA**

- Hospitalization may be indicated for management of severe spasms, spasticity, and pain.
**Medications**

**DRUG(S) OF CHOICE**
- **Diazepam** was the first studied and is the most widely used medication. Many patients take 40–60 mg/day; a few take >100 mg/day. Mood changes and sedation are common and should be screened for. Although no controlled trials have been done, most patients with SPS respond to diazepam to some degree and for an extended period of time. The required doses, however, are often so high that diazepam is not easily tolerated and other agents are used as needed.
- **Vigabatrin**, which decreases GABA catabolism, and **tiagabine**, which interferes with GABA uptake, may be helpful.
- **Baclofen** increases GABA activity and thus is efficacious in reducing rigidity and spasms when administered orally/intrathecally. Intrathecal administration has the advantage of minimizing sedation side effects.
- **Corticosteroids** and **azathioprine** have been shown to be effective in treating patient symptoms. Some side effects of corticosteroid use are of particular concern in patients with SPS. IDDM is present in 30% of patients with SPS and complicates therapy, but is not an absolute contraindication. Azathioprine can be effectively used as a steroid sparing agent. Screening for leukopenia and liver dysfunction is important.

**ALTERNATIVE DRUGS**
- Experience with **intravenous immunoglobulin** and **plasma exchange** is limited but promising.

**Follow-Up**

**PATIENT MONITORING**
- Regular visits to screen for patient comfort and quality of life are important to the patient, as is routine laboratory work to screen for toxic effects of therapies such as steroids and azathioprine.

**EXPECTED COURSE AND PROGNOSIS**
- Patients with SPS generally have a progressive course with variable response to treatment.

**PATIENT EDUCATION**
- Patients can learn more about this disorder through the National Institute of Neurological Disorders and Stroke. Website: www.ninds.nih.gov

**SYNONYMS**
- Woltman-Moersch syndrome
- Stiff man syndrome

**ICD-9-CM:** 333.91 Stiff man syndrome

**SEE ALSO:** NA

**REFERENCES**

**Author(s): Edward A Goldberg, MD**
**Sturge-Weber Syndrome**

**DESCRIPTION**
- Sturge-Weber syndrome (SWS) is a congenital condition affecting the cephalic venous microvasculature.
- The hallmark intracranial vascular anomaly is leptomeningeal angiomatosis, which most often involves the occipital and posterior parietal lobes but can affect both cerebral hemispheres.
- An ipsilateral facial cutaneous capillary vascular malformation usually affects the upper face in a distribution consistent with the first branch of the trigeminal nerve.
- Other findings include glaucoma, buphthalmos, enlargement of the choroid plexus, and seizures.
- Hemiparesis, hemiatrophy, hemianopia, and stroke-like events may occur contralateral to the cortical abnormality.
- Calcifications are noted in the external layers of the atrophic cerebral cortex underlying the angiomatosis.
- Nervous, cutaneous, and ophthalmic systems are affected.

**ETIOLOGY**
- Congenital. There is a malformation of an embryonic vascular plexus arising within the cephalic mesenchyme between the neuroectoderm and the telencephalic vesicle. Interference with vascular drainage development within these areas between weeks 5 and 8 of gestation subsequently affects the face, eye, leptomeninges, and brain.

**GENETICS**
- Inheritance is sporadic

**RISK FACTORS**
- N/A

**PREGNANCY**
- N/A

**ASSOCIATED CONDITIONS**
- Glaucoma
- Headache
- Seizure

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Facial capillary vascular malformation
- Isolated cutaneous malformation without accompanying glaucoma or CNS disease
- Partial Seizures
  - Idiopathic
  - CNS malformation (neuronal migration)
  - Mesial temporal sclerosis
  - Hemorrhage
  - Tumor
  - Other

**SIGNs AND SYMPTOMS**
- From 75%–90% of patients with SWS have epilepsy. Seizures probably are caused by hypoxia and microcirculatory stasis.
- From 85%–90% of patients with SWS have facial capillary vascular malformation.
- Other accompanying symptoms are vascular headaches (40%–60%), developmental delay (30%–70%), choroidal hemangioma (40%), hemianopia (40%–45%), and hemiparesis (25%–60%).

**LABORATORY PROCEDURES**
- N/A

**IMAGING STUDIES**
- Skull x-ray film shows classic "tram-line" or "tram-track" calcifications. These may be a late finding and may not be present initially.
- Angiography demonstrates a lack of superficial cortical veins, nonfilling of the dural sinuses, and a tortuous course of veins toward the vein of Galen. Evidence of venous stasis is characteristic. Arterial distribution is normal.
- CT scan shows calcifications, brain atrophy, and ipsilateral choroid plexus enlargement.
- MRI with gadolinium enhancement shows leptomeningeal angiomatosis.
- SPECT demonstrates decreased cortical perfusion.
- PET demonstrates hypometabolism in areas that correspond to decreased perfusion.
- EEG show electromagnetic abnormalities localized to areas underlying the leptomeningeal angiomatosis. Rarely, affected infants have infantile spasms.

**SPECIAL TESTS**

**Pathology**
- Leptomeningeal angiomatosis usually involves the occipital and posterior parietal lobes. It can affect the entire cerebral hemisphere.
- Leptomeninges appear thickened and discolored by the leptomeningeal angiomatosis.
- Enlarged choroid plexus is seen.
- Calcifications are seen in meningeal arteries, cortical and subcortical veins, and cortex underlying the leptomeningeal angiomatosis.
- Laminar cortical necrosis can accompany calcifications, suggesting ischemic damage secondary to venous stasis in leptomeninges and in the cerebral capillary bed.
- Neuronal loss and gliosis can occur.

**MANAGEMENT**

**GENERAL MEASURES**
- Seizure control
- Symptomatic and prophylactic headache therapy
- Glaucoma treatment to reduce intraocular pressures
- Laser therapy for facial cutaneous vascular malformation
- Management of behavior and learning problems

**SURGICAL MEASURES**
- For patients with refractory focal seizures, surgery is an option. Procedures include focal cortical resection, hemispherectomy, corpus callosotomy, and vagal nerve stimulation.
- Surgical therapy for intractable epilepsy from SWS uses the same guiding principles as surgical therapy for epilepsy in general.
- There is no conclusive evidence that surgery in infancy is indicated in SWS.
- If glaucoma is poorly controlled by medications, then surgery may be indicated. Trabeculectomy and goniotomy are options.

**SYMPTOMATIC TREATMENT**
- Seizures: Antiepileptics with focal seizure efficacy and limited side effects
- Stroke-like events: Aspirin to inhibit platelet aggregation
- Headaches: Combination analgesics; antimigraine therapy
- Facial cutaneous vascular malformation: Laser therapy started as soon as possible is most successful. Reports show psychological benefits of early removal.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- Incidence in the United States is unknown. An estimated 5,000 Americans are affected.

**AGE**
- The typical patient presents at birth with facial capillary vascular malformation.
- Most children have partial seizures by age 3 years.
- Early onset of seizures does not clearly indicate a poor prognosis.

**SEX**
- N/A

**RACE**
- N/A

**ASSOCIATED CONDITIONS**
- Glaucoma
- Headache
- Seizure

**DIFFERENTIAL DIAGNOSIS**
- Facial capillary vascular malformation
- Isolated cutaneous malformation without accompanying glaucoma or CNS disease
- Partial Seizures
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Sturge-Weber Syndrome

Follow-Up

PATIENT MONITORING
- Child neurologist, ophthalmologist, and dermatologist should follow children with SWS as associated problems dictate.

Possible Complications
- Status epilepticus
- Prolonged stroke-like episode
- Hearing disorder
- Behavior problem
- Irretractable headaches

EXPECTED COURSE AND PROGNOSIS
- Some patients are minimally affected, if at all. Others have early-onset seizure, stroke-like episodes, and neurologic deterioration. The course is too variable to predict prognosis in any patient.
- Life expectancy is thought to be normal.

Patient Education
- The Sturge-Weber Foundation provides patients with mentors and allows families to network and communicate about emotional and therapeutic management. It is the "first stop" for families of children with SWS. Website www.sturge-weber.com
- No restrictions to activity except as dictated by associated conditions. Some patients with SWS report severe headache after minor head trauma.
- No special diet is required.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
N/A

Medications

DRUG(S) OF CHOICE
- Carbamazepine (Tegretol)
- Valproic Acid (Depakote, Depacon)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Oxcarbazepine (Trileptal)
- Aspirin

Contraindications
N/A

Precautions
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up Miscellaneous

SYNONYMS
- Encephalotrigeminal angiomatosis
- Angio-encephalo-cutaneous syndrome

ICD-9-CM: 759.6 Sturge-Weber syndrome

SEE ALSO: N/A

REFERENCES

Author(s): Bernard Maria, MD, MBA; Kristin Thomas-Sohl, BA
Subclavian Steal Syndrome

**Basics**

**DESCRIPTION**
- Subclavian steal phenomenon describes a state of retrograde vertebral artery flow in the setting of proximal arterial stenosis to the upper limb, causing rerouting of blood from the vertebral circulation. This is a relatively common phenomenon usually recognized by ultrasound.

- Subclavian steal syndrome refers to the rare situation where neurologic symptoms are caused by this retrograde flow. The treatment of this syndrome is not fully characterized due to its rarity. Subclavian steal phenomenon may be characterized by the territory from which blood is "stolen," or by the severity of hemodynamic disturbances. Territories are classified as vertebral, carotid-basilar, external carotid, or carotid-subclavian. Severity is classified as stage I: reduced antegrade vertebral flow; stage II: reversal of flow during arm exercise; and stage III: permanent retrograde vertebral flow. The left vertebral is most commonly affected in this disorder (4:1 ratio).

**ETIOLOGY**
- The Joint Study of Extracranial Arterial Occlusion showed angiographic steal occurred in 2.5% (168/6,534) of cases in the study. Of these, only 9/168 (5.3%) of angiographic cases had neurologic symptoms. A European survey showed subclavian steal phenomenon in 324 of 25,000 patients referred for cerebrovascular Doppler ultrasound; of these, only 5% had symptoms suggestive of vertebral dysfunction.
- Males are affected more than females for atherosclerotic subclavian steal phenomenon (approximately 2:1), but females are more likely to suffer from Takayasu's disease. Older patients are more likely to have subclavian steal syndrome of atherosclerotic type; subclavian steal syndrome in Takayasu's disease usually presents in young adults.

**RISK FACTORS**
- Usual risk factors for atherosclerotic disease, including smoking, hyperlipidemia, hypertension, diabetes, cardiovascular disease, peripheral vascular disease, family history, and age

**PREGNANCY**
- N/A

**ASSOCIATED CONDITIONS**
- Most patients with subclavian steal phenomenon have associated carotid circulation stenosis (in the Joint Study of Extracranial Arterial Occlusion, 80% had associated extracranial obstructions). Other atherosclerotic disorders, including cardiac and peripheral vascular diseases, are common in this patient population.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Differential includes other causes of transient neurologic dysfunction, particularly of the posterior circulation. Intracranial vertebral or basilar stenosis should be considered in this patient population. Embolic lesions from cardiac and other proximal sources may cause similar symptoms. Bickerstaff variant of migraine is characterized by vertebrobasilar symptoms that usually last minutes and are accompanied by headache. Focal seizures occasionally cause vertigo lasting seconds to minutes, representing a simple partial seizure.

**SIGNS AND SYMPTOMS**
- Subclavian steal syndrome is defined by the presence of vertebrobasilar symptoms in the presence of subclavian steal phenomenon, i.e., retrograde flow in the vertebral arteries precipitated by arm exercise. Symptoms may include vertigo, unsteadiness, visual blurring, and occasionally diplopia and sensory symptoms. Provoking maneuvers for symptoms include ipsilateral arm exercise and neck movement. Hemispheric symptoms have been described in subclavian steal syndrome (aphasia, unilateral field cut, hemi-motor or sensory symptoms.) Whether these symptoms are due to subclavian steal syndrome or concomitant anterior circulation disease is unclear.

**IMAGING STUDIES**
- There is no specific role for plain radiographs. Magnetic resonance angiography (MRA) may be useful for characterizing the presence of subclavian steal phenomenon. Special techniques, such as phase-contrast MRA and head and neck coils with gadolinium enhancement, may depict the presence of proximal subclavian artery stenosis or occlusion. Angiography can directly show the anatomic features of subclavian stenosis or occlusion, the presence of retrograde vertebral flow, and associated extracranial and intracranial stenoses. Angiography is attended by risks of arterial puncture and reactions associated with contrast medium.

**SPECIAL TESTS**
- Subclavian steal phenomenon is identified during Doppler ultrasound examination of the carotid and vertebral circulation. Findings may vary from transient decrease in ipsilateral vertebral artery mid-systolic velocity (mild) to total vertebral flow (severe). Doppler ultrasound assists in documentation of other vascular lesions (internal and external carotid, contralateral vessels). Transcranial Doppler may further characterize intracranial flow dynamics in the posterior circulation.

**LABORATORY PROCEDURES**
- There are no specific blood tests for subclavian steal syndrome.

**SIGNS AND SYMPTOMS**
- Signs of subclavian steal syndrome include weak or absent radial and ulnar pulses. Blood pressure measured in both arms may show a reduction >20 mm Hg compared to the contralateral arm. A bruit over the subclavian artery may be audible. Unless the patient is symptomatic at the time of neurologic examination, there are no neurologic signs suggestive of subclavian steal syndrome. All should be examined for evidence of peripheral vascular disease and carotid disease.

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**LABORATORY PROCEDURES**
- There are no specific blood tests for subclavian steal syndrome.
**Subclavian Steal Syndrome**

**Management**

**GENERAL MEASURES**
- Avoiding specific inciting maneuvers (e.g., arm exercise, neck position changes) may be beneficial.

**SURGICAL MEASURES**
- Surgical measures may be used when symptoms are severe and well defined by imaging and Doppler ultrasound techniques. Various techniques are used, including carotid-subclavian bypass and axillo-axillary bypass. Published mortality rates for these vary between 0.4% and 2.5%

**SYMPTOMATIC TREATMENT**
- N/A

**ADJUNCTIVE TREATMENT**
- Percutaneous transluminal angioplasty (PICA) with or without stent placement is becoming the intervention of choice for subclavian stenosis syndrome. Risks of these procedures include stroke, access site hematoma, and arterial dissection. The decision to intervene is largely dominated by the nature of the symptoms. If the symptoms are mild and not debilitating, avoiding intervention may be the treatment of choice.

**ADMISSION/DISCHARGE CRITERIA**
- Most patients are evaluated on an outpatient basis unless there are prolonged neurologic symptoms or the differential of TIA is being evaluated. Patients may require admission for surgical procedures or short-stay admission for PICA with or without stent placement.

**Follow-Up**

**PATIENT MONITORING**
- Patients will require monitoring for their course, as well as progression of concomitant cerebrovascular disease. Repeated Doppler ultrasound is a safe method of monitoring for worsening of vertebral flow reversal.

**EXPECTED COURSE AND PROGNOSIS**
- The prognosis for subclavian steal syndrome has not been fully characterized due to its rarity. The course varies and depends on the extent of symptoms with exercise and neck movement, as well as the presence of concurrent cerebrovascular disease.

**PATIENT EDUCATION**
- Patients should be apprised of the pathophysiology of their symptoms, various options for therapy, treatment of risk factors, and proper notification of physicians in case of increasing symptoms.

**Drugs**

**DRUG(S) OF CHOICE**
- There are no specific drug approaches to subclavian steal syndrome. The appropriate use of antiplatelet agents, lipid-lowering medications, and antihypertensives are similar to that for patients with ischemic stroke or transient ischemic attack syndromes.

**Contraindications**
- N/A

**Precautions**
- N/A

**ALTERNATIVE DRUGS**
- N/A

**Medications**

**SYNONYMS**
- N/A

**ICD-9-CM:** 435.2 Subclavian steal syndrome

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** Alexander D. Rae-Grant, MD

**Missellaneous**

**SYNONYMS**
- N/A

**ICD-9-CM:** 435.2 Subclavian steal syndrome

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** Alexander D. Rae-Grant, MD
Sydenham's Chorea

Basics

DESCRIPTION
- First described by Sydenham in 1686, Sydenham's chorea is an immune-mediated acquired chorea that occurs after streptococcal pharyngitis. It may be associated with other features of rheumatic fever (Jones criteria). Chorea refers to involuntary, forceful, random jerks that involve any part of the body. They can include abnormal movements of the respiratory muscles, producing grunts and other sounds. Chorea is present at rest and increases with voluntary movements. Chorea at rest and with posture gives rise to the appearance of a restless child who is unable to sit still. "Flapping" movements of fingers, when the hand is held outstretched, and the "milkmaid's grip" when grasping an object, are features of chorea. Volitional movements often are jerky, and the gait often has a lurching quality. Chorea may be accompanied by athetosis, which consists of involuntary movements that have a more writhing, sinusoidal quality.

EPIDEMIOLOGY

Incidence/Prevalence
- Most prevalent acquired chorea in childhood.
- There has been a previous decline in the incidence, with a more recent resurgence of cases.
- Occurs in 10%-20% of patients with rheumatic fever.
- Seen mostly between the ages of 5 to 15 years.
- Female predominance occurring at a ratio of approximately 2:1 that becomes more evident after age 10 years.

ETIOLOGY
- It is thought that group A/3-hemolytic streptococci (GABHS) trigger antistreptococcal antibodies that, by molecular mimicry, cross-react with epitopes on the basal ganglia of susceptible hosts. Genetic susceptibility is suggested by the higher than expected familial incidence of this condition. Although the nature of the relationship between antineuronal antibodies and neuropsychiatric symptoms is not yet known, one hypothesis is that when genetically vulnerable children are exposed to GABHS, antibodies are produced that mistakenly recognize cells within the basal ganglia and cause an inflammatory response. This inflammation is manifest by involuntary movements and psychiatric symptoms. Symptom expression may depend on the epitope recognized by the antineuronal antibody, extent of inflammation, chronicity of the insult, developmental stage of the child's immune system, inherited vulnerability, or a combination of these factors.

RISK FACTORS
- Family history of rheumatic fever, Sydenham's chorea, or post-streptococcal carditis appears to increase the risk of an individual developing Sydenham's chorea.

PREGNANCY
- Women who had Sydenham's chorea in childhood may rarely have a recurrence of symptoms during pregnancy.

ASSOCIATED CONDITIONS
- Rheumatic fever
- Cardiac involvement in 33.7%
- Other neurologic symptoms: Approximately 38.7% had dysarthria. Encaphalopathy, with personality changes, emotional lability, disorientation, confusion and, more rarely, delirium, occurred in 10%.
- Other psychiatric symptoms: Obsessive-compulsive symptoms were seen in 82%. Other symptoms included emotional lability, irritability, distractibility, motoric hyperactivity, age-regressed behavior, nightmares, and anxiety. These symptoms may start 2-4 weeks prior to onset of chorea, peak as the motor severity does, and remit shortly after the chorea disappears.

Signs and Symptoms
- Chorea and emotional lability appear abruptly several months after streptococcal pharyngitis. Although usually fairly abrupt in onset, symptoms may progress in severity over a few weeks and persist for months. In a retrospective study of 240 patients between 1951 and 1976 at the University of Chicago, 81% had generalized chorea and 19% had hemichorea. Duration of chorea ranged from 1-22 weeks (median 12 weeks). Eighty percent had no recurrences.
- Diagnosis is made by establishing a preceding exposure to GABHS, either by history or by elevated antistreptococcal antibody titers (ASO [antisera] or anti-DNase B). However, in about 20% of cases, no clinical or serologic evidence of a preceding GABHS can be established, because the chorea can lag behind the etiologic infection by 6 months. Without documentation of an antecedent streptococcal infection, the diagnosis of Sydenham's chorea is made by excluding other causes of childhood chorea.

Differential Diagnosis
- Primary central nervous system vasculitis
- Systemic lupus erythematosus
- Acute encephalitis
- Toxins/drugs
- Wilson's disease
- PANDAS (pediatric autoimmune neuropsychiatric disorders after streptococcal infections)
- GM1 and GM2 gangliosidoses
- Glutaric aciduria
- Methylmalonic and propionic academia
- Antiphospholipid antibody syndrome
- Thyrotoxicosis

LABORATORY PROCEDURES
- Search for evidence of a previous streptococcal infection with ASO titer, anti-DNase B titer, and a throat swab to determine whether the patient still has streptococcal colonization of the throat. Other tests should include a rheumatological screen with ESR, ANA, RF, and antiphospholipid antibodies. If there is evidence suggesting an acute primary central nervous system infection, cerebrospinal fluid analysis should be performed. When Sydenham's chorea is a consideration, a search should be undertaken for cardiac involvement with electrocardiography and echocardiography.

IMAGING STUDIES
- MRI: Analysis of cerebral MRIs of subjects with Sydenham's chorea and controls in one study demonstrated increased size of the basal ganglia in the Sydenham's chorea group. However, as a diagnostic tool in Sydenham's chorea, cerebral MRI appears to be more helpful in eliminating certain other mimickers than in confirming the diagnosis, as it may often look fairly normal in Sydenham's chorea.

SPECIAL TESTS
- SPECT scan of the brain may show hyperperfusion in the basal ganglia.

Diagnosis

Management

General Measures
- Eradication of streptococcus if still present in the pharynx with antibiotics, and prevention of further infection with antibiotic prophylaxis
- Treatment of cardiac dysfunction if present
- Treatment of chorea
- Treatment of behavior/neuropsychiatric symptoms

Surgical Measures
N/A
**SYMPTOMATIC TREATMENT**

- Treatment of chorea (see below). Psychiatric manifestations warrant evaluation and appropriate therapy depending on severity. Cardiac manifestations should be treated and monitored closely.

**ADJUNCTIVE TREATMENT**

- Measures for physical safety in patients with significant difficulties in ambulation. Difficulties in the realms of behavior, fine motor skills, and cognition should be addressed by a team consisting of the medical provider, psychology/psychiatry, educators, and physical and occupational therapists.

**ADMISSION/DISCHARGE CRITERIA**

- Admission for rapid evaluation and monitoring if symptoms suggest a primary central nervous system infection or if there are symptoms of cardiac dysfunction. Patients with severe chorea who are unable to ambulate may benefit from initial inpatient rehabilitation.

**DRUG(S) OF CHOICE**

- **Prednisone.** In one retrospective study, children treated with prednisone appeared to have a shorter course of chorea than those treated with haloperidol, valproate, or diazepam. Prednisone can cause weight gain, cushingoid appearance, mood lability, psychosis, hypertension, hyperglycemia, electrolyte imbalances, and gastritis. It can suppress the immune system, thereby decreasing the individual's ability to fight off intercurrent infections.
- **Valproate.** In a study of 18 children with Sydenham's chorea, valproate appeared to have a better efficacy than carbamazepine and haloperidol. Side effects can include an allergic skin rash, weight gain, thrombocytopenia, pancytopenia, pancreatitis, hepatic failure, and gastritis.
- **Carbamazepine.** Side effects can include liver dysfunction, an allergic skin rash, leukopenia, pancytopenia, drowsiness, ataxia, and hyponatremia.
- **Haloperidol.** Potential side effects include an acute dystonic reaction, weight gain, hyperthermia, and drug-induced dyskinesias.
- **Pimozide.** Potential side effects include those of haloperidol, with the potential for cardiac dysrhythmias.
- **Benzodiazepines.** Sedation appears to be the main side effect.

**PATIENT MONITORING**

- Monitor response to treatment and for potential side effects of the drug used. Gradually wean medications as symptoms resolve.

**EXPECTED COURSE AND PROGNOSIS**

- Sydenham's chorea is considered benign and self-limiting. However, on occasion chorea can be so severe as to cause significant impairment in motor function and ambulation. Psychological manifestations may range from minimal to extremely severe. Without treatment the symptoms tend to gradually remit, but may take weeks to a year. Recurrent attacks can occur in up to 20% of cases. Usually there was only one recurrence, on average 1.8 years, after the first attack. Recurrences many years after the initial attack are uncommon and suggest that late chorea may be due to reactivation by another mechanism, such as pregnancy or drugs. Patients with Sydenham's chorea may have chorea during pregnancy (chorea gravidarum) and are at higher risk for chorea induced by phenytoin or oral contraceptives.

**PATIENT EDUCATION**

- Compliance to antibiotic prophylaxis against further streptococcal infection should be stressed.
- Good source for patient information is the website: [www.wemove.org](http://www.wemove.org)

**REFERENCES**


**Author(s):** S. Anne Joseph, MD

**ALTERNATIVE DRUGS**

N/A

**SYNONYMS**

- Rheumatic chorea
- Chorea minor
- St. Vitus dance
- Encephalitis rheumatica

**ICD-9-CM:** 392.9 Rheumatic chorea NOS

**SEE ALSO:** N/A
Syphilis, Neurologic Complications

Basics

DESCRIPTION

- Syphilis is a systemic infection that can involve the central nervous system (CNS) during any stage. Neurosyphilis can produce vascular and parenchymatous disease in the cerebrum and spinal cord.

Forms of Neurosyphilis

- Early and late asymptomatic neurosyphilis: No clinical neurologic disease. Persistence of CSF abnormalities for >5 years after infection (late asymptomatic neurosyphilis) almost always is followed by clinical neurologic disease.
- Acute syphilitic meningoencephalitis: Incubation period for meningitis is <1 year. Seen most commonly in HIV-infected individuals.
- Meningovascular syphilis: Vascular neurosyphilis is an endarteritis that results in infarction in any vessel territory, but most commonly the middle cerebral artery distribution. Occurs 5-12 years after initial infection. Involvement often occurs with or progresses to parenchymal disease.
- General paresis: Meningoencephalitis associated with direct invasion of the cerebrum by Treponema pallidum. Develops 15-20 years after initial infection and progresses subacutely over years. Terminal if untreated.
- Tabes dorsalis: Parenchymatous form involves the periganglionic portion of the dorsal nerve roots and the spinal cord posterior columns. It is now rare and occurs in untreated patients after 20-25 years of latency. Neurologic damage often irreversible despite therapy.
- Optic (neuro)syphilis: Optic involvement takes many forms, including uveitis, retinitis, optic atrophy, perineuritis, and papillitis.
- Gummas of the CNS: Gummas, or granulomas, may remain asymptomatic or cause symptoms through compression of CNS meninges and/or parenchyma (extremely rare).
- HIV and neurosyphilis: Most common presentations in HIV-infected persons include acute syphilitic meningitis and meningoencephalitis. Syndromes associated with neurosyphilis in HIV-infected individuals include acute meningovascular neurosyphilis, which may mimic aseptic meningitis or subarachnoid hemorrhage, and syphilitic meningitis, which may mimic acute bacterial meningitis.
- Concurrent syphilis infection and HIV infection poses a small increased risk, if untreated, syphilis at any stage increases the risk of progression to neurosyphilis.

SIGNS AND SYMPTOMS

- Clinical presentation depends on the particular syndrome. Overlap occurs.
- Acute syphilitic meningitis: Symptoms may include stiff neck, confusion, or delirium; fever typically is low grade or absent. Signs may include those of elevated intracranial pressure and cranial nerve palsies. Sensorineural deafness can develop over 1-2 weeks.
- Meningovascular syphilis: Most common presentation is hemiparesis, aphasia, or seizures. Symptoms often preceded by premonitory headache, memory loss, or psychiatric disease lasting for weeks to months. Cord involvement may present with paraparesis or paraplegia, sensory abnormalities, urinary or fecal incontinence, or hyperreflexia.
- General paresis: Manifestations are variable and can mimic any neuropsychiatric disorder. Onset is insidious, with early manifestations usually psychiatric in nature. Depression is the most common early symptom. Papillary abnormalities are common and may progress to the Argyll Robertson type (small, fixed pupils that do not react to light and mydriatics, but accommodate normally). Early neurologic features include facial tremors, intention tremors, and impaired speech. Untreated disease may progress to dementia.
- Tabes dorsalis: Classic presentation includes lightning pains, paresthesias, diminished deep tendon reflexes, and poor pupillary responses to light. Argyll Robertson pupils are more commonly seen than with paresis. Lightning pains are sudden paroxysms of severe stabbing pain that last for minutes. They may occur anywhere; including viscera (e.g., gastric crisis may mimic appendicitis), but most commonly affect the lower extremities. Loss of vibration sense occurs early and leads to ataxia. Cranial nerve involvement is common.
- Gummas of the CNS: Presentation depends on location of the granuloma and mimics a mass lesion. Involvement of the brainstem or hypothalamus may mimic multiple sclerosis.
- Congenital neurosyphilis: Presentation is highly variable, but includes optic complications, aseptic meningitis, and cranial nerve palsies.

LABORATORY PROCEDURES

- All patients with suspected neurosyphilis should receive a serum nontreponemal antibody test (e.g., Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] tests), a confirmatory treponemal antibody test (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] or microhemagglutination assay for antibody to T. pallidum [MHA-TP] tests), and an HIV test. In neurosyphilis, screening nontreponemal antibody test in most cases will be positive, whereas treponemal antibody test will always be positive.
- Lumbar puncture (LP) recommended when signs or symptoms of neurosyphilis are present, when there is evidence of active tertiary syphilis, with treatment failure during any stage of syphilis, and in HIV infection with latent syphilis or syphilis of unknown duration.
Syphilis, Neurologic Complications

- The VDRL-CSF test is the standard serologic test. When reactive is diagnostic of neurosyphilis, however, negative CSF serology does not exclude the diagnosis.
- The CSF FTA-ABS yields more false-positive results, but some experts believe that a negative test excludes neurosyphilis.
- In neurosyphilis, CSF changes may include elevated pressure, mononuclear pleocytosis (up to 2,000 cells per mm³), elevated protein concentration, reduced glucose, and elevated globulin levels.
- CSF findings are variable and can reflect acute disease or remain completely normal, as in the case of inactive or treated disease.
- In congenital syphilis, CSF findings in the neonatal period and infancy are extremely variable.

**IMAGING STUDIES**
- CNS imaging is nonspecific but has a role in managing complications of syphilitic disease (e.g., hydrocephalus).
- Typical findings of vascular neurosyphilis are seen on cerebral angiography.

**SPECIAL TESTS**
- N/A

**GENERAL MEASURES**
- The main focus of treatment for neurosyphilis is administration of appropriate antibiotics.

**SURGICAL MEASURES**
- Surgical intervention is required for biopsy of a suspected CNS gumma or the management of syphilitic complications (e.g., shunt placement for hydrocephalus).

**SYMPTOMATIC TREATMENT**
- Antiemetics, hydration, analgesics, and control of fever for those with acute syphilitic meningitis

**ADJUNCTIVE TREATMENT**
- Physical therapy for gait disorders
- Antiepileptic medications such as gabapentin may be tried for lancinating pains
- Antiepileptic medications if associated with seizures

**ADMISSION/DISCHARGE CRITERIA**
- N/A

**Follow-Up**

**PATIENT MONITORING**
- Patient follow-up is critical to document clinical and serologic improvement/failure, observe for a Jarisch-Herxheimer reaction, and ensure compliance with therapy.
- Serial serum serologic evaluations (with the nontreponemal antibody test, as the treponemal antibody test will remain positive for life) should be performed every 3 months for up to 48 months (or until it normalizes).
- Serial CSF examinations should be repeated 3 months after antibiotic therapy, then every 6 months until the CSF normalizes. Once normal, CSF examination should be repeated annually for the next 2 years.
- Criteria for failure include persistence or development of clinical symptoms, elevation of serum nontreponemal antibody test titer (by two dilutions), failure of serum nontreponemal antibody test to decrease by two dilutions at 24 months, and failure of the CSF to normalize by 6 months (VDRL-CSF test may take up to 2 years to normalize).
- Failure in any form warrants retreatment with penicillin.

**Medications**

**DRUG(S) OF CHOICE**
- Penicillin is the only proven therapy for neurosyphilis.
- Current recommended treatment regimen is aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours for 10-14 days. Alternative regimen is procaine penicillin 2.4 million units PO four times per day, both for 10-14 days.
- For infants and children, recommended regimen is aqueous crystalline penicillin G 200,000-300,000 units/kg/day IV, administered as 50,000 units/kg every 4-6 hours for 10 days.

**Contraindications**
- N/A

**Precautions**
- In those with confirmed penicillin allergy, skin testing and desensitization are recommended.

**ALTERNATIVE DRUGS**
- Other antibiotics as an alternative regimen have not been studied and their routine use is not recommended.

**Expected Course and Prognosis**
- Penicillin is effective in clearing CSF abnormalities and preventing progressive clinical disease in all types of neurosyphilis.
- Antibiotic therapy cannot reverse structural damage that has already occurred.

**Patient Education**
- Syphilis is a sexually transmitted disease, so patients should be educated regarding safe sexual practices.
- Sexual contacts of patients (over the prior 12 months), should be serologically/clinically evaluated. Epidemiologic treatment is cost effective.

**Synonyms**
- N/A

**ICD-9-CM:**
- 094 Neurosyphilis; 094.0 Tabes dorsalis; 094.1 General paresis; 094.2 Syphilitic meningitis; 094.3 Asymptomatic neurosyphilis; 094.8 Other specified neurosyphilis; 094.81 Syphilitic encephalitis; 094.82 Syphilitic parkinsonism; 094.85 Syphilitic retrolubar neuritis; 094.87 Syphilitic ruptured cerebral aneurysm; 094.89 Other; 094.9 Neurosyphilis, unspecified

**References**

**Author(s):** Thomas D. Lamarre, Jr., MD; Julie E. Mangino, MD
Syringomyelia

**DESCRIPTION**

Syringomyelia refers to an abnormal fluid collection (syrinx) within the spinal cord (myelia).

Terminology describing a syrinx (pl. syringes) often is confusing. Expansion of the ependymal lined central canal is termed hydromyelia. Expansion of the cavity into the cord and the resultant nonependymal lined cavity is termed syringohydromyelia. Often syringomyelia is used as a generic term before an etiology is determined. The accumulation of fluid within the spinal cord is not thought to be the primary manifestation of any disease process. Syringohydromyelia is a secondary process with many etiologies. A useful classification is to divide these accumulations into communicating and noncommunicating varieties. Cavities with cerebrospinal-like fluid are communicating are usually associated with altered CSF flow at the craniocervical junction (e.g., Chiari malformation) or occult spinal dysraphism (OSD; e.g. diastematomyelia). Highly proteinaceous fluid cavities are generally found in noncommunicating varieties caused by arachnoiditis, vascular anomalies, neoplasm, or trauma to the spinal cord.

**ETIOLOGY**

- Precise cause of syrinx formation is still unknown; however, inappropriate CSF flow at the craniocervical junction (Chiari malformation) is associated with syrinx production.

**Genetics**

- N/A, although up to 2% of syringes have been found in siblings and twins both monozygotic and dizygotic.

**Causes**

- Chiari malformation (Type 0, I and II)
- Arachnoiditis (Tuberculosis, fungus, syphilis, following subarachnoid hemorrhage, etc.)
- Neoplasm of the spinal cord (usually glial in origin)
- Vascular malformation of the spinal cord
- Trauma of the spinal cord
- Following iatrogenic penetration of the subarachnoid space e.g. lumbar puncture
- Idiopathic

**PREGNANCY**

- Not applicable.

**ASSOCIATED CONDITIONS**

- Myelomeningocele
- OSD
- Chiari malformation
- Disseminated tumor
- Systemic infection

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- Disseminated tumor
- Systemic infection

**IMAGING STUDIES**

- MRI
  - MRI is the test of choice in evaluation of a syrinx. A syrinx will have a CSF signal (black) on T1-weighted images. Contrast may be helpful in discerning tumor or inflammation as a cause of the syrinx. Flow studies (cine mode) of the craniocervical junction often are not useful, yielding many false-negative and false-positive results.
  - Always evaluate the craniocervical junction in the presence of syrinx (i.e., is a Chiari malformation present?).
  - Syringes produced by a Chiari malformation often involve the cervicothoracic region, whereas syringes from OSD are found in the distal cord.
  - If a Chiari I malformation is the cause of the syrinx, hydrocephalus and cervical spine instability should be ruled out first.
- Spine radiographs. Often a syrinx is first appreciated when uncommon curvatures (produced by the underlying syrinx) are found on x-ray films (e.g., a single-curve scoliosis with convexity to the left).

**SPECIAL TESTS**

- Abdominal reflexes often are diminished or absent in the presence of syrinx, especially in patients with scoliosis

**DIAGNOSIS**

**SIGNALS AND SYMPTOMS**

- Syringomyelia symptoms tend to be chronic and often are subtle compared to the clinical signs because the patient has years to become accustomed to them. Symptoms include balance disorders, loss of pain/temperature appreciation in the hands and arms, sphincter disturbance, weakness in the hands, and dysphagia.
Syringomyelia

Management

GENERAL MEASURES
• No specific measures; attention to issues such as bladder function, bowel regimen, decubiti in severely disabled patients, and deep vein thrombosis prophylaxis in hospitalized patients

SURGICAL MEASURES
• Communicating syrinx: Consider surgical decompression at hydrostatic sites such as the posterior fossa. Insertion of a tube into the syrinx may provide for chronic decompression. Patients with severe scoliosis may require surgical correction with Harrington rod implantation.
—Posttraumatic: Reestablish an open subarachnoid space, usually at the site of a spine fracture. If unsuccessful, then a syringopleural shunt should be placed.
—Secondary to Chiari Malformation: Cranio-cervical decompression with or without removal of a cerebellar tsoni
— Secondary to neoplasm/vascular malformation: Resection of primary lesion — Secondary to arachnoiditis: Syringopleural shunt
— Secondary to OSD: Syringo-subarachnoid stent
—Idiopathic: Verify CSF egress from the fourth ventricle. If physiologic result: syringopleural/peritoneal shunt. If no egress and no other cause of syrinx is found: cranio-cervical decompression.
—Asymptomatic: If the syrinx is small, consider observation and serial MRI. If the syrinx is large and expanding the spinal cord and no other cause is found, consider cranio-cervical decompression.

SYMPTOMATIC TREATMENT
• As per general measures, consider measures for spasticity and pain management if applicable.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
• If surgery is chosen, patients are brought in electively and observed carefully postoperatively. For both shunt procedures and decompressive procedures, patients normally are discharged in 1-2 days.

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Symptoms
• If operative intervention is necessary, patients may resume normal activities once the wound is healed and they are physically back to baseline, usually in a period of weeks. Patients should be educated about the risk of burning their hands due to insensitivity, gait disorders, and bowel and bladder function, if applicable. Patients should become acquainted with the nature of the illness and the mechanism of neurologic dysfunction.

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
• Patients are seen 1 week postoperatively, then in 2 months. At the next follow-up in 6 months, a repeat MRI is obtained to assess the size of the syrinx. If the syrinx is shunted, observe for neurologic deterioration from either shunt malfunction or migration. Shunt infection may occur. Examples of complications of cranio-cervical decompression are cerebellar ptosis, continued presence of the syrinx, further neurologic compromise, acute hydrocephalus, and ventral compression from a retroflexed dens.

EXPECTED COURSE AND PROGNOSIS
• Approximately 90% of patients in whom hindbrain herniation is the cause of the syrinx have resolution on follow-up imaging.
• Syringopleural shunts and syringo-arachnoid stents do well in combating syringes but require close follow-up and maintenance.
• Syringes of tumor/vascular anomaly origin require that the mass be dealt with efficiently.

PATIENT EDUCATION

Medications

DRUG(S) OF CHOICE
• There is no medical treatment for syringomyelia.

ALTERNATIVE DRUGS
N/A

SYNONYMS
N/A

ICD-9-CM: 336.0 Syringomyelia/syringobulbia

SEE ALSO: SPINAL CORD SYNDROMES, CHRONIC; CHIARI MALFORMATION

REFERENCES

Author(s): R. Shane Tubbs, MS, PA-C, PhD; W. Jerry Oakes, MD
Systemic Lupus Erythematosus, Neurologic Complications

**Basics**

**DESCRIPTION**
- Systemic lupus erythematosus (SLE) is a systemic inflammatory disorder that affects almost every organ of the body. Clinical course varies from indolent to fulminant.
- Neuropsychiatric SLE (NPSLE) includes both the central and peripheral nervous systems.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- SLE: 15-50 per 100,000; neurologic involvement: 60%-75% of all SLE patients at some point in disease. Prevalence may be up to 91%, including mood disorder, headache, and cognitive dysfunction.

**Race**
- All races appear susceptible, although it occurs more frequently in black and Hispanic individuals. Black individuals tend toward increased severity.
- Women outnumber men 5-10:1. No known gender differences for neurologic involvement.

**Age**
- Most cases of SLE are diagnosed between 15 and 40 years, although all ages may develop SLE. NPSLE may develop at any time during SLE.

**ETIOLOGY**
- Although the etiology of SLE is unknown, aberrant regulation of autoreactive antibody production and clearance may be the under-lying pathogenesis of SLE. Tissues are damaged by deposition of autoantibodies and immune complexes, which induce antigen-specific immunologic damage or non-antigen-specific complement fixation. The mechanisms of neurologic injury in SLE include direct antibody (antineuronal)-mediated effects, distant effects of systemic inflammation (e.g., cardiac emboli from valvular disease, hemorrhagic stroke from thrombocytopenia), or secondary effects, such as infection, toxicity of medications, or metabolic abnormalities. Although common in other organs (including peripheral nerve), cerebral blood vessel inflammation (vasculitis) is unusual.

**Genetics**
- Several genes predispose to SLE: HLA classes I and II, including DR2, DR3, and several C4 genes. Ten percent of patients have affected family members.

**RISK FACTORS**
- Risk factors for NPSLE include antiphospholipid antibody syndrome (positive anti-cardiolipin IgG in high titer, arterial thrombosis), cutaneous vasculitis lesions, thrombocytopenia, positive anti-SS-B/La, and depressed C3 or C4. Arthralgias/arthritis and discoid rash are protective. Drug-induced lupus rarely involves the nervous system.

**PREGNANCY**
- SLE does not interfere with conception, and there is no increase in flares during pregnancy. However, there are increased rates of spontaneous abortion, prematurity, and intrauterine death. Differentiating SLE flare from preeclampsia/eclampsia can be difficult, but laboratory abnormalities (anti-DNA antibody titer, decreased complement levels) can assist clinical impression. Prednisone does not cross the placenta and is given safely during pregnancy.

**ASSOCIATED CONDITIONS**
- CNS autoimmune disorders: multiple sclerosis; primary CNS vasculitis
- Systemic autoimmune disorders: rheumatoid arthritis, polymyositis, scleroderma ("mixed connective tissue diseases"); dermatomyositis; Raynaud’s syndrome
- Toxic: drug-induced lupus: procainamide (52%-75% with positive ANA); chlorpromazine, methyldopa, hydralazine, isoniazid, phenytoin, penicillamine. Drug-induced lupus is rarely associated with CNS involvement.
- Anti-phospholipid antibody syndrome (may be separate or a part of SLE)
- Premature atherosclerosis (late-stage SLE)
- Sneddon’s syndrome: generalized livedo reticularis and stroke
- Reversible posterior leukoencephalopathy syndrome: associated with SLE nephritis and hypertension

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Autoimmune: multiple sclerosis, primary isolated CNS vasculitis, Behçet’s disease, sarcoidosis
- Psychiatric: depression, schizophrenia
- Epilepsy: partial, partial complex, generalized epilepsy
- Drugs of abuse
- Stroke: cardioembolic, hemorrhagic
- Guillain-Barré syndrome
- Infections: fungal meningitis, bacterial meningitis, herpes simplex virus, Lyme disease, cytomegalovirus, HIV, syphilis, tuberculosis meningitis
- Metabolic: hyperuricemia, electrolyte imbalances
- Severe hypertension: usually with active nephritis

**SIGNS AND SYMPTOMS**
- May be seen in isolation or during systemic activity. Non-SLE disorders must be evaluated and ruled out. Generalized disorders are probably from primary CNS involvement of SLE, whereas focal disorders are from distant effects of SLE.

**Generalized NPSLE (≥ 5% Incidence)**
- Organic brain syndrome: psychosis (6%), delirium or marked emotional instability
- Differentiation between SLE-induced or, steroid-induced psychosis is on clinical grounds only. Therapeutic trial of increased or decreased steroids is guided by clinical improvement.
- Mood disorder; depression (44%), anxiety disorder (13%), personality change
- Cognitive impairment (41%-80%); varies from subclinical impairment to severe dementia
- Headaches (40%-54%): can be migrainous or nonmigrainous; often unresponsive to narcotics
- Chorea: rarely clinically similar to Sydenham’s chorea, usually early in disease course; can be associated with antiphospholipid antibodies.
- Retinopathy: usually secondary to vasculitis and accompanies CNS activity
- Vasculopathy: chronic, small-vessel occlusive disorder with cognitive impairment, possibly secondary to chronic immune complex deposition
- CNS vasculitis: rare cause of stroke
- Aseptic meningitis: rare
- Myasthenia gravis: rare

**Focal NPSLE**
- Seizures (9%-40%): usually secondary to focal ischemia, but must consider infectious and metabolic etiologies
- Peripheral neuropathy (16%-28%): sensory, motor, mixed sensory/motor polyneuropathies, or mononeuritis simplex/multiplex (vasculitic axonal polyradiculopathy). Plexopathy, Guillian-Barré syndrome, autonomic disorder, and transverse myelitis also are seen.
- Cranial neuropathy (6%): visual loss, facial palsy, trigeminal neuritis, trinitus, vertigo
- Stroke—Stroke usually due to complications from therapy or end-organ damage

**Therapy or end-organ damage
- Arterial or venous occlusion: related to cardiac emboli, antiphospholipid antibodies
- Hemorrhagic: often secondary to thrombocytopenia or hypertension
- Visual disturbances: transient monocular blindness (6%), migraine (10%)
- Myelopathy: due to transverse myelitis, spinal cord infarct, or subdural-epidural hematoma
- Focal demyelinating syndrome: similar to multiple sclerosis, but often has serologic and clinical evidence for antiphospholipid syndrome

**Diagnosis**

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Systemic Lupus Erythematosus, Neurologic Complications

LABORATORY PROCEDURES
• CNS involvement of SLE is a clinical diagnosis.
• Serologic evidence for increased disease activity (increased anti-DNA titers, depressed complement levels) can correlate with disease activity. Although studies are conflicting, serum anti-ribosomal-P antibodies appear to correlate with CNS involvement, especially psychosis.
• CSF studies frequently find pleocytosis (usually mononuclear cells, 18%/°), elevated protein (32%/°), elevated albumin ratio (24%), oligoclonal bands (28%-70%), and elevated IgG index (70%-90%°°), although NPSLE did not differ from SLE without neuropsychiatric involvement. Protein and albumin ratio may increase during relapse but is not specific.
• CSF studies (including routine and fungal culture, viral studies) are important to exclude infectious complications of immunosuppression. Pleocytosis may be absent despite ongoing fungal infection.

IMAGING STUDIES
• Brain MRI is more useful than CT, reveals distant effects of systemic disease (cardioembolic stroke, hemorrhage), and can show diffuse abnormalities. MR angiography can visualize medium and large vessels.
• Spine MRI can visualize focal lesions (transverse myelitis, infarct) and should be considered when symptoms localize to the spine.
• Conventional angiography is rarely necessary.

GENERAL MEASURES
• Infections must be considered when new symptoms develop. Postmortem studies in patients with presumed active SLE frequently find active CNS infection (fungal, viral) and quiescent SLE.
• Toxicity/side effects of current medications must be considered.
• Evaluation of seizures includes screening and treatment of active systemic disease, such as uremia, electrolyte abnormalities, metabolic encephalopathy, and hypertension.

SURGICAL MEASURES
• Brain biopsy is rarely needed to confirm diagnosis.
• Surat nerve biopsy can confirm SLE peripheral neuropathy.

SYMPTOMATIC TREATMENT
• See Medications

ADJUNCTIVE TREATMENT
• Counseling is effective for mood disorders and emotional instability.

ADMISSION/DISCHARGE CRITERIA
• Admission may be required for acute confusional state, stroke, infection, or other neuropsychiatric complications. Treatment with high-dose corticosteroids or intravenous cyclophosphamide often requires hospitalization.

DRUG(S) OF CHOICE

• Evidence from controlled clinical trials data is either negative or absent, and most treatment is empirical. Cyclophosphamide is commonly used, but there is little clinical trial evidence supporting its use.

• General: Intravenous cyclophosphamide with high-dose corticosteroids appears to be effective.

• Encephalopathy: Plasmapheresis and cyclophosphamide either 500 mg IV biweekly or 75-100 mg/day PO.

• Seizures: Anticonvulsant usually is sufficient; further immunosuppression usually is not needed.

• Movement disorders: Plasmapheresis with azathioprine or cyclophosphamide is better than corticosteroids.

• Stroke: Treatment is directed by etiology.

• Thrombosis: Antiplatelet agents

• Emboli: Antibiotics or anticoagulants

• Coagulopathy: Plasmapheresis, antiplatelet agents, anticoagulation

• Stroke itself is treated according to standard stroke protocols.

• If part of antiphospholipid syndrome: warfarin with target INR 3-4

• Transverse myelopathy: High-dose corticosteroids (methylprednisolone >500 mg/day)

• Peripheral neuropathy/plexopathy: Corticosteroids, equivalent of 60-80 mg prednisone daily

• Necrotizing vasculitis: Corticosteroids, immunosuppressive agents, plasmapheresis

Precautions
• It is often difficult to differentiate adverse effects of medications from disease activity. Empiric titration in immunosuppression with careful monitoring is required.

• It is imperative that infectious, metabolic, and hypertensive etiologies be excluded prior to treating neurologic dysfunction as a primary or distant effects of SLE.

• Nonsteroidal antiinflammatory drugs are commonly used in SLE but can cause aseptic meningitis, dizziness, confusion, depression, headache, and worsening of renal dysfunction.

ALTERNATIVE DRUGS
• Autologous stem cell transplant has demonstrated promising preliminary results.

• Azathioprine may be steroid sparing, but efficacy in NPSLE is unknown.

• Plasmapheresis is ineffective in some manifestations of SLE (nephritis).

• Antimalarials (hydroxychloroquine, chloroquine, and quinacrine) are used for cutaneous SLE but can have CNS side effects.

• Methotrexate is used for cutaneous and articular SLE; experience in NPSLE is minimal.

PATIENT MONITORING
• Clinical monitoring is the best method to follow patients over time. In some patients, serologic studies parallel clinical activity and can be useful for early detection of exacerbations.

EXPECTED COURSE AND PROGNOSIS
• Most CNS events are self-limiting, reversible, and not associated with poor outcome unless disease is progressive.

PATIENT EDUCATION
• Lupus Foundation of America, 1300 Pittard Drive, Suite 200, Rockville, MD 20850-4303.

Phone: 301-670-9292; fax: 800-558-0121, website: www.lupus.org/lupus/
Tardive Dyskinesia

**Basics**

- Tardive dyskinesia (TD) is a disorder of abnormal involuntary movements most often affecting the orobuccolingual musculature but also truncal and limb musculature. It is associated with antipsychotic drug therapy. TD usually develops after >1 year of treatment, but cases where symptoms of TD appeared within 3-6 months of antipsychotic use have been reported in the literature. Most cases are mild to moderate, but a small percentage can be severely disfiguring and disabling.

**Epidemiology**

- **Incidence/Prevalence**
  - The incidence of TD is estimated at 2%—5% per year over the first 5-10 years of treatment with neuroleptic agents.
  - Lifetime prevalence is estimated to be approximately 20%, but the range is extremely wide (1%-80%) for those requiring chronic treatment with neuroleptics.

- **Race**
  - No information available

- **Age**
  - Elderly patients are much more vulnerable.

- **Sex**
  - Women are more at risk, with a female-to-male ratio of 1:7.1

**Etiology**

- The onset of TD is linked to the use of dopamine receptor-blocking agents, but the exact mechanism is not known.
- There are data suggesting that prolonged receptor blockade by antipsychotic agents may cause hyperactivity of the CNS dopaminergic and noradrenergic systems coupled with reduced activity in the GABAergic and cholinergic systems.
- The onset of TD usually has been associated with exposure to antipsychotic agents. Other dopamine receptor-blocking agents, such as the antihypertensive metoclopramide and prochlorperazine, and the antidepressant amoxapine also can result in TD.
- TD should be distinguished from spontaneous (idiopathic) movement disorders associated with schizophrenia (prevalence of 15%), old age, and brain damage.

**Genetics**

- No information available

**Risk Factors**

- Higher dose of administered antipsychotic medication
- Longer duration of antipsychotic exposure
- Older age

**Diagnosis**

**Differential Diagnosis**

- Tardive dystonia, which consists of
  - Irregular postures (e.g., Pisa syndrome)
  - Slow, involuntary twisting movements of face, trunk, or limbs (patients may present with torticollis, blepharospasm, retrocolis, grimacing)
  - It occurs in 2% of patients treated with antipsychotic agents.
  - It may coexist with TD and may be even more distressing and disabling.
  - Use of anticholinergic drugs may lessen symptoms of tardive dystonia.
- Tardive akathisia, which consists of
  - Motor restlessness
  - Subjective discomfort
  - Treatment with benzodiazepines, blockers, or clozapine may be beneficial
  - Dopamine depletors, such as reserpine, are effective
- Huntington's disease
  - Other basal ganglia disorders

**Diagnosis**

- Careful clinical assessment is the sole basis for the diagnosis of TD.
- Several quantitative assessment tools have been published, but the most widely used one is the Abnormal Involuntary Movements Scale (AIMS). The AIMS should be assessed for all patients when dopamine receptor-blocking agents are initiated and at least every 3 months while patients continue to be treated with these agents.
- Physicians should not rely solely on patient complaints to make a diagnosis of TD because the early signs and symptoms of this disorder can easily escape notice.
- There are no laboratory procedures, imaging studies, or special tests to diagnose TD.
- TD often becomes evident upon antipsychotic dose reduction or discontinuation.

**Signs and Symptoms**

- TD is a complex syndrome of irregular, abnormal, repetitive, involuntary movements of the mouth, lips, tongue, limbs, or trunk.
- The buccolingualomasticatory triad of symptoms is most common and consists of—
  - Smacking, puckering movements of the lips
  - Lateral movements of the jaws
  - Puffing of the checks with the tongue
- Chewing motions (patients frequently bite the inside of their mouths or tongues).
- Athetoid and choreiform movements of the extremities. These movements are involuntary and purposeless.
- Trunk movements: Either anterior-posterior or rhythmic side to side swaying may be present.
- All involuntary movements are exacerbated by stress or anxiety and dramatically subside during sleep.

**Laboratory Procedures**

N/A

**Imaging Studies**

N/A

**Special Tests**

N/A
Tardive Dyskinesia

**GENERAL MEASURES**

- Prevention is the most important aspect of TD management. There is no reliable treatment other than discontinuation of the offending drug.
- Long-term use of antipsychotic agents should be restricted to patients whose chronic illness clearly necessitates it (e.g., schizophrenia). It should be avoided in patients suffering from depression, mania, anxiety, or personality disorders, except in unusual clinical circumstances.
- Ongoing periodic evaluations of the patient's need for long-term antipsychotic agents must be done with an assessment of the risks and benefits of treatment. The dose of medication must be adjusted so that patients receive the lowest antipsychotic dose that is still effective.
- There is no reliable treatment of TD other than discontinuation of the offending agent.
- Many patients recover spontaneously when antipsychotic agents are discontinued.
- TD may improve in some patients even when they continue treatment with antipsychotics.
- Anticholinergic medications should be avoided because they may aggravate TD, and it is not known whether long-term use of these agents increases the risk of developing TD.
- If an antipsychotic agent is necessary, use clozapine (Clozaril; which has antidysskinetic effects) or one of the new atypical antipsychotics (risperidone, olanzapine, quetiapine), which seem to have a much lower incidence of TD.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

N/A

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

- Admission is rarely required unless dyskinesias become so severe that they interfere with breathing or swallowing.

**MEDICATIONS**

**DRUG(S) OF CHOICE**

- Clozapine (an atypical antipsychotic agent) has been found to decrease symptoms of TD in several large studies and may be the treatment of choice, especially for patients who need medications for their psychiatric disorder. Severe TD and particularly tardive dystonia seem to respond best to doses ranging from 300-750 mg/day. The main disadvantages to using clozapine are the potential side effects of agranulocytosis, seizures, and the need for weekly blood monitoring.
- There have been anecdotal reports indicating that risperidone or olanzapine may improve TD, but further controlled studies are necessary to confirm this. One needs to keep in mind that all neuroleptics that have antidyskinetic properties also have been associated with the occurrence of TD.
- Vitamin E (an antioxidant) in doses of 1,600 IU/day has not been consistently shown to be beneficial in all studies. Several case reports have found positive results, but a recent long-term trial found no efficacy of vitamin E in this condition. Patients who have had TD for <5 years appear to have a better response than patients with long-standing TD.
- Clonazepam in doses of 0.5-3 mg/day has been found to reduce movements of TD, but caution must be exercised in chronic use of benzodiazepines.
- Dopamine-depleting medications, such as reserpine in doses of 1-5 mg/day, may alleviate symptoms in up to 50% of patients.
- Calcium channel blockers may help alleviate TD symptoms. Nifedipine in doses of 20-80 mg/day may be the most effective agent in this class, but further studies are needed to assess its overall place in TD management.

**FOLLOW-UP**

**PATIENT MONITORING**

- Patients should be given an AIMS test every 3 months while taking dopamine-blocking agents so that any symptoms of TD can be identified early and discussed at length with the patient.

**EXPECTED COURSE AND PROGNOSIS**

- We used to believe that the course of TD was progressive and irreversible. More recent data show that in most patients, TD develops to a certain degree and then stabilizes and may even improve. The most frequent pattern is waxing and waning of mild-to-moderate symptoms over many years. Progression to severe TD is not common.

**PATIENT EDUCATION**

- Each patient should be informed about the long-term risk of developing TD and that the involuntary movements may be irreversible and treatment resistant. At the same time, the patient should be assured that the clinician will make every attempt to minimize the risk of TD and to closely monitor early signs and symptoms.
- Every clinician should obtain informed medical consent from the patient and/or the patient's family. Ongoing education and open communication should occur and should be clearly documented in the patient's record.
- Tardive Dyskinesia/Tardive Dystonia National Association, P.O. Box 4573, Seattle, WA 98145-0732. Phone: 206-522-3166.

**SYNONYMS**

N/A

**ICD-9-CM:** 333.82 Orofacial dyskinesia

**SEE ALSO:** N/A

**REFERENCES**


**Author(s):** Radu Saveanu, MD
Tetanus

DESCRIPTION
- Tetanus is a noncommunicable and potentially fatal infection caused by Clostridium tetani. Clinically it is characterized by the acute onset of generalized rigidity and reflex spasms.

EPIDEMIOLOGY

Incidence/Prevalence
- The disease is seen worldwide. Tetanus is seen more often in the summer season.

Race
- No information available

Age
- Newborns, because of nonsterile birth conditions, and the elderly have the highest risk for the disease.

Sex
- Male-to-female ratio of 2.5:1

ETIOLOGY
- C. tetani is a Gram-positive anaerobic, spore-forming bacteria that is universally found in the environment. The spores enter the body through contaminated wounds. They germinate under anaerobic conditions and produce tetanus toxin (tetanospasmin), which is responsible for the disease. Tetanospasmin inhibits neurotransmitter release presynaptically at the neuromuscular junction, autonomic terminals, and inhibitory neurons of the central nervous system.

GENETICS
- N/A

RISK FACTORS
- Nonsterile obstetric delivery and contamination of umbilical stump with the organism
- Wounds bearing necrotic tissue, foreign bodies, and associated infection
- Chronic lesions (decubitus ulcers, abscesses)
- Parenteral drug abuse
- Absent or incomplete immunization

PREGNANCY
- Poor obstetric conditions and lack of maternal immunization are risk factors for neonatal tetanus.

ASSOCIATED CONDITIONS
- N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Other causes of bacterial and viral meningitis
- Rabies
- Hypocalcemic tetany
- Strophanthine poisoning
- Torsillitis
- Peritonsillar abscess
- Dystonic reactions due to tophenothiazines

SIGNS AND SYMPTOMS
- The incubation period usually is between 5 and 14 days, although it can be prolonged up to 3 weeks. The distance of injury from the central nervous system determines the length of incubation period. Stiffness of jaw (trismus) usually is the first symptom. A characteristic facial appearance (risus sardonicus) results from sustained contractions of facial muscles. Generalized muscle rigidity involving neck, trunk, and extremity muscles follows. Rigidity of back muscles causes opisthotonus.
- Paroxysmal tonic spasms can occur spontaneously or be precipitated by external stimuli. Pharyngeal muscular spasms cause dysphagia, and spasms of the glottis may lead to death by asphyxiation. Spasms of diaphragmatic, intercostal, and laryngeal muscles are life threatening.
- Autonomic dysfunction (labile hypertension, tachycardia, arrhythmias, hyperhidrosis) can be seen in severe cases.
- Reflexes are increased and sensory examination is normal. Irritability and restlessness are seen, but consciousness is preserved.
- High fever up to 41°C can be seen and signifies poor prognosis.
- Rarely tetanus is localized to an area close to site of injury (local form). Muscles in the region of injury go into intermittent painful spasms. This form is benign and muscular spasms subside spontaneously within weeks. When localized to the head, it is called the cephalic form.

LABORATORY PROCEDURES
- Diagnosis should be made by clinical features and history. There is no single laboratory procedure that gives definite diagnosis in every patient. Routine blood work is nonspecific. Mild leukocytosis is seen.

IMAGING STUDIES
- Imaging studies are not helpful.

SPECIAL TESTS
- Cerebrospinal fluid examination is normal
- Specimens from the wound may reveal Gram-positive bacilli.
- Anaerobic cultures usually are unsuccessful.
- Neutralization of toxin in mice is the standard method for detection of antitoxin in the serum.

- Manifestations of tetanus increase in severity during the first 3 days after onset; remain stable for 5-7 days, and resolve within 1-2 weeks.
- Neonatal tetanus: Occurs 3-14 days after delivery. Disease is due to nonsterile birth conditions and contamination of the umbilical cord stump. Mothers are unimmunized women. Difficulty in sucking, excessive crying, trismus, opisthotonus, and spasms are clinical signs.
GENERAL MEASURES

• Be sure that the airway is open and ventilation is adequate. Respiratory insufficiency due to laryngospasm or spasms of respiratory muscles is a major problem. Tracheostomy not only facilitates mechanical assistance of ventilation but also reduces the risk of aspiration and protects against suffocation due to laryngospasm. Although some milder cases can be managed without it, every patient should be considered a candidate for tracheostomy.
• Avoid external stimuli and keep the patient in a dim and quiet room.
• All treatments and manipulations should be kept to a minimum to prevent provocation of reflex spasms.
• Stop oral intake to prevent aspiration and start fluid and electrolyte balance.
• Apply intermittent catheterization if urinary retention develops.
• Prevent deep vein thrombosis with low-dose heparin.

SURGICAL MEASURES

• Surgical debridement of wounds and drainage of abscesses is mandatory because anaerobic conditions are necessary for spore germination. Wounds should be irrigated with 3% hydrogen peroxide three times daily after the procedure.

SYMPTOMATIC TREATMENT

• Muscle relaxation is necessary and mild sedation is desirable.
• Diazepam is very effective. It not only relieves rigidity but also provides sedation. Administer diazepam 0.5-5 mg/kg/day IV in divided doses every 2-8 hours or 5-10 mg whenever spasms occur.
• Phenobarbital 50-100 mg every 3-6 hours or pentobarbital 50-200 mg IV, chlorpromazine 200-300 mg daily, dantrolene, or intrathecal baclofen can be used as muscle relaxants.
• If spasms cannot be controlled by these measures, curarization may be necessary.
• D-Tubocurarine 15 mg/hour IM can be given after ventilatory support. Propofol can be given as sedative.
• Propranolol with phentolamine or labetalol 0.25-1.0 mg/min can be used to decrease sympathetic activity.

ADJUNCTIVE TREATMENT

• Physical therapy can be started 2-6 weeks after the onset of infection, when the spasms disappear. Many patients will also require psychotherapy.

ADMISSION/DISCHARGE CRITERIA

• All patients should be treated in an intensive care unit.

DRUG(S) OF CHOICE

• Antiserum: Administer human tetanus immune globulin (HTIG) 3,000-6,000 units IM as soon as possible, because antiserum neutralizes only the toxin that has not entered the nervous system. 
• Antibiotics: The organism is susceptible to several antibiotics. Metronidazole is first choice: 20-30 mg/kg/day IV over 1 hour in three or four divided doses following a loading dose of 15 mg/kg. Metronidazole should be given for 7-14 days. If metronidazole is not available, penicillin G 100,000 U/kg/day IV in six divided doses can be given. 
• Tetanus toxoid: Because tetanus infection does not provide natural immunity against further attacks, active immunization of patients is necessary at the time of diagnosis or during convalescence. Contraindications:
• Known drug allergies
• Precautions:
• Respiratory function should be monitored during heavy sedation.

Prophylaxis

• Tetanus vaccine (toxoid) is administered with diphtheria and pertussis vaccines at ages 2, 4, 6 months, 12-18 months, and before school (4-6 years). Routine boosters of tetanus with diphtheria (Td) should be given every 10 years.
• Adults who have not been immunized previously should receive two doses of Td 4-8 weeks apart and the third dose 6 months to 1 year after the second dose.
• Nonimmunized female should receive two doses of tetanus toxoid (at least 4 weeks apart) during pregnancy, the last one at least 2 weeks before delivery.
• Management of wound prophylaxis of tetanus depends on current immunization status of the patient. If a patient has received at least three doses of toxoid, there is no need for HTIG. Toxoid booster is required if >5 years (10 years for minor clean wounds) has elapsed.
• For patients who received fewer than three doses, primary immunization series should be started. HTIG 250 units IM should be given prophylactically, except for fresh, clean, minor wounds. Toxoid and antiserum must be given with separate syringes to different sites.

ALTERNATIVE DRUGS

• Pooled human intravenous immunoglobulin may be an alternative to HTIG.

Follow-Up

• Sequela are uncommon once the patient heals, although focal deficits such as exotropia and facial muscle paresis have rarely been reported. However, because the infection does not provide natural immunity, primary immunization should be completed.

EXPECTED COURSE AND PROGNOSIS

• Tetanus is self-limited, and patients who recover from the disease have no residual defect. The disease usually subsides within 3-6 weeks. Mortality rate is 50%. For neonatal tetanus, mortality goes up to 60%-80%. Death usually occurs 3-10 days after infection, mostly due to asphyxiation during spasms, cardiovascular insufficiency, or superimposed infections.

PATIENT EDUCATION

• Centers for Disease Control and Prevention. Website: www.cdc.gov/nip/vaccine/nip-dtp.htm
• World Health Organization. Website: www.who.int/gpv-dvacc/diseases/NeonatalTetanus.htm

Miscellaneous

SYNONYMS

N/A

ICD-9-CM: 037 Tetanus; 771.1 Tetanus neonatorum; 670 Puerperal tetanus

SEE ALSO: N/A

REFERENCES


Author(s): Sevim Erdem, MD
**SURGICAL MEASURES**
- There are a few reports of patients with severe motor and phonetic tics controlled by high-frequency deep brain stimulation

**SYMPTOMATIC TREATMENT**
- Symptomatic treatment consists of behavioral management:
  - Positive reinforcement
  - Target behaviors
  - Skill deficiencies
  - Behavior excesses

**ADJUNCTIVE TREATMENT**
N/A

**ADMISSION/DISCHARGE CRITERIA**
- Admission for management of tics is rarely necessary.

**DRUGS OF CHOICE**
- Dopamine D₂ receptor antagonists: Chlorpromazine was reported to dramatically improve tic severity. Since then, several placebo-controlled randomized allocation studies with various neuroleptics (e.g., haloperidol, fluphenazine, pimozide) have confirmed these initial reports. On average, tic severity declines by approximately 50%-80% with neuroleptic treatment.
  - Haloperidol (Haldol): FDA indication for treatment of tics
  - Pimozide (Orap): FDA indication for treatment of tics
  - Fluphenazine (Prolixin): FDA indication for treatment of tics
- Clonidine (Catapres) 0.05 mg PO bid to 0.1 mg PO qid
- Guanfacine: This agent was tested in a 2001 randomized controlled trial (Children’s National Medical Center). In 47 patients with tic disorders, 50%-80% with neuroleptic treatment. It is not clear whether some of the new atypical neuroleptics, such as clozapine and olanzapine, will be effective in the treatment of tics or other manifestations of burrette’s syndrome.
- Clonidine: This drug has been used frequently to treat tics. However, no proof exists for anti-tic efficacy after several small trials. A meta-analysis concluded that clonidine has clear efficacy. It may be most appropriate as a first agent in patients with problematic attention deficit hyperactivity disorder (ADHD) and mild tics.
- Mild-to-moderate tic disorder medications
  - Pimozide superior to Haldol in one double-blind study
  - Clonidine (Catapres) 0.05 mg PO bid to 0.1 mg PO qid

**ALTERNATIVE DRUGS**
- Benzodiazepines: Retrospective reports suggest that benzodiazepines, such as clonazepam, reduce tic severity in some patients. The effect is less than that of neuroleptics and is probably nonspecific. Clonazepam (Klonopin) 0.25 mg PO bid to 1 mg PO tid.
- Botulinum toxin injections in motor tics: Botulinum toxin injections may improve urges or sensory tics, as well as observable tics, and may be the treatment of choice for patients with a single, especially problematic, dystonic tic.
- Tetraabenazine: This is a presynaptic dopamine-depleting agent. It has not been reported to cause tardive movement disorders. A retrospective report noted “marked” clinical improvement in 57% of 47 patients with tics. It is not available in United States.
- Guanfacine: This agent was tested in a 2001 randomized controlled trial in children with both ADHD and chronic tic disorders. The drug showed clear superiority to placebo in reduction of both ADHD and tic symptoms, with few adverse effects. It also has been shown to be efficacious in adults with non-tic ADHD.
- An open trial using nicotine patch indicates that nicotine may suppress tics in some patients not treated with D₂ receptor-blocking drugs.

**PRECAUTIONS**
- Use the lowest dose of medication that achieves acceptable tic suppression.
- Neuroleptics may be associated with various extrapyramidal side effects, including dystonia, akathisia, and tardive dyskinesia in up to 20% of children.
- Sedation, depression, weight gain, school phobia, tardive dyskinesia, hepatotoxicity, prolongation of QT interval with pimozide, akathisia, and acute dystonic reaction

**CONTRAINDICATIONS**
- None of these drugs should be used if there is a known hypersensitivity.
- Pimozide is contraindicated in patients with the long QT syndrome because it may prolong the QT interval. There are a few reports of deaths when pimozide is used in conjunction with macrolide antibiotics, so this drug combination should be avoided.

**PATIENT MONITORING**
- Because a medication for tics may not have any impact on obsessions or compulsions, and medications for ADHD may worsen tics in some patients, the selection of medications and combination of medications can become quite complex in a situation with associated comorbid conditions.

**EXPECTED COURSE AND PROGNOSIS**
- The prognosis for children who develop this disorder between the ages of 6 and 8 is good.
- Symptoms may last 4-6 years and then disappear without treatment in early adolescence.
- When the disorder begins in older children and there is no remission or reduction of symptoms well into the 20s, a chronic, lifelong disorder may be anticipated.

**PATIENT EDUCATION**
- WeMove. Website: www.wemove.org

**REFERENCES**

**Author(s):** Muhammad I. Akhtar, MD
**Torticollis**

**Basics**

**Description**
- Torticollis is a term used to describe disorders characterized by abnormal postures of the head and neck. Cervical dystonia (CD) is the preferred term for the idiopathic movement disorder that causes involuntary contraction of the cervical muscles, resulting in clinoc (spasmodic, tremor) head movements and/or tonic (sustained) head deviation. Head deviation can be described as follows: torticollis, torsion or rotation of the head; anterocollis, flexion of the neck, head forward; retrocollis, extension of the neck, head backward; or laterocollis, tilt of the head to one side.

**Epidemiology**
- CD is the most common form of focal dystonia, onset most commonly in early to mid life with a female predominance. Torticollis and laterocollis are the most common head deviations; retrocollis and anterocollis are more rare. Most patients have combinations of neck deviations depending on the cervical muscles involved: Tremor is common with the tonic head deviation. There may be other dystonias and tremor involving facial, buccal-lingual, mandibular, and other body parts. The clinical course of CD is variable; most patients report some progression of symptoms. Spontaneous remission is rare (10%—20%). Torticollis is a disorder of middle and late life. Torticollis in childhood is more likely to be acquired and nondystonic. In infancy, congenital muscular torticollis is the most common cause of restricted range of motion of the head.

**Etiology**
- Torticollis may be dystonic (either idiopathic, cause unknown, or secondary, related to some other process) or nondystonic. In infancy, congenital muscular torticollis is the most common cause of restricted range of motion of the head. 

**Genetics**
- Genetic mechanisms may play a role.

**Risk Factors**
- Torticollis usually occurs spontaneously, and there are no specific risk factors for its development.

**Diagnosis**

**Differential Diagnosis**

**Dystonic Conditions**
- Idiopathic:
  - Primary focal dystonia (CD)
  - Associated with more generalized dystonia
- Secondary:
  - Associated with neurologic degenerative illnesses, e.g., parkinsonism (MSA, PSP, IPD), Huntington's disease, Wilson's disease
  - Associated with metabolic disorders, e.g., amino acid disorders (such as homocystinuria), lipid storage disorders (such as metachromatic leukodystrophy), Leigh's disease
  - Associated with other causes, e.g., perinatal injury (cerebral palsy), infection (encephalitis, Jakob-Creutzfeld disease, syphilis), head trauma/cervical trauma, multiple sclerosis, stroke
  - Associated with toxins, e.g., manganese, carbon monoxide, methanol
  - Associated with drugs, e.g., levodopa, dopamine agonists, neuroleptics, dopamine-blocking agents

**Nondystonic Head Tilt**
- Structural (mechanical):
  - Cervical spine fracture
  - Dislocation
  - Disc herniation
  - Cervical region abscess — Congenital fibrous bands
- Neurologic:
  - Vestibulo-visual: fourth nerve palsy, hemianopia
  - Posterior fossa tumor
  - Spinal cord tumor
  - Arnold-Chian malformation
  - Focal seizures
  - Cervical myopathy
  - Myasthenia gravis
  - Psychogenic

**Pregnancy**
- Torticollis is not associated with pregnancy. In terms of treatment, botulinum toxin is not approved for use during pregnancy. Other medications should be avoided if possible during pregnancy.

**Associated Conditions**
- Torticollis may be idiopathic or secondary to other conditions (listed below). Head tremor is commonly associated with torticollis and may confuse the examiner.

**Management**

**Signs and Symptoms**
- Head deviation: rotation, tilt, flexion, extension, or some combination
- Tremor: if present, may be essential type involving head (no direction), oscillatory, jerky, or spasmodic
- Cervical pain: nonradicular, aching, or radical
- Palpable spasm and hypertrophy of muscle may be present
- Head deviation can be controlled temporarily by counterpressure and sensory tricks, geste antagonist: touching chin, face, or back of head
- Exacerbation occurs during periods of fatigue and stress.

**Laboratory, Procedures**
- With onset in patient <50 years old, obtain serum ceruloplasmin and liver function tests to exclude Wilson's disease.
- Review drug exposure (especially dopamine-blocking agents, i.e., neuroleptics, metoclopramide).
- Consider magnetic resonance imaging of neck to exclude structural etiologies.
- Consider testing if there is a strong family history of dystonia.
- Consider other laboratory studies (ANA, ESR, RPR, CBC, electrolytes, renal, and liver function tests) if history or physical examination suggests the condition.

**Imaging Studies**
- There is imaging demonstrable in idiopathic CD. However, appropriate imaging studies maybe indicated to identify nondystonic forms of torticollis.

**Special Tests**
- N/A

**General Measures**
- Physical measures such as stretching, heat, and physical therapy may be considered. The role of such measures is limited in idiopathic torticollis.

**Surgical Measures**
- Rhizotomy, neuromyotomy, or myotomy has been advocated for patients who do not respond to chemodenervation and medical management. Currently the application of basal ganglia ablative surgery (i.e., thalamotomy) and deep brain stimulation is considered only for treatment of more generalized forms of dystonia.
Torticollis

SYMPTOMATIC TREATMENT
• Nonpharmacologic therapies such as biofeedback, hypnosis, relaxation techniques, acupuncture, and other modalities have been used in torticollis but are generally unhelpful. Botulinum therapy has become the standard of care.

ADJUNCTIVE TREATMENT
• There occasionally may be a role for sensory feedback therapy or relaxation techniques in the relief of associative symptoms such as pain.

ADMISSION/DISCHARGE CRITERIA
N/A

DRUG(S) OF CHOICE
Chemodenervation, Botulinum Toxin

Treatment
• Botulinum injections are the treatment of choice for torticollis (CD), both idiopathic and secondary forms. Botulinum toxin injections block acetylcholine release, causing focal neuromuscular junction blockade. By selectively injecting various doses into affected muscles, the symptoms of CD and other dystonias often are dramatically relieved. Repeated injections often are necessary every few weeks or months, depending on the response.

Contraindications
• Neuromuscular disorders such as Lambert-Eaton syndrome and myasthenia gravis are relative contraindications to botulinum toxin use. It also should be avoided in myopathies and in motor neuron disorders.

Precautions
• Botulinum injections should be administered only by a physician expert in the diagnosis and treatment of dystonias and in the administration of this medication. Side effects are rare when used appropriately. Subcutaneous hematomas and pneumothorax have been reported. Temporary muscle weakness is a predictable response to this therapy. Occasionally temporary dysphagia occurs with higher doses. Secondary resistance to botulinum toxin is becoming an issue in clinical practice.

ALTERNATIVE DRUGS
• Anticholinergic agents (trihexyphenidyl) — Often require high doses with significant side effects
  —Dry mouth, urine retention, psychosis
• Tricyclic antidepressants (amitriptyline)
  —Often requires high doses with significant side effects
  —Dry mouth, urine retention, weight gain
• Benzodiazepines (clonazepam, lorazepam)
  —Antispasticity agents (baclofen)
• For tremor component of torticollis
  —Primidone
  —Benzodiazepine
  —/3-Blocker

PATIENT MONITORING •
• Patients undergoing botulinum toxin injections should be monitored for response to medication and evaluated at regular appointments, usually every 3 months, for repeated injections. No routine laboratory or imaging studies required.

EXPECTED COURSE AND PROGNOSIS
• Approximately 60%-80% of patients benefit from botulinum toxin injections, usually with reduced but not completely abolished symptoms.

PATIENT EDUCATION
• Patients should be made aware of the risk of muscle weakness, dysphagia, bruising, and rarely pneumothorax with botulinum injections. They should know that treatment is temporary and needs close follow-up. They should understand that torticollis is a treatable condition that usually does not cause major disability.

SYNONYMS
• Cervical dystonia
• Spasmodic torticollis
• Wry neck
• Stiff neck
• Capitium obstipum
• Rhaebocrania
• See Description

ICD-9-CM: 723.5 Torticollis, unspecified; excludes: 754.1 Congenital; 767.8 Due to birth injury; 300.1 Hysterical; 306.0 Psychogenic; 333.83 Spasmodic; 847.0 Traumatic, current; 333.7 Due to drugs; 333.83 Spasmodic torticollis (idiopathic cervical dystonia)

SEE ALSO: DYSTONIA; DYSTONIC REACTION (BOTULINUM TOXIN, ACUTE CERVICAL DYSTONIA); PARKINSON'S DISEASE

REFERENCES

Author(s): Peter Barbour, MD
Tourette's Syndrome

Basics

DESCRIPTION
- Tics are a movement disorder characterized by brief, repetitive, stereotyped movements or sounds. Tic disorders are classified along a spectrum based on severity.
  - Transient tic disorder: single or multiple motor and/or vocal tics, which have occurred for <1 year
  - Chronic tic disorder: single or multiple motor or vocal tics, but not both, which have persisted for >1 year
  - Burettes' syndrome (TS): multiple motor and one or more vocal tics, which have persisted for >1 year

EPIDEMIOLOGY
Prevalence
- The exact prevalence of TS is unknown, but estimates range from 2.9-49.5 per 100,000 children.

Race
- TS has been reported in all races, with no ethnic predominance.

Age
- Tics begin most commonly by age 6-7 years and always before 18 years.

Sex
- Males are more commonly affected than females.

ETIOLOGY
- Penetrance is 70% in females and 99% in males.
- Streptococcal infection may play a triggering role in genetically susceptible individuals.

Genetics
- TS is a genetic disorder with an autosomal dominant pattern of inheritance, although the gene has not yet been identified.

RISK FACTORS
- There are no identified risk factors other than genetic and possibly streptococcal infection.
- In patients with IS, however, stress, fatigue, and excitement may exacerbate tics.

PREGNANCY
N/A

ASSOCIATED CONDITIONS
- 50% of patients with IS have attention deficit hyperactivity disorder (ADHD).
- 50% of patients with TS have obsessive-compulsive disorder (OCD).
- There is a higher incidence of learning disabilities in children with IS.
- Self-injurious behaviors, such as hitting or biting oneself, may occur.

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Chorea
- Myoclonus
- Seizures

SIGNS AND SYMPTOMS
- Tics develop abruptly, with initial tics usually being motor tics. Common motor tics include eye blinking, head jerking, and facial grimacing.
- Vocal tics include throat clearing, sniffing, grunting, and coughing. Coprolalia, which is involuntary swearing, develops in about 10% of patients and is not usually present until 4-7 years after initial symptoms.
- Tics vary in frequency, location, type, and severity. Although initial tics may involve the head, over time the tics often involve the limbs and trunk.
- Tics may spontaneously wax and wane, and there may be periods of days to months when all symptoms disappear. They also change over time, with one tic disappearing and another developing.
- Patients can voluntarily suppress tics for varying periods of time; however, the suppression creates an inner tension and eventually the tics must be released.
- Tics may occur during sleep.

LABORATORY PROCEDURES
- There is no laboratory test that is diagnostic for TS.
- The diagnosis is based on clinical criteria.
  - If there is a preceding history of sore throat, tests for streptococcal infection including ASO titer or streptozyme may be indicated.

IMAGING STUDIES
- Neuroimaging studies do not show any structural abnormalities and are not helpful in making the diagnosis

SPECIAL TESTS
- No special tests are indicated.
- EEG and CSF examinations are not helpful.

Admission/Discharge Criteria
- It is very unusual for patients with TS to require admission for their symptoms.

Management

GENERAL MEASURES
- Explaining the nature of TS to the child and family is the most important initial intervention.
- Parents need to know that tics are involuntary and that children should not be punished for symptoms they cannot control.
- They also need to understand that tics are not a sign of psychological disease but that stress can exacerbate the symptoms.

Any events or conditions that exacerbate tics should be identified and eliminated if possible.
- Parents should be educated to ignore tics as much as possible, because focusing attention on them often increases the frequency of tics.
- Management should focus on educational issues that may result from the tics or associated ADHD or OCD.

SURGICAL MEASURES
- There is no surgical treatment for TS.

SYMPTOMATIC TREATMENT
- Pharmacotherapy is indicated for children whose symptoms impair their psychosocial or educational functioning.

ADJUNCTIVE TREATMENT
- In patients with obsessive-compulsive symptoms, behavioral therapy in conjunction with pharmacotherapy may be helpful.
- Educational intervention may be required to optimize academic success.

Adverse effects:
- Haloperidol may cause tardive dyskinesia, a potential side effect from use of haloperidol, but this rarely occurs in children with TS.
- Clonidine reduces tics in some children and can also be helpful for treatment of ADHD.
- A dose of 0.05 mg qd is started and increased by 0.05 mg q5-7 days to a maximum of 0.2-0.3 mg/day. Clonidine has a short half-life, so tid or qid dosing often is required. The patch form has the advantage of providing a constant level of medication.

Space

Medications

DRUG(S) OF CHOICE
- Haloperidol is effective in decreasing tics in about 80% of patients.
- A dose of 0.5 mg qhs is started, with an increase of 0.25-0.5 mg weekly until satisfactory tic control is achieved. Doses >4 mg qd rarely are required. After the tics are controlled for a few months, the medication can be slowly tapered as tolerated.

Contraindications
- None in children with tics other than hypersensitivity to the drug.

Precautions
- Patients need to be monitored for lethargy, weight gain, personality changes, cognitive impairment, and school phobia. Tardive dyskinesia is a potential side effect from use of haloperidol, but this rarely occurs in children with TS.
- Clonidine reduces tics in some children and can also be helpful for treatment of ADHD.
- A dose of 0.05 mg qd is started and increased by 0.05 mg q5-7 days to a maximum of 0.2-0.3 mg/day. Clonidine has a short half-life, so tid or qid dosing often is required. The patch form has the advantage of providing a constant level of medication.

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**Tourette's Syndrome**

**Contraindications**
- Hypotension

**Precautions**
- Patients need to be monitored for sedation and hypotension and, in those treated with the transdermal form, skin reaction. It is advisable not to abruptly stop the medication because of the risk of hypertension.

**ADHD**
- Stimulants such as methylphenidate or dextroamphetamine can improve the attention span and help with impulsive behavior.
- The dose of methylphenidate is 0.3-0.6 mg/kg per dose given 2-3 times qd.

**Contraindications**
- None

**Precautions**
- Stimulants may exacerbate tics in some children. Decreased appetite and insomnia may occur.

**OCD**
- Clomipramine or one of the newer serotonin reuptake inhibitors, such as fluoxetine, sertraline, fluvoxamine, or paroxetine, may help decrease OCD symptoms. These medications usually must be given for 4-6 weeks before improvement is seen.
- The daily dose of clomipramine is 1-3 mg/kg in children and 250 mg in adults. Usual doses of fluoxetine range from 10-40 mg/day, sertraline 50-100 mg/day, fluvoxamine 50-200 mg/day, and paroxetine 20-40 mg/day.

**Contraindications**
- Clomipramine is contraindicated in patients with hypersensitivity to tricyclic antidepressants. Fluoxetine, fluvoxamine, and paroxetine should not be used in combination with MAO inhibitors. Fluvoxamine also cannot be used with terfenadine, astemizole, and cisapride.

**Precautions**
- ECG monitoring before and during treatment with clomipramine is recommended.

**Follow-Up**

**PATIENT MONITORING**
- Patients with mild symptoms who do not need medications can be followed on an as-needed basis. Patients with more severe symptoms will need follow-up every few weeks to months to monitor medication response, school progress, and psychosocial issues.

**EXPECTED COURSE AND PROGNOSIS**
- Approximately one third of patients have complete remission of tics by late adolescence. An additional third of patients report that their tics significantly lessen in frequency and severity by late adolescence. The remaining third of patients continue to be symptomatic into adulthood, although in some there is continuing gradual improvement throughout life.
- ADHD symptoms tend to improve during the adolescent years, although some patients continue to have symptoms that may affect their occupation.
- OCD symptoms, which tend to begin later than tics, may persist and have a negative impact on the patient’s life.

**PATIENT EDUCATION**
- The Tourette Syndrome Association provides many services for patients, families, physicians, and caregivers. Local chapters throughout the country provide additional services, including support groups. Tourette Syndrome Association, 42-40 Bell Boulevard, Bayside, NY 11361-2820. Phone: 718-224-2999, fax: 718-279-9596, website: http://tsa.mgh.harvard.edu

**Miscellaneous**

**SYNONYMS**
- Gilles de la Tourette syndrome

**ICD-9-CM:**
- 307.21 Transient tic disorder; 307.22 Chronic motor or vocal tic disorder; 307.23 Tourette’s disorder; 307.20 Tic disorder not otherwise specified

**REFERENCES**

**Author(s):** Sarah M. Roddy, MD
Transverse Myelitis

DESCRIPTION
- Transverse myelitis (TM) is a syndrome of inflammation of the spinal cord, usually involving multiple segments and both gray and white matter, with resultant myelopathy or spinal cord dysfunction.

EPIDEMIOLOGY
- TM is uncommon, with an incidence estimated at 1-5 cases per million.
- No study has demonstrated any ethnic predominance.

AGE
- All ages affected, with peak incidence in the third and fourth decades.

SEX
- Males and females are equally affected.

SEXUALITY
- The cause of TM is largely unknown.

ETIOLOGY
- The cause of TM is largely unknown. Approximately one third of cases occur during or shortly after an infectious illness such as mycoplasma, schistosomiasis, cytomegalovirus, Epstein-Barr virus, mumps, and varicella.
- Although some infections may attack the spinal cord by direct invasion, it has been hypothesized that other systemic infections may invoke a cell-mediated autoimmune response with sensitization of lymphocytes to spinal cord antigens.
- Another subset of TM is associated with autoimmune disorders including systemic lupus erythematosus (SLE), Sjogren’s syndrome, sarcoidosis, and multiple sclerosis.
- None identified

RISK FACTORS
- Systemic illness, especially respiratory

PREGNANCY
- Little is known about any relationship of TM to pregnancy.

ASSOCIATED CONDITIONS
- Multiple sclerosis
- SLE
- Devic’s disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Extrinsic cord compression
  - Verbal metastases
  - Benign tumors such as meningioma
  - Disc herniation
  - Spinal canal stenosis
  - Spinal arteriovenous malformation
  - Epidural abscess
  - Spinal cord infarction
  - Autoimmune disorders
    - Multiple sclerosis
    - SLE
    - Sjogren’s syndrome
    - Sarcoidosis
    - Paraneoplastic
    - Infectious myelitis: bacterial, viral, tuberculous, syphilitic, fungal, parasitic
    - Myelopathy associated with intravenous opiate use

SIGNS AND SYMPTOMS
- TM symptoms develop rapidly over several hours to several weeks. Approximately 45% of patients reach maximal deficit within 24 hours. Most patients develop leg weakness of varying degrees of severity. The arms are involved in a minority of cases. Initial muscle tone is flaccid, with spasticity developing over hours to days. Sensation is diminished below the level of spinal cord involvement. Some patients experience tingling paresthesias or numbness. Bowel and bladder dysfunction occurs in the majority of patients. Many patients with TM complain of a tight banding or girdlelike sensation around the trunk.

LABORATORY PROCEDURES
- Blood work: There are no specific blood tests to diagnose TM, but the following tests should be obtained to identify potential underlying causes: CBC/differential, RPR, ANA, double-stranded DNA, anti-SSA antibody, anti-SSB antibody, serum vitamin B12 level, human immunodeficiency virus antibody, human T-cell leukemia virus (HTLV-1) antibody, and serum angiotensin-converting enzyme.

IMAGING STUDIES
- MRI with T2-weighted images over several cord segments are often found in TM. Sometimes the cord is swollen. Cranial MRI is helpful to explore the possibility of multiple sclerosis.

SPECIAL TESTS
- Cerebrospinal fluid (CSF) should be sent for cell count, differential, total protein, protein electrophoresis, IgG index, Gram stain, and bacterial culture, cryptococcal antigen, fungal culture, acid-fast bacilli smear and culture, and viral titers or cultures. CSF examination typically shows a lymphocytic pleocytosis with normal or elevated total protein level. Oligoclonal bands are present in 20%-40% of patients with TM.

MANAGEMENT

GENERAL MEASURES
- Specific treatment should be given if any underlying cause of TM is detected. Examples include antibiotics for bacterial infections and antiviral agents such as acyclovir for TM associated with varicella-zoster or herpes simplex virus. More aggressive immunosuppression with cyclophosphamide generally considered if the patient is identified to have SLE. Otherwise, most neurologists would administer high-dose intravenous methylprednisolone for idiopathic postinfectious TM.
- Respiratory function should be monitored closely with forced vital capacity for hypoventilation in the acute phase for high cervical TM. Patients with high cervical lesions may require intubation with high cervic al lesions may require intubation for airway protection if they are not handling secretions well.
- Prophylactic treatment should be given for deep vein thrombosis (DVT) in patients who are immobilized with either air compression boots or SQ heparin 5,000 U bid. A high index of suspicion should be maintained for DVT and pulmonary embolism (PE) should suggestive symptoms arise.
- Urinary retention is frequent. Bladder function should be checked frequently in the acute phase to rule out retention. Intermittent catheterization often is required to prevent bladder distention. A bowel program should be taught. Patients with immobilization should have attention to frequent repositioning and padding to prevent decubitus ulceration. Splints and range of motion may be required to prevent joint contractures.
Transverse Myelitis

**SURGICAL MEASURES**
- There are no surgical procedures for TM. Sometimes the cord is shown to be swollen and a spinal cord tumor cannot be excluded. Biopsy of the cord should be cautiously considered in that case.

**SYMPTOMATIC TREATMENT**
- Spasticity may be a subacute or even long-term problem. It may be ameliorated by:
  - Baclofen at a dosage of 10 mg 1-2 times daily titrated up to an effective dose to maximum of 100 mg or even 200 mg daily if severe, divided in 3-4 doses per day.
  - Tizanidine may be used as an alternative agent if baclofen is not tolerated. Start with 2 mg daily and gradually increase by 2 mg every 3-4 days up to a maximum of 32 mg daily in three doses per day. Tizanidine may cause less weakness than baclofen. Liver function tests must be monitored.
  - Diazepam 2-10 mg 3 times a day or clonazepam 0.5-1.0 mg 3 times a day may relieve spasticity but use often is limited to nighttime because of concomitant sedation.
- Bladder dysfunction: Patients may develop several different patterns of bladder dysfunction. Checking postvoid residuals and cystometric studies may help to sort out the problem.
  - Hypertonic bladder: Oxybutynin 2.5-5 mg PO taken 2-3 times per day or propantheline bromide 15-30 mg PO qhs and 7.5-15 mg tid during the day.
- Constipation:
  - Patient's fluid intake should be increased to 2 to 2.5 L daily.
  - Bulking agents, stool softeners, rectal stimulation (e.g., with glycerin or Dulcolax suppositories), and Theravac mini-enemas may be helpful.
- Neuropathic pain: Many patients complain of neuropathic pain as a long-term residuum of TM. This should be managed with trials of agents such as gabapentin 100-900 mg PO tid, amitriptyline 25-150 mg PO qhs, or carbamazepine 100-200 mg daily, with gradual increase to 600-1,600 mg daily in 3-4 doses.

**ADJUNCTIVE TREATMENTS**
- Physical therapy with passive and active range of motion and occupational therapy should be started as soon as possible to prevent contractures and hasten functional recovery.

**ADMISSION/DISCHARGE CRITERIA**
- Patients are generally admitted for acute evaluation and administration of intravenous steroid therapy. Patients with significant weakness should be evaluated for consideration of inpatient acute rehabilitation.

**MEDICATIONS**

**DRUGS OF CHOICE**
- Methylprednisolone 1 g IV qd for 3-5 days followed by an oral taper of prednisone is given for patients with no identifiable infectious. There is no standard taper used in practice, but a typical regimen might be to start with 1 mg/kg prednisone qd and then taper by 10 mg every 3 days.

**Contraindications**
- Known hypersensitivity to corticosteroids

**Precautions**
- Diabetes mellitus, hypertension

**ALTERNATIVE DRUGS**

**Follow-Up**

**PATIENT MONITORING**
- Patients should be monitored to make sure that they are stabilized and followed as outpatients to facilitate rehabilitation during recovery.

**EXPECTED COURSE AND PROGNOSIS**
- Approximately 45% of patients develop maximal neurologic deficit within 24 hours. In one series, recovery was judged to be good in 33%, fair in 48%, and poor in 25%. Recovery generally begins between 1 and 3 months after onset of symptoms. Back pain or spinal shock at onset is associated with poorer outcome. Recovery is unlikely if no improvement is seen in the first month. TM is generally a monophasic illness, but relapses have been reported in idiopathic or postinfectious TM. Recurrent myelopathic symptoms are frequent in patients with underlying autoimmune illnesses such as SLE or spinal vascular malformations. TM is the first manifestation of multiple sclerosis for some patients. However, most long-term studies record rates of subsequent development of MS of <25%. The presence of abnormal cerebral white matter lesions on MRI at the time of presentation with TM is associated with a significantly higher risk for subsequent development of MS.

**PATIENT EDUCATION**
- Transverse Myelitis Association, 3548 Tahoma Place W, Tacoma, WA 98466.
  Phone: 614-766-1806,
  website: www.myelitis.org

**SYNONYMS**
- N/A

**ICD-9-CM:** 323 Encephalitis, myelitis, encephalomyelitis; 323.9 Unspecified cause of encephalitis. There are other descriptors for viral, postinfectious, and other causes of myelitis.

**SEE ALSO:** N/A

**REFERENCES**

**Author(s):** D. Joanne Lynn, MD
Trauma, Intracranial

Basics

DESCRIPTION

- Intracranial trauma can be described in terms of mechanism and morphology of injury. Mechanism of injury refers to blunt versus penetrating trauma, whereas morphology describes the presence of focal or diffuse intracranial injury. The initial primary injury results in both global and focal disruption of neural networks. The vulnerable tissue is at high risk for secondary insult.

ETIOLOGY

- Alcohol and drug intoxication

RISK FACTORS

- Males to females ratio of 3:1.
- Higher incidence in African Americans; appears to be related to increased exposure to firearms and higher rates of homicide.

AGE

- Occurs in all ages; majority 15-24

SEX

- Male to females ratio of 3:1.

EPIDEMIOLOGY

- Estimate in the United States is 200 per 100,000 (80% mild, 10% moderate, 10% severe)

RACE

- Occurs in all ages; majority 15-24

INCIDENCE

- Half of all traumatic brain injuries are related to sports-related injuries with resultant concussions.

ASSOCIATED CONDITIONS

- N/A

PREGNANCY

- N/A

SIGNS AND SYMPTOMS

- Immediate loss or alteration of consciousness
- Period of confusion and posttraumatic amnesia (retrograde and antegrade)

SIGNS AND SYMPTOMS

- Racing of confusion and posttraumatic amnesia
- Difficulty speaking

ASSOCIATED CONDITIONS

- N/A

PREGNANCY

- Alcohol and drug intoxication

GENETICS

- N/A

RISK FACTORS

- N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of coma

- Alcohol and drug intoxication

- N/A

ASSOCIATED CONDITIONS

- N/A

Management

GENERAL MEASURES

- Appropriate emergency department/intensive care unit management is critical. Treatment differs based on severity of injury.
- Multidisciplinary teams consisting of trauma surgeons, neurosurgeons, orthopedic surgeons, neurologists, and rehabilitation services frequently are necessary.

SPECIAL TESTS

- Head CT: initial study assesses for intracranial blood. Perform on anyone with loss of consciousness for >15 minutes.
- Brain MRI is useful for detecting brainstem involvement and diffuse axonal injury.

LABORATORY PROCEDURES

- Platelet count, PT, PTT, INR, glucose
- Electrolyte abnormalities
- Hypernatremia
  - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
  - Treatment: fluid restriction and avoid hypotonic IV fluids. Refractory cases: demeclocycline (300 mg every 6 hours), fludrocortisone (0.1-0.2 mg/day), hypertonic saline (500 cc over several hours), or oral salt replacement
- Cerebral salt wasting
  - Clinical signs: hyponatremia with hypovolemia, normal serum osmolality, low urine osmolality
  - Treatment: fluid restriction and avoid hypotonic IV fluids. Refractory cases: hypertonic saline (500 cc over several hours), or oral salt replacement
- Hyponatremia
  - Symptoms: hyponatremia with hypovolemia, normal serum osmolality, low urine osmolality
  - Treatment: fluid restriction and avoid hypotonic IV fluids. Refractory cases: hypertonic saline (500 cc over several hours), or oral salt replacement
- Hypertension
  - Treatment: fluid restriction and avoid hypotonic IV fluids. Refractory cases: hypertonic saline (500 cc over several hours), or oral salt replacement

- Cerebral perfusion pressure = MAP — ICP
- Signs of trauma
  - Raccoon's sign
    - Bilateral dilated, nonreactive pupils
    - GCS: defines severity of injury.
  - Occipital: eyes open spontaneously = 4, to voice = 3, to pain = 2, no opening = 1
- Verbal: oriented = 5, disoriented = 4, inappropriate = 3, incomprehensible = 2, no response = 1
- Motor: follows commands = 6, localizes = 5, draws = 4, flexion posturing = 3, extenders posturing = 2, no response = 1

IMAGING STUDIES

- Head CT: initial study assesses for intracranial blood. Perform on anyone with loss of consciousness for >15 minutes.
- Brain MRI is useful for detecting brainstem involvement and diffuse axonal injury.

- Electroencephalogram (EEG)
  - Evoked potentials (EPs)
    - Combination of somatosensory, visual, and brainstem EPs have high correlation with 1-year clinical outcome.

- Video-EEG monitoring
  - May be useful for detecting seizures

- Intracranial pressure (ICP) monitors:
  - Camino bolts, ventriculostomy; ICP goal: <15 mm Hg
  - Ventriculostomy provides acute treatment; ventriculoperitoneal shunting may be necessary

- Transcranial Doppler ultrasound
  - May be useful for detecting cerebral perfusion

- Transcranial magnetic stimulation
  - May be useful for detecting cerebral function

- Functional magnetic resonance imaging (fMRI)
  - May be useful for detecting cerebral function

- Positron emission tomography (PET)
  - May be useful for detecting cerebral function

- Single-photon emission computed tomography (SPECT)
  - May be useful for detecting cerebral function

- Positron emission tomography (PET) and single-photon emission computed tomography (SPECT)
  - May be useful for detecting cerebral function

- Functional magnetic resonance imaging (fMRI) and single-photon emission computed tomography (SPECT)
  - May be useful for detecting cerebral function

- Transcranial magnetic stimulation and functional magnetic resonance imaging (fMRI)
  - May be useful for detecting cerebral function

- Transcranial Doppler ultrasound and single-photon emission computed tomography (SPECT)
  - May be useful for detecting cerebral function

- Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)
  - May be useful for detecting cerebral function

- Video-EEG monitoring and transcranial Doppler ultrasound
  - May be useful for detecting cerebral perfusion

- Transcranial magnetic stimulation and functional magnetic resonance imaging (fMRI)
  - May be useful for detecting cerebral function

- Transcranial Doppler ultrasound and video-EEG monitoring
  - May be useful for detecting cerebral perfusion and seizures

- Functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation
  - May be useful for detecting cerebral function and seizures

- Positron emission tomography (PET) and single-photon emission computed tomography (SPECT)
  - May be useful for detecting cerebral function and seizures

- Video-EEG monitoring and functional magnetic resonance imaging (fMRI)
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  - May be useful for detecting cerebral function and perfusion

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  - May be useful for detecting cerebral function and seizures

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Trauma, Intracranial

**Moderate TBI**
- Generally ICP is not a concern in this group. Similar management as severe TBI for seizures, agitation, and general care.

**Mild TBI**
- Treatment should focus on the symptomatic treatment of sequelae. Patients should not engage in activities placing them at risk for recurrent injury until they have been symptom-free for at least 1 week.

**SURGICAL MEASURES**
- Early surgery warranted for resectable lesion causing a midline shift of >5 mm on CT.
- Decompressive hemicraniectomy with or without tissue resection may be used for refractory increased ICP.

**SYMPTOMATIC TREATMENT**
- Discussed under General Measures. Sequelae may require treatment of headaches, spasticity, cognitive deficits, and pain.

**ADJUNCTIVE TREATMENT**
- Rehabilitation services: physical, occupational, and speech therapy; neuropsychological testing and counseling.

**ADMISSION/DISCHARGE CRITERIA**
- All severe and moderate injuries, as well as mild injuries with an abnormal CT, should be admitted. Discharge may be considered when responsive and clinically stable >24 hours.

**Follow-Up**

**PATIENT MONITORING**
- Monitor through neurology and rehabilitation services for delayed complications.

**EXPECTED COURSE AND PROGNOSIS**
- **Mortality:** Directly related to severity of injury, overall rate = 20/100,000. Higher mortality seen in ages <5 and >65. Severe injury carries 30% mortality rate.
- **Morbidity:** Some degree of neurologic impairment remains in 10% of patients with mild TBI, 67% with moderate, and 100% with severe. Annual disability rate is 35/100,000.

**Posttraumatic Seizures**
- Risk is greatest in first year after injury. Recurrent seizures occur in >85% with an unprovoked late posttraumatic seizure.
- Risk factors for posttraumatic seizures: 
  - Intracerebral contusion
  - Subdural hematoma
  - Prolonged coma or posttraumatic amnesia
  - Skull fracture

**Delayed Hydrocephalus**
- Difficult to distinguish hydrocephalus ex vacuo from symptomatic hydrocephalus. Sequential head CTs are beneficial.
- Presents any time, from >1 month to years after injury. Incidence is 4%.
- Usually a communicating hydrocephalus. May see the classic triad of dementia, gait ataxia, and urinary incontinence.

**Suspect in patients who deteriorate or fail to progress in their rehabilitation.**

**Treatment:** Ventriculoperitoneal or lumbo-peritoneal shunt.

**Postconcussion Syndrome (PCS)**
- Diverse symptom constellation: headaches, dizziness, visual blurring, tinnitus, fatigue, sleep disruption, mood changes, impairments in memory, and attention.
- Usually improves over 3 months in >90%.
- Persistence 6 months after injury raises concerns of psychological factors.

**Neuropsychological Issues**
- Five years after injury, 50% of severe, 14% of moderate, and 3% of mild injuries may still demonstrate neuropsychological impairments.
- Neuropsychological testing can assist with planning of appropriate rehabilitation programs, prediction of functional recovery, and long-term prognosis.

**Rehabilitation**
- Majority of recovery following any brain injury occurs in first 6 months after injury.
- Specialized postacute rehabilitation programs have been developed to address community reentry and vocational rehabilitation.

**PATIENT EDUCATION**
- Brain Injury Association, 105 North Alfred Street, Alexandria, VA 22314. Website: www.biausa.org

**Medications**

**DRUGS OF CHOICE**
- Increased ICP
  - Mannitol at 1 gm/kg loading dose, then repeat boluses of 12.5-50 g
  - Barbiturates (pentobarbital, thiopental) at 5 mg/kg loading dose, then steady infusion of 1-3 mg/kg/hour to maintain burst-suppression EEG pattern
- Seizures
  - Acute period: phenytoin at 15-20 mg/kg loading dose, then maintenance dose for a therapeutic level; discontinue after 1 week if there are no witnessed seizures
  - Long-term: carbamazepine, valproic acid, or levetiracetam are preferred anticonvulsants due to fewer adverse effects on cognition

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- Persistence 6 months after injury raises concerns of psychological factors.

**Neuropsychological Issues**
- Five years after injury, 50% of severe, 14% of moderate, and 3% of mild injuries may still demonstrate neuropsychological impairments.
- Neuropsychological testing can assist with planning of appropriate rehabilitation programs, prediction of functional recovery, and long-term prognosis.

**Rehabilitation**
- Majority of recovery following any brain injury occurs in first 6 months after injury.
- Specialized postacute rehabilitation programs have been developed to address community reentry and vocational rehabilitation.

**Patient Education**
- Brain Injury Association, 105 North Alfred Street, Alexandria, VA 22314. Website: www.biausa.org
Trauma, Mild Brain Injury.

**DESCRIPTION**
- Mild traumatic brain injury (MTBI) or mild head injury is difficult to define compared to moderate or severe injury in which structural damage is evident. Currently, MTBI is considered a traumatically induced physiologic disruption of brain function that may or may not be associated with loss of consciousness.

**EPIDEMIOLOGY**
- It is estimated that two million persons in the United States suffer closed head injuries each year. Approximately 80% of these are due to mild head injury.
- Motor vehicle accidents are the most frequent cause of head injuries. Males between 15 and 24 years old are the group at highest risk.

**ETIOLOGY**
- Estimates of the relative causes of MTBI in the United States are as follows:
  - Motor vehicle accidents 45%
  - Falls 30%
  - Occupational accidents 10%
  - Recreational accidents 10%
  - Assaults 5%
- Mechanisms of head injury or MTBI include:
  - Direct contact injuries
  - Indirect or nonimpact injury (whiplash)
  - Soft tissue injuries
  - Cervical or ocular strain
- Most injuries may overlap, i.e., in acceleration/deceleration head movement, forehead collision on the steering wheel, and cervical strain. There is increasing evidence supporting an organic basis in the pathophysiology of MTBI. After both mild and severe head injuries, damage to nerve fibers and nerve fiber degeneration are evident. Cerebral circulation can be slowed and rotational forces may cause shearing of axons. Generally an injury sustained with the head free (such as an automobile accident) is more damaging than an injury sustained with the head fixed (such as sports injuries).

**RISK FACTORS**
- Motor vehicle accidents are the main cause in the young. Falls are more common in the elderly. Rates of head injury are higher for males at all ages.

**PREGNANCY**
- No association

**ASSOCIATED CONDITIONS**
- Alcohol intoxication has been found in almost two thirds of those tested following MTBI due to automobile accidents.

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Usually mild head injury has an apparent source as noted above. Other medical or neurologic conditions may have been responsible for the head injury, such as a seizure disorder or syncope.

**SIGNS AND SYMPTOMS**
- Headaches are the most common symptom following MTBI. Headache prevalence actually is greater in people with mild head injury than in those with more severe trauma. The onset of headache usually occurs within 2 weeks. There may be more than one type of headache, i.e., they often are mixed with tension and vascular features.
- Neck injuries commonly accompany head injuries and can cause headache. Tension-type headaches may account for 75% of headaches. Recurring attacks of migraine with or without aura can occur. Cluster-type headaches are rare.
- Dizziness is reported by almost half of patients with MTBI. This can have a central origin but probably is more likely from labyrinthine concussion. The dizziness usually is triggered by head movement.
- Other common symptoms include difficulty with attention, concentration, memory; depression; fatigue; and irritability.

**LABORATORY PROCEDURES**
- Usually not significant imaging studies.

**SPECIAL TESTS**
- The most common imaging study is CT scan, although MRI probably is superior in most circumstances. In MTBI, imaging studies usually are normal. Some have recommended CT brain scan for all patients with a Glasgow Coma Score (GCS) <15, an abnormal mental status examination, or any neurologic deficit. Even mild lethargy or memory deficit justifies a CT scan.
- EEG evaluation in MTBI remains uncertain. The EEG may be abnormal, usually with slowing, in some patients shortly after a head injury, and this abnormality may decrease or disappear within days to weeks. Some studies have found no EEG abnormalities if there was not a period of amnesia or loss of consciousness.
- Brainstem auditory evoked potentials are useful for assessing the integrity of the auditory pathway. Abnormalities can be found in 10%–20% of patients with posttraumatic syndrome or after MTBI. Approximately 30% of patients with mild MTBI and symptomatic dizziness will have abnormal studies. The degree of abnormality usually increases with the extent of injury.
- Electronystagmography (ENG) has been noted to be abnormal in 40%–50% of patients with MTBI or even "whiplash." ENG may be more sensitive to traumatic abnormalities than the brainstem auditory evoked response.
Management

GENERAL MEASURES
• Treatment is individualized for each of the problems diagnosed. Treatment for headaches is similar to treatment of headache in general. If there is a posttraumatic migraine syndrome, the triptan-type medications can be helpful. Education of the patient, family members, other physicians, and, when appropriate, employers and attorneys can be very helpful.

SURGICAL MEASURES
• Generally none for MTBI

SYMPTOMATIC TREATMENT
• Patients with daily posttraumatic headache may need to be placed on some type of preventative medication, usually an antidepressant. Tricyclic antidepressants usually are given first, but selective serotonin reuptake inhibitors also can be tried. Dosing antidepressants for posttraumatic headache is essentially the same as for treatment of depression, although occasionally patients will respond to lower doses. Patients with posttraumatic migraine may benefit from propranolol or a calcium channel blocker (verapamil). Using analgesic medication to decrease pain levels may enable the patient to better concentrate and relax and allow greater benefits from non-drug therapies. Care must be taken that analgesic rebound headaches do not occur. Antiinflammatory medication and muscle relaxants may be useful for some patients, usually for a limited time frame, i.e., 1-2 weeks.

ADJUNCTIVE TREATMENT
• Headaches associated with myofascial trigger points in the neck or upper back often will respond to trigger point injections of local anesthetic, with or without steroids. These often are helpful but typically last only 2-4 weeks. Other nondrug therapies include biofeedback, physical therapy, massage, and counseling. Psychotherapy may be helpful if there is significant depression, anxiety, frustration, excessive expectations, anger, and unresolved grief and loss. Depression should be treated with antidepressant medication.

ADMISSION/DISCHARGE CRITERIA
• MTBI typically does not require neurosurgical intervention or hospitalization. If there is any uncertainty as to the degree or head injury, a brief hospitalization for observation is perfectly reasonable. Patients with MTBI may be admitted if there are concurrent injuries to other parts of the body. Patients with GCS scores <15, an abnormal mental status, or any neurologic deficit should be considered for admission. The majority of patients with mild head injuries can be sent home and observed.

Follow-Up

PATIENT MONITORING
• Outpatient follow-up usually is all that is necessary, but patients may take several weeks because of multiple symptoms and concerns. Follow-up should be individualized.

EXPECTED COURSE AND PROGNOSIS
• Approximately 80% of patients will recover without significant sequelae. Twenty percent may continue to have symptomatic headache, neck pain, or dizziness. Some will continue to have difficulty with attention, concentration, and memory. Although most patients have a favorable outcome. Some guidelines exist to identify patients at risk for longer periods of incapacity. These include:
  — Older patients
  — Patients with previous head injuries
  — Persons who have been high achievers or in demanding occupations
  — Patients who have family or social stressors

Medications

DRUGS OF CHOICE
• Analgesics
• Nonsteroidal inflammatory medications
• Muscle relaxants
• Antidepressants
• Anticonvulsants
• Tricyclics

Follow-Up

PATIENT MONITORING
• Outpatient follow-up usually is all that is necessary, but patients may take several weeks because of multiple symptoms and concerns. Follow-up should be individualized.

EXPECTED COURSE AND PROGNOSIS
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  — Older patients
  — Patients with previous head injuries
  — Persons who have been high achievers or in demanding occupations
  — Patients who have family or social stressors

Patient Education
• Patients should be educated as to the expected outcome for MTBI. Most MTBI patients do not enroll in support groups for brain injury associations. If patients have symptoms that persist beyond 1 year, they may benefit from contacting the Brain Injury Association.

Miscellaneous

SYNONYMS
• Concussion
• Mild head injury
• Mild traumatic brain injury
• Postconcussive syndrome.

ICD-9-CM: 850.0 Concussion; 310.20 Postconcussive syndrome

SEE ALSO: N/A

REFERENCES

Author(s): Russell C. Packard, MD
Trauma, Spinal Cord

Basics

DESCRIPTION
- Spinal cord injury can be divided into complete or incomplete injuries. Extrication, stabilization, and transport guidelines are followed to prevent exacerbation of current injuries and increase rehabilitation potential.

EPIDEMIOLOGY
Incidence
- Between 30 and 50 per 1,000,000

Injury Levels
- C-spine 55%, T-spine 30%, L-spine 15%

Prevalence
- Approximately 721 per 1,000,000

Age
- All ages; majority 25-44 years; median age at injury is 26 years.

Sex
- Males outnumber females by a ratio of 2.5:1

Race
- Higher incidence in Caucasians

ETIOLOGY
- Motor vehicle accidents 45%
- Falls 17%
- Violence

Genetics
N/A

RISK FACTORS
- Alcohol, drug intoxication, violence

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Transverse myelitis, myelopathy
- Spinal cord ischemia

SIGNS AND SYMPTOMS
- Depend on level of injury, which is defined as the lowest spinal cord segment with intact motor and sensory function.
- Loss of motor control, tone and reflexes
- Loss of sensory function within three levels of injury
- Hand paresthesias should raise concern for cervical injury.
- Loss of bowel, bladder, and sexual function.

DESCRIPTION
- Testing involves voluntary motor control, sensory sparing, tone, and reflexes (bulbocavemosus reflex).
- Key levels:
  - Motor:
    - C-5: Elbow flexors
    - C-6: Wrist extensors
    - C-7: Elbow extensors
    - C-8: Finger flexors to the middle finger
    - T-1: Small finger abductors
    - L-2 Hip flexors
    - L-3: Knee extensors
    - L-4: Ankle dorsiflexors
    - L-5: Long toe extensors
    - S-1: Ankle plantar flexors
    - S-4-5: Rectal tone
  - Sensory: T-4: nipple line, T-10:umbilicus
- Tetraplegia results from cervical region injury.
- Paraplegia results from injury to the thoracic, lumbar, or sacral segments; conus medullaris; or cauda equina.

Spinal cord syndromes
- Complete
  - Loss of all sensory and motor function
  - Reflexes initially flaccid, but hyperreflexia develops over time.
  - Autonomic pathways are disrupted, resulting in urinary, rectal, and sexual dysfunction.
- Incomplete syndromes
  - Brown-Séquard syndrome (hemisection of cord)
    * Ipsilateral motor weakness and proprioception/vibration loss
    * Contralateral pain and temperature loss
  - Tetraplegia
    * Weakness of arms greater than legs due to involvement of anterior horn cells
    * Pain/temperature loss at level of injury
    * Reflexes decreased in arms; normal to hyperactive in legs
    * Frequently occurs with hyperextension injuries in the elderly due to cervical spondylosis
  - S-1 level and completeness of injury.

ETIOLOGY
- Motor vehicle accidents 45%
- Falls 17%
- Violence

Genetics
N/A

RISK FACTORS
- Alcohol, drug intoxication, violence

PREGNANCY
N/A

ASSOCIATED CONDITIONS
N/A

Management

GENERAL MEASURES
- Early immobilization of the spine is mandatory. A detailed neurologic examination, including rectal tone, is necessary to identify level and completeness of injury.
- Megadose steroids: methylprednisolone, initial bolus 30 mg/kg over 1 hour.
- Follow with continuous infusion of 5.4 mg/kg/hour for 23 hours if treatment is started within 3 hours of injury. Continue for 48 hours if treatment was started 3-8 hours after injury.
- No indication for megadose steroids beyond the 8-hours window.

Neurogenic shock
- Decreased peripheral vascular tone results in expanded vascular space and relative hypovolemia, with hypotension, bradycardia, and warm dry skin.
- Monitor central venous and pulmonary wedge pressures, with appropriate use of vasopressors.

SPECIAL TESTS
- Cervical magnetic resonance angiography (MRA) to assess integrity of vertebral arteries with cervical injury.
- Head CT or MRI should be done if traumatic brain injury is suspected.

GENERAL MEASURES
- American Spinal Injury Association (ASIA) Impairment Scale describes the extent of spinal cord injury:
  - A = Complete: Npreserved motor or sensory function
  - B = Incomplete: Npreserved motor function, sensation preserved below the neurologic level
  - C = Incomplete: Motor function below the neurologic level with <50% key muscle grades >3/5
  - D = Incomplete: Motor function below the neurologic level with >50% key muscle grades >3/5
  - E = Normal: Motor and sensory function

LABORATORY PROCEDURES
- CBC, PT, PTT, INR, glucose

IMAGING STUDIES
- Anteroposterior and lateral plain x-ray films of bony spine
- Spinal CT of bony strutures if abnormalities present on conventional imaging
- Spinal MRI of spinal cord, and intervertebral and paravertebral soft tissue

STANDARD CARE
- Extrication, stabilization, and transport guidelines are followed to prevent exacerbation of current injuries and increase rehabilitation potential.

IMAGING STUDIES
- Spinal CT of bony structures if abnormalities present on conventional imaging
- Spinal MRI of spinal cord, and intervertebral and paravertebral soft tissue

SPECIAL TESTS
- Cervical magnetic resonance angiography (MRA) to assess integrity of vertebral arteries with cervical injury.
- Head CT or MRI should be done if traumatic brain injury is suspected.

GENERAL MEASURES
- Megadose steroids: methylprednisolone, initial bolus 30 mg/kg over 1 hour.
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Neurogenic shock
- Decreased peripheral vascular tone results in expanded vascular space and relative hypovolemia, with hypotension, bradycardia, and warm dry skin.
- Monitor central venous and pulmonary wedge pressures, with appropriate use of vasopressors.
**Spinal Shock**
- Loss of tone and spinal reflexes below level of injury. Duration is 2-4 weeks.
- Pulmonary complications
- High tetraplegics require ventilatory support and/or phrenic nerve pacemakers.
- Pain management
- Difficult to distinguish between neuropathic and musculoskeletal pain.
- Gabapentin rather than narcotics should be considered for neuropathic pain.
- Autonomic dysreflexia
- Noxious stimuli below the lesion level result in sympathetic discharge with hypertension, reflex bradycardia, sweating, headache, flushing, and piloerection.
- Noted in 45%-85% of injuries at or above T6. Onset >2 months after injury. Common causes:
  - Bladder and/or bowel distention
  - Pressure ulcers, skin infections
  - Uterine contractions during labor and delivery
- Management:
  - Treat underlying inciting factor
  - Raise head of bed and treat hypertension pharmacologically
- General care
  - Prophylaxis for deep vein thrombosis.
  - Gastrointestinal care: Nasogastric tube to manage ileus prior to return of GI motility. Bowel program.
  - Monitor for spasticity. Early ranging and medications may prevent contractures.
  - Prevent decubitus ulcers.

**Surgical Measures**
- Early surgery warranted for locked and dislocated facet joints, or marked spinal instability or deformity that does not respond to closed realignment.
  - Decompress and prevent further injury to spinal elements to maximize recovery.
  - Prevent delayed spinal instability and deformity.
  - Allow early mobilization and rehabilitation.

**Symptomatic Treatment**
- Sequelae of trauma may require treatment of orthopedic, internal, and pulmonary injuries, spasticity, and pain.

**Adjunctive Treatment**
- Rehabilitation services: physical, occupational, and speech therapy; neuropsychological counseling

**Admission/Discharge Criteria**
- Any evidence of spinal cord injury warrants admission. Transfer to specialized rehabilitation services when the patient is stabilized.

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**Medications**

**DRUG(S) OF CHOICE**
- Acute injury
  - Methyldprednisolone
  - Vasopressors for shock and hypotension
- Pain
  - Neuropathic pain: gabapentin, levetiracetam (Keppra), carbamazepine dilantin — Musculoskeletal pain: narcotics acutely, nonsteroidal antiinflammatory drugs
- Deep Vein Thrombosis
  - Prophylaxis: Enoxaparin (Lovenox) 30-60 mg bid, SQ heparin 5,000 U bid
  - Treatment: Anticoagulation with heparin, then coumadin. If contraindicated, IVC Greenfield filter is necessary.
- Spasticity
  - Useful drugs: gabapentin, baclofen, tizanidine, diazepam, dantrolene sodium — Intrathecal baclofen pumps are helpful for excessive spasticity.
- GI issues
  - ULCER prophylaxis: H2 receptor antagonists or sucralfate
  - Bowel program: adequate fluid, diet, and activity level, stool softeners, and glycerin or bisacodyl suppositories

**Contraindications**
- Hypotension worsens clinical outcome.
- Precautions
  - Monitor closely for pulmonary complications, DVT, infections, and skin care.

**Alternative Drugs**

**Follow-Up**

**Patient Monitoring**
- Long-term monitoring by neurology and rehabilitation for delayed complications

**Expected Course and Prognosis**
- Clinical course is based on level of injury — High tetraplegia (C1-C4)
  - Requires long-term ventilatory support
  - 05: Functional biceps allows greater independence through splinting and orthotics. Generally able to feed self and assist with upper body dressing.
  - 06: Presence of wrist extension allows use of tenodesis for greater hand use.
  - Generally able to feed self and perform oral-facial hygiene.
  - C7: Triceps function significantly increases independence.
- Most are independent with dressing, and bowel and bladder management.
  - Thoracic and lumbar paraplegia
  - Should achieve full independence with self-care and wheelchair mobility.

- Prognosis for ambulation recovery based on assessment at 1 week:
  - ASIA A: 80%-90% remain complete. Only 3%-6% recover functional leg strength.
  - ASIA B: 50% become ambulatory. — ASIA C: 75% become community ambulators. ASIA D: 95% become community ambulators.

- Equipment needs
  - Proper wheelchair positioning, cushions
  - Bracing may assist with ambulation
- Sexual function
  - Education and counseling are essential.
  - Adaptive strategies, alternative techniques, mechanical devices, and medications may be useful.
- Psychological
  - Depression in 25%-50%.
  - Chemical dependency in up to 5010.
- Counseling should be available.

**Patient Education**
- American Spinal Injury Association, 2020 Peachtree Road, NW, Atlanta, GA 30309.
  - Phone: 404-355-9772.
  - Website: www.asia-spinalinjury.org

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**Miscellaneous**

**SYNONYMS:** N/A

**ICD-9-CM:** 952.00 Spinal cord injury, cervical region; 952.1 Spinal cord injury, dorsal (thoracic); see multiple qualifiers for 952 codes

**SEE ALSO:** TRANSVERSE MYELITIS

**REFERENCES**

**Author(s):** Lori Shutter, MD
Trichinosis

**Basics**

**DESCRIPTION**

- Trichinosis is the systemic illness that results from infestation with larvae of the nematode worm *Trichinella spiralis*. It may consist of general, gastrointestinal, neurologic, cardiac, and respiratory manifestations.

**EPIDEMIOLOGY**

- Incidence in United States has been declining over the past 50 years. Currently, cases in United States average <40 years.
- May be acquired by travel in foreign countries.

**ETIOLOGY**

- Invasion of tissue by worm larvae
- Inflammatory response to infection

**RISK FACTORS**

- Consumption of undercooked pork or wild game such as deer, bear, horse meat, which contain larvae of *T. spiralis*.
- Recommendations are to cook pork and game meats until well done (not pink), to temperatures of at least 77°C (171°F).

**PREGNANCY**

- There are reports of trichinosis being transmitted in utero from mother to fetus.
- Maternal trichinosis has been associated with spontaneous abortion. Lactation has been reported to be suppressed in postpartum women with trichinosis.

**ASSOCIATED CONDITIONS**

- N/A

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**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**

- Typhoid fever
- Food poisoning
- Leptospirosis
- Periarteritis nodosa
- Dermatomyositis
- Poliomyelitis
- Meningitis/encephalitis

**SIGNS AND SYMPTOMS**

- The diagnosis is suggested by the symptom complex of fever, malaise, myalgia, periorbital edema, and eosinophilia.
- The incubation period for appearance of generalized symptoms from time of ingestion varies from approximately 1 day to 7 weeks, with earlier appearance of symptoms generally presaging a more severe course. After the ingested cyst wall is digested in the stomach, the larvae are released and enter the general circulation from the gut. Although they may invade multiple organs, they encyst in striated muscle and may persist there for many years. An allergic vasculitis may occur and is responsible for edema and hemorrhage.

**GENERAL/ABDOMINAL**

- Fever, malaise
- Cramping, diarrhea
- Periorbital edema
- Subconjunctival hemorrhages
- Myocarditis
- Maculopapular rash

**NEUROLOGIC**

- Myalgia
- Muscles painful to palpation
- Rim at.w.st.. l.at.watse.with movement
- Vvitis, t-Ast,cim) 'muscles, k.em*.vt , respiratory, neck muscles
- Weakness and stiffness in affected muscles CNS involvement occurs in 10%-20% of cases, and may result from direct invasion of affected muscles CNS invasion. In untreated patients with neurologic manifestations, mortality may be as high as 50%.
- Headache
- Seizures
- Meningitis/encephalitis

**LABORATORY PROCEDURES**

**Blood Tests**

- Eosinophilia
- Elevated muscle enzymes
- Hypoalbuminemia
- Leukocytosis

**IMAGING STUDIES**

- Neuroimaging may reveal focal areas of infarction, hemorrhage, or thrombosis, in cases where there has been larval invasion of the brain. In some cases, larvae may be found in spun samples of CSF. In cases of pulmonary complications, there may be pneumonia or pleural effusion present on chest x-ray film.

**SPECIAL TESTS**

- The definitive test for trichinosis is the presence of *T. spiralis* larvae in muscle biopsy of the affected individual. Biopsy may be positive as early as 2 weeks after infection. Serology may be obtained for the presence of *T. spiralis* antibodies. Serologic tests become positive 3-4 weeks after initial infection.
- ECG
  - T wave changes, e.g., inversion
  - Decreased QRS voltage
  - ST-segment depression
  - Premature ventricular contractions
  - Conduction disturbances

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Trichinosis

Management

**GENERAL MEASURES**

- Other than specific treatment of complications, therapy is directed at stopping infection and eradicating the parasite within the host (vide infra). Management of complications is symptom specific, e.g., anticonvulsant therapy for seizures. Corticosteroids may be indicated in moderate-to-severe cases of allergic vasculitis, e.g., prednisone at doses of 60-120 mg/day or higher if needed. Steroids should not be used alone in early cases (<6 weeks after ingestion) because they may prolong the presence of adult worms in the gut.

**SURGICAL MEASURES**

N/A

**SYMPTOMATIC TREATMENT**

- Symptomatic therapy is aimed at specific complications. Fluids may be needed for dehydration, or diuretics in cases of severe edema. Antiarrhythmics may be indicated in cases of cardiac complications. Rarely, with severe pulmonary involvement, assisted ventilation may be necessary. Myalgia may respond to conventional doses of salicylates or nonsteroidal antiinflammatory drugs. After the act phase, physical or occupational therapy may be indicated to restore function in affected muscles.

**ADJUNCTIVE TREATMENT**

N/A

**ADMISSION/DISCHARGE CRITERIA**

- Patients with moderate or severe trichinosis will need to be admitted primarily for management of systemic manifestations and complications, e.g., dehydration, or cardiopulmonary or CNS manifestations. The most common cause of death in trichinosis is myocardial/cardiac failure, which most frequently occurs in weeks 4-8 of infection.

**Follow-Up**

**PATIENT MONITORING**

- Patients should be monitored in the first few weeks of the illness for development of neurologic, cardiac, pulmonary, and respiratory complications. Patients may develop hypersensitivity reactions as the result of larval death due to antihelminthic therapy.

**EXPECTED COURSE AND PROGNOSIS**

- Recovery is complete in a few months in most cases.
- Encysted larvae in muscle may persist for up to decades and be asymptomatic.
- Rarely, there is a chronic syndrome that consists primarily of fatigue.

**PATIENT EDUCATION**

- Patients should be warned against eating raw or undercooked pork or wild game products, particularly when traveling abroad. They should be instructed in proper cooking and freezing procedures when home processing pork and game products.

**Medications**

**DRUGS OF CHOICE**

- **Intestinal Phase**
  - Mebendazole 200-400 mg PO tid for 3 days, followed by 400-500 mg PO tid for 10 days
  - Albendazole 400 mg bid

- **Acute Phase**
  - Corticosteroids 0.5-2.0 mg/kg/day in divided doses for 4-10 days
  - Mebendazole 200-400 mg PO tid daily for 3 days, followed by 400-500 mg PO tid for 10 days

**Contraindications**

- These drugs are contraindicated for use in pregnant women.

**PRECAUTIONS**

- Side effects include neutropenia, abnormal liver function tests, myalgia, and fatigue. In patients who develop allergic vasculitis or hypersensitivity reactions, steroids may be combined with antihelminthic treatment.

**ALTERNATIVE DRUGS**

N/A

**References**


Author(s): Barbara S. Giesser, MD

**Synonyms**

- Trichinellosis

**ICD-9-CM: 124 Trichinosis**

**Miscellaneous**

- Trichinella infection and clinical disease.
Trigeminal Neuralgia

**Basics**

**DESCRIPTION**
- Trigeminal neuralgia is a clinical syndrome characterized by recurrent paroxysmal lancinating pain in the trigeminal distribution. The pathogenesis in most cases is idiopathic but may be caused by a local lesion.

**ETIOLOGY**
- The pathogenesis of trigeminal neuralgia is unclear and probably multifactorial.
- Cerebelloptine tumors, schwannoma, multiple sclerosis, or other lesion involving or near the trigeminal nerve or its nucleus may cause trigeminal neuralgia in a minority of cases.
- The proposed theories of pathogenesis for both the idiopathic and symptomatic cases focus on aberrant repetitive discharges that could arise from:
  - The vascular compression theory holds that a tortuous artery or vein near the trigeminal nerve compresses the nerve root. The compression increases with age and causes changes in the sensory root entry zone that result in prolongation of electrical impulses in the nerve and reexcitement of the axon leading to repetitive neural discharges.
  - Inflammation near or in the trigeminal nerve

**RISK FACTORS**
- N/A

**PREGNANCY**
- Currently, there is no particular relation of trigeminal neuralgia with pregnancy.

**ASSOCIATED CONDITIONS**
- Multiple sclerosis
- Brainstem neoplasms
- Vascular compression/vertebrobasilar dolichoectasia
- Trigeminal schwannoma
- Cerebroptine angle tumors: acoustic neuroma, meningioma
- Metastatic infiltration of the base of the skull
- Cavernous sinus lesions: cavernous carotid aneurysm, meningioma, pituitary adenoma, Tolosa-Hutksyndrome, metastasis

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Need to differentiate from other causes of pain or cranial pain.
  - Neuralgia
    - Glossopharyngeal neuralgia
    - Atypical neuralgia
  - Migraine headaches
    - Cluster headache
    - Temporal arteritis
    - Musculoskeletal pain
    - Temporomandibular joint pain
  - Myofascial pain syndrome
  - Local diseases
    - Ocular and per ocular diseases, e.g., uveitis, orbital tumor, orbital cellulitis
    - Nasal and paranasal sinus diseases
    - Odontogenic diseases

**SIGNS AND SYMPTOMS**
- The characteristic pain in trigeminal neuralgia is a paroxysmal, sharp, shooting or lancinating pain in the distribution of one or more divisions of the trigeminal nerve, most commonly in the second and third divisions.
- Pain classically consists of a burst of multiple very brief sharp jabs, each lasting <1 second but adding to 1 to several seconds. The bursts themselves may occur repeatedly for a period of a few seconds to 1 minute. The pain may be excruciating to the point of deep depression or even suicide.
- The pain is triggered by sensory stimuli to the skin, mucosa, or teeth within the area innervated by the trigeminal nerve. Pain sometimes can be initiated by chewing, brushing the teeth, or talking.
- In classic idiopathic trigeminal neuralgia, the neurologic examination is normal. There is no sensory or motor impairment in the trigeminal distribution.
- When trigeminal neuralgia results from a lesion involving the trigeminal nerve roots or ganglion, the neurologic examination may show sensory deficits in the trigeminal distribution, weakness or atrophy of the muscles of mastication, or abnormalities in the adjacent cranial nerves, depending on the location.
- Atypical trigeminal neuralgia is characterized by atypical characteristics of pain (e.g., no bursts, continuous pain) or an abnormal neurologic examination that would prompt investigations for an associated structural lesion.

**LABORATORY PROCEDURES**
- In classic trigeminal neuralgia, there are no accompanying laboratory or radiographic abnormalities. Blink reflexes are normal.
- Additional laboratory tests may be required for other disorders in the differential diagnosis of facial pain, such as ESR for temporal arteritis, or X-ray film of sinus or temporomandibular joint.

**IMAGING STUDIES**
- Neuroradiologic imaging is recommended in patients undergoing surgical treatment for trigeminal neuralgia, patients with atypical trigeminal neuralgia, or patients with any associated neurologic deficit compatible with an underlying structural lesion.
- In the case of trigeminal neuralgia due to structural lesions such as meningioma, schwannoma of the trigeminal nerve, or infiltration of the base of skull by malignant tumors, CT or MRI with contrast may reveal a lesion along the pathway of trigeminal nerve.
- In idiopathic trigeminal neuralgia, neuroimaging will be normal.

**Management**

**GENERAL MEASURES**
- Initial management begins with a trial of carbamazepine, which is the agent of choice. Doses are gradually increased until pain is controlled or side effects become intolerable. Other agents listed in the Medications section can be tried alone or in combination. Approximately 25%-50% of patients eventually will fail to respond to drug therapy and require some sort of surgical intervention.

**SURGICAL MEASURES**
- Surgical measures are reserved for patients with:
  - Surgical lesions
  - Inadequate response to nonsurgical treatment
  - High-dosage medication requirement with intolerable side effects

**Extracranial Peripheral Denervation**
- Temporary denervation or blocks of the peripheral branches of trigeminal nerve
- Nerve block performed at supraorbital, infraorbital, or mental foramen with alcohol or lidocaine
- Advantages: May be performed in the office. The area of denervation is focal and small. The corneal does not become denervated and permanent dysesthesias are unlikely. Major complications are rare.
- Disadvantages: The procedure is very painful when it is performed without sedation or analgesia in the office. Pain can return in a short period.
- Even with the more permanent peripheral denervations, pain commonly returns within 6-12 months, and repeating the procedure could be more difficult with shorter period of pain relief.
Percutaneous Denervation of Gasserian Ganglion and Retrogasserian Ganglion Rootlets
- Several methods may produce partial denervation of the trigeminal ganglion or its rootlets. A specially designed device is inserted under radiographic control into the cheek, through the foramen ovale, into the gasserian or retrogasserian ganglion. Partial destruction of the trigeminal nerve then is accomplished with radiofrequency thermoagulation or glycerol.

Percutaneous Radiofrequency Thermocoagulation
- Initial pain relief occurs in >90% of the patients, with recurrence in 22% at 2-6 years and up to 80% with long-term (12 years) follow-up. A smaller area of denervation is associated with a higher recurrence rate.
- Procedure can be repeated, usually with good probability of pain relief.
- Severe dysesthesia follows the procedure in 2%-10% of the patients. Denervation of cornea and keratitis occur in 1%-3% of patients. The incidence of dysesthesias and keratitis tends to increase with more aggressive denervation.

Glycerol Trigeminal Rhizolysis
- Injection of sterile glycerol into the gasserian ganglion and retrogasserian rootlets instead of radiofrequency thermoagulation.
- Glycerol is a mild denervating agent.
- Denervation of cornea and keratitis occur in 1%-3% of patients. The incidence of dysesthesias and keratitis tends to increase with more aggressive denervation.

Microvascular Decompression
- Procedure is based on the proposed mechanism that trigeminal neuralgia results from chronic vascular compression of the trigeminal nerve at the root entry zone.
- Procedure is performed through the suboccipital retrosigmoid craniectomy. The trigeminal nerve then is decompressed by placing a synthetic material, usually a Teflon felt, between the nerve and the vessel.
- One year after the procedure, 75% have pain relief and 9% have partial relief. After 10 years, 64% continue with excellent results and 4% with partial relief of pain.
- Death occurs in 0.2%-2.4% of patients, and other major intracranial complications occur in 1%/2% of patients. Hearing loss occurs in 1%/2% of patients. Facial weakness occurs in approximately 1% of patients, and burning and aching facial pain occur in 3.3%-4.8% of patients.

Choosing the Surgical Procedure
- Due to the invasiveness of microvascular decompression, radiofrequency thermoagulation or other less invasive procedures are preferred in patients with (i) older age, (ii) significant medical illness, (iii) contralateral hearing loss, (iv) previously good results with radiofrequency thermoagulation, or (v) multiple sclerosis, because pain recurrence is frequent regardless of procedure type.

SYMPTOMATIC TREATMENT
- See Medications

ADJUNCTIVE TREATMENT

ADMISSION/DISCHARGE CRITERIA
- Admission may be required when pain is so severe that it has resulted in dehydration.

Medications

DRUG(S) OF CHOICE
- Carbamazepine is the most effective medication with pain relief achieved in 75% of patients.

Dosage
- Medication may be started at a small dose of 50-100 mg twice per day to prevent side effects and increased slowly as tolerated. Usual therapeutic doses range from 600-1,200 mg/day, with the therapeutic drug level of 40-100 g/mL.

Side Effects
- Common side effects include drowsiness, vertigo, nausea, and ataxia.

Contraindications
- History of previous bone marrow depression, hypersensitivity to carbamazepine. Combination with monoamine oxidase (MAO) inhibitors is contraindicated. MAO inhibitors should be discontinued for 14 days before starting carbamazepine.

Precautions
- Hyponatremia can occur. In patients taking carbamazepine, CBC should be taken in the first few months and periodically because of increased risk for agranulocytosis. Obtaining these counts may or may not influence risk for these rare but devastating complications. Patients should be advised to contact their physician if they develop symptoms of a hematologic problem, such as prolonged fever, infection, easy bruising, petechial hemorrhage, and symptoms of anemia.

ALTERNATIVE DRUGS
- Alternative medications are phenytoin, baclofen, gabapentin, valproate, mexiletine, and clonazepam, which are generally less effective than carbamazepine but may be better in particular individuals.

Follow-Up

PATIENT MONITORING
- Neurologic examination should be performed periodically. A neurologic deficit suggests an occult structural lesion.

EXPECTED COURSE AND PROGNOSIS
- The clinical course is exacerbating and remitting over many years. Spontaneous remission may occur at any time and last for months or years.
- Medications should be tapered periodically to uncover a remission.

PATIENT EDUCATION
- Trigeminal Neuralgia Association (TNA), P.O. Box 340, Barneget Light, NJ 08006. Phone: 609-361-1014, fax: 609-361-0982; website: www.tna-support.org

SYNONYMS
- Tic douloureux

ICD-9-CM: 350.1 Neuralgia, trigeminal

SEE ALSO: N/A

REFERENCES

Author(s): Thomas C. Chelimsky, MD
Tuberculosis

**DESCRIPTION**
- Tuberculous involvement of the nervous system occurs as meningitis, tuberculoma formation, or spinal arachnoiditis.

**ETIOLOGY**
- More common in males than females.
- American Indians have higher rates than African Americans, who in turn have higher rates than Caucasians.

**EPIDEMIOLOGY**

**Incidence/Prevalence**
- Tuberculous meningitis develops in 1%-2% of tuberculosis cases. Immunodeficiency increases the incidence. From 5%-10% of AIDS patients have tuberculosis, and up to 10% of these patients develop central nervous system (CNS) involvement.

**Age**
- Seen at any age, but peaks in the pediatric and elderly populations.

**Sex**
- More common in males than females.

**GENETICS**
- N/A

**RISK FACTORS**
- Immunodeficiency
- HIV infection
- Hematologic and reticuloendothelial malignancies
- Immunosuppressive therapy
- Malnutrition
- Chronic renal failure
- Alcohol and drug abuse

**PREGNANCY**
- A pregnant woman with tuberculosis should be treated because the infection is more hazardous to the patient and fetus than are the drugs. Isoniazid, rifampin, and ethambutol cross the placenta but do not have demonstrated teratogenic effects. Streptomycin can cause congenital deafness. There are no adequate data on pyrazinamide. Tuberculosis during pregnancy is not an indication for therapeutic abortion.

**ASSOCIATED CONDITIONS**
- N/A

**DIAGNOSIS**

**DIFFERENTIAL DIAGNOSIS**
- Fungal or viral meningitis
- Partially treated bacterial meningitis.
- Parasitic infections (cysticercosis, toxoplasmosis)
- Carcinomatous meningitis
- Neurosyphilis
- Sarcoidosis
- Pyogenic brain abscess

**SIGNALS AND SYMPTOMS**
- CNS tuberculosis presents as three different clinical pictures.
  - Tuberculous meningitis results from hematogenous dissemination or, more frequently, rupture of granulomas into the subarachnoid space. The cause of the neurologic symptoms is the thick fibrous exudate that especially fills the basal cisterns. Inflammation and compression of blood vessels cause cerebral infarctions. Cranial nerves traversing the exudate are affected. A communicating type of hydrocephalus commonly develops. The onset of symptoms is subacute. Signs of meningeal irritation (headache, vomiting, neck stiffness) are preceded by a prodromal phase lasting 2-3 weeks. Prodromal symptoms are fatigue, night sweats, low-grade fever, anorexia, malaise, and myalgia. Altered consciousness will follow meningeal irritation signs. Cranial nerve palsies, especially involvement of cranial nerves III, IV, and VI, are seen in 20%-30% of patients. Papilledema, seizures, and hemiparesis occur in 10%-15% of patients. Signs of pulmonary or extrapulmonary tuberculosis are often present. If not treated, coma and death will occur within 5-8 weeks.
  - Tuberculomas are slow-growing granulomas that can be found in the cerebral, cerebellum, brainstem, subarachnoid, subdural and epidural spaces, and rarely within the spinal cord. They can occur in isolation or associated with meningitis. They cause headache, seizures, and focal neurologic deficits. Tuberculomas can cause an obstructive type of hydrocephalus.
  - Spinal arachnoiditis usually follows intracranial meningitis. Resultant root and cord compression causes pain, paralysis, sensory loss, and sphincter disturbances.

**LABORATORY PROCEDURES**
- Routine blood tests are nonspecific. Mild anemia, leukocytosis, and increased erythrocyte sedimentation rate are seen. Inappropriate antidiuretic hormone secretion can lead to mild-to-moderate hyponatremia in about half of the patients.
- From 50%-75% of patients with tuberculous meningitis have a positive tuberculin skin test (PPD).

**IMAGING STUDIES**
- Chest x-ray film shows findings of pulmonary tuberculosis in about 50%-90% of patients with meningitis.
- Cranial CT with contrast and postgadolinium magnetic MRI demonstrate uniform and intense enhancement of basal cisterns and meninges early in the disease. Ischemic infarctions are also detected by either CT or MRI.
- Hydrocephalus is seen as the disease evolves, more commonly in children. Serial CT examinations will help to follow the progression of hydrocephalus.
- Tuberculomas are seen as hypodense, avascular, solid, or ring-enhancing lesions on CT scans. Occasionally they may have central calcification surrounded by a hypodense area with ring enhancement (target sign). On MRI tuberculosis appears isointense to gray matter on T1-weighted images and are either hyperintense (noncaseating lesions) or isointense to hypointense (caseating tuberculomas) on T2-weighted images. They may have surrounding edema. Most often they are located at the corticomedullary junction and periventricular regions. Tuberculomas tend to be infratentorial in children but supratentorial in adults.

**SPECIAL TESTS**
- CSF examination is the most important investigation. CSF pressure is increased, usually over 300 mm H2O, and there is pleocytosis. Polymorphonuclear leukocytes predominate in the earlier stages. Lymphocytic pleocytosis is seen within 24-48 hours. White cell count is between 100 and 400 cells/mm3. CSF protein concentration is high (between 100 and 200 mg/dl) and glucose is decreased (<45 mg/dl). Acid-fast bacilli can be detected by Ziehl-Neelsen stain on CSF examination. The chance of detection of acid-fast bacilli increases with repeated examinations.
- CSF cultures reveal the microorganism in 50%-60% of patients; however, it takes several weeks to obtain the results. Cultures are important for drug sensitivity studies.
- Detection of bacterial DNA with polymerase chain reaction amplification is more sensitive than cultures and provides results within 24-72 hours.
- In tuberculosis without meningitis, CSF is either normal or may show lymphocytic pleocytosis with elevated protein and normal glucose.
Tuberculosis

GENERAL MEASURES

- Routine supportive care of the unconscious or paralyzed patient, maintenance of fluid, and electrolyte balance and nutrition, and care of urinary bladder are important.

SURGICAL MEASURES

- Ventriculoperitoneal shunt insertion is only indicated in the presence of intolerably high intracranial pressure or in medical failures.

SYMPTOMATIC TREATMENT

- Symptomatic treatment for headaches, vomiting, fever, and seizures is necessary.

ADJUNCTIVE TREATMENT

N/A

ADMISSION/DISCHARGE CRITERIA

- Tuberculosis patients with neurologic involvement must be hospitalized.

DRUGS OF CHOICE

- Multiple-drug therapy is necessary because of the possibility of resistant strains of bacteria. Treatment should include bactericidal drugs that penetrate inflamed and noninflamed meninges. Isoniazid and pyrazinamide always pass the blood-brain barrier, whereas penetration of rifampin, streptomycin, and ethambutol through noninflamed meninges is poor.

- Centers for Disease Control and Prevention recommends a combination of three drugs as initial therapy in adults:
  - Isoniazid (INH) 5 mg/kg/day (maximum 300 mg/day) with pyridoxine 50 mg/day
  - Rifampin 10 mg/kg/day (maximum 600 mg/day)
  - Pyrazinamide 15-30 mg/kg/day (maximum 2 g/day)

- After 8 weeks, stop pyrazinamide and continue INH and rifampin. Short-duration (6 months) treatment is as effective as long-duration (9-18 months) treatment. In persons with delayed response, therapy should continue at least 6 months after the cultures become negative.

- In areas where drug resistance is common or if drug resistance is suspected, either ethambutol 15-25 mg/kg/day (maximum 2.0 g/day) or streptomycin 15 mg/kg/day (maximum 1 g/day) should be added as a fourth drug for 2 months.

For immunosuppressed individuals, streptomycin should be added to the regimen, and continued at least 6 months after cultures are negative for a total length of 6-9 months.

- Steroid therapy is controversial but recommended for patients with focal neurologic signs, increased intracranial pressure, hydrocephalus, spinal block, and altered consciousness. Steroids 1-3 mg/kg/day can be given for 2-3 weeks. The dose should be reduced after 2-3 weeks and stopped at 4-6 weeks.

Contraindications

- Drug allergy

Precautions

- Side effects: Isoniazid causes an axonal sensorimotor polyneuropathy, interfering with pyridoxine metabolism. Supplemental pyridoxine should be administered. Slow acetylators of the drug are more susceptible to neuropathy, whereas fast acetylators are prone to hepatotoxicity. Rifampin causes orange discoloration of body fluids, leukopenia, thrombocytopenia, and hemolytic anemia. Streptomycin is ototoxic, and ethambutol carries a risk of optic neuropathy.

ALTERNATIVE DRUGS

- If resistance or allergy to the standard regimen exists, susceptibility studies should guide treatment.

PATIENT MONITORING

- Repeat lumbar punctures are necessary to monitor response to treatment, and CSF pressure should be measured. Serial CT scans are used to follow hydrocephalus and resolution of tuberculomas. Patients receiving isoniazid should be followed monthly for hepatotoxicity. Color vision and visual acuity should be followed in patients receiving ethambutol, and patients should be asked to report any decrease in acuity.

EXPECTED COURSE AND PROGNOSIS

- Although discovery of antituberculosis agents increased survival, tuberculosis meningitis still carries 20%-40% mortality risk. The prognosis mainly depends on the severity of findings at the initiation of therapy. Therefore, early treatment is the most important factor in the prognosis. Empiric therapy should be started as soon as tuberculosis meningitis is suspected. Other factors that affect the prognosis are:
  - Age of the patient (children < years and the elderly have worse prognosis)
  - Nutritional status
  - Presence of miliary tuberculosis
  - Presence of hydrocephalus or cerebral infarction

PATIENT EDUCATION

- Centers for Disease Control and Prevention. Website: www.cdc.gov/nchstp/phfagq/qa.htm
- American Thoracic Society. Website: www.thoracic.org/statemnt.html

SYNONYMS

N/A

IJD-9-IM: 013 Tuberculosis of meninges and central nervous system; 013.0 Tuberculous meningitis; 013.1 Tuberculosis of meninges; 013.2 Tuberculosis of brain; 013.3 Tuberculous abscess of brain; 013.4 Tuberculosis of spinal cord; 013.5 Tuberculous abscess of spinal cord; 013.6 Tuberculous encephalitis or myelitis

SEE ALSO: N/A

REFERENCES


Author(s): Ersin Tan, MD
Tuberous Sclerosis

DESCRIPTION

• The tuberous sclerosis complex is a multi-system autosomal dominant neurocutaneous syndrome that most commonly affects the brain, eye, skin, kidneys, and heart. The clinical manifestations of tuberous sclerosis can be identified in organs derived from all primary stem cell lines, e.g., ectoderm, endoderm, and mesoderm.

ETIOLOGY

• Tuberous sclerosis is inherited in an autosomal dominant fashion, with a penetrance of almost 100%. There is considerable variation in the expressivity of tuberous sclerosis. Recent advances in genetic identification have led to the identification of two genes that result in the phenotype of tuberous sclerosis. The first to be identified was TS2, located on chromosome 16p13.3. This gene encodes for the protein tuberin. More recently, TS1 has been identified. This gene, which encodes for the protein hamartin, is found on chromosome 9p34. Tuberin plays a role in cellular growth regulation, and hamartin appears to have an interactive function with tuberin. Approximately 50% of tuberous sclerosis families show genetic linkage to TS2 and 50%/o to TS1. Approximately 60% of patients have no prior family history and represent new mutations.

RISK FACTORS

N/A

PREGNANCY

N/A

ASSOCIATED CONDITIONS

• Mental retardation. Mental function varies greatly among patients with tuberous sclerosis. Although mental retardation is a characteristic of the disease, approximately 30% of patients have normal intelligence.
• Seizures. Seizures can be refractory and can start in infancy. The following seizure types can be seen in tuberous sclerosis:
  — Neonatal seizures
  — Infantile spasms
  — Lennox-Gastaut syndrome
  — Simple and complex partial seizures
• Behavioral abnormalities
  — Hyperactivity
  — Aggression

LABORATORY PROCEDURES

• The following diagnostic studies are recommended in the evaluation of a new patient with tuberous sclerosis.
  — Electroencephalogram. The test is recommended for patients who present with episodes suggestive of seizures but are not particularly useful in the routine evaluation of a patient with tuberous sclerosis.
  — Electrocardiography. Cardiac arrhythmias sometimes occur even in patients without a cardiac rhabdomyoma. A baseline study is recommended at the time of diagnosis or before surgery.

IMAGING STUDIES

• MRI/cranial CT, MRI may be the more sensitive test to determine the presence of cerebral hamartomas, subependymal nodules, radial migrational lines, and giant cell astrocytomas. Larger calcified lesions can be seen on CT scan.
• Renal ultrasound for renal angiomyolipomas.
• Echocardiography reveals one or more cardiac rhabdomyomas in more than half the younger individuals with tuberous sclerosis. These tumors tend to involute dramatically and often disappear by adulthood. The most rapid reduction in size occurs in the first 3 years of life.

SPECIAL TESTS

• Molecular diagnosis. DNA-based testing is not yet routinely available. Once molecular testing becomes available and there are sufficient data to determine which phenotypes correlate with which gene defects, gene typing at the time of initial diagnosis could be useful.
• Ophthalmologic evaluation for retinal hamartomas.
• Dermatologic evaluation.
GENERAL MEASURES
• There is no specific treatment for tuberous sclerosis: Care centers for management of symptomatic problems related to tuberous sclerosis, such as epilepsy, mental retardation, and autism, and for monitoring cardiac, renal, and dermatologic manifestations are discussed below.

SURGICAL MEASURES
• Patients with refractory epilepsy may be epilepsy surgery candidates. Large lesions that obstruct cerebrospinal fluid flow should be surgically removed. Occasionally if skin lesions are continually irritated or subjected to trauma, they can be removed surgically or by other dermatologic therapeutic measures.

SYMPTOMATIC TREATMENT
• Associated conditions such as epilepsy should be treated with the appropriate antiepileptic agents.

ADJUNCTIVE TREATMENT
N/A

ADMISSION/DISCHARGE CRITERIA
N/A

Medications

DRUG(S) OF CHOICE
N/A

ALTERNATIVE DRUGS
N/A

Follow-Up

PATIENT MONITORING
• Once the diagnosis has been established and the extent of organ involvement determined, management includes ongoing monitoring and treatment of associated conditions. Long-term surveillance testing should concentrate on complications that are significant, relatively common, and more easily managed when found early. The following guidelines are designed for long-term clinical management of an asymptomatic patient. Additional studies may be necessary and tailored to clinical symptoms.

Cranial CT and MRI
• Children should undergo neuroimaging once every 1-3 years to monitor for subependymal giant cell astrocytomas and cerebral hamartomas. If cerebral lesions are already present, more frequent neuroimaging may be needed to monitor progression.

Renal Ultrasonography
• By age 10 years, nearly 75% of children with tuberous sclerosis have sonographic evidence of one or more renalangiomyolipomas. During the first decade, the number and size of these lesions tend to increase. The current recommendation is for renal ultrasonography to be done once every 1-3 years. The frequency depends on the results of previous examinations. Patients with large or numerous renal tumors may require referral to a urologist, as well as either CT or MRI of the kidneys to better define the extent of kidney disease.

Echocardiography
• Most patients with tuberous sclerosis who have a cardiac rhabdomyoma remain asymptomatic. It is unusual for patients to become symptomatic after the neonatal period. Occasionally asymptomatic patients may need follow-up echocardiography because the original study raised specific concern about the size and location of a cardiac rhabdomyoma.

Lung Disease
• Pulmonary function tests should be reserved for patients with suspected lung dysfunction.

EXPECTED COURSE AND PROGNOSIS
• Course and prognosis depend on the organ systems involved and the extent of involvement.

PATIENT EDUCATION
• Education with regard to the long-term nature of this disease, as well as the potential for multiple organ involvement, should be outlined in detail.
• Genetic counseling, as well as screening of family members, is an important part of management.
• Seizure care should be explained, and seizure precautions should be followed by patients with seizures.
• Tuberous Sclerosis Alliance offers a comprehensive website for patients and professionals. Website:
  www.tsalliance.org/default.asp

SYNONYMS
• Bourneville’s cerebral sclerosis

ICD-9-CM: 759.5

SEE ALSO: N/A

REFERENCES

Author(s): S. Anne Joseph, MD
Vasculitis, Central Nervous System

DESCRIPTION

- Central nervous system (CNS) vasculitis is characterized histologically by inflammation and necrosis of blood vessel walls. Primary (also called isolated) CNS vasculitis is clinically and pathologically limited to the CNS. Secondary vasculitis is associated with widespread systemic vasculitis and at times an identifiable underlying disorder.

EPIDEMIOLOGY

Incidence

- Uncommon with an annual incidence of 30-45 cases per million

Age

- Occurs at all ages, with cases reported as young as 3 years and up to age 78 years.

Sex

- Affects both males and females. Some specific entities show a male preponderance, others a female preponderance.

Race

- No investigations have been done to determine a racial predominance. Some systemic conditions, such as sarcoidosis, may be more common in African Americans.

ETIOLOGY

- CNS vasculitis is a segmental necrotizing vasculitis. The pathogenic events leading to vasculitis are not understood, but several mechanisms have been proposed. Isolated CNS vasculitis usually is granulomatous with infiltrates consisting of monocytes, lymphocytes, and plasma cells. The infiltrate usually is adjacent to a disrupted elastic lamina and involves the intima and adventitia with sparing of the media. It affects mainly small artery and veins, especially in the leptomeninges. Deposition of antigen-antibody immune complexes containing activated complement in blood vessel walls has been implicated in initiating the vascular injury. It leads to endothelial damage, infiltration of neutrophils and monocytes, activation of clotting and kinin pathways, and free radical and proteolytic enzyme release. Other mechanisms include neutrophil and natural killer (NK) cell-mediated vascular damage; a T-cell mediated immune response directed against a specific antigen with secondary macrophage activation and direct damage by cytotoxic T cells; and direct vascular damage by infectious agents and tumor. CNS vasculitis can be associated with a number of systemic conditions. It occurs with systemic vasculitides, autoimmune diseases, infectious diseases, neoplasia, and toxic exposures.

RISK FACTORS

- Risk factors are associated with specific conditions known to cause a secondary vasculitis.

PREGNANCY

There is no known relationship to pregnancy.

ASSOCIATED CONDITIONS

- Systemic necrotizing arthritis: Wegener’s granulomatosis, sarcoidosis
- Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, dermatomyositis
- Infectious diseases: Herpes zoster, cytomegalovirus, syphilis, Lyme disease, fungal infections
- Neoplastic disease: Malignant histiocytosis, meningeal carcinomatosis
- Toxins: Radiation, cocaine, heroin, amphetamine
- Childhood: Kawasaki disease, Henoch-Schönlein purpura, juvenile rheumatoid arthritis

DIFFERENTIAL DIAGNOSIS

- Primary isolated CNS vasculitis
- Giant cell arteritis
- Takayasu’s disease
- Polycystic nodosa
- Wegener’s granulomatosis
- Behcet’s disease
- Syphilitic vasculitis
- Multiple sclerosis
- Malignant hypertension
- Moyamoya
- Sarcoidosis
- Mixed connective tissue disease
- Infectious vasculitis
- Drugs of abuse (cocaine)
- Neoplasia (intrasellar lymphoma)

SIGNS AND SYMPTOMS

- CNS vasculitis presents with an acute or subacute onset. Initial symptoms are frequently headache, hemiparesis, confusion, lethargy, and personality change. The disease is progressive, with an accumulation of multifocal symptoms. Among the symptoms are ataxia, aphasia, nausea or vomiting, cranial nerve dysfunction, memory deficits, seizures, and visual changes. CNS vasculitis can cause hemorrhagic and ischemic strokes. Fever and hypertension are sometimes present early in the disease. Funduscopic examination can reveal papilledema or vasculopathy.

LABORATORY PROCEDURES

- Blood tests may be useful for identifying an inflammatory process and possible underlying systemic conditions. These include a CBC with differential, erythrocyte sedimentation rate, serology for syphilis, liver function tests, ANA, anti-ds-DNA, c-ANCA and p-ANCA, lupus anticoagulant, and anticardiolipin antibody. CSF can be normal or have nonspecific abnormalities such as a lymphocytic pleocytosis, mildly elevated protein, and oligoclonal bands. It is critical to rule out CNS infection and examine CSF cytology to rule out a neoplastic meningeal infiltrate.

IMAGING STUDIES

- CT and MRI may identify multiple CNS lesions, but do not evaluate angiitis. An MR angiogram and a cerebral angiography may show sausage-shaped beading appearance of affected vessels, but in many cases they appear normal.

SPECIAL TESTS

- In isolated angiitis of the CNS, a biopsy that includes the leptomeninges and cortical parenchyma is the gold standard for diagnosis and often is necessary to rule out a neoplastic meningial infiltrate. Some systemic conditions, such as sarcoidosis, may be more common in African Americans.

MANAGEMENT

- Treatment requires identification of the specific vasculitic syndrome, assessment of organ damage, and treatment of the underlying cause. Medical therapy is primarily immunosuppression with steroids and/or cyclophosphamide. High-dose prednisone 1.5 mg/kg/day or IV methylprednisolone 15 mg/kg/day is the initial treatment. If the response to steroid therapy is poor, oral cyclophosphamide 2 mg/kg/day can be added and often is given with steroids as initial therapy. Long-term maintenance therapy consists of prednisone 5-10 mg/day and azathioprine 2 mg/kg/day. IV immunoglobulin has been reported in specific cases to be effective in treating CNS vasculitis.
Vasculitis, Central Nervous System

SURGICAL MEASURES
- There is no surgical treatment, but biopsies may be required for diagnosis.

SYMPTOMATIC TREATMENT
- Aggressive treatment of hypertension, especially if there is renal involvement. Monitor specific organ dysfunction and treat appropriately. Cardiac involvement, such as coronary artery dilatation in Kawasaki disease, may require monitoring with an echocardiogram.

ADIJUNCTIVE TREATMENT
- Physical, occupational, speech, and cognitive therapy may be needed, depending on the specific benefits.

ADMISSION/DISCHARGE CRITERIA
- Patients are admitted for the severity of symptoms and deficits, and evaluation for etiology. Certain institutions may require admission for IV methylprednisolone and/or cyclophosphamide therapy. After induction therapy, patients may need subacute inpatient rehabilitation care.

Medications

DRUG(S) OF CHOICE
- Induction therapy: Methylprednisolone 15 mg/kg a day, cyclophosphamide 2 mg/kg
- Maintenance therapy: Prednisone 10 mg/kg/day (tapering over 1 year, alternate-day therapy, and azathioprine 2 mg/kg/day)

Contraindications
- Immunosuppression should be avoided or minimized if an infection is identified. Prior history of hypersensitivity or allergic reaction to any of the above drugs may preclude their use.

Precautions
- Steroid therapy can be associated with hypertension and hyperglycemia. Urine should be examined for glucose. Steroids are associated with gastric ulcers, and prophylaxis with H₂ antagonists is recommended. If azathioprine is used, liver enzymes and CBC must be closely monitored. Cyclophosphamide has been associated with hemorrhagic cystitis, infertility, and numerous other toxicities. All of these drugs should be prescribed only by individuals experienced with their potential toxicity.

ALTERNATIVE DRUGS
- Other immunosuppressive drugs may be useful in specific situations (e.g., cyclosporine, methotrexate), but experience is limited.

EXPECTED COURSE AND PROGNOSIS
- Isolated angiitis of the CNS is relatively rare and its clinical course may vary. It may be acute with rapid progression to coma and then death in 3 days to 6 weeks. It also can wax and wane before a spontaneous resolution, followed by a stepwise progression of symptoms. There may be relapses and remissions with long periods of remission or a slow gradual progression over years. Most patients die within 1 year of this diagnosis. A poor outcome is associated with diffuse cerebral dysfunction and altered mental status. Prognosis is better if the symptoms are primarily focal neurologic deficits or perhaps with early treatment. In secondary CNS vasculitis, success depends on treating the underlying autoimmune collagen/vascular, infectious, or neoplastic disorder.

PATIENT MONITORING
- Patients are followed to monitor progression of symptoms and efficacy of therapy. This can be done with serial physical examinations. Also, if an abnormality is detected in the CSF, on MRI, or on angiogram, it can be followed serially to evaluate efficacy of therapy. There may be relapses and remissions of the underlying disorder. If an abnormality by angiography was identified, a response to treatment may be seen on serial angiograms.

REFERENCES

Author(s): Raymond Ferri, MD; Peter Calabresi, MD
Vertebrobasilar Insufficiency

DESCRIPTION
- Vertebrobasilar insufficiency (VBI) describes a wide spectrum of clinical symptoms caused by compromise of the posterior cerebral circulation. The reduction of blood flow to the brainstem leads to a constellation of brainstem signs and symptoms that are essentially transient ischemic attacks (TIAs) in this vascular territory.

EPIDEMIOLOGY
- Incidence of VBI is about 5-6 per 1,000; vertebrobasilar atherothrombotic disease (VBATD) is about 3 per 1,000; and vertebral artery dissection (VAD) about 1-2 per 1,000.
- As with atherosclerosis, VBATD affects men twice as often as it does women. For spontaneous VAD, the female-to-male ratio is 3:1.
- Age: VBATD occurs in the late decades of life (70s and 80s). Traumatic causes and vascular anomalies leading to VBI are more common in the younger age group (30s and 40s).

ETIOLOGY
- VBATD is by far the most common cause of VBI, making VBI most common among patients with cardiovascular risk factors such as age, hypertension, diabetes, smoking, and dyslipidemias.
- VBI may result from any disease process that impacts arterial supply to the posterior fossa.
  - Fibromuscular dysplasia
  - Rotational occlusion (Bow hunter’s stroke): mechanical occlusion or stenosis of the vertebral artery at the Cl-2 level caused by lateral flexion as in traumatic insults
  - Vertebral artery dissection, spontaneous and traumatic
  - Verteobasilar aneurysms
  - Dolichoectasia of basilar artery

RISK FACTORS
- As above and hypercoagulable states

PREGNANCY
- The risk of ischemic stroke is not increased during pregnancy but is increased during the first 6 weeks postpartum.

ASSOCIATED CONDITIONS
- Subclavian steal syndrome
- Posterior circulation migraine
- Posterior fossa tumor
- Transient cerebral herniation
- CNS vasculitis

DIFFERENTIAL DIAGNOSIS
- Benign positional vertigo
- Vestibular neuritis
- Labyrinthitis
- Multiple sclerosis
- Hemorrhagic stroke
- Ischemic stroke
- Neurosyphilis
- Hypothyroidism/hyperthyroidism
- Meningoencephalitis

SIGNS AND SYMPTOMS
- Vertigo is the hallmark symptom of patients experiencing ischemia in the vertebrobasilar distribution. Many patients describe their vertigo as a nonviolent swaying sensation. Exact incidence is unknown, but up to one third of VBI patients may experience vertigo as the sole manifestation of their illness.
- Visual disturbances (including diplopia)
- Facial numbness or paresthesias
- Dysphagia, dysarthria, hoarseness
- Syncope or presyncope
- Hemisensory or hemotor extremity symptoms (most commonly contralateral to facial component)

LABORATORY PROCEDURES
- Blood work: There are no specific blood tests to diagnose VBI, but the following blood tests should be obtained to help with differential and treatment options: CBC/differential, electrolyte profile, glucose, coagulation profile, ESR, ANA, RPR, and thyroid function testing.

IMAGING STUDIES
- CT scan helps to rule out CNS hemorrhage or mass effect secondary to cerebellar infarction.
- MRI is far superior to CT scan for brainstem and posterior fossa imaging. MRI is more sensitive to small ischemic areas that characterize branch occlusion of the vertebrobasilar circulation.
- Magnetic resonance angiography (MRA) may be as good as cerebral angiography for detecting occlusions and stenoses of the vertebrobasilar circulation, but because it is a dynamic study it may not be as good for quantifying degree of stenosis.
- Doppler ultrasound and MRA may provide important hemodynamic data on degree of vertebrobasilar stenosis.
- Transcranial Doppler helps assess and monitor vertebrobasilar patency in patients who received intraarterial thrombolysis or underwent balloon angioplasty.
- Cerebral angiography is still the gold standard. The characteristic angiographic finding in a dissected vertebral artery is the string or “string and pearl” appearance of the stenotic vessel lumen. Because of the high incidence (up to 40% in some series) of multiple extracranial cervical artery dissections occurring simultaneously in the same patient, four-vessel angiography is the technique of choice in all patients with potential VAD.

SPECIAL TESTS
- Chest x-ray film
- Electrocardiogram
- Consider a lumbar puncture when differential diagnosis is possible meningoencephalitis.

GENERAL MEASURES
- Management is dependent on the underlying etiology, and patient’s symptoms and condition
- Airway issues must be addressed for patients with brainstem infarction. —Compromise of ninth and tenth cranial nerves can blunt the gag reflex and inhibit even a conscious or awake patient from handling secretions effectively.
- Secure airway of patient with an unstable course or severe deficits before starting prolonged diagnostic imaging studies.
- Patients with ischemic stroke often are hypertensive, even in the absence of premorbid blood pressure elevations. —Given the autoregulatory curve’s tendency to shift to the right during hypertension, most experts caution against lowering the blood pressure in the first 24-48 hours after onset of stroke unless extremely elevated.
- Precipitous drop in blood pressure can significantly impact cerebral perfusion pressure and extend infarction.
- Consider antihypertensive medication only in cases of concomitant hypertensive emergency (ongoing end-organ damage), mean arterial pressure (MAP) >130 mm Hg, or systolic BP >220 mm Hg.
- Prevent arterial occlusion. If hemorrhagic lesion has been excluded, patients with VBATD and VAD are managed with antplatelet agents or, in certain circumstances, an anticoagulant such as heparin.
**Vertebrobasilar Insufficiency**

**SURGICAL MEASURES**
- Endovascular surgery
  - Intraarterial thrombolyis: High mortality associated with basilar artery occlusion and resulting brainstem infarction has prompted research into reperfusion therapy via intraarterial infusion of thrombolytic agents.
  - Percutaneous transluminal cerebral angioplasty (PTCA): Increasingly, investigators have described successful dilation of high-grade vertebral artery stenoses in VBATD patients who did not respond to medical therapy.
  - Balloon angioplasty and stenting: Still experimental in CNS disease. It has been used successfully for cardiovascular diseases. It is now becoming increasingly popular for treatment of VAD and certain cases of VBATD.

**SYMPTOMATIC TREATMENT**
- Intravenous fluid therapy to provide isotonic hydration and to prevent hyperglycemia, which appears to exacerbate neuronal injury in stroke.
- Treat vomiting with antiemetics. Vomiting may be severe in some brainstem infarctions.
- Intravenous thrombolysis (tissue plasminogen activator [tPA]) is now approved for acute complicated by hydrocephalus.
- Lipid-lowering statin agents have been shown to be effective in slowing the progression of atherosclerosis.

**ADJUNCTIVE TREATMENT**
- Lipid-lowering statin agents have been shown to be effective in slowing the progression of atherosclerosis.

**ADMISSION/DISCHARGE CRITERIA**
- Admission is warranted for stuttering VBI symptoms or acute stroke.

**Follow-Up**

**PATIENT MONITORING**
- Patients with VBI warrant admission and close neurologic monitoring until therapy is optimized and patients clinical condition is stable.

**EXPECTED COURSE AND PROGNOSIS**
- VBI generally has a more favorable prognosis than carotid territory TIsAs because there is less risk of developing a completed stroke. Better collateral circulation may account for improved outcome in these patients.
- Basilar artery occlusion is a rare but devastating complication of VBI. It is associated with a 75%-85% mortality and high rate of neurovegetative states in survivors. — Extracranial dissection: Most patients do remarkably well if they survive the initial crisis. As many as 88% of patients demonstrate complete clinical recovery at follow-up. Severity of neurologic deficits at the time of presentation usually is related directly to the functional outcome. - Patients with intracranial vertebrobasilar dissection constitute a more severely affected subgroup of all patients with VAD and is associated with higher mortality rate.

**MEDICATIONS**

**DRUG(S) OF CHOICE**
- Antiplatelet medications constitute first-line treatment for patients with VBATD.
  - Aspirin 81-650 mg PO qd, not to exceed 1.3 g/day
  - Clopidogrel (Plavix) 75 mg PO once per day
  - Aggrenox (combination of extended release dipyridamole 200 mg and aspirin 25 mg) 1 cap PO bid
- Acute heparinization is indicated for stuttering VBI symptoms (crescendo TIsAs) or progressive stroke. There is no definite consensus regarding duration of anticoagulation.
- Heparin (Hep-Lock) start with 50 U/kg/hour, followed by continuous infusion of 15-25 U/kg/hour. Increase dosage by 5 U/kg/hour q4h PRN using PTT results. If no contraindication, convert heparin to coumadin with INR of 2-3 for 3-6 months.
- tPA (Activase, Alteplase) 0.9 mg/kg IV over 60 minutes, with 10% of the dose given as initial IV bolus. Maximum dose: 90 mg.
- Alternatively, intraarterial therapy 0.6 mg/kg over 30-60 minutes is given. Maximum dose: 60 mg.

**Contraindications**
- Contraindications for tPA include uncontrolled hypertension, recent surgery or hemorrhage, coagulopathy.

**PRECAUTIONS**

**ALTERNATIVE DRUGS**

**REFERENCES**

**AUTHOR(S):** Jawid F. Kirmani, MD; Abutahaer M. Yahia, MD
**Vitamin B<sub>12</sub> Deficiency**

**Basics**

**DESCRIPTION**
- Subacute combined degeneration (SCD) is the name given to the spinal cord dysfunction that arises from vitamin B<sub>12</sub> deficiency. Subacute implies a time course over a few weeks, combined refers to involvement of both the corticospinal tracts (resulting in motor weakness) and the dorsal columns (resulting in vibratory and proprioceptive loss).

**EPIDEMIOLOGY**
- Incidence/Prevalence
  - SCD is uncommon.
  - Race: N/A
  - Sex: N/A
  - Age: B<sub>12</sub> deficiency is more common in the elderly.

**ETOLOGY**
- The cause of SCD is vitamin B<sub>12</sub> deficiency. Rarely the deficiency is not in quantity of B<sub>12</sub> but rather the precursors of the pathway that processes B<sub>12</sub> (methylmalonic acid [MMA] and homocysteine [HC]). The classic etiology for B<sub>12</sub> insufficiency is that of pernicious anemia (PA), wherein the gastric mucosa does not release B<sub>12</sub> binding factor and patients present with megaloblastic anemia, mental status changes, and evidence of myelopathy. B<sub>12</sub> is released from bound food in the stomach and bound to intrinsic factor (IF) in the IF complex then travels to the distal ilium, where B<sub>12</sub> is released from IF and absorbed. Pernicious anemia results from antibody formation to IF, reducing the free IF available to bind the vitamin. Pernicious anemia also can result from gastric achlorhydria, most often seen in the elderly, in which increased stomach pH prevents the release of bound B<sub>12</sub> from food. Also, in today’s medical era, malabsorption of B<sub>12</sub> from the distal ilium may occur from either resection or chronic inflammation of the stomach or ileum, such as sprue or ulcerative colitis. Intestinal bacteria or parasites occasionally may compete for dietary vitamin B<sub>12</sub>, most notably the fish tapeworm (Diphyllobothrium latum).
- An environmental cause of B<sub>12</sub> deficiency is that of nitrous oxide abuse; NO<sub>2</sub> interferes with the B<sub>12</sub> processing pathway and causes an intrinsic deficiency. Patients receiving excess folk acid with B<sub>12</sub> deficiency may present with spinal cord dysfunction withdrawal, as the folate may correct the anemia.

**DIFFERENTIAL DIAGNOSIS**
- Myelopathy
- Syringomyelia
- Epidural abscess
- Infectious myelitis, especially tabetic

**SIGNS AND SYMPTOMS**
- The signs and symptoms of SCD develop subacutely over days to weeks and may vary from overt to insidious in presentation. Patients primarily complain of weakness and imbalance. They may complain of variable degrees of sensory disturbance and even may have a “cord level,” i.e., sensory changes ascending to, and ending at, a certain point. Sensory abnormalities vary from numbness to tingling and paresthesias. The imbalance may present as falling, impaired gait, or inability to stand upright without assistance. The weakness may be mild or profound. Reflecting the injury to several, (“combined”) neurologic pathways, the neurologic examination may reveal a combination of upper and lower motor neuron signs that may be confusing for non-neurologists. Spasticity and positive Babinski signs may coexist with hyporeflexia.
- Signs and symptoms in the upper extremities may or may not be present; this may manifest as the disease progresses. Many patients will have a Lhermitte’s sign, which is an electric-like sensation through the spine produced by flexion of the neck, signaling localization to the spinal cord.

**RISK FACTORS**
- Infiltrative gastric carcinomas or gastric resection, strict vegetarian diet

**PREGNANCY**
- Pregnancy may exacerbate an occult B<sub>12</sub> deficiency, as the needs of the developing fetus may deplete reserves of stored vitamin ins.

**ASSOCIATED CONDITIONS**
- Nitrous oxide abuse
- Pernicious anemia
- Terminal ileal resection

**DIAGNOSIS**

**LABORATORY PROCEDURES**
- Blood work: Vitamin B<sub>12</sub> and RBC folate acid levels are initially indicated. If they return normal (or low normal) values, then serum MMA and HC levels are checked. MMA and HC both are precursors in the B<sub>12</sub> metabolic pathway. If B<sub>12</sub> is deficient, production halts at this point and precursors accumulate; therefore, MMA and HC often will be elevated in B<sub>12</sub> deficient states.
- If folate is taken to excess in a B<sub>12</sub> deficient state, HC levels may normalize, whereas MMA levels will remain high.

**IMAGING STUDIES**
- In any patient with suspected spinal cord dysfunction, MRI of the entire cord, specifically focusing on the region of the presu med level, is indicated. This is done to ensure that abscess or compression is not mimicking SCD. In SCD, high signal on T2-weighted images in the dorsal columns in sagittal views can be seen and is indicative of ongoing degeneration.

**DIFFERENTIAL DIAGNOSIS**
- Myelopathy
- Syringomyelia
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- Signs and symptoms in the upper extremities may or may not be present; this may manifest as the disease progresses. Many patients will have a Lhermitte’s sign, which is an electric-like sensation through the spine produced by flexion of the neck, signaling localization to the spinal cord.
Management

GENERAL MEASURES

- Management of B12 deficiency (and SCD) depends upon the underlying etiology. If B12 malabsorption is the cause, the vitamin must be replaced.
- Patients should be questioned regarding recreational drug use, specifically abuse of nitrous oxide, or "whippets." Persons with access to NO2 obviously are at higher risk; this includes those in the dental field and the food industry, where whippets are used in the preparation of whipped cream. NO2 consumption must be stopped to prevent further CNS injury.
- If a gastric etiology is the cause of B12 deficiency, there is a small risk of an underlying gastric carcinoma and consideration should be given for an EGD study.
- The main treatment in the United States is intramuscular (IM) cyanocobalamin. IM replacement should be performed once per week for 2-3 months, then once every 2 weeks for 2-3 months, and then lifelong monthly injections. The level may be checked approximately 2-3 months into treatment to ensure adequacy of therapy. Some resolution of acquired deficits may be observed. The goal of treatment is to prevent further degeneration and dysfunction of the spinal cord.
- Controversy exists as to whether oral vitamin B12 is adequate. Oral B12 is available in 1,000-µg “nuggets.” Currently, some researchers are making a case for large doses of oral B12; oral absorption without IF is 110-2%, therefore, a 1,000-µg tablet would provide the daily recommended dose of 1-2 µg. However, this is clearly not acceptable as replacement therapy for diminished levels. Oral B12 may have a role in maintenance therapy. If the underlying etiology is distal deal dysfunction, oral treatment may be ineffective.

SURGICAL MEASURES
N/A

ADJUNCTIVE TREATMENT

- Treatment of gait abnormalities and balance difficulties is best performed by physical therapy.

ADMISSION/DISCHARGE CRITERIA

- Patients are admitted if they are unable to ambulate at presentation. Discharge considerations after evaluation and treatment include ability to perform safely activities of daily living upon discharge. If this is not possible, discharge to inpatient rehabilitation may be necessary.

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Meditations

DRUG(S) OF CHOICE

- Intramuscular cyanocobalamin

Contraindications

- Anaphylactic reactions

Precautions

- Infections, muscle soreness, focal muscle atrophy from repeated injections

ALTERNATIVE DRUGS

- Oral hydroxycobalamin is sometimes used as a maintenance drug when gastrointestinal absorption of vitamin B12 is intact, but careful long-term monitoring of serum B12 levels is necessary.
- Cyanocobalamin gel for intranasal administration (500 µg intranasally every week) is indicated for long-term maintenance after a course of replacement with intramuscular cyanocobalamin

Follow-Up

PATIENT MONITORING

- Once a patient has been diagnosed with B12 deficiency, levels should be followed lifelong. Once replacement has occurred and levels have normalized, periodic evaluations (once per year or as needed) is adequate. Patients with a history of nitrous oxide abuse should be offered counseling and periodically assessed for possible relapses.

EXPECTED COURSE AND PROGNOSIS

- Treatment should begin promptly once the diagnosis of B12 deficiency is made. Theoretically, degeneration desists as soon as B12 levels return to normal. However, acquired abnormalities may not be reversible. Therapy is lifelong.

PATIENT EDUCATION

- Patients should be counseled regarding the necessity of lifelong therapy in case of B12 malabsorption. For patients whose underlying etiology is NO2 abuse, counseling regarding drug abuse is indicated, because some of these patients may relapse.

REFERENCES


Author(s): Holli A. Horak, MD

Surgical Measures

SYNONYMS

- Subacute combined degeneration
- B12 deficiency
- Pernicious anemia

ICD-9-CM: 236.2 Subacute combined degeneration of spinal cord in diseases classified elsewhere; Deficiency of B.complex components: 281.0 Pernicious anemia; 281.1 Other vitamin B12 deficiency anemia; 266.2 Vitamin B12 deficiency

SEE ALSO: N/A

Miscellaneous

SYNONYMS

- Subacute combined degeneration
- B12 deficiency
- Pernicious anemia

ICD-9-CM: 236.2 Subacute combined degeneration of spinal cord in diseases classified elsewhere; Deficiency of B.complex components: 281.0 Pernicious anemia; 281.1 Other vitamin B12 deficiency anemia; 266.2 Vitamin B12 deficiency

SEE ALSO: N/A

REFERENCES


Author(s): Holli A. Horak, MD
Wernicke-Korsakoff Syndrome

**Basics**

**DESCRIPTION**
- Wernicke-Korsakoff syndrome (WKS) is a disorder of the central nervous system in which a lack of thiamine causes an initial acute illness (Wernicke syndrome) followed occasionally by a chronic illness (Korsakoff syndrome). Classic signs of Wernicke syndrome include nystagmus, ataxia, and confusion. Korsakoff syndrome is characterized by a disorder of memory.
- Early replacement of thiamine may abort the acute syndrome, but delay in diagnosis and treatment can cause permanent injury.

**EPIDEMIOLOGY**
- Wernicke syndrome is frequently under-diagnosed. In one series, only 20% of autopsy cases were suspected in life. Autopsy series frequency for Wernicke syndrome ranges from 0.8%-2.8%. A high level of clinical suspicion is necessary. It is likely that the disease is underreported and underdiagnosed. An estimated 25% of WKS cases were missed when the brains were not examined microscopically.

**ETIOLOGY**
- WKS occurs in the setting of thiamine deficiency. Various states with nutritional deficits may cause this syndrome. Chronic alcoholism with deficient nutritional intake is the most common cause, but other causes include hyperemesis gravidarum, systemic malignancy, chronically ill patients, anorexia nervosa, acquired immunodeficiency syndrome, and postgastroplasty states.
- Thiamine is a vitamin cofactor in many enzymatic reactions important for energy metabolism. Specific areas of the brain susceptible to injury include the paraventricular regions of the thalamus and hypothalamus, the mamillary bodies, the periaqueductal region of the midbrain, the floor of the fourth ventricle, and the superior cerebellar vermis. These areas may show necrosis and gliosis, with vacuolation of the affected brain.

**Genetics**
- Transketolase in cultured fibroblasts from alcoholics with WKS bind thiamine pyrophosphate less well than control lines. This finding may implicate a hereditary basis for WKS in this population. Recent research suggests that the genetic marker APOE4 is a significant predictor of global intellectual deficits in people with WKS.

**RISK FACTORS**
- Any condition causing reduced thiamine intake, absorption, or excessive utilization of thiamine can cause WKS.

**PREGNANCY**
- Hyperemesis gravidarum may precipitate WKS.

**ASSOCIATED CONDITIONS**
- Alcoholism
- Alcoholic polyneuropathy
- Alcoholic beriberi
- Alcoholic myopathy
- Marchiafava-Bignami disease
- Alcoholic cerebellar degeneration

**Diagnosis**

**DIFFERENTIAL DIAGNOSIS**
- Diagnosis is based on a high index of suspicion in the appropriate clinical situation. Consider in patients with alcoholism, chronic disease, or poor nutritional intake who show evidence of nystagmus, diplopia, ataxia, confusion, or ophthalmoplegia. Patients with cerebellar or thalamic infarction may have some of the same symptoms. Head injured patients may have unrecognized WKS. Rarely, Creutzfeldt-Jacob syndrome may mimic WKS. Paraneoplastic or toxic cerebellar disorders may mimic WKS.

**SIGNS AND SYMPTOMS**
- The triad of ophthalmoplegia, ataxia, and confusion is classic, but only 19% of patients determined to have Wernicke syndrome show all of these signs. Oculomotor signs: horizontal nystagmus on lateral gaze, bilateral lateral rectus palsies, conjugate gaze palsies, ptosis. Other signs: Paresis of vestibular function may be shown by absent cold water caloric, Confusion with reduced attention, indifference to environment. Unsteady gait due to ataxia. Korsakoff syndrome is diagnosed in the presence of appropriate risk factors, and a defect in learning new material (anterograde amnesia) and a loss of prior memories (retrograde amnesia). Signs of peripheral neuropathy, an associated nutritional disorder, are common. Postural hypotension and syncope are common and related to autonomic insufficiency.

**LABORATORY PROCEDURES**
- WKS is a clinical diagnosis. Laboratory testing usually is not helpful. Blood pyruvate levels are elevated in untreated cases of Wernicke syndrome. Blood transketolase activity is reduced to as low as one third of normal values, but assays are not readily available.

**IMAGING STUDIES**
- CT scanning is of no use in WKS. It may help rule out concurrent syndromes causing altered consciousness, such as subdural hematoma, intracerebral hemorrhage, or ischemic disease.
- MRI occasionally can show atrophy of the mamillary bodies or small hemorrhages in affected brain areas. The sensitivity and specificity of this test for WKS are unknown.

**SPECIAL TESTS**
- N/A
**Wer nicke-Korsakoff Syndrome**

**Management**

**GENERAL MEASURES**
- Care must be taken to stabilize the patient medically, particularly noting the presence of hypothermia and treating it if present. Appropriate fluid resuscitation is key, because patients may be dehydrated. Patients should be examined for trauma and assessed for the presence of alcohol intoxication or withdrawal, as well as concurrent drug intoxication or withdrawal. Concurrent pneumonia, subdural hematoma, GI bleeding, pancreatitis, and other sequelae of alcoholism may be present and need to be considered and treated.

**SURGICAL MEASURES**
N/A

**SYMPTOMATIC TREATMENT**
N/A

**ADJUNCTIVE TREATMENT**
- Treatment for alcohol withdrawal or delirium tremens may be necessary (see appropriate sections).

**ADMISSION/DISCHARGE CRITERIA**
- Patients with Wernicke syndrome usually are acutely ill and require admission. Patients with Korsakoff syndrome may require long-term care.

**Medications**

**DRUG(S) OF CHOICE**
- Thiamine: 100 mg IV stat, followed by 50—100 mg IM/IV qd until normal intake is reestablished.

**Contraindications**
- Hypersensitivity to thiamine

**Precautions**
- Rare cases of angioedema, cyanosis, or anaphylaxis may occur. Common reactions include pruritus, urticaria, and injection site pain.

**ALTERNATIVE DRUGS**
N/A

**Follow-Up**

**PATIENT MONITORING**
- Patients with WKS are acutely ill and need to be monitored in an ICU or other monitored setting until they are stable.

**EXPECTED COURSE AND PROGNOSIS**
- Although treatable if caught early enough, the death rate from WKS is relatively high, about 10%—20%. Ataxia improves > nystagmus > cognitive dysfunction.

**PATIENT EDUCATION**
- When stable, patients should be counseled on avoiding alcohol intake (if appropriate) and maintaining good dietary intake.

**Miscellaneous**

**SYNONYMS**
N/A

**ICD-9-CM:** 291.1 (alcoholic); 294.0 (non-alcoholic)

**SEE ALSO:** ALCOHOL, NEUROLOGIC COMPLICATIONS

**REFERENCES**

**Author(s):** Alexander D. Rae-Grant, MD
Whipple's Disease

DESCRIPTION
• Whipple's disease is a rare systemic disorder caused by infection with *Tropheryma whippelii*. It is characterized by diarrhea, migratory arthralgias, lymphadenopathy, fever, dementia, ophthalmoplegia, and myoclonus.
• CNS involvement occurs in 5%-40% of cases and may be present without systemic symptoms.
• Oculomasticatory myorhythmia and oculofacial-skeletal myorhythmia are infrequent but pathognomonic signs of the disease.

EPIDEMIOLOGY
Incidence/Prevalence
• <1,000 cases reported since 1907.
Occupational association with farmers, construction workers, and machinists
Race
• Nearly all reported cases are Caucasians.
Age
• Peak in the fifth decade
Sex
• 86% male

ETIOLOGY
• *Tropheryma whippelii*, a Gram-positive bacillus
• Humans are the only known host
• Reservoir unknown
• Infection probably from ingestion
• Pathogenesis unknown
• Spread to CNS is likely hematogenous; several reported cases of endocarditis and embolic strokes

RISK FACTORS
• Exposure to soil or animals

PREGNANCY
• No reported cases

ASSOCIATED CONDITIONS
• Arthritis
• Fever of unknown origin
• Malabsorption
• Diarrhea
• Weight loss
• Pneumonia
• Dementia
• Seizures
• Headache

LABORATORY PROCEDURES
• Biopsy: Jejunum is the most common site, but *T. whippelii* has been identified in CNS tissue, lymph nodes, serum, and pleural fluid.
  — Staining with periodic acid-Schiff (PAS) is strongly suggestive but not diagnostic.
  — Negative biopsy should be repeated in 1 month if clinical suspicion is high.
• Polymerase chain reaction (PCR) testing provides a sensitive and specific means of diagnosis and monitoring.
• Organisms can be seen by electron microscopy

IMAGING STUDIES
• MRI of brain or spinal cord: Lesions enhance without edema.
  — May mimic stroke, tumor, demyelinating plaques, or vascular abnormalities.
• CT of brain: Lesions enhance with contrast.
• KUB: Enlarged small intestine, thickened mucosa.

SPECIAL TESTS
• PAS staining
• PCR
• Electron microscopy

Management

GENERAL MEASURES
• Malabsorption: intravenous hydration and nutritional supplementation

SURGICAL MEASURES
N/A

SYMPTOMATIC TREATMENT
• Antiepileptics for seizures
• Analgesics for headache and arthralgias
• Hydration and symptomatic treatment of diarrhea

ADJUNCTIVE TREATMENT N/A

ADMISSION/DISCHARGE CRITERIA
• Seizure control
• Facilitate diagnosis
• Parenteral nutrition
• Intravenous antibiotics

DIFFERENTIAL DIAGNOSIS
Systemic
• Celiac sprue
• Rheumatoid arthritis
• Lymphoma
• Inflammatory bowel disease
• Pancreatitis
• Systemic lupus erythematosus
• Lyme disease
• Waldenstrom's macroglobulinemia

Neurologic
• Alzheimer's disease
• Sarcoidosis
• Vasculitis
• Primary or metastatic tumor
• Cerebrovascular accident
• Multiple sclerosis
• Encephalitis
• HIV-related CNS infections
• Tuberculosis
• Creutzfeldt-Jakob Disease

SYSTEMIC SIGNS AND SYMPTOMS
• Arthralgias
• Fever
• Abdominal pain
• Weight loss
• Diarrhea
• Malabsorption
• Uveitis
• Lymphadenopathy
• Increased skin pigmentation

Neurologic
• Dementia
• Ophthalmoplegia, particularly upward gaze palsy
• Myoclonus
• Nystagmus
• Oculomasticatory myorhythmia (OMM): 1-Hz pendular convergent nystagmus with synchronous contraction of muscles of mastication
• Oculofacial-skeletal myorhythmia (OFSM): 1-Hz pendular convergent nystagmus with synchronous contraction of facial and skeletal muscles
  — OMM and OFSM have not been reported in other diseases.
• Personality changes
• Ataxia
• Cranial nerve deficits
• Hypothalamic symptoms
  — Insomnia, temperature sensitivity, altered appetite
• Headache
• Seizures
• Focal neurologic deficits
Whipple's Disease

**DRUG(S) OF CHOICE**

- Induction treatment for 2-4 weeks —
  - Ceftriaxone 2 gm IV bid ± streptomycin 1 gm IV/IM qd or
  - Penicillin G 4 million units IV q4h and streptomycin 1 g IV/IM qd
- Maintenance treatment for 1 year —
  - Trimethoprim-sulfamethoxazole DS PO bid or
  - Cefepime 400 mg PO bid
- Recurrence or clinical decline on oral antibiotics requires repeat course of intravenous ceftriaxone for at least 1 month.

**Contraindications**
- Allergy to cephalosporins or sulfonamides

**Precautions**
- Folinic acid supplementation should be given with chronic trimethoprim-sulfamethoxazole administration.
- Because of the rare nature of this disease, consultation with an infectious disease specialist is recommended.

**ALTERNATIVE DRUGS**
- Doxycycline or chloramphenicol may be used for patients allergic to cephalosporins and sulfonamides.

**PATIENT MONITORING**
- Repeat jejunal biopsy or CSF PCR at 1 year to verify clearance
- Serial MRI to assess response

**EXPECTED COURSE AND PROGNOSIS**
- Uniformly fatal prior to advent of antibiotics
- Systemic symptoms routinely respond to antibiotics
- CNS manifestations, nystagmus, and ophthalmoplegia show the most improvement.
- Recurrence rate is high.

**PATIENT EDUCATION**

**SYNONYMS**
- Intestinal lipodystrophy
- ICD-9-CM: 040.2 Whipple's disease

**REFERENCES**


**Author(s)**: Todd Czartoski, MD; Christina Marra, MD
Wilson's Disease

DESCRIPTION

• Wilson's disease (WD) is an inherited disorder of copper metabolism with a wide spectrum of clinical manifestations.

EPIDEMIOLOGY

Incidence/Prevalence

• Estimates of prevalence vary widely (10-30 per million), with a heterozygous carrier rate of 1 in 90.

Race

• No known difference

Age

• Age at diagnosis of WD varies from 3-61 years. Hemolytic anemia presents in early childhood (ages 7-14), chronic liver disease between ages 5 and mid-30s, and neuropsychiatric symptoms between ages 14 and 40.

Sex

• No known difference

ETIOLOGY

• The cause of the illness is a gene mutation causing absence or dysfunction of production of a copper transporting ATPase ATP7B. This ATPase is localized to the hepatocyte trans-Golgi network and transports copper into the secretory pathway for incorporation into ceruloplasmin and excretion into bile. The normal rate of excretion of copper in the bile is deficient, and copper accumulates in the liver. When hepatic storage is exceeded, hepatocyte death occurs with copper release into the plasma (where it is bound by ceruloplasmin) and tissue deposition.

Genetics

• WD is inherited as an autosomal recessive disease due to mutation of the ATPase ATP7B gene on chromosome 13. The risk of WD is 40% in a sibling of an index case and 0.5% in a child of an index parent.

RISK FACTORS

N/A

PREGNANCY

• Both penicillamine and trientine have been used successfully for treatment of WD during pregnancy with reports of fetal agenesis.

ASSOCIATED CONDITIONS

N/A

DIAGNOSIS

Differential Diagnosis

• The differential diagnosis of WD is very large given the wide spectrum of potential presentations and includes the differential diagnosis for each of the conditions listed under Signs and Symptoms.

• Neurologic disorders that are in the differential include
  — Huntington's disease — Essential tremor
  — Parkinson's disease — Neurologic complications of chronic hepatic encephalopathy
  — Multiple sclerosis

SIGNS AND SYMPTOMS

Hepatic

• Chronic active hepatitis
• Cirrhosis
• Fulminant hepatic failure

Hematologic

• Coombs' negative hemolytic anemia
• Hypersplenism
• Coagulopathy due to liver disease

Renal

• Fanconi's syndrome
• Urolithiasis
• Hematuria
• Proteinuria
• Peptiduria
• Nephrocalcinosis

Neuropsychiatric

• Neurologic symptoms occur at initial presentation in 80% of patients, usually in the third or fourth decade of life.
• Tremor: "wing beating," titubation
• Dystonia of bulbar musculature with resultant dysarthria and dysphagia
• Gait disorder (parkinsonian and/or ataxic)
• Seizures (approximately 6%)
• Personality change: emotional lability, impulsiveness, disinhibition
• Affective symptoms
• Cognitive impairment
• Psychosis

Ophthalmologic

• Kayser-Fleisher (KF) pigmented corneal rings
• Sunflower cataracts
• Night blindness

Other

• Ototoxicity
• Arthralgias/arthritis
• Cardiomyopathy/arrhythmias
• Amenorrhea
• Hypoparathyroidism

LABORATORY PROCEDURES

• Total serum copper levels are of little value.
• Free serum copper is generally elevated.
• Serum ceruloplasmin: Reduced level <20 mg/dL is strongly supportive (normal: 20-40 mg/dL). False-positive low levels may occur in protein deficiency states, heterozygotes for the WD gene who will not develop disease, and hypoceruloplasminemia. False-negative results may be due to elevated levels of ceruloplasmin.
• Twenty-four-hour urinary copper excretion often is increased (>100 µg in 24 hours).

IMAGING STUDIES

• Cranial CT scan is abnormal in the majority of patients having neuropsychiatric WD, with generalized atrophy, dilatation of the ventricles, and focal areas of low attenuation in the basal ganglia and more diffusely. Brain MRI shows abnormal low signal lesions on T1-weighted images and high signal on T2-weighted images in the putamen, and dorsal and central aspects of the pons.

SPECIAL TESTS

• Slit-lamp ophthalmologic examination for KF rings: Despite a clinical tradition that KF rings must be present once neuropsychiatric signs are present in WD, there are reports of a small percentage of patients with neuropsychiatric signs without KF rings.
• Hepatic copper content via liver biopsy is considered the gold standard for diagnosis by some (normal: 15-55 µg per gram).
• Definitive diagnosis often is based on the presence of two of the following:
  — KF ring
  — Serum ceruloplasmin level <20 mg/dL
  — Typical neuropsychiatric finding
GENERAL MEASURES

• Treatment of WD centers on efforts to restore and maintain normal copper balance within body tissues. Primary treatment is systemic chelation therapy to restore hepatic copper balance.

SURGICAL MEASURES

• Orthoptic hepatic transplantation is recommended for patients with progressive liver failure unresponsive to chelation therapy or acute liver failure due to fulminant hepatitis. Hepatic transplantation results in improvement of neuropsychiatric symptoms.

SYMPTOMATIC TREATMENT

• Physical therapy and treatments that address the many manifestations of WD

ADJUNCTIVE TREATMENT

• Zinc salts should be prescribed in addition to chelation therapy to reduce gastrointestinal copper absorption. Dietary copper should be restricted.

ADMISSION/DISCHARGE CRITERIA

• Admission is required if symptoms are life threatening (e.g., hepatic failure) or if hydration, mobility, and nutrition are compromised.

DRUGS OF CHOICE

• Penicillamine (dimethylcysteine), the traditional mainstay for treatment of WD, avidly chelates copper; the complexed copper is excreted in urine. The traditional initial recommended dosage is 1–2 g daily on an empty stomach, but many advocate beginning with a significantly lower dose, such as 250 mg/day with gradual upward titration. Because of the high adverse reaction profile, some authorities recommend induction therapy with less toxic alternatives.

• Zinc acetate or zinc sulfate should be administered at a dose of 50-mg elemental zinc three times per day on an empty stomach.

CONTRAINDICATIONS

• Renal disease and history of penicillamine-induced aplastic anemia or agranulocytosis

Medications

PRECAUTIONS

• Initiation of penicillamine therapy is frequently associated with neurologic deterioration. This has been attributed to mobilization of copper from the liver with redistribution to the brain, although there is evidence against this hypothesis. This problem has led some authorities to recommend induction of therapy with alternative agents such as zinc or ammonium tetrathiomolybdate. Penicillamine therapy may cause acute sensitivity reactions, including skin rash, fever, eosinophilia, thrombocytopenia, leukopenia, and lymphadenopathy. Penicillamine should be discontinued until the fever and rash clear. It may then be re instituted at a reduced dose with concomitant prednisone, or an alternative agent may be considered. Many other adverse reactions are associated with penicillamine, including nephrotic syndrome, Good-pasture’s syndrome, a lupus-like syndrome, myasthenic syndrome, polyarthr itis, thrombocytopenia, retinal hemorrhages, dysgeusia, and dermopathy.

ALTERNATIVE DRUGS

• Ammonium tetrathiomolybdate (TM) complexes copper in the gut to prevent absorption and in the bloodstream to reduce tissue deposition. TM is administered in a regimen of 6 doses daily: 3 with meals and 3 between meals, at starting doses of 20 mg at meal time and 20 mg between meals gradually titrated upward (20–60 mg/dose). In initial studies, patients were switched to zinc maintenance therapy after 8 weeks. TM is associated with reversible bone marrow depression and damage to epiphyses in growing bone.

• Triethylene tetramine dihydrochloride (trientine) is a copper chelation therapy. It should be taken on an empty stomach. A typical daily dosage is 750–2,000 mg in three divided doses. Trientine is less toxic than penicillamine, but it has been associated with lupus nephritis and sideroblastic anemia.

EXPECTED COURSE AND PROGNOSIS

• Most patients will become asymptomatic within 4 months of chelation therapy. After significant improvement occurs, the dose of penicillamine may be reduced by half for lifetime maintenance chelation therapy.

PATIENT EDUCATION

• Compliance with long-term chelation therapy must be encouraged because rapid deterioration has been reported after abrupt discontinuation of penicillamine. Patients should be instructed to follow a low-copper diet.

• Wilson’s Disease Association International. Website: www.wilsonsdisease.org

• Wilson’s Disease Association Copper Content of Various Foods. Website: www.wilsonsdisease.org/copper.html

REFERENCES


SECTION IV

Short Topics
**Abetalipoproteinemia**

Bassen-Kornzweig syndrome; autosomal recessive; disorder of lipid metabolism, develops in first decade of life; symptoms and signs consist of steatorrhea, distal sensorimotor neuropathy, retinitis pigmentosa, ataxia, areflexia, and dysarthria; metabolic defect involves inability to synthesize B-lipoprotein, which reduces concentration of chylomicrons and causes deficiencies of fat-soluble vitamins A, K, and E; neurologic syndrome resembles vitamin E deficiency in other situations; treatment consists of vitamin E supplementation, restricted intake of long-chain fats, substitution with polyunsaturated fats, and rehabilitation.

**Adrenomyeloneuropathy**

Most common phenotypic variant of ALD; accounts for 25% of phenotypes associated with mutations at ALD locus; onset between 18 and 36 years of age; main clinical features include spastic paraparesis, peripheral neuropathy, and adrenal insufficiency; other commonly noted signs are hypogonadism, impotence, cerebellar dysfunction, and dementia; MR reveals demyelination, which always precludes symptoms; diagnosis requires presence of elevated levels of VLCFA in plasma and cultured fibroblasts; treatment is similar to ALD and includes replacement and stress steroids, methods to reduce VLCFA, such as dietary restriction of VLCFA and Lorenzo’s oil (glycerol trirurate oil, glycerol trioleate oil), and bone marrow transplantation.

**Adie’s Syndrome**

Tonic pupil syndrome; incidence of 4.7 per 100,000; usually sporadic in origin; female preponderance with typical onset between 20 and 50 years of age; unilateral in 80% of cases; usually develops acutely, with pupillary dilation and poor reaction to light; over time the pupil often becomes miotic; symptoms include difficulty with dark adaptation and reading, photophobia, blurred near vision, and anisocoria; reduced or absent deep tendon reflexes are often noted; cholesteric denervation supersensitivity can be demonstrated with a 0.1% pilocarpine solution; cause of Adie’s syndrome remains unclear; symptomatic treatment is not required for most patients.

**Alexander Disease**

Degenerative disease of unknown etiology that affects astrocytes; autosomal inheritance may be noted in some families; usually occurs in childhood; infantile form most common, which presents with severe psychomotor retardation, progressive spasticity, seizures, megalencephaly, and frequent hydrocephalus; juvenile and adult variants are less severe; CT and MRI demonstrate diffuse demyelination with a frontal predominance; pathologic hallmark is diffuse presence of Rosenthal fibers within astrocytic footplates; alpha B-crystallin and HSP27 levels may be elevated in CSF; therapy is nonspecific and consists of seizure medications and other supportive care.

**Andersen Syndrome**

Type of familial periodic paralysis; autosomal dominant inheritance; linked to mutations of potassium channel Kir2.1 subunit on chromosome 17q23 in some families; attacks may be associated with high, low, or normal potassium levels; administration of potassium may provoke attacks of weakness or arrhythmias; presentation is in childhood or adolescence with dysmorphic features (low-set ears, broad nose, hypertelorism), short stature, periodic paralysis, potassium sensitivity, myotonia, and cardiac disease (prolonged QT interval, ventricular arrhythmias); EMG demonstrates progressive drop in CMAP amplitude during exercise, without myotonic discharges; serum CK shows mild-to-moderate elevation; high incidence of death from arrhythmia and cardiac arrest; acetazolamide may control periodic weakness; antiarrhythmic therapies.

**Aicardi’s Syndrome**

Disorder of cerebral cortical development, with abnormal neuronal migration; only noted in females, probably due to X-linked dominant transmission (lethal to males); presents with severe mental retardation, early seizures (infantile spastic), agenesis or hypoplasia of the corpus callosum, periventricular and subcortical band heterotopias, choroidreinal lacunae, cerebellar abnormalities, fused vertebrae, and hemivertebrae; associated with an increased incidence of choroid plexus papillomas; there is no specific therapy except anticonvulsant treatment; supportive care.

**Alpers’ Syndrome**

Degenerative disease with adult onset in the fifth or sixth decade; usually associated with a deficiency of the branching enzyme, but there appear to be other biochemical variants; inheritance is autosomal recessive; characterized by progressive upper and lower motor neuron dysfunction, sensory loss, sphincter abnormalities, neurogenic bladder, and dementia; 50% of patients; electrodiagnostic testing demonstrates axonal sensorimotor neuropathy; polyglucosan bodies are periodic acid-Schiff (PAS)-positive, diastase-resistant cellular inclusions; pathology reveals polyglucosan bodies in processes of neurons and astrocytes of gray and white matter, and in the axoplasm of peripheral myelinated fibers; there is no specific therapy.
Angelman's Syndrome

Genetic disorder that usually is sporadic but may be familiar, associated with DNA deletion within chromosome 15q11-13, inherited maternally in most cases; mouse models suggest UBE3A is a strong candidate gene within 15q2; infants are typically normal at birth, with rapid onset of feeding abnormalities and failure to thrive; other features include small head circumference, severely delayed motor development and hypotonia, early onset of seizures, lack of speech development, wide-based and ataxic gait, hyperactivity, rounded faces with a protruding tongue, delayed puberty, and very short adult height; no specific treatment, except anticonvulsants.

Apert Syndrome

Acrocephalosyndactyly; a subtype of craniosynostosis; autosomal dominant; abnormal skull development with coronal suture closure, shortening of the head in the anteroposterior dimension, prominent forehead, and flat occiput; typical features include shallow orbits and proptosis of eyes, hypertelorism, maxillary hypoplasia, small nose, low-set ears, and narrow or cleft palate; osseous and cutaneous synostosis not noted often; occasional cardiac, gastrointestinal, and genitourinary malformations are present; mental deficiency often occurs; development of the limbic structures, corpus callosum, and gyri may occur; no specific therapy.

Ataxia-Telangiectasia

Early-onset ataxia syndrome; autosomal recessive inheritance; involves mutations of ATM gene on chromosome 11q22-23, results in dysfunction of DNA repair processes and impaired cell cycle control; clinical features include truncal ataxia, delayed motor development, dysarthria, conjunctival and cutaneous telangiectasias, immune dysfunction with reduced concentrations of IgA and IgG2, recurrent respiratory and cutaneous infections, growth retardation, premature aging, and delayed sexual development; mild mental retardation, oculomotor abnormalities, myoclonus, and peripheral neuropathy may be noted; 15%–20% incidence of malignancies, especially leukemias and lymphomas; serum α-fetoprotein level is elevated; median age at death is 20 years, from respiratory infections and cancer; treatment is supportive (antibiotics).

Behcet's Disease

Inflammatory disorder of unknown etiology, characterized by relapsing remitting uveitis and recurrent genital and oral ulcers. CNS involvement occurs in 25%–30% of patients; age at onset is the third and fourth decades; men are affected more frequently than women; neurologic signs and symptoms include headache, cranial nerve palsies, seizures, mental confusion, dementia, aphasia, hemiparesis, and papilledema; low-grade fever may be common; laboratory data may include elevated sedimentation rate, anemia, mild leukocytosis, elevated CSF pressure and protein, CSF pleocytosis; CNS involvement may be multifocal (similar to multiple sclerosis); CT/MRI demonstrate focal CNS lesions; immunosuppressive therapy may be of benefit for CNS involvement.

Brill-Zinsser Disease

Recurrent typhus; flare-up of epidemic louse-borne typhus fever in mild form months to years after the primary attack; infectious agent is obligate intracellular Rickettsia prowazekii, which has remained latent in the tissues; symptoms and signs are similar to epidemic typhus fever, lasts 7-12 days, and may include the characteristic rash (often absent), mild fever, headache, malaise, myalgias, photophobia, dizziness, stroke, and mild somnolence or encephalopathy; diagnosis is made by demonstration of organisms in blood, CSF, or biopsy materials, or by serologic and CSF antibody testing; treatment with rifampin or benzimidazole is usually effective in acute stage.

Balint's Syndrome

Symptom complex due to bilateral damage to posterior parietal lobes (e.g., angular gyrus and superior parietal cortex); most commonly caused by watershed infarction; cerebral control of precise eye movements is impaired; clinical features include optic ataxia (defect in reaching under visual guidance), simultanagnosia (inability to recognize a whole picture despite perceiving its parts), and ocular apraxia (defect in voluntary eye movements); delayed visual field defects and bilateral hemineglect may be present; patients may deny having any visual dysfunction or deficits.

Carnitine Deficiency

Carnitine is an essential cofactor to transport long-chain fatty acids into mitochondrial for β-oxidation; muscle carnitine concentration is decreased or absent; primary carnitine deficiency presents in first or second decade as progressive, proximal muscle weakness and hypotonia, reduced or absent reflexes, normal motor milestones, mentation and sensation preserved; atrophy of extremities may be noted; ECHO shows diffuse myopathic process; secondary carnitine deficiency occurs with short-chain and medium-chain acyl-coenzyme A dehydrogenase deficiencies, Reye syndrome, and valproate therapy; primary carnitine deficiency is diagnosis of exclusion; treatment consists of oral carnitine, with or without prednisone.

Cerebrotendinous Xanthomatosis

Cholesterol storage disease; caused by mutations in the sterol 27-hydroxylase gene; autosomal inheritance often noted; clinical features become apparent in early adolescence and include cataracts, tendon xanthomas, progressive spasticity and ataxia, dysarthria, mental deterioration (in most cases), sensorimotor neuropathy, distal muscle wasting, and Babinski signs; pseudobulbar palsy, dementia, and myocardial infarction may be noted in late stages; cholesterol and sterol levels increase in plasma, brain, bile, and tendon xanthomas; cholesterol level usually normal in serum; chenodeoxycholic acid level is reduced or absent in bile; treatment with a low cholesterol diet or certain bile acids may be of benefit.

Chagas Disease

South American trypanosomiasis (Trypanosoma cruzi); infection is transmitted by an animal host (e.g., rodents, cats) to humans by blood-sucking reduviid bugs (i.e., "kissing bugs"); clinical features include an acute febrile stage with conjunctivitis, facial edema, lymphadenopathy, and hepatosplenomegaly; chronic infection may lead to diffuse (encephalopathy, seizures, chorea) or focal (hemiplegia, ataxia, aphasia) neurologic involvement; disease is slowly progressive without treatment; laboratory abnormalities may include elevated ESR and anemia, and CSF lymphocytic pleocytosis with elevated protein and y-globulins; diagnosis made by demonstration of organisms in blood, CSF, or biopsy materials, or by serologic and CSF antibody testing; treatment with nitrofurantoin or benzimidazole usually effective in acute stage.
**Chediak-Higashi Syndrome**

Autosomal recessive inheritance; characterized by partial oculloucaneous albinism, immunologic defects, hepatosplenomegaly, pancytopenia, and progressive neurologic dysfunction, including pyramidal, extrapyramidal, cerebellar, and sensory neuropathies; linked to mutation of CHS1 gene on chromosome 1q42-44; results in defective transport of intracellular proteins, leading to giant peroxidasepositive granules and reduced function of leukocytes and other granule-containing cells (e.g., monocytes, hepatocytes, renal tubular cells); neurons and Schwann cells may have inclusions; predisposition to frequent pyogenic infections; increased risk of lymphoreticular malignancies; therapy consists of anticonvulsants, antibiotics, and other supportive care; no specific therapy exists.

**Corticobasal Ganglionic Degeneration**

Corticodentatonigral degeneration; degenerative dementia syndrome characterized by diffuse accumulation of pathologic tau proteins within neurons; clinical features reflect dysfunction in corticobasal ganglionic and sensorimotor areas; clinical features include asymmetric rigidity, dysphagia, postural instability, frontal release signs, oculomotor impairment, asymmetric hyperreflexia, myoclonus, and hypokinetic dysarthria; pathology demonstrates asymmetric frontoparietal atrophy with neuronal loss and gliosis, substantia nigra degeneration, and swollen achromatic neurons; MRI shows asymmetric cortical atrophy mostly severe in the parietal lobes; PET and SPECT reveal hypoperfusion and hypometabolism in affected areas; treatment involves symptomatic and supportive care; levodopa occasionally may result in modest reduction of rigidity.

**Chorea-Acanthocytosis**

Neuroacanthocytosis; Levine-Critchley syndrome; multisystem degenerative disease; characterized by acanthocytes, normal plasma lipids and lipoproteins, and variable neurologic involvement; autosomal dominant; linked to recessive or sporadic; linked to chromosome 1q21; onset in fourth or fifth decade; clinical features include hyperkinetic movement disorder (chorea, orofacial dyskinesia, dystonia); personality changes such as obsessive-compulsive disorder, dementia in late stages, axial neuropathy with muscle wasting and weakness, reduced deep tendon reflexes, pseudobulbar palsy, and seizures in 40% of patients; MRI shows generalized atrophy and atrophy of caudate nuclei; treatment is symptomatic and supportive.

**Cowden's Syndrome**

Gingival multiple hamartoma syndrome; familial cancer syndrome with autosomal dominant inheritance; linked to mutations of PTEN gene on chromosome 10q23; symptoms in young children include progressive macrocephaly, mental retardation, mild-to-moderate delay in motor development, lingua plicata; adults present with facial trichilemmomas, oral papillomas, skin changes; childhood cancers; autosomal dominant or recessive inheritance patterns can occur; clinical features include nevus, hypothyroidism, skin hyperpigmentation, and peripheral edema; treatment of underlying disease may stabilize or improve the neuropathy.

**Crouzon's Syndrome**

Progressive multisystem disease with autosomal recessive inheritance pattern; clinical features include extreme dwarfism, dysmorphic faces, cachectic habitus, and neurologic deterioration; children are normal at birth; then develop failure to thrive and decreased height, weight, and head circumference by 24 months; cognitive development and speech are rudimentary; gait is limited by progressive spasticity and ataxia; deafness and impaired vision occur frequently; peripheral neuropathy may develop; the brain is small, with atrophic white matter and calcification of the basal ganglia; patchy demyelination is noted in the white matter and peripheral nerves; underlying biochemical abnormality is unknown; no specific treatment.

**Crow-Fukase Syndrome**

POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly; endocrinopathy, monoclonal gammapathy, and skin changes); characterized by progressive, symmetric demyelinating sensorimotor neuropathy in association with osteosclerotic and multiple myeloma, Waldenstrom's macroglobulinemia, Kaposi's sarcoma, or angiofollicular lymph node hyperplasia; pathophysiology unknown; probably mediated by immune effectors; mean onset in the fifth decade; often in males; clinical features include moderate-to-severe weakness affecting distal more than proximal muscles, less prominent sensory loss (mostly large fiber), uncommon autonomic symptoms and cranial nerve involvement; common systemic features include hepatomegaly, diabetes mellitus, hypothyroidism, skin hyperpigmentation, and peripheral edema; treatment of underlying disease may stabilize or improve the neuropathy.

**Cysticercosis**

Most common parasitic disease of the CNS; acquired by ingestion of food contaminated by Taenia solium eggs (often undercooked pork); hatched eggs spread via blood to eyes, skeletal muscles, and CNS (brain parenchyma, subarachnoid space, ventricles, spinal cord); parasites may live for years within cysts or die and leave calcified granulomas; cysts in subarachnoid space may incite intense inflammation, causing fibrosis and hydrocephalus; clinical features include new-onset seizures, cognitive impairment, confusion, headache, gait disturbance, focal neurologic deficits, and signs of elevated intracranial pressure; cysts well visualized by CT and MRI; CSF ELISA and complement fixation tests are diagnostic; treatment consists of albendazole and praziquantel, and anticonvulsants.

**Dejerine-Sottas Syndrome**

Progressive hypotrophic neuropathy; form of hereditary peripheral neuropathy (HSNM type III); autosomal dominant or recessive inheritance patterns can occur; presentation in infancy with progressive generalized muscle weakness, severe sensory loss, limb ataxia, muscular atrophy, and marked hypertrophy of peripheral nerves; appears to be more severe phenotype of Charcot-Marie-Tooth disease; mutations within several different genes involved in peripheral nerve myelinization result in a similar phenotype, including PMP22 (17p11.2), myelin PO (1q22.1), and EGFR (10q21); treatment is supportive and consists of physical and occupational therapy, orthotic devices, and genetic counseling.
**Dandy-Walker Syndrome**

Dandy-Walker malformation; 1 in 30,000 births; posterior fossa malformation characterized by complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle, enlarged posterior fossa, elevation of the forcula and straight sinus, and hydrocephalus; aterias of the foramina of Luschka and Magendie may be present; patients display delayed motor development, nystagmus, spasticity, ataxia, and abnormal cognition; treatment consists of shunting of the ventricles and/or posterior fossa cyst; early shunting and decompression of the cyst may allow more normal development of the cerebellar hemispheres.

**DiMauro Syndrome**

Carnitine palmitoyl transferase (CPT1 or CPT2) deficiency; enzymes involved in fatty acid oxidation and energy metabolism within mitochondria; autosomal recessive inheritance pattern; CPT1 deficiency manifests in infancy with nonketotic hyperglycemic coma, hepatomegaly, hypertriglyceridemia, and abnormal liver function, including hyperammonemia (similar to Reye syndrome); condition may improve with medium-chain triglycerides; CPT2 deficiency is lethal in infants but more benign in adults; clinical features include metabolic myopathy with recurrent pain and myoglobinuria; symptoms provoked by fasting, prolonged exercise, cold exposure, infection, or emotional stress; permanent weakness in 10% of cases; no specific treatment.

**Dystonia Musculorum Deformans**

Idiopathic torsion dystonia; inherited disorder of the basal ganglia with autosomal dominant inheritance; initial onset between 5 and 15 years of age; clinical features include early dystonic involvement of the legs, with rapid progression to involve the arms, neck, head, and trunk; torticollis, lordosis, and scoliosis often develop; pain with movements is unusual; over time, axial muscle atrophy may become more impaired than limb muscles; affected muscles often become hypertrophic; MRI usually unremarkable; PET scans may demonstrate reduced glucose metabolism in the basal ganglia; treatment with anticholinergic agents, levodopa, bromocriptine, baclofen, or carbamazepine occasionally improves symptoms.

**Emery-Dreifuss Muscular Dystrophy**

X-linked muscular dystrophy syndrome characterized by an unusual pattern of weakness: humeroperoneal, which predominantly affects the biceps and triceps in the arms and distal musculature of the legs; severity of myopathic weakness is quite variable; early onset of severe contractures of elbows, knees, ankles, fingers, and spine; a rigid spine typically develops, with limited neck flexion; prominent muscular wasting occurs; heart block is common and often requires a pacemaker; linked to mutation of EDMD gene, localized to the Xq28 locus; expression of the EDMD gene product emerin, which normally is present in the nuclear membrane of muscles and other tissues, is absent; treatment is symptomatic.

**Encephalitis Lethargica**

von Economo Disease; disease of unknown etiology, presumed to be viral, responsible for worldwide epidemic from 1917 to 1928; epidemic form possibly extinct; now occurs sporadically; affects patients of all ages and sexes; clinical features include acute stage (duration 3–4 weeks) with onset of fever, headache, lethargy, impairment of eye movements and oculomotor control, motor symptoms characteristic of basal ganglia dysfunction, and acute organic psychosis; CSF demonstrates lymphocytic pleocytosis with elevated protein in 50% of patients; parkinsonian syndrome common in postencephalitic phase, unusual features include early age of onset, torticollis, torsion spasms, myoclonus, and facial tics; no specific treatment.

**Encephalotrigeminal Angiomatosis**

Sturge-Weber-Dimitri syndrome; form of neurocutaneous disorder characterized by a cutaneous vascular port-wine nevus of the face (follows distribution of trigeminal nerve), contralateral hemiparesis and hemihypertrrophy, glaucoma, seizures, frequent homonymous hemianopsia, and mental retardation; inheritance usually sporadic, may be dominant or recessive; seizures are early onset and difficult to control, they can be focal, motor, generalized, or partial complex; occipital lobe most often affected, also involves the temporal and parietal lobes; atrophy noted ipsilateral to facial nevus; calcification involves the cortex and small vessels; skull radiographs reveal trolley-track curvilinear calcifications; treatment includes cosmetic surgery, anticonvulsants, physical and occupational therapy, and supportive care.

**Eosinophilia-Myalgia Syndrome**

Interstitial form of eosinophilic myositis and fasciitis; characterized by severe myalgias, muscle cramps, edema and induration of the skin, pulmonary symptoms (e.g., cough, dysnea), and peripheral blood eosinophilia; in one third of cases, an associated inflammatory polyneuropathy can occur and cause neuropathic symptoms (may be painful); myokymia, myoclonus, and movement disorders occur in some patients; in most cases, related to patients taking certain preparations of L-tryptophan that contained a chemical contaminant (e.g., 1,1'-ethylenedien); the condition has been most prevalent in the United States; symptoms respond well to glucocorticoids; nonsteroidal antiinflammatory agents and rehabilitation also may be beneficial.
Erb-Duchenne Syndrome

Upper radicular syndrome; weakness of the upper extremity caused by damage to the upper nerve roots (fourth, fifth, sixth cervical roots or upper trunks) of the brachial plexus; weakness affects the deltoid, biceps, brachioradialis, pectoralis major, supraspinatus, infraspinatus, subscapularis, and teres major muscles; flexion of the forearm, abduction and internal and external rotation of the arm, and apposition of the scapula are all severely affected; sensory loss is variable and consists of hypesthesia on the outer surface of the arm and forearm; the biceps reflex is absent; recovery is likely if complete avulsion has not occurred; rehabilitation is of benefit.

Fabry Disease

X-linked disorder of the skin (angiokeratoma corporis diffusum), kidney, blood vessels, neurons, and peripheral and autonomic nervous systems; caused by defective enzyme, α-galactosidase A, with abnormal storage of ceramide trihexoside in affected tissues; incompletely recessive, as some female heterozygotes may be affected; clinical features include paroxysmal burning pains in the limbs, parasthesias, anhidrosis, fever, pruritis, hemiplegia, hemianesthesia, dysphasia, and seizures; psychosis and dementia may occur in older patients; cardiac abnormalities may include myocardial ischemia or infarction, congestive heart failure, and aortic stenosis; progressive renal failure is common; no specific treatment; kidney transplant may be lifesaving; phenytoin or carbamazepine may improve neuropathic pain.

Familial Amyloidotic Polyneuropathy

Inherited neuropathy characterized by amyloid deposition into peripheral and autonomic nerves; pathologic evaluation reveals both demyelination and axonal damage; autosomal dominant inheritance pattern; linked to mutations of transthyretin gene, mapped to chromosome 18q11.2-g12.1; onset is between ages 20 and 35 years; initial clinical features include acral sensory loss, chronic diarrhea, and impotence; followed by progressive weakness, sphincter dysfunction, and orthostatic hypotension; cardiomypathy with heart block may occur; requiring a pacemaker; nephrosis is a late manifestation; the disease is inexorable progressive, no specific therapy exists; liver transplantation and plasma exchange have had little impact on the neuropathy; symptomatic treatment.

Familial Dysautonomia

Riley-Day syndrome; autosomal recessive, slowly progressive condition that affects children, typically of Jewish heritage; clinical features include diminished lacrimation, lack of reflexes, hyperhidrosis, abnormal blood pressure regulation, postural hypotension, intermittent skin blanching, poor temperature control, subnormal growth, and multiple sensory deficits; in addition, children have poor motor coordination, emotional instability, frequent vomiting, and relative insensitivity to pain; seizures, frequent breath-holding episodes, and abnormal EEGs may be noted; overall intelligence is preserved; pathology reveals progressive loss of neurons in sympathetic and parasympathetic ganglia; betahaneol chloride may provide relief from crises, improve gastrointestinal motility, increase tearing, and reduce the incidence of aspiration.

Farber Lipogranulomatosis

Onset in first few weeks to months of life; clinical features include painful swollen joints, hoarseness, vomiting, respiratory difficulties, and limb edema; subcutaneous nodules develop near joints, tendon sheaths, and at pressure points; less common findings include cardiac enlargement, lymphadenopathy, hepatosplenomegaly, macrocytosis, and difficulty swallowing; mental development may be impaired; syndrome caused by severe deficiency of acid ceramidase, with accumulation of ceramide and related materials in foam cells within affected tissues; diagnosis is clinical, finding deficiency of acid ceramidase in cultured fibroblasts or leukocytes; no specific treatment.

Fatal Familial Insomnia

Prion disease (spongiform encephalopathy) with autosomal dominant inheritance and onset between 18 and 60 years of age; clinical features include progressive insomnia, dysautonomia (hyperhidrosis, tachycardia, tachypnea, hyperthermia, hypertention), dementia, myoclonus, and motor dysfunction (pyramidal tract and cerebellar signs); EOG shows diffuse slowing with infrequent periodicity; pathology reveals prominent neuronal loss and gliosis in the thalamus, with minimal spongiform change; neocortex, basal ganglia, cerebellum, and brainstem are variably affected; syndrome caused by mutation within PrP gene at codon 178, coupled with a methionine at codon 129; no specific treatment; family genetic counseling is indicated.

Fazio-Londe Syndrome

Form of juvenile spinal muscular atrophy, with onset in late childhood or early adolescence; inheritance usually is autosomal recessive, although sporadic cases can occur; clinical features include progressive bulbar weakness, dysarthria, dysphagia, and, in some cases, less severe weakness of the arms and legs; wasting of the tongue with visible fasciculations is noted; upper motor neuron signs are absent; respiration may be affected in patients with long-standing disease; symptoms typically remain restricted until end-stage disease; death occurs within 2 years of presentation in most patients, usually from respiratory failure.

Foster Kennedy Syndrome

Defined as ipsilateral optic nerve atrophy and contralateral papilledema; caused by tumors that arise in the retro-orbital region, anterior skull base (e.g., medial sphenoid wing), or inferior frontal lobe and compress the optic nerve; initial tumor growth causes optic nerve damage and atrophy, further growth elevates intracranial pressure and leads to papilledema in the contralateral, intact optic nerve; ipsilateral anomaia may be noted; a central scotoma often is present ipsilateral to the tumor; typically occurs with frontal tumors and meningiomas of the olfactory groove and sphenoid wing.

Friedreich's Ataxia

Autosomal recessive inheritance; prevalence is 2 per 100,000; GAA triplet repeat expansion found in first intron of X25 gene, located on chromosome 9q13-21, codes for a conserved protein, frataxin; onset in early teen years; clinical symptoms include progressive gait ataxia, areflexia of lower limbs, impaired vibration and position sense, diffuse weakness, dystonia, nystagmus, frequent Babinski sign, and hypertrophic cardiomyopathy; MRI usually is normal, may show mild cerebellar atrophy; most patients become nonambulatory within 15 years of symptom onset; treatment is symptomatic (e.g., physical therapy); no specific treatment; death from infection or cardiac disease occurs between 40 and 60 years of age.
Frontotemporal Dementia

Group of rare progressive dementia syndromes, Pick's disease is the best characterized subtype; clinical features of Pick's disease include initial mild memory impairment, with more pronounced dysphasia (reduced speech output), personality changes, apathy, inattentiveness, and extrapyramidal motor dysfunction; dementia become severe later in the disease; MRI demonstrates focal atrophy of the frontal and temporal lobes; pathology reveals argyrophilic intraneuronal inclusion bodies (Pick bodies) and gliosis in affected areas; associated with mutations in tau gene (involved in microtubule assembly and stabilization) on chromosome 17, with accumulation of abnormal tau proteins in Pick bodies; memory may improve or stabilize with anticholinergic agents.

Fucosidosis

Storage disease with onset during the first 2 years of life; clinical features include progressive intellectual and motor deterioration, initial hypotonia that gradually evolves into clinical features of the juvenile and adult forms include dementia with variable onset, seizures, incoordination, splenomegaly, and tics; diagnosis made by demonstration of xesimed p-glucosidase in leukocytes or presence of a mutation in the /3-glucosidase gene; no specific treatment.

Gaucher Disease

Lysosomal storage disease with autosomal recessive inheritance; glucocerebroside accumulates within affected tissues because of a deficiency of /3-glucocerebrosidase; infantile, juvenile, and adult neuronopathic forms exist, as well as an adult non-neuronopathic form; the infantile form has onset in the first 6-12 months, with poor suck and swallow, dementia, strabismus, opsoclonus, spasticity, organomegaly, and seizures; clinical features of the juvenile and adult forms include dementia with variable onset, seizures, incoordination, splenomegaly, and tics; diagnosis made by demonstration of xesimed p-glucosidase in leukocytes or presence of a mutation in the /3-glucosidase gene; no specific treatment.

Hirayama Syndrome

Monomelic muscular atrophy; disorder of unknown origin, often diagnosed in Japan, usually affects young males; onset at approximately 20 years of age in most patients; initial symptoms are progressive weakness and muscular atrophy affecting one limb, typically an arm and hand; patients often are athletes, but the disorder is not clearly related to cervical trauma; symptoms usually stabilize after several years; EMG consistent with a lower motor neuron process; patients must be followed closely even after stabilization of symptoms to rule out other signs of motor neuron disease; no specific treatment; physical therapy may be of benefit.

Hepatolenticular Degeneration

Wilson's disease; inborn error of copper metabolism with autosomal recessive inheritance, due to mutations and deletions of P-type ATPase located on chromosome 13q14.3; onset variable in late childhood or adolescence; accumulation of copper in liver leads to cirrhosis; neurologic features are quite variable but can include rigidity, tremor (often "wing beating"), dystonic movements, dysarthria, unsteady gait, reduced dexterity, hypophonic speech, seizures, behavioral abnormalities (affective disorder or psychosis), drooling, and dysphagia; Kayser-Fleischer ring noted in 75% of patients; MRI demonstrates diffuse atrophy, esbe.6a% of the basal ganglia, and ventricular dilation; initial therapy involves penicillamine, tetraethylthiuram disulfide, triethylentetramine, or zinc; optimum maintenance treatment is with zinc.

Gaucher Disease

Autosomal recessive disorder with onset in childhood and adolescence; symptoms typically begin with stiffness of gait, distal extremity wasting (hands may become useless), pes cavus, toe walking, risus sardonicus, spasticity and rigidity (painful spasms can develop), speech difficulty with eventual anarthria (comprehension is maintained), hyperactive reflexes, and occasional mild dementia; dystonia, ataxia, and tremor may occur; MRI demonstrates low-signal abnormality in the globus pallidus (eye-of-the-tiger sign); pathology reveals neuronal loss and thinning of myelin in the medial segment of the globus pallidus; underlying biochemical defect unknown, but disease linked to chromosome 20p12.3-p13 in some families; no specific treatment.

Hand-Schiller-Christian Disease

Multifocal form of Langerhans cell histiocytosis; caused by proliferation of antigen-presenting dendritic cells and antigen-processing phagocytic cells; core features are calvarial lesions, exophthalmus, and diabetes insipidus; short stature; orbita media, constitutional symptoms (fever, weight loss), visual loss, and other endocrine manifestations may occur; symptoms linked to granuloma formation within skull, orbits, and hypothalamic-pituitary axis; MRI reveals multifocal intraparenchymal lesions that may enhance; diagnosis is made by demonstration of Langerhans cells in brain or calvarial biopsy tissue, with a consistent immunohistochemical analysis; treatment consists of corticosteroids and localized radiotherapy; chemotherapy is reserved for refractory disease.
Hunter Syndrome

X-linked recessive lysosomal storage disease, with accumulation of mucopolysaccharides (dermatan sulfate, heparan sulfate) within affected tissues; caused by deficiency of iduronate-2-sulfatase; two forms, mild and severe; clinical features of the severe form include juvenile onset of joint stiffness, coarse facies, dysostosis multiplex, hepatosplenomegaly, mental deterioration, growth retardation, diarrhea, and occasional pigmentary retinal deterioration; the mild form may be asymptomatic, with short stature, joint stiffness, coarse features, normal intelligence, and hepatosplenomegaly; neither form has corneal clouding; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of iduronate-2-sulfatase in cultured fibroblasts; no specific treatment.

Hurler Syndrome

Autosomal recessive lysosomal storage disease, with accumulation of mucopolysaccharides (dermatan sulfate, heparan sulfate) within affected tissues; caused by reduced expression of a-L-iduronidase gene (chromosome 4p); most severe form of the mucopolysaccharidoses; onset in infancy with stiff joints, coarse clulng, pericardial swelling, clawhands, chest deformity, dwarfing, coarsening of facial features, hypertelorism, enlarged tongue, mental retardation and deterioration, minimal speech development, and deafness; cardiac disease, abdominal distention, visual loss, and cervical cord compression may occur; zebra bodies containing lipids are noted in the brain; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of a-L-iduronidase in cultured fibroblasts; no specific treatment.

Hyperekplexia

Form of exaggerated startle response; can result from a brainstem disorder or can be inherited as an autosomal dominant trait with mutations of the α subunit of the glycine receptor (chromosome 5q); clinical features include a sudden motor response to unexpected auditory, tactile, or visual stimuli; the motor response involves a blink, contraction of the face, flexion of the neck and trunk, and abstraction and flexion of the arms; the response can be brief or prolonged, falling can occur; in infancy may result in "stiff baby syndrome" due to prolonged tonic spasms; excessive startle syndromes can be regional, such as the "jumping Frenchman of Maine" in Quebec; may respond to clonazepam or valproic acid.

Hyperviscosity Syndrome

Can develop in all forms of leukemia with significant leukocytosis (most severe in myeloid forms), as well as in IgM paraproteinemia; clinical features include headache, blurred vision, tinnitus, vertigo, ataxia, somnolence, severe lethargy and fatigue, and cerebrovascular events (transient ischemic attacks or stroke); encephalopathy, reduced level of consciousness and coma, subarachnoid hemorrhage, spinal cord dysfunction, and seizures may develop; acute treatment consists of leukapheresis or plasmapheresis; definitive treatment of the underlying disease with chemotherapy is beneficial.

Isaacs Syndrome

Neuromyotonia; slowly progressive myokymia (visible and continuous muscle twitching) that affects children, adolescents, or young adults; clinical features include slowed movements, clawing of the fingers, toe walking, stiffness of muscles, abnormal postures of the limbs (similar to carpal spasm), pseudomyotonia, frequent cramps, and hyperhidrosis; percussion myotonia is not present; oropharyngeal and respiratory muscles may be affected; stiffness and myokymia are present during rest and sleep; rarely occurs as a paraneoplastic syndrome (antibodies to potassium channels); muscle activity abolished by botulinum toxin; disorder may be due to peripheral neuropathy or dysfunction of nerve terminal; phenytoin and carbamazepine usually control symptoms; plasmapheresis and intravenous immunoglobulin may be beneficial.

Jumping Frenchman of Maine

Regional form of hyperekplexia (see above).

Kennedy Disease

Spinobulbar muscular atrophy; X-linked recessive inheritance pattern; onset usually after age 40; clinical features include slowly progressive dysarthria, dysphagia, tongue fasciculations, twitching of limb muscles, and delayed limb weakness, which is more severe proximally; reflexes are lost; upper motor neuron signs and dementia may occur but are extremely rare; gynecomastia is common; disorder caused by CAG expansion mutation within the androgen receptor gene, linked to chromosome Xq11-12; expansion mutation probably causes toxic gain of function of gene product; inverse relationship between the number of repeats and the severity of the disease; no specific therapy.

Klippel-Feil Syndrome

Congenital fusion of two or more cervical vertebrae (usually C2-3 or C5-6); embryonic failure of segmentation of chorda-mesoderm that form cervical vertebrae; can be part of other syndromes (i.e., Turner's, Noonan's, Wildeveand's), sporadic, or inherited as autosomal dominant; radiographic evaluation of cervical spine is diagnostic; patients have a short neck, limited head and neck movement; frequent kyphosis, scoliosis, platybasia, and hearing loss; may have weakness and atrophy of arm muscles, mental retardation; craniofacial instability may lead to spinal cord compression and progressive paraplegia; laminctomy is indicated for cord compression.

Klumpke Syndrome

Lower radicular syndrome; weakness of the upper extremity caused by damage to the lower nerve roots (eighth cervical and first thoracic roots or lower trunk) of the brachial plexus; weakness affects the flexor carpi ulnaris, flexor digitorum, interossei, and the thenar and hypothenar muscles; pattern of weakness is similar to a combined lesion of the median and ulnar nerves, with a flattened or simian hand; sensory deficit consists of hypesthesia on the inner side of the arm and forearm, and on the ulnar side of the hand; triiceps reflex is absent; Horner syndrome may occur if the inferior cervical ganglion is injured; rehabilitation is of benefit.
Krabbe Leukodystrophy

Lysosomal storage disease with deficiency of galactocerebrosidase and accumulation of galactocerebroside and psychosine in affected tissues; typical onset in infancy; occasionally can develop in juvenile or adult years; patients are normal at birth, then have progressive irritability, inexplicable crying, fevers, limb stiffness, seizures, feeding difficulty, vomiting, and slowing of mental and motor development; followed by psychomotor deterioration marked hypertonia, extensor posturing, and optic atrophy; reflexes eventually decrease or disappear, with loss of tone and flaccidity; death by 2 years in most cases; CSF protein is elevated; nerve conduction velocities are reduced; global cells are noted in demyelinated regions of affected brain; no specific treatment.

Kugelberg-Welander Syndrome

Spinal muscular atrophy type 3; inheritance can be autosomal recessive or dominant; onset usually is in middle to late childhood, with slow progression into adult middle age; clinical features include proximal weakness of the extremities (most often the legs), with variable amounts of muscle wasting, fasciculations, and occasional elevation of serum creatine kinase activity; bulbar musculature usually is spared; corticospinal tract signs, sensory deficit, autonomic involvement, and mental deterioration do not occur; linked to mutations in SMN gene, located on chromosome 5q11.3-13.1; no specific treatment.

Landau-Kleffner Syndrome

Disorder of childhood characterized by an acquired aphasia, typically in association with a seizure disorder, which occurs in children with previously normal language and motor development, between ages 4 and 7; occasionally the disorder can affect very young children, so speech never develops properly; the disorder can precede or follow the occurrence of seizures and often persists, even though seizures may be well controlled; EEG shows temporal or temporoparietal spikes, or spike-and-wave discharges, which may be almost continuous in some cases; MRI is normal; etiology unknown, possibly a focal encephalitis; valproic acid, ethosuximide, and benzodiazepines may improve the condition.

Laurence-Moon-Biedl Syndrome

Congenital disorder of development with an autosomal recessive inheritance pattern; characterized by early-onset obesity, mental retardation, retinal dystrophy, hypogonadism and hypospadia (mostly in males), and coloboma; polycystic, syndactyly, or both may occur; less common features include renal dysfunction, hypertension, cardiac abnormalities, and liver defects; night vision is impaired early by retinitis pigmentosa, patients often are blind by age 20; lifespan may be normal, although frequently shortened by cardiac and renal disease; no specific neuropathologic changes have been described yet; treatment is symptomatic, with supportive care.

Leber Hereditary Optic Neuropathy

Maternally inherited disorder of the optic nerve, caused by mutations in mitochondrial (mtDNA) genes; mutations have been noted in several genes of complex I of the respiratory chain (e.g., ND1, ND4, ND6); clinical features include onset in adolescence or early adulthood, with progressive, painless clouding of central vision (may be asymmetric); results in bilateral loss of vision (20/200 or finger counting) within several months; optic atrophy is always present; possible associated findings include cardiac preexcitation, postural tremor, dystonia, motor tics, and peripheral neuropathy; treatment remains unclear; corticosteroids, hydroxocobalamin, optic nerve sheath fenestration, and cranialotomy with lysis of optic sheath fenestration and craniotomy with lysis of optic sheath are of unproved value.

Letterer-Siwe Disease

Disseminated form of Langerhans cell histiocytosis; caused by proliferation of antigen-presenting dendritic cells and antigen-processing phagocytic cells; affects children <2 years of age; clinical features include a granulomatous rash, lymphadenopathy, hepatomegaly, splenomegaly, fever, and weight loss; pulmonary and bone involvement is common; granulocytosis usually is present; pancytopenia may occur with severe hypersplenism; neurologic involvement usually is absent; course often is full-him-it, with poor prognosis; symptoms may improve with corticosteroids; focal lesions may respond to radiotherapy; chemotherapy may be required to achieve clinical remission.

Levine-Critchley Syndrome

Neuroacanthocytosis; familial multisystem neurodegenerative disorder with autosomal dominant or recessive inheritance linked to chromosome 9q21; sporadic cases are rare; onset is usually in the fourth or fifth decade, juvenile onset is uncommon; clinical features include acanthocytosis, hyperkinetic movement disorder (chorea, orofacial dyskinesias, dystonia), psychiatric symptoms (obscene-compulsive disorder, personality changes), dementia, and axonal neuropathy; neuropathy causes muscle wasting, weakness, and absent reflexes; epileptic seizures occur in 40% of patients; MRI shows atrophy of the caudate nuclei and high signal within the striatum; pathology reveals neuronal degeneration and gliosis within the basal ganglia and substantia nigra; no specific treatment.

Lesch-Nyhan Syndrome

Pyrohexanthine-guanine phosphoribosyltransferase (HPRT) deficiency; X-linked recessive; HPRT necessary for recycling of purine bases into nucleotide forms during DNA and RNA synthesis; leads to accelerated synthesis of uric acid and hyperuricemia; onset by 6 months of age with developmental delay, axial hypotonia, appendicular spasticity, mental retardation, choreathetoid movements, self-mutilation, dystonia; diagnosis by demonstrating reduced tissue levels of HPRT; allopurinol reduces serum uric acid but does not effect neurologic symptoms; no effective treatment; supportive care.

Lhermitte-Ducros Disease

Dysplastic gangliocytoma of the cerebellum; rarely noted in hypothalamus and spinal cord; age of onset typically in the third or fourth decade; usually sporadic in origin; clinical features include cerebellar dysfunction (ataxia, dysdiadochokinesia, nystagmus), and symptoms of increased intracranial pressures secondary to hydrocephalus; may be associated with CNS malformations such as hydromyelia, brain heterotopia, and megalencephaly; MRI shows low signal lesion on T1 images, with minimal enhancement; pathology demonstrates altered cerebellar architecture, with pleomorphic ganglion cells replacing the granule cell layer; treatment is surgical resection; role of radiotherapy and chemotherapy is unclear.
Lowe Syndrome

Oculocerebrorenal syndrome; X-linked (long arm) recessive disorder of amino acid metabolism; clinical features include severe mental retardation, delayed physical development, myopathy, and congenital glaucoma or cataracts; general aminoaciduria of the Fanconi type occurs, with renal tubular acidosis and rickets; histidine is the predominant amino acid in the urine; MRI shows various patterns of white matter damage; CNS pathology is inconsistent; the gene encodes a protein similar to inositol polyphosphate-5-phosphatase; no specific treatment.

Lytic-Bodig Disease

Parkinson-dementia-amyotrophic lateral sclerosis complex of Guam; syndrome indigenous to the Chamorro natives of Guam; also noted in emigrants from Guam; clinical features include those of Parkinson's disease and dementia, often in combination with amyotrophic lateral sclerosis; supranuclear gaze palsy may be present; pathology reveals the presence of neurofibrillary tangles in degenerating neurons of the substantia nigra and locus ceruleus, loss of anterior horn cells, and scattered granulovascular bodies; Lewy bodies and senile plaques are absent; possibly related to exposure to a neurotoxin, 2-granulovascular bodies; Lewy bodies and senile plaques are present in the brain of the patient; symptoms include those of Parkinson's disease and dementia, often in combination with amyotrophic lateral sclerosis; early-onset ataxia syndrome; autosomal recessive inheritance pattern; clinical features include ataxia, bilateral cataracts (congenital or can develop in infancy), mental retardation, limited sexual maturation, and short stature; cerebellar dysfunction is manifested by dysarthria, nystagmus, and ataxia of the trunk and limbs; developmental delay always occurs but can vary from mild to severe; other associated features that may be noted are strabismus, hypertonia, pes valgus, and scoliosis; disease progression is slow, with most patients being wheelchair bound by the third or fourth decade; underlying cause is unknown, possibly a lysosomal storage disorder; no specific treatment.

Maroteaux-Lamy Syndrome

Mucopolysaccharidosis type VI; form of lysosomal storage disease, with deficiency of N-acetylgalactosamine-4-sulfate sulfatase or arylsulfatase B; accumulation of dermatan sulfate within affected tissues; disease severity can be variable, with mild, intermediate, and severe forms; manifestations of the severe form include growth retardation by 2 or 3 years of age, coarse facial features, corneal clouding, severe skeletal abnormalities, short stature, valvular heart disease, and heart failure; intelligence remains normal; hydrocephalus and cervical cord compression can develop from hypoplasia of the odontoid process; patients may survive into the second or third decade; treatment is supportive and symptomatic.

Meige's Syndrome

Oromandibular dystonia; form of oral-facial dyskinesia; characterized by the combination of blepharospasm and other cranial dystonias; clinical features include forceful blinking and sustained eye closure (with or without spasms of the orbicularis oculi), spasms of the jaw muscles that cause slow forceful involuntary opening of the mouth, deviation of the jaw to one side, protrusion of the tongue, spasms may be forceful enough to dislocate the mandible or fracture teeth; dystonia may spread over time to include the cervical and shoulder musculature; treatment with anticholinergic agents may give partial relief of symptoms.

Menkes Syndrome

X-linked, localized to gene at Xq13.3, in family of cation-transporting ATPases that transport ions across membranes; lack of gene causes insufficient intestinal absorption of copper and dysfunction of copper-containing enzymes; develops in first few months of life; symptoms and signs consist of male infants with developmental arrest and regression, hypotonia, seizures, failure to thrive, wiry and friable hair, recurrent infections, and hypothermia; very low serum copper levels; no effective treatment; supportive care.

Miller-Fisher Syndrome

Miller-Fisher variant of Guillain-Barré syndrome (GBS); consists of the triad of ophthalmoplegia, gait ataxia, and areflexia occurring in isolation; pupillary abnormalities may be noted; limb weakness does not develop; similar to GBS, the disorder often is preceded by a respiratory infection; typically benign course with progression over weeks, followed by improvement; CSF protein usually is elevated; nerve conduction testing is unremarkable; MRI may show high-signal abnormalities within the brainstem; no specific immune therapy is required in most cases.
**Mobius Syndrome**

Developmental anomaly of the posterior fossa; core features include congenital complete oculomotor nerve palsy, ataxia, and dysmetria. Associated findings may include other cranial nerve deficits (hearing loss, dysarthria, dysphasia, ptosis, complete ophthalmoplegia), congenital anomalies of the limbs or heart, hypogonadism and anosmia, and mental retardation; facial weakness is more severe in the upper face than below (i.e., more difficulty with eye closure than lip movement); infants have difficulty suckling and lack facial expression when they cry; etiology unclear, may be due to congenital absence of cranial nerve nuclei or vascular damage within the brainstem.

**Neuronal Ceroid-Lipofuscinosis (NCL)—Adult Variant**

NCL type 4; Kuf's disease; form of lysosomal storage disease with adult onset in the third or fourth decade; abnormal autofluorescent lipopigments are present in granular cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive, may be dominant or sporadic; patients present with either late-onset epilepsy and progressive dementia or progressive motor deficits (ataxia, rigidity); myoclonus may be present; MRI may show cortical and/or cerebellar atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment; anticonvulsant therapy and supportive care; disease progression is slow over several decades.

**Neuronal Ceroid-Lipofuscinosis (NCL)—Juvenile Variant**

NCL type 1; Batten's disease; form of lysosomal storage disease with onset between ages 5 and 15 years; abnormal autofluorescent lipopigments are present in fingerprint cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive; early symptoms include behavioral changes, visual dysfunction, and learning difficulty; symptoms progress to dementia and blindness, with the addition of seizures, myoclonus, and motor dysfunction (pyramidal and extrapyramidal); reduced or absent electroretinogram; MRI may show cortical atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment; anticonvulsant therapy and supportive care.

**Neuronal. Ceroid Lipofuscinosis (NCL)—Late-Infantile Variant**

NCL type 2; Jansky-Bielschowsky disease; form of lysosomal storage disease with onset between ages 1.5 and 4 years; abnormal autofluorescent lipopigments are present in curvilinear cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive; clinical features include severe seizures, psychomotor deterioration, and ataxia; seizures often are refractory to anticonvulsant treatment; progressive retinal deterioration, optic atrophy, and visual loss occur, with abolition of the electroretinogram; rapid progression to a vegetative state or death in a matter of months to several years; MRI may show atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment; anticonvulsant therapy and supportive care.

**Opsoclonus-Myoclonus Syndrome**

Form of paraneoplastic syndrome, most often noted in children with neuroblastoma and adults with solid tumors (e.g., breast, small cell lung); clinical features consist of constant, arrhythmic motion of the eyes, irregular in direction or tempo, in combination with myoclonus affecting the facial muscles, limbs, or trunk; in adults, may be associated with the presence of anti-Ri antibodies and encephalomyelitis or a cerebellar disorder; eye movement disorder attributed to dysfunction of the paramedian pontine reticular formation; pathology occasionally reveals Purkinje cell loss, neuronal loss in the dentate nucleus, and demyelination of the cerebellar white matter; no specific treatment.

**Parinaud Syndrome**

Dorsal rostral midbrain syndrome; characterized by supranuclear paralysis of upgaze, defective convergence, convergence-retraction nystagmus, and skew deviation may be noted; most often caused by compression of the dorsal midbrain and superior colliculi from tumors of the pineal region (e.g., pinealoma, germ cell tumor, glioma); other causes include ischemia and stroke, and demyelinating disease; symptoms are caused by impairment of fiber connections between the oculomotor nuclei; treatment is directed toward the initiating disease process.

**Pelizaeus-Merzbacher Disease**

X-linked recessive degenerative disease of childhood; linked to defects in the proteolipid protein (PLP1) gene on Xq22; two forms exist, one that is present at birth (connatal variant) and an infantile variant; both forms present with dystroglycogen and head tremor; the connatal form also has floppiness, head lag, psychomotor retardation, ataxia, spasticity, and failure to thrive; the classic infantile form shows initial slowing of motor and speech development, in association with ataxia, spasticity, hyperreflexia, optic atrophy, choreorethetatic movements, and eventual regression of psychomotor skills; patients often develop kyphoscoliosis, joint contractures, and incontinence; hearing is preserved; sensory loss does not occur; pathology reveals loid changes of the white matter; no specific treatment.

**Pick's Disease**

Also known as frontotemporal dementia. An uncommon, progressive dementia syndrome that has a prominent language component. Patients present with variable degree of memory impairment, aphasia, and personality changes. In association with progression of disease, the frontal and anterior temporal regions become mute. The brain demonstrates focal atrophy of the frontal and anterior temporal lobes (may be "knife-edge"), with neuronal loss, gliosis, Pick bodies (eosinophilic cytoplasmic masses), swollen ballooned neurons (Pick cells), and sparing of the nucleus basalis. Marked caudate and hippocampal atrophy may be noted. Treatment consists of supportive care; there are no specific therapies for Pick's Disease.

**Platybasia**

Autosomal dominant congenital malformation, affecting the base of the skull; defined as a skull base in which the angle between the planes of the anterior cranial fossa and the clivus is greater than 140 degrees; foramen magnum is narrowed; patients generally remain asymptomatic; if symptoms occur, the onset is in the second or third decade, related to progressive compression of the cervical spinal cord; clinical features include spasticity, incoordination, nystagmus, and lower cranial nerve palsies; can occur in other syndromes, such as Chiari types 1 and II, and aqueductal stenosis; treatment requires surgical decompression of the posterior fossa and upper cervical cord.
POEMS Syndrome

Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; associated with osteosclerotic myeloma or plasmacytoma; electrodagnostic testing of the neuropathy is consistent with demyelination and axonal degeneration, which may be similar to CIDP; see Crow-Fukase syndrome.

Quadruplegic Myopathy

Syndrome of acute quadriparesis that occurs in critically ill patients; usually develops after administration of high-dose corticosteroids, nondepolarizing neuromuscular blocking agents, or both; most often under treatment for status asthmaticus, organ transplantation, and trauma; clinical features include onset of severe, diffuse extremity weakness, loss of reflexes, and persistent respiratory weakness; ophthalmoplegia and facial weakness may occur; serum creatine kinase levels often are elevated; muscle biopsies reveal myopathic changes with fiber atrophy, fiber necrosis, loss of thick filaments (myosin); treatment consists of discontinuation of offending agents and supportive care.

Rasmussen Encephalitis

Disorder of childhood and preadolescence characterized by a unilateral focal seizure disorder, including epilepsy partialis continua, and a progressive hemiplegia induced by focal cortical inflammation and destruction; seizures manifest as repeated clonic or myoclonic jerks that may remain focal or regional; MRI shows focal or hemispheric atrophy; underlying etiology is a chronic focal encephalitis, although an infectious agent is not consistently identified; an autoimmune etiology also has been postulated; treatment with anticonvulsants such as valproic acid or clonazepam often is unsuccessful but may give partial relief; surgical hemispherectomy should be considered for intractable seizures.

Pompe's Disease

Infantile acid maltase deficiency; glycogenosis type 2; lysosomal storage disease with autosomal recessive inheritance; combination of a metabolic myopathy and motor neuron disease; clinical features include initial normal development (for several weeks to months), followed by severe hypotonia, retained mental alertness, generalized weakness, weak cry, dysphagia, anorexia, enlarged tongue, cardiomegaly with congestive failure, and hepatomegaly; respiratory weakness usually will develop, along with an inability to handle oropharyngeal secretions; cardiac failure is the usual cause of death by 12-18 months of age; no specific treatment; supportive care.

Prader-Willi Syndrome

Sporadic cytogenetic disorder affecting chromosome 15q11-q13; deletions of this region may occur in up to 50% of cases; clinical features include decreased fetal movement in utero, infants will have a feeble suck and severe hypotonia; older children have short stature, small hands and feet, narrowed cranial bifrontal diameter, almond-shaped eyes with strabismus, and mild mental retardation; MRI may show anomalous cortical growth around the sylvian fissure, possibly due to misrouting of long projection aseans; may be due to defective hypothalamic function; no specific treatment.

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Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; associated with osteosclerotic myeloma or plasmacytoma; electrodagnostic testing of the neuropathy is consistent with demyelination and axonal degeneration, which may be similar to CIDP; see Crow-Fukase syndrome.

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Rubella

Infection by rubella, a single-stranded RNA virus, acquired by droplet inhalation; neurologic syndromes include congenital infection, acute encephalitis, postrubella polyradiculoneuropathy, and progressive panencephalitis; congenital rubella infection manifests as intrauterine growth retardation, deafness, cataracts, glaucoma, microcephaly, and mental retardation; rubella encephalitis is rare, symptoms include headache, dizziness, lethargy, seizures, behavioral changes, and coma; polyradiculoneuropathy presents similar to GBS but has a brief course; rubella panencephalitis presents with dementia, cerebellar syndrome affecting gait and extremity function, spasticity, optic atrophy and retinopathy, lymphocytic CSF pleocytosis, and occasional seizures and myoclonus; no specific treatment.

Scheie's Syndrome

Milder version of Hurler syndrome; autosomal recessive lysosomal storage disease, with accumulation of dermatan sulfate and heparan sulfate within affected tissues; caused by deficiency of a-L-iduronidase; juvenile onset of stiff joints, clawhands, deformed feet, corneal clouding, pigmentary degeneration of the retina, coarse facial features, glaucoma, carpal tunnel syndrome, and deafness; stature and intelligence are normal; psychological disturbances and cardiac dysfunction may be noted; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of a-L-iduronidase in cultured fibroblasts; no specific treatment.

Schwartz-Jampel Syndrome

Chondrodystrophic myotonia; three forms are recognized; the most common is the late-infantile variant, which is autosomal recessive and mapped to 1p34-p36.1; a neonatal variant, which is more severe and often fatal, is not linked to chromosome 1; and an autosomal dominant variant, which is unmapped; muscles are stiff, especially in the face and thighs; muscle hypertrophy may be noted; wasting and weakness of muscles in the hand may occur with membrane-stabilizing drugs (phenytoin).

Sericin Syndrome

Lactotrophic disorder caused most often by the use of serotonin reuptake inhibitor drugs, either alone or in combination with other medications; clinical features include altered mental status and confusion, agitation, myoclonus, hyperreflexia, tremor, incoordination, nausea and diarrhea, low-grade fever, autonomic instability, diarrhea, and rigidity; occurs after a serotoninergic drug is started or the dosage increased; also may be induced by the use of a selective serotonin reuptake inhibitor (SSRI) in combination with a monoamine oxidase inhibitor or tricyclic antidepressant; other etiologies must be ruled out (i.e., infection, metabolic alteration, substance abuse); treatment consists of drug withdrawal and supportive care.

Sjogren's Syndrome

Vasculitic and inflammatory disorder of unknown etiology, defined by two or more of the following symptoms: xerostomia, xerophthalmia, or keratoconjunctivitis sicca (diagnosed by Shimer test) ; most common neurologic complications are sensorimotor peripheral neuropathy and polyneuropathies; ocularmotor and trigeminal sensory neuropathies may occur; CNS involvement can manifest as aseptic meningitis, focal cerebral deficits, seizures, cognitive decline, personality changes, and optic neuropathy; spinal cord may present as myelopathy, transverse myelitis, or intraspinal hemorrhage; CSF may show pleocytosis and elevated protein; MRI can demonstrate high-signal regions of ischemia; symptoms related to vasculitis respond well to corticosteroids; supportive care.

Subacute Sclerosing Panencephalitis (SSPE)

Dawson disease; chronic viral infection caused by a defective measles virus (deficient viral M protein); preadolescent children and young adults are affected (males more often than females); early clinical features include the gradual onset of forgetfulness, difficulty with homework, and restlessness; followed in weeks to months by incoordination, ataxia, myoclonic jerks of the trunk and extremities, apraxia, loss of speech, and seizures; late-stage disease reveals loss of vision, hearing, dementia, and a rigid quadriplegia; pathology demonstrates neuronal degeneration, perivascular infiltration, demyelination, and glosis in the cortex, white matter, and deep nuclei; no definitive treatment; stabilization may occur with intrathecal interferon alfa.

Sydenham Chorea

St. Vitus dance; rheumatic chorea; acquired chorea of childhood caused by an autoimmune reaction to infection with group A 0-hemolytic streptococcus; clinical features include the onset of rapid, irregular, aimless, involuntary movements of the muscles of the limbs, face, and trunk; patients appear to be very restless; other findings include muscular weakness, hypotonia, emotional lability, irritability, and obsessive-compulsive symptoms; less common manifestations are speech impairment, headache, seizures, and cranial neuropathy; EEG reveals diffuse slowing; CSF often normal, may show pleocytosis; MRI normal or may demonstrate enlargement of the basal ganglia; course benign, with improvement in 4–6 weeks; symptoms may improve with benzodiazepines, valproic acid, or corticosteroids.

Tay-Sachs Disease

GM2-gangliosidosis type I; infantile variant of storage disease with deficiency of hexosaminidase A; autosomal recessive inheritance pattern; normal development until onset of symptoms by 6 months of age; clinical features include irritability and hypereexcitability, exaggerated startle response, delayed cognitive development, motor retardation with hypotonia, hyperactive reflexes, dorum, extensor plantar responses, progressive visual impairment, complete blindness by 1 year in most cases, presence of macular cherry-red spot, and occasional myoclonic seizures; vegetative state occurs by the second year; pathology reveals ballooned neurons in brain, cerebellum, and spinal cord; no specific treatment; supportive care.

Thrombotic Outlet Syndrome

Group of disorders that cause compression of the nerves or blood vessels of the brachial plexus; C6 and T1 nerve roots and lower trunk of the plexus can be compressed by cervical ribs, fibrous bands, and hypertrophic scalenus muscles; pain is present in the shoulder, arm, and hand (fourth and fifth digits); use of the limb may exacerbate the pain and induce fatigue; hypoxia of affected areas may be noted; wasting and weakness of muscles in the hand occurs; EMG is consistent with the appropriate nerve injury; MRI may show distortion or impingement along the pathway of nerves or vessels; surgery and physical therapy are the appropriate treatment.
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### 3.1 ACR - Chest (Learning file) (American college of Radiology)

1. chest Trauma 2. Cardiac Disease 3. Vascular Disease 4. Airway Disease

این شامل عناوین زیر می‌باشد:

2001
### 5.1 ACR - Genitourinary (Learning file) (American college of Radiology)

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### 9.1 ACR - Pediatric (Learning file) (American college of Radiology) (Beverly P. Wood, M.D., David C. Kushner, M.D.)

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### 10.1 ACR - Skeletal (B.J Manaster, M.D., Ph.D.) (Learning file)

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### 13.1 Breast Implant Imaging (SALEKAN E-BOOK) (MICHAEL S. MIDDLETON, PH.D., M.D, MICHAEL P. MCNAMARA JR., M.D.)

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### 14.1 Carotid Duplex Ultrasonography Extracranial and Intracranial (Michael Jaff DO, Serge Kouwator MD, Alain Voorons Audlouslue)

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**شماره مطالب: 2000**

**شماره مطالب: 2003**

**شماره مطالب: پس از 2003**
CASE REVIEW Obstetric and Gynecologic Ultrasound WITH CROSS-REFERENCES TO THE REQUISITES SERIES (Pamela T. Johnson, Alfred B. Kurtz)  

CD Roentgen (Michael McDermott, M.D., Thorsten Krebs, M.D.) (Williams & Wilkins)  

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CD-ROM to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)  

CD to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)  

CD to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)  

CD to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)  

CD to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)  

CD to complement the book (A. Gregory Sorenson, Peter Reimer) (Thieme)
21.1 Computed Body Tomography with MRI Correlation (Joseph K. T. Lee, Stuart S. Sagel, Robert J. Stanley, Jay P. Heiken) (3rd Edition) (Lippincott Williams & Wilkins)

22.1 CT Teaching Manual (Matthias Hofer) (Thieme) (Salekan E-Book)


24.1 DIAGNOSTIC ULTRASOUND A LOGICAL APPROACH (JOHN P. McGahan, BARRY B. GOLDBERG)

25.1 Diagnostic Ultrasonography of Fetal Anomalies: Principles and Techniques (CD II, III)

26.1 EBUS (Endo Bronchial Ultrasound)

27.1 Endoscopy and Gastrointestinal Radiology (Gregory G. Ginsberg, Michael L. Kochman) (2004)
28.1 Essentials of Radiology

Case 1: Four Patients at a Hospital Case 2: A Case of a Lung Tumor

29.1 Exam Preparation for Diagnostic Ultrasound

Adenob and OB/GYN (Roger C. Sanders, Jann D. Dolk, Nancy Smith Miner)

30.1 Image Data Bank

RADIOGRAPHIC ANATOMY & POSITIONING (APPLETON & LANGE)

31.1 Imaging Atlas of Human Anatomy

(version 2.0) (Mosby)

32.1 Imaging of Diffuse Lung Disease

(David A. Lynch, MB, John D. Newell Jr, MD, FCCP, Jin Seong Lee, MD)

1998

33.1 Imaging of Spinal Trauma in Children

(Lawrence R. Kuhns, M.D.) (University of Michigan Medical Center)

34.1 MAGNETIC RESONANCE IMAGING

(Third Edition) (Dauld Stark, William Bradley)

1998

Principles AND TECHNIQUES

1. Generation and Manipulation of Magnetic Resonance Images
2. Magnetic Resonance: Bioeffects and Safety
3. Three-Dimensional Magnetic Resonance Rendering Technique
4. Principles of Echo Planar Imaging: Implications for Musculoskeletal System
5. MR Imaging of Articular Cartilage and of Cartilage Degeneration
6. The Hip
7. The Knee
8. The Ankle and Foot
9. The Shoulder
10. The Elbow
11. The Wrist and hand
12. The Temporomandibular Joint
13. Kinematic Magnetic Resonance Imaging
14. The Spine
15. Marrow Imaging
16. Bone and Soft-Tissue Tumors
17. Magnetic Resonance Imaging of Muscle Injuries

ATLAS OF SPINAL INJURIES IN CHILDREN

Epidemiology Normal Spine Variants and Anatomy Special Views and Techniques Cervical Spine Lumbar Spine

Measurements Mechanisms and Patterns of Injury Experimental and Necropsy Data Thoracic Spine Sacroccygeal Spine

Occipitocervical Injuries Thoracic Spine Injuries Sacral Injuries

Lumbar
35.1 Magnetic Resonance Imaging in Orthopedics and Sport Medicine (David W. Stoller)

36.1 Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

37.1 MR Angiography Thoracic Vessels (O. Ratib & D. Didier)

38.1 MR Imagin Expert (Geir Torhim, Peter A. Rinck) 4th Edition

39.1 MRI of the BRAIN & SPINE (SCOT W. ATLAS) (LIPPINCOTT-ROVEN)

40.1 Normal Findings in CT and MRI (Torsten B Moeller, Emil Reif) (Thieme)

20.3 Obstetric Ultrasound Principles and Techniques

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Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

This version is a special adaptation for "Magnetic Resonance in Medicine The Basic Textbook of the European Magnetic Redonson Forum"

2000

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Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

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Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

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Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

2000

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Mammography Diagnosis and Intervention (Ralphl. Smathers, M.D.)

2000
8.2 **Coblation Assisted Tonsillectomy (CAT) — Coblation Assisted Procedures (VCD)**

**VCD 1**

1. Cadaveric Rhinoplasty Dissection Technique
2. Role of Component Dorsal Reduction: Spreader Grfts in the Deviated Nose

**VCD 2**

1. Exposure/Nasal incisions
   - Closed endonasal approach
   - Intracartilaginous (IC) incision
   - Cartilage delivery technique
   - Intracartilaginous incision
   - Interdomal incision
   - Open Rhinoplasty approach
   - Transcolumnar incision

2. Tip Alteration
   - Columnar Stat placement
   - Intercartilageal tunnel placement
   - Controlling dome augmentation
   - Pinching/notchig

3. Septal reconstruction
   - Sequest excision
   - Submucosal excision
   - Modification of the dorsum

4. Osteotomies
   - Medial Osteotomy
   - Lateral Osteotomy
   - External Osteotomy

5. Adequate techniques/Closure
   - Alar base rebaseling
   - Correction of alar flaring
   - Diminishing nostril shape
   - Bllow
   - Splints

**9.2 DALLAS RHINOPLASTY**

**Nasal Surgery by the Masters (Reducing Tip Projection and Nostrill Show Via the Open Approach) (CD I, II)**

**10.2** **EENT**

*Welch Allyn Institute of Interactive Learning*
Endoscopic Assisted Procedures used in Astatic Facial Plastic Surgery (VCD) (CD 1, II)

Endoscopic forehead rhytidectomy and brow elevation

Gregory S. Keller

Diseases of the Sinuses Diagnosis and Management (Darid W. Kennedy, MD, FRCSI, William E. Bolger, MD, FACS, S. James Zinreich, MD)

Endoscopic Sinus Surgery

The Endonasal sinusectomy with correction of the nasal cavity (Takahashi's method)

Facial Plastic & Reconstructive Surgery (Terence M. Davidson, MD)

Head and Neck Surgery (Jatin P Shah, MD, MS (Surge), FACS) (Mosby)

Introduction to Ear Acupuncture (Martin Franke)

La Rhinoplastica Ragionata (Valerio Micheli-Pellegrini, Roberto Polselli)

Nasal Aesthetics and Anatomy: A Cadaver Study (Rollin K. Daniel, M.D.)

Open Tip Graft in Twin Patient (Rollin K. Daniel, M.D.)

OPEN RHINOPLASTY Cadaver Dissection Program (Dean M. Toriumi, MD.) (Vol I, II) (College of Medicine at Chicago)
1. Access to nasal Septum
   - Hemitrans Fixatu incision
   - Havwestion Septal Cartilage

2. Harvesting of Conchal Cartilage
   - Anterior approach for harvesting Cartilage
   - Flap elevation
   - Cartilage excision
   - Closure and dressing

3. Open Rhinoplasty approach
   - Incisions
   - Flap elevation

4. Structural grafts used in Secondary
   - Anterior approach for harvesting Cartilage
   - Flap elevation
   - Incision and dissection
   - Cartilage excision
   - As a case study, Presented by Dr. Ali

5. Management of Middle Nasal Vault
   - Division of upper lateral Cartilages from septum
   - Application of spreader grafts

6. Major septal reconstruction
   - Hemitransfixation incision
   - Flap elevation
   - Septal excision
   - As a case study, Presented by Dr. Ali

7. Management of Lower third of the nose
   - Cephalic trimming of lateral Crura
   - Saturation in-place Collarllar strut
   - Transdomal Sutur
   - Sutured in-place tip

8. Chin augmentation
   - Preparation of the implant
   - Incision and dissection
   - Placement of implant

24.2 Otorhinolaryngology Head and Neck Surgery (SIXTEENTH EDITION) (James B. Snow Jr, MD, John Jacob Ballenger, MD.)

25.2 Plastic Surgery (Fifth Edition) (Grab and Smith's) (Salekan E-Book)
29.2 Rhinoplasty The American Academy of Facial Plastic and Reconstructive Surgery (CD I, II) (E. Gaylon McCollough, M.D.) (the St. Louis Aging Face Symposium)

In neonates, the first step is the only step...

29.2 Rhinoplasty The American Academy of Facial Plastic and Reconstructive Surgery (CD I, II) (E. Gaylon McCollough, M.D.) (the St. Louis Aging Face Symposium)

Aging Face Journal of ENT Micorsurgery of the Skull Base

30.2 RHINOPLASTY DOUBLE DOME UNIT (CD I, II) (E. Gaylon McCollough MD, Birmingham, Alabama)

These two dome units are also available in the Double Dome Unit.

31.2 Rhinoplasty The Overly Projected Nasal Tip (Trent W. Smith, M.D.F.A.C.S.)

In the year 2000, the first step is the only step...

32.2 SURGERY of the EAR (Fifth Edition) (Glasscock-Shambaugh) (Michael E. Glasscock III, MD, FACS, Aina Julianna Gulya, MD)

2003

33.2 The MEDPOR Lower Eyelid Spacer (James Patrinely, M.D.F.A.C.S., and Charles N.S. Soparkar, M.D., Ph.D.) (VCD)

34.2 The MEDPOR Nasal Shell Implant (Paul O'Keefe, M.B, B.S., (SYD), F.R.C.S., F.R.A.C.S.) (VCD)

35.2 VCD Journal of ENT APPROACH VESTIBULAR NEURECTOMY-TRANSTEMPORAL SUPERFACIALINE APPROACH

40.2 San Diego Classics in Soft Tissue & Cosmetic Surgery Rhinoplasty (Part 1-6) (Richard C. Webster, MD, Terence M. Davidson, Alan M. Nahum)
15

12.3 Core Curriculum in Primary Care Gynecology (Michael, Isaac Schiff, Keith, Thomas, Annkeathryn) (SALEKAN E-BOOK) 2003

13.3 Danforth's Obstetrics and Gynecology (James R. Scott) (9 Edition) (SALEKAN E-BOOK)

14.3 Diagnosis of Benign Breast Disease (Dorothy M. Barbo, MD) (VCD) Submitted Subject The Limits of Laparoscopy: Diapharbmatic Endometriosis (David B. Redline, MD) (SALEKAN E-BOOK)

15.3 Endoscopic Surgery for Gynecologists (Suttond & diamond) (second Edition)


17.3 INTERACTIVE COLOR GUIDES Obstetrics Gynecology Neonatology (David James, Mary pillai, Janice rymer, Andrew N. J. Fish, Warren Hye) (SALEKAN E-BOOK)

18.3 LAVM: Our First one Hundred Cases; What have We Learned? (Dr. G. F. Stohs, MD & Dr. L. P. Johnson, MD) (CD I, II)

19.3 Nine Month Miracle (A.D.A.M. Software, Inc.)

20.3 Obstetric Ultrasound Principles and Techniques

21.3 Operative Obstetrics (Larry C. Gilstrap III) (2nd Edition) (SALEKAN E-BOOK)

22.3 Safety principles for surgical techniques in minimally invasive gynecologic surgery (Dr. Samir Sawalhe) (CD 1, II) (SALEKAN E-BOOK)

23.3 Single Puncture Laparoscopic Technique (Marco Pelosi, MD) (VCD)
Submitted Subject: Transvaginal Sonographic Assessment of Pelvic Pathology: Preoperative Evaluation (Frances R. Batzer, MD)

Limiting Physician Exposure to Hepatitis B and HIV: Ob / Gyns (V. Scolarelli, MD)

Laparoscopic Retropubic Colposuspension For Stress urinary incontinence (Gordon, D. Davis, MD & R.W. Lobel, MD)

Bi-polar Desiccation of Vascular Tissue: Laparoscopic Hysterectomy (Paul, D. Indman, MD)

TEXT AND ATLAS OF Female in Fertility Surgery (Robert B. Hunt) (Third Edition) (Mosby) (SALEKAN E-BOOK)

Triplet Pregnancies and their Consequences (Louis G. Keith, MD, Isaac Blickstein, MD) (SALEKAN E-BOOK)

TVT Tension-free Vaginal – Tape

Urogynecology: Evaluation and Treatment of Urinary Incontinence (Bruce Rosenweig, MD, Jeffrey S. Levy, MD, Donald R. Ostergard, MD)

2. Consideration for the OB/GYN Generalist

Types of Incontinence • Incontinence Awareness • Patient misconceptions • affected women • incontinence

: \( \text{incontinency} \)

1. Introduction & Defining Incontinence

: Cystoscopy • uroflowmetry • Postvoid residual • Cystometrogram • Pad test • Voiding diary • un , w / / • Pessary test • Multi-Channel urodynamic

: Stress urinary incontinence

Incontinence is the leaking of urine which may occur with coughing, sneezing, or any other cause of abdominal pressure. This can be due to weak muscles, injury, or neurological problems.

Types of incontinence can be classified into two main categories:

1. Urge incontinence: Occurs when the bladder contracts unexpectedly, causing urine to leak out. This may be due to an overactive bladder or nerve damage.

2. Stress incontinence: Occurs when the muscles around the urethra (the tube that carries urine out of the body) are weak, allowing urine to escape. This may be caused by pregnancy, childbirth, or surgery.

Patient misconceptions about incontinence can be common. Some patients may think:

- It is a natural part of aging.
- It is not treatable.
- It is only a problem for women.

These misconceptions can lead to delays in seeking treatment and maintaining a healthy lifestyle.

Complication: Incontinence can lead to skin irritation and infection, as well as social and emotional problems.

: Consideration for the OB/GYN Generalist

: Incontinence management to private patients • Non surgical therapy • Urogynecology as a subspecialty

: Breast examination

Breast examination is a crucial part of women's health checkups. It involves examining the breasts for any lumps, swelling, or changes. The examination may be done by hand or using a specialized device.

Procedure:

1. Inspection:
   - Look for any asymmetry, palpation
   - Inspect the nipples and areolae for texture, color, and symmetrical position

2. Palpation:
   - Feel for any masses, lumpiness, or induration
   - Demonstrate the method

3. Ultrasound:
   - Use an ultrasound machine to visualize the breasts
   - Interpret the findings

4. Mammography:
   - Use X-ray to assess the breast tissue
   - Evaluate the results

5. Biopsy:
   - Take a biopsy of any suspicious areas
   - Send the sample to pathology

: Pelvic Examination

Pelvic examination is a routine part of obstetric and gynecologic care. It involves examining the reproductive organs for any abnormalities.

Procedure:

1. Rectal examination:
   - Insert a gloved finger into the rectum
   - Feel for any masses, lumps, or asymmetry

2. Vaginal examination:
   - Insert a gloved finger into the vagina
   - Feel for any masses, lumps, or asymmetry

3. Vaginal speculum:
   - Use a speculum to visualize the cervix and vaginal walls
   - Check for any abnormalities

4. Pap smear:
   - Collect cells from the cervix
   - Send the sample to pathology

: CNG CD

: UTEROSALPINGOGRAPHY IN GYNECOLOGY

It's Application in Physiological And Pathological Conditions

(A) Hysterosalpingography (HSG)

(B) Ultrasonography (USG)

(C) Magnetic Resonance Imaging (MRI)

(D) Fiber Optic Endoscope (FOE)

: Pelvis E-Book

SALEKAN E-BOOK 2003
4- علوم آزمایشگاهی

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این محتوای آزمایشگاهی شامل توصیف و نمایش تصویر از بیسیج آزمایشگاهی و نحوه اجرای آزمایشات حاوی در سایر کتاب‌ها و کتاب‌های آزمایشگاهی است.
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<td>(SECOND EDITION)</td>
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15.4 COMMON PROBLEMS IN CLINICAL LABORATORY MANAGEMENT (Judith A. O'brien, M.S. CLSup (NCA)) (Salekan E-Book)

- COMPLYING WITH CLIA '88
- OVERCOMING OSHA'S OBSTACLES THE EXPOSURE CONTROL PLAN
- OVERCOMING OSHA'S OBSTACLES THE CHEMICAL HYGIENE PLAN
- Taming Technology: Laboratory Information System (LIS)
- OVERCOMING OSHA'S OBSTACLES THE OPERATING PROCEDURE MANUAL (GOMP)
- RE-ENGINEERING FOR THE FUTURE: THE CORE LABORATORY AUTOMATION, OUTREACH NETWORKING, AND THE MILLENNIUM BUG
- PROVIDING AND USING PERSONAL PROTECTIVE EQUIPMENT
- FULFILLING QUALITY CONTROL GUIDELINES
- REGULATIONS
- GENERATING LABORATORY NUMBERS: STATISTICS LINEARITY, CALIBRATION, REFERENCE, AND CRITICAL VALUES: CALCULATIONS
- THE GENERAL OPERATING PROCEDURE MANUAL (SOPM)
- MANAGING THE PHYSICIAN OFFICE LABORATORY (POL)
- PURSUING PERSONNEL PERSPECTIVES

16.4 Concise Histology (A data of multiple choice question in microscopic) (Bloom & Fawcett's) (Second Edition)

17.4 Diagostic Hematology

This textbook, 'Diagnostic Hematology: A pattern approach', is accompanied by a CD-ROM with three knowledge-based systems applied to 237 case studies. The 3 knowledge-based systems are:

1. Professor Petrushka for peripheral blood analysis
2. Professor Fidelio for flow cytometry immunophenotyping
3. Professor Belmonte for bone marrow interpretation

18.4 Discover Biology


20.4 EMBRYO (CD Color Atlas for Developmental Biology) (Gary C. Schoenwolf)

21.4 Essential Cell Biology (with the voice of Julie Theriot designed and programmed by Christopher Thorpe)

22.4 Fields Virology (Forth Edition) (Volume 1) (Lippincott Williams & Wilkins)

23.4 Functional HISTOLOGY WHEATER'S (FOURTH EDITION) (BARBARA YOUNG, JOHN W. HEATH) (ALAN STEVENS JAMES S. LOWE) (PHILIP J. DEAKIN)

24.4 Genetics From Genes to Genomes (Ann Reynolds, Ph.D.) (University of Washington)

- 1. Transmission Genetics
- 2. General Dogma
- 3. Molecular Genetics
- 4. Chromosomes FISH (نکات اورون لاکتوز، سیگنال ترسلاکتن و ... می‌باشد که تحت برآم‌های Quick time

25.4 Gram Stain TUTOR (ANINTERACTIVE TUTORIAL THAT TEACHES THE MICROSCOPIC EXAMINATION OF URINARY SEDIMENT)

26.4 HISTOLOGY EXPLORER

27.4 HUMAN HISTOLOGY CD-ROM (Alan Stevens. James Lowe)
### Images of Disease
An image database for the teaching of Pathology (Nick Hawkins, Mark Dziegielewski)

- **28.4** Images of Disease case
  - **Images of Disease** (Version 1.0) (Leslie P. Gartner James L. Hiatt) (LIPINCOTT WILLIAMS & WILKINS)

### Immunology
(Blackwell Science)

- **29.4** Immunology
  - **Immunology**

### Interactive Color Atlas of Histology

- **30.4** Interactive Color Atlas of Histology
  - **Interactive Color Atlas of Histology**

### Interactive Embryology The Human Embryo Program

- **31.4** Interactive Embryology The Human Embryo Program (Jay Lash Ph.D.)

### Laboratory Medicine: URINALYSIS

- **32.4** Laboratory Medicine: URINALYSIS
  - **Laboratory Medicine: URINALYSIS** (Version 1.0)

### Media Supplement for Biochemistry

- **33.4** Media Supplement for Biochemistry
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### Microbes in Motion III

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  - **Microbes in Motion III** (Dr. Gloria Delisle and Dr. Lewis Tomalty Queen's University)

### MICROBIOLOGY AND IMMUNOLOGY

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### MOLECULAR CELL BIOLOGY 4.0

- **36.4** MOLECULAR CELL BIOLOGY 4.0
  - **MOLECULAR CELL BIOLOGY 4.0**

### PATHOLOGIC BASIS OF DISEASE

- **37.4** PATHOLOGIC BASIS OF DISEASE
  - **PATHOLOGIC BASIS OF DISEASE** Interactive Case Study Companion to ROBBIMS (W. B. Saunders Company) (Sixth Edition)

### PATHOLOGY

- **38.4** PATHOLOGY
  - **PATHOLOGY** (Alan Stevens. James Lowe)

### Peripheral Blood TUTOR

- **39.4** Peripheral Blood TUTOR

### PRINCIPLES OF Molecular Virology

- **40.4** PRINCIPLES OF Molecular Virology (Third Edition)
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44.4 RAPID REVIEW HISTOLOGY AND CELL BIOLOGY (E. ROBERT BURNS, M. DONALD CAVE) (MOSBY) 2002

45.4 Samter's Immunologic Diseases (SIXTH EDITION) (K. Frank Austen, M.D, Michael M. Frank, M.D., John P. Atkinson, M.D., Harvey Cantor, M.D.)

46.4 The American Society of Hematology (41st Annual Meeting and Exposition) 1999

47.4 The Cell 1.0 A Molecular Approach (Many Animations, Movies, Photos, and drawn images) (Geoffrey M. Cooper) 2000

48.4 THE HUMAN GENOME PROJECT 2003

49.4 The Metabolic and Molecular Bases of Inherited Disease 1999

50.4 UNDERSTAND! Biochemistry (3/e Version) (Lehninger Principles of Biochemistry) 2000

51.4 UNDERSTAND! Biochemistry (VERSION 1.0) 1999

52.4 UNDERSTAND! Biology: Biochemistry (Molecules, Cell & Genes) 2000

53.4 Urinalysis TUTOR ( ANINTERACTIVE TUTORIAL THAT TEACHES THE MICROSCOPIC EXAMINATION OF URINARY SEDIMENT) (Carla M. Phillips, MLM, ML(ASCP), Paul J. Henderson, MS, MT(ASCP), Claudia Bein, BS, MT(ASCP)) 1999
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Challenging established treatment patterns in chronic heart failure

A Satellite Symposium held during the ESC Heart Failure meeting

Clinical TRANSESOPHAGEAL ECHOCARDIOGRAPHY (A PROBLEM-ORIENTED APPROACH) (Second Edition) (Steven N. Konstadt)

Clinical Utility of Contrast Echocardiography
Sonovue: An ideal contrast agent for Low MI myocardial Perfusion (Dr. Daniela Bokor, Bracco sa, Milano)

What's new in cardic echography (Dr. Luciano Agati, University "La Sapienza Roma"

Ischemic coronary artery disease (Dr. Harld Becher, John Radcliffe Hospital, Oxford)

Congestive Heart Failure (NOVARTIS) (CD I, II)

Coronary Heart Disease (J. Hurley Myers, Ph.D., Frank H. Netter, M.D.)

Dynamic Practical Electrodiography (Lippincott Williams & Wilkins)

ECG (Jay W. Mason, MD)

ECG DIAGNOSIS MADE EASY ROMEO VEGHT

ECG-SAP III (Jay W. Mason, MD, FACC)

Echo Lecture (VIDEO SERIES) (Mayo)

Intraoperative echocardiography has become an essential component to the surgical approach to valvular disease. Dr. Bijoy Khandheria discusses the utility of intraoperative echocardiography and its impact on the surgical management of cardiovascular disease.

Dr. James Seward Presents Adult Congenital Heart Disease. A generation of Children Have Grown into adulthood and Present with postoperative congenital heart disease. Transesophageal echocardiography is extremely helpful but may not always be necessary in the assessment of adult congenital heart disease. Learn from the expert regarding appropriate use of transesophageal echocardiography and assessment of residual and sequelae of adult congenital heart disease.

Understanding Operative Procedures for Patients with Univentricular Heart from Palliation to Fontan (James B. Seward, M.D.)

Dr. Seward gives a detailed overview of complex anomalies and their applicable corrections. Topics included are Blalock, Mustard, Glenn and Fontan corrections. Graphic depictions of each corrective procedure, possible complications and echocardiographic example are included.

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4. Mitral Valve Regurgitation: Essential Measurements. Pitfalls and Limitations. (Fletcher A. Miller, Jr., MD)

Dr. Fletcher Miller discusses and presents the current approach to the quantitative evaluation of mitral valve regurgitation. This is an excellent review of current quantitative assessment of mitral valve regurgitation including pitfalls and limitations.

5. Mitral Valve Regurgitation: Evidence-Based Practice (A. Jamil Tajik, MD)

A classic presentation by Dr. A. Jamil Tajik on a change in clinical practice with regard to the quantitation of regurgitation and then a change in medical management with early surgery and repair of the mitral valve.

6. Evaluating the Patient with Prosthetic Valve (Fletcher A. Miller, Jr., MD)

Dr. Fletcher Miller, an expert on the echocardiographic assessment of prosthetic valves, presents a detailed in-depth review of the quantitative echo Doppler approach to the prosthetic valve. It is important to understand the hemodynamic pitfalls and limitations of the echocardiographic assessment of cardiac prosthetic valves.

7. Stress Echocardiography and Contrast (Patricia A. Pellikka, M.D.)

Using illustrative cases, Dr. Pellikka gives an expert presentation and discussion on the role of contrast in stress echocardiography. Pitfalls and limitations of contrast stress echocardiography are also discussed. New Horizons in Stress Echocardiography Dr. Pellikka, an expert in stress echocardiography, discusses Dobutamine stress echocardiography and its role in preoperative risk stratification. Also discussed are new advances in stress echocardiography such as color kinetics and acoustic quantification, color Doppler imaging, and strain and strain rate imaging.

20.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (UPDATE NO. 1) (TRANSESOPHAGEAL- ECHOCARDIOGRAPHY)

21.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 1) (VCD) (ECHOCARDIOGRAPHY Normal 2-D And M-MODE EXAM))

22.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 10) (VCD) (CARDIAC MASSES)

23.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 11-A,B) (VCD CD I, ii) (ECHOCARDIOGRAPHIC ASSESSMENT OF PROSTHETIC HEART VALVES)

24.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 12) (VCD) (INTERVENTIONAL ECHOCARDIOGRAPHY)

25.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 2) (VCD) (DOPPLER AND COLOR FLOW IMAGING PHYSICS, INSTRUMENTATIONS AND THE NORMAL EXAM)

26.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 4) (VCD) (ECHOCARDIOGRAPHY IN AORTIC VALVE DISEASE)

27.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 5) (VCD) (ECHOCARDIOGRAPHY IN CORONARY HEART DISEASE)

28.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 6) (VCD) (ECHOCARDIOGRAPHY IN CONGENITAL HEART DISEASE IN THE ADULT)

29.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 7) (VCD) (ECHOCARDIOGRAPHY IN CARDIOMYOPATHIES: DILATED, RESTRICTIVE AND HYPERTROPHIC)

30.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 8) (VCD) (ECHOCARDIOGRAPHY IN PERICARDIAL DISEASE)

31.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME 9) (VCD) (ECHOCARDIOGRAPHY IN TRICUSPID AND PULMONIC VALVE DISEASE AND DISEASES OF THE AORTA)

32.5 ECHOCARDIOGRAPHY 2-D/DOPPLER WITH COLOR FLOW IMAGING (VOLUME3) (VCD) (ECHOCARDIOGRAPHY IN MITRAL VALVE DISEASE)

33.5 EchoSAP III (Echocardiography Self-Assessment Program) (Echocardiography Overview: Technique and Applications) (Volume 1)

(James D. Thomas, MD, Ellen Mayer-Sabik, MD)

-Introduction and Overview -Examinations -Applications -Self-Assessment Questions -Evidence-Based Medicine -Conclusions

34.5 Electronic Image Collection of Comprehensive Vascular and Endovascular Surgery (John W. Hallet, Joseph L. Mills, Jonathan J. Eamsbaw, Jim A Reekers)

2004


35.5 ENDOVASCULAR TECHNIQUES (Abdominal Aortic Aneurysms) (Workshop) (I. Flessenkämper) (15th Endovascular Symposium Berlin)

2004

36.5 ESC Congress

2004

37.5 EVOLVING ISSUES IN THE MANAGEMENT CHD (National Lipid Education Council™)

2002

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- Effect of Maneuvers and Perturbations
- Hermosis to Cardiac Imaging Modalities

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- Valve Closure Sounds and Splitting of Sounds
- Opening Sounds
- Third Sounds
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- Diastolic Murmurs
- Continuous Murmurs versus “To and Fro” Murmurs
- Friction Rubs

Catalog of Lesions
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- Valvular Lesions
- Pericardial Disease
- Congenital Heart Disease
- Cardiomyopathies
- Myxoma

1. From a new perspective: mitral valve prolapse aortic dissections and aneurysms

2. Surgical and medical management of ascending and descending aortic dissections liporoten (A): a cardiovascular risk factor

3. Radionocency ablation: Ablation of AV Node reentry tachycardias

4. Laser Angioplasty for coronary Atherosclerotic Disease

5. Video Journal of Cardiology (LAWRENCE S. COHEN, M.D, JOHN ELEFTERIADES, M.D.) (VCD)

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Video Journal of Cardiology (LAWRENCE S. COHEN, M.D, JOHN ELEFTERIADES, M.D.) (VCD)
AQUAMIDE: Poly Acryl Amide Gel (an injectable gel for correction of soft Tissue Deficiencies)

2.6

ATLAS OF COSMETIC SURGERY (Michael S. Kaminer, MD, Jeffrey S. Dover, MD, FRCP, Kenneth A. Arndt, MD) (W.B. Saunders Company)

3.6

PART II

ANESTHESIA
7 Regional Anesthesia for Aesthetic Surgery
8 Office-Based Sedation and Monitoring
9 Postoperative Pain and Nausea Management

PART III

COSMETIC SURGERY PROCEDURES AND TECHNIQUES
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11 Lasers in the Treatment of Vascular Lesions
12 Lasers in the Treatment of Pigmented Lesions
13 Laser Hair Removal
14 Liposuction
15 Hair Transplantation
16 Soft Tissue Augmentation
17 Botulinum A Exotoxin Injections for Photographing and Hyerhidrosis,
18 Chemical Peels
19 Lasers in Skin Resurfacing
20 Blepharoplasty
21 Surgical Rhytidectomy: Face Lifts and the Endoscopic Forehead Lift
22 Leg Vein Management: Sclerotherapy, Ambulatory Phlebectomy, and Laser Surgery
23 Scar Management: Keloid, Hypertrophic, Atrophic, and Acne Scars

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4 Photoaging: Mechanisms, Consequences, and Prevention
16 Soft Tissue Augmentation
5 Beauty and Society
20 Blepharoplasty
21 Surgical Rhytidectomy: Face Lifts and the Endoscopic Forehead Lift
22 Leg Vein Management: Sclerotherapy, Ambulatory Phlebectomy, and Laser Surgery
23 Scar Management: Keloid, Hypertrophic, Atrophic, and Acne Scars
8 Office-Based Sedation and Monitoring
9 Postoperative Pain and Nausea Management

Atlas of Dermatology (Jhon’s Hopkins) (SALEKAN E-BOOK) (CD I, II)

Atlas of Dermatology (T.L.Diepgen, M. Simon, A. Bittorf, M. Fartasch, G. Schuler) (with the DOIA team G. Eysenbach, J. Bauer, A. Sager) (springer)

Atlas of Differential Dermatology (Klaus F. Helm, M.D., James G. Marks, M.D.)

Color Atlas and synopsis of Clinical Dermatology Common and Serious Diseases Thomas B. (Fitzpatrick, M.D. Richard Allen Johnson, M.D. Dick Suromund, M.D.)

Correction of Wrinkles & Augmentation of lip and cheek with Restylane & Perlane

for as long as you like

Skin filler

Lip enhancement

Post-op

Pre-op

Cyst

Hair transplant

Co2

Procedural wound healing

Erbium:Yag

Incisional laser

Tinas.Alster

Tissue healing

Scar revision

manual of cutaneous laser techniques

Cutaneous Laser Surgery (Second edition) The Art and Science of Selective Photothermolysis (Goldman, Fitzpatrick)
16.6 EVIDENCE-BASED DERMATOLOGY (Howard I. Maibach, MD, Sagid J. Bashir, BSc(Hons), CHB, Minn A. Khan, BSc, MLS) این کتاب دو سال اخیر در این زمینه شایع شده است و یکی از اولویت‌های آن‌ها به‌طور قابل توجهی در تحقیقات بهره‌برداری از آزادی خواهد بود.

18.6 Hair Removal with Intense Pulsed Laser (IPL) (طراحی استفاده از لوکس - مدل هایی که برای موهای زادن به کار می‌روند): این کتاب در مورد تحقیقات در این زمینه می‌باشد.

20.6 HANDBOOK OF ORAL DERMATOLOGY: DIAGNOSIS AND MANAGEMENT (Cripian Scully (MARTIN DUNITZ) کتاب فوکه در مرکز خدمات فردی سالمان دبیری به کتاب دندانپزشکی اشاره کرده است.

21.6 Laser Hair Removal (David J. Goldman) (Martin Dunitz) کتاب فوکه در مرکز خدمات فردی سالمان دبیری به کتاب دندانپزشکی اشاره کرده است.

23.6 Dermatology: A Multi-Media Teaching File (Disc 1.2) (Gross & Microscopic Symposium) (Mosby) کتاب فوکه در مرکز خدمات فردی سالمان دبیری به کتاب دندانپزشکی اشاره کرده است.

31.6 Cutaneous Medicine Cutaneous Manifestations of Systemic Disease (THOMAS T. PROVOST, MD, JOHN A.FLYNN, MD) (Johns Hopkins Medical Institutions Baltimore, Maryland) کتاب فوکه در مرکز خدمات فردی سالمان دبیری به کتاب دندانپزشکی اشاره کرده است.

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2002

1999

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REFINEMENT IN HAIR TRANSPLANTATION: Micro and minigraft Megasession (Alfonso Barrera, M.D.)

Skin Rejuvenation with skin filler (E.E.A. Derm)

Textbook of Pediatric Dermatology (JOHN HARPER ANDRANOY NEIL PROSE) (VOLUME 1 & 2)

The Aging Face: A Systematic Approach (Calvin M. Johnson, Jr., Ramsey Alasrarr)

### 36.6 USING BOTULINUM TOXINS COSMETICALLY

*Jean Carruthers, Alastair Carruthers*

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### 1.7 A New Generation in Cemented Hip Design (VCD) (Part I, II)

*David S. Hungerford, Clayton R. Perry*

**Segment I:** Core Decompression

**Segment II:** Trauma Case Studies: Retrograde Femoral Nailing

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### 2.7 AO Image Collection

*AO Principles of Fracture Management* (T.P. Ruedi, W.M. Murphy)

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### 3.7 AO International AO Teaching Series-LCP

*Thomas P. Ruedi, Prof. Michael Wagner*

---

### 4.7 AO Principles of Fracture Management

*Thomas P. Ruedi, William M. Murphy* (CD I , II)

1. AO philosophy and Its basis
2. Decision making and planning
3. Reduction and fixation techniques
4. Specific fractures
5. General topics
6. Complications

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### 5.7 CCC (Core Curriculum in Primary Care)

**Orthopedics/Sport Medicine Section**

1. Introduction
2. Orthopedic Procedures: A Rheumatology's Perspective
3. Exercise and Aging A Prescription for life
4. Foot and Ankle Problems Part Two

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### 6.7 Atlas of Orthopaedics Surgery (Disk 1-6)

**Disk 1:** Condylar Plate Fixation in the Distal Femur, Malleolar Fracture Fixation, Malleolar Fracture Type B, Malleolar Fracture Type C, Tension Band Wiring on the Elbow

**Disk 2:** Techniques of Absolute Stability, Proximal Humerus Fracture, Reduction with Clamps, Posterior Wall Fracture, Posterior + Transverse Wall Fracture, Undeamed Tibial Nail (UTN), Intrarticular Fracture of the Distal Humerus

**Disk 3:** Fracture of the Tibiaplateau, Tibia Fracture in Femur, UTN, Reduction Technique, The Undeamed Femoral Nail System, Dynamic Condylar Screw (DCS), Dynamic Hip Screw (DHS), Pilon Tibial Fractures (Foamed Foot)

**Disk 4:** Application of Large Distractor, AO Asil External Fixator, PC-FIX Point Contact Fixator an Internal Biologicl, The Proximal Femoral Nail (PFN), Bicondylar Fracture of Tibia Plateau, Minimal Invasive Plating of the Tibia

**Disk 5:** Direct and Indirect Reduction Techniques, Short Oblique Radius Fracture, Small External Fixator, Intraarticular Fracture Distal Radius, Distal Radius, Open Reduction & Fractures of the Calcaneus, Postoperative Treatment, Internal Fixation of a Humeral Shaft Fracture

**Disk 6:** High Cinematography of a Butterfly Fracture, Posterior, Pelvic Fixations Symphysis Pubis & Pubic Rami, Pelvic Fixations, Anterior Plate Fixation 53028, The Pelvic C-Clamp, Liss Less Invasive Stabilization System, LCP Locking Compression Plate

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### 7.7 Click’X VenttoFix SynCage

*J. Webb, O. Schwarzenbach J. Thalgott* (VCD) (AO ASIF OFFICIAL TAPE)

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### 8.7 FRACTURES IN ADULTS

*ROCKWOOD AND GREENS*

1. General Principles
2. Upper Extremity
3. Spine
4. Lower Extremity
### Principles AND TECHNIQUES

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### Imaging of Spinal Trauma in Children

**Epidemiology**
- Normal Spine Variants and Anatomy
- Special Views and Techniques
- Cervical Spine
- Thoracic Spine
- Lumbar Spine
- Sacroccygeal Spine

**Measurements**
- Mechanisms and Patterns of Injury
- Experimental and Necropsy Data
- Thoracic Spine
- Lumbar Spine
- Sacroccygeal Spine

**Occipitocervical Injuries**
- Cervical Spine
- Thoracic Spine
- Lumbar Spine
- Sacroccygeal Spine

**ATLAS OF SPINAL INJURIES IN CHILDREN**

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### Internal Fixation of a Humeral Shaft Fracture with the UHN

- Technical Information
- Postoperative Concept
- Post-op – X-ray control
- Post-op treatment

### Master Techniques in Orthopedic Surgery

**Reconstructive Knee Surgery**
- Southern California Center for Sports Medicine Long Beach, California
- (DOUGLAS W. JACKSON, M.D.)

**Operative Arthroscopy**
- John B. McGinty)
- Lippincott, Williams & Wilkins

**Operative Arthroscopy** (Third Edition)
- (John B. McGinty)
- (Lippincott, Williams & Wilkins)

**Magnetic Resonance Imaging in Orthopedics and Sport Medicine**
- (David W. Stoller)

**Mathys Orthopaedics (VCD)**
- (Video-Atelier Othmar Keel AG)

**Mathys Orthopaedics Hip Prostheses (VCD)**
- (Video-Atelier Othmar Keel AG)

**Shoulder:**
- Arthroscopic Cuff Repair
- Slap Lesions

**Magnetic Resonance Imaging in Orthopedics and Sport Medicine (David W. Stoller)**

**Mathys Orthopaedics (VCD)**
- (Video-Atelier Othmar Keel AG)

**Mathys Orthopaedics Hip Prostheses (VCD)**
- (Video-Atelier Othmar Keel AG)
16.7 Operative Arthroscopy (Third Edition) (John B. McGinty) (Lippincott, Williams & Wilkins)

**Hip:**
- Southern Sport Medicine & Orthopaedic Center
- Operative Hip Arthroscopy: Dense Soft Tissue Envelope - Constrained Ball and Socket Anatomy - Thick Capsule, Limited Compliance

17.7 Operative Arthroscopy (Third Edition) (John B. McGinty) (Lippincott, Williams & Wilkins)

**Ankle:**
- Ankle Arthroscopy (James Tasto M.D.)
  - Ankle & Subtalar Arthroscopy

18.7 Operative Arthroscopy (Third Edition) (John B. McGinty) (Lippincott, Williams & Wilkins)

**Wrist:**
- Portal Markings - Establishing the 3/4 Portal - Radiocarpal Arthroscopy

19.7 Operative Arthroscopy (Third Edition) (John B. McGinty) (Lippincott, Williams & Wilkins)

**Knee (CD-2):**
- ACL - Complex articular surface injuries - Fractures - Patellofemoral

20.7 Operative Arthroscopy (SECOND EDITION)

1- Basic Principles 2- The Knee 3- The Shoulder 4- The Elbow 5- The Wrist 6- The Foot and Ankle 7- The Temporomandibular Joint 8- The Spine 9- The Hip

21.7 Operative Orthopaedics (Ninth Edition) (CAMPBELL'S) (S. TERRY CANALE)

22.7 OPERATIVE ORTHOPAEDICS (CAMPBELL'S)

Trochanteric osteotomy-hip revision  Arthroscopic assisted ACL reconstruction  Screw fixation  Trochanteric osteotomy-hip revision  Arthroscopic assisted ACL reconstruction  Screw fixation  ORIF calconeal fracture

23.7 ORTHOPAEDIC SURGERY (Third Edition) (CHAPMAN)

Surgical Principles and Techniques  Sport Medicine  Skeletal Disorders  Joint Reconstruction, Arthritis, and Arthroplasty

24.7 PEDIATRIC ORTHOPAEDICS (Lovell and Winter's) (Fifth edition) (Salekan E-Book) (Volume II)

KYPHOSIS THE UPPER LUMB SLIPPED CAPITAL FEMORAL EPIPHYSIS
- Spondyloysis and Spondylolisthesis
- The Cervical Spine
- Leg Length Discrepancy
- Sports Medicine in Children and Adolescents

25.7 Photographic manual of Regional Orthopaedic and Neurological Tests

45.1 Radiology imaging Bank: Orthopaedic

26.7 **Range of Motion-AO Neutral-O Method**

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27.7 **SPINE (VCD 1-A)**

(J. o’Dowd, P. Moulin, E. Morscher P. Moutin, J. Webb, M. Aebi)

| CS-Titanium Locking Plate (E. Morscher P. Moutin) | Cervical Spine Locking Plate (P. Moulin) | | |

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28.7 **SPINE (VCD 1-B)**


| Cervix Fixation C3-C7 in Presence of a Laminectomy (B. Jeanneret) | USS: Lumbosacral Fusion Sacral Implants (J. Webb M.Aebi P.Bryne) |
| U.S.S: Lumbar Degenerative Scoliosis Side-Opening Pedicle Screws (M. Aebi J. Webb) | |

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29.7 **SPINE (VCD 1-C)**


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30.7 **SPINE (VCD 1-D)**


| ClickX (J. Webb) | The Interior Rod System (J. Thalgott & J. Webb) |
| | Contact Fusion Cage (J. Webb) |

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31.7 **SPINE implants (CD I, II)**

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32.7 **Surgery of the Foot and Ankle**

(Michael J. Coughlin, Roger A. Mann)

**Volume One:**
1. General Considerations
2. The forefoot
3. Postural Disorders
4. Neurologic Disorders
5. Arthritic Conditions

**Volume Two:**
1. Miscellaneous Disorders
2. Sports Medicine
3. Pediatrics
4. Trauma

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33.7 **Surgery of the Knee (Third Edition)**

(John N. Insall, W. Norman Scott)

1- Video
2- Photos
3- Illustrations
4- 3D Knee
5- Imaging
- Anatomy
- Anatomical Aberrations
- Biomechanics
- Imaging
- Surgical Approaches

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34.7 **The Adult Hip On CD**

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35.7 **The Shoulder (2nd Edition)**

(Rockwood and Matsen)

1- Disorders of the Acromioclavicular Joint
2- Disorders of the Sternoclavicular Joint
3- Glenohumeral Instability
4- Glenohumeral Arthritis and Its Management

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36.7 **The Unreamed Femoral Nail System**

(N. Sudkamp P. Duwelius)

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37.7 **Video Collection Labor for Experimental Orthopaedics Surgery**

AO/ASIF VCD (CD 1-10)

**VCD 1-A**

(R Texhammar, P Holzach)

| AO/ASIF Instrumentation Care and Maintenance | PreOperative Preparation of the Patient |
| | Approaches to the Femur, Pelvis Knee and Elbow |

**VCD 1-B**

(P Matter M.D., S.M. Perren, B Noesberger)

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| | |

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### VCD 1-C

- **S. Perren, K.M. Pfeiffer M.D.**
- Correctional Osteotomy (dist. Radius)
- Basic Lag Screw Techniques
- Internal Fixation of a Closed Butterfly Fracture of Right Tibia (Operation Video)

### VCD 2-A

- **S. Perren, K.M. Pfeiffer M.D.**
- Correctional Osteotomy (dist. Radius)
- Basic Lag Screw Techniques
- Internal Fixation of a Closed Butterfly Fracture of Right Tibia (Operation Video)

### VCD 2-B

- **B. Noesberger, J. Stadler, P. Holzach, Th. Ruedi**
- DCP 4.5 Butterss Tibial Plateau
- LC-DCP 4.5 for the Distal Tibia
- DCP 3.5 Radius Shaft 3.5 LC-DCP
- DCP 4.5 Neutralization Plate of a Spiral Fracture
- Fracture of the Radius Shaft 3.5 LC-DCP with Shaft screws

### VCD 2-C

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### VCD 3-B

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### VCD 4

- **B. Noesberger, J. Stadler, P. Holzach, Th. Ruedi**
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- LC-DCP 4.5 for the Distal Tibia
- DCP 3.5 Radius Shaft 3.5 LC-DCP
- DCP 4.5 Neutralization Plate of a Spiral Fracture
- Fracture of the Radius Shaft 3.5 LC-DCP with Shaft screws

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### CD 1

**Atlas of Clinical Oncology Tumors of the Eye and Ocular Adnexa** (American Cancer Society) (Devron H. Char, MD)

- Lid and Conjunctival Tumors
- Uveal and Intraocular Tumors
- Retinal and Optic Nervehead Tumors
- Orbital Tumors

**Basic and Clinical Science Course Retina and Vitreous** (Section 12) (American Academy of Ophthalmology) (SALEKAN E-BOOK)

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### CD 2

**Atlas of Ophthalmology** (Richard K. Parriss II) (CD 1, II) (Mosby)

### CD 3

**ATLAS OF OPHTHALMOLGY** (SUE FORDORNSAL MARSH) (Mosby)

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### CD 4

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<td>Incomitant Deviations (4th edition)</td>
<td>a supplement chapter 17 of Pickwell's Binocular Vision Anomalies</td>
<td>2000</td>
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<td>40.8</td>
<td>Intraocular Inflammation and Uveitis</td>
<td>(Section 9) (SALEKAN E-BOOK)</td>
<td>2003</td>
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<td>41.8</td>
<td>LEO Clinical Update Course on Retina</td>
<td>(H. Michael Lambert, Charles. Arr, J. Paul Diechert, Mark W. Johnson, James S. Tiedeman)</td>
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<td>LEO Clinical Update Course on Cataract</td>
<td>(Stephen L. Lane, MD, Alan S. Candall, MD, Douglas D. Koch, MD, Roger F. Steinert, MD)</td>
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<td>43.8</td>
<td>LEO Clinical Update Course on Pediatric Ophthalmology and Strabismus</td>
<td>THE AMERICAN ACADEMY OF OPHTHALMOLOGY (American Academy of Ophthalmology)</td>
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- Reconnaissance des structures oculaires
- Anatomie endoscopique normale et Pathologie de la base du vitre antérieur
- Le Phaco Chop: Pour que les noyaux durs deviennent un plaisir

Roussat B, Chourkron J (Paris)

2003

MOVIMENTQ NATURAL PARA EL OJO ARTIFICIAL (VCD), (AJL OPHTHALMIC, S.A.)

New England Eye Center Imaging in Glaucoma

New England Eye Center Photorefractive Keratotomy (PRK) Course (Helen K. WU, MD, Roger F. Steinert, MD, Michael B. Raizman, MD)

Ocular Pathology (FIFTH EDITION) (MYRON YANOFF, MD AND BEN S. FINE, MD) (Mosby)

Ophthalmic Lenses & Dispensing (Mo JALIE)

Ophthalmic Surgery: principles and Techniques (BLACKWELL SCIENCE)

Orbital Floor Reconstruction Using Medpor Surgical Implant (Joseph M. Serletti, MD, Paul Manson, MD)

Phacoemulsification Cataract Surgery (Multimedia Oculosurgical Module) (Robert M. Schertzer, David X. Pang, MSE, Luanna R. Bartholomew, PhD) (Mosby)

Physiology of the Eye

Anatomy of the Eye  3-D Tour of the Eye  Development of Vision  Physics of Light & Color  Illusions & Your Vision  Common Eye Conditions
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| 56.9      | The Clinical Diagnosis of Alzheimer's Disease (An Interactive Guide for Family Physician) | Alzheimer disease group:  
- Flowchart 
- RiverView 
  - Case Studies 
  - Case Studies
- Shred 
  - Shred
| 57.9      | THE HUMAN BRAIN (Marion Hall David Robinson)                               | THE HUMAN BRAIN
| 58.9      | THE HUMAN NERVOUS SYSTEM (Springer)                                      | THE HUMAN NERVOUS SYSTEM
| 59.9      | The Massachusetts General Hospital Handbook of Pain Management (Second Edition) (Jane Ballantyne, Scott M. Fishman, Salahadin Abd) (SALEKAN-e-book) | THE HUMAN NERVOUS SYSTEM
| 60.9      | The Movement Disorder Society's Guide to Botulinum Toxin Injections       | THE HUMAN NERVOUS SYSTEM
| 61.9      | Thinking a head (Critical question in ms therapy)                         | THE HUMAN NERVOUS SYSTEM
| 62.9      | Understanding and Diagnosing Restless Legs Syndrome                       | THE HUMAN NERVOUS SYSTEM

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| 3.10     | Adult Airway Management Principles & Techniques American Association (afael A. Ortega, M.D., Harold Arkoff, M.D.) | 2001
| 4.10     | Advanced Therapy of INFLAMMATORY BOWEL DISEASE (Theodore M. Bayless, MD, Stephen B. Hanauer, MD) | 2001
| 5.10     | AGA Postgraduate Course CONTROVERSIES And CLINICAL CHALLENGES (An Intensive Two-Day Course Covering A Diversity of Topics Related to the Pancreas) | 2001
|          | Expanded Content | Includes Results of the Q&A | Section Challenge Sessions |
6.10 Atlas of GASTROINTESTINAL in Health and Disease (Marvin M. Schuster, Michael D. Crowell, Kenneth L. Koch)

Part 1: Physiologic Basis of Gastrointestinal Motility
Part 2: Motility Test for the Gastrointestinal Tract

7.10 Atlas of GASTROINTESTINAL MOTILITY in Health and Disease (Second Edition) (Marvin M. Schuster, MD, FACP, FAPA, FACG, Michael D. Crowell, PhD, FACG, Kenneth L. Koch, MD)

Part I: Physiologic Basic of Gastrointestinal Motility
Part II: Motility Tests for The Gastrointestinal Tract

8.10 Atlas of Clinical Oncology Soft Tissue Sarcomas American Cancer Society (Raphael E. Pollack, MD, Phd)

9.10 Atlas of Clinical Oncology Cancer of the Lower Gastrointestinal Tract (Christopher G. Willett, MD)

10.10 Atlas of Clinical Rheumatology (2nd Edition) (David J. Nashel, Chief, Rheumatology Section Va Medical Center, Washington, Professor of Medicine Georgetown University)


12.10 Case Studies in GASTROENTEROLOGY (Second Edition) (Ingram Roberts, MD)

13.10 CD-ATLAS OF DIAGNOSTIC ONCOLOGY

14.10 Clinical Endocrinology (G. Michael Besser MD, DSc, FRCP, Michael O. Thorner MB BS, DSc, FRCP)

Adrenals
Gonads
Growth
Hormone Assay
Imaging Techniques
Pancreas

15.10 Clinical Immunology PRINCIPLES AND PRACTICE (Second Edition) (Robert R Rich, Thomas A Fleisher, William T Shearer, Brain L Kotzin, Harry W Schroeder)

16.10 CLINICAL ONCOLOGY (Raymond E. Lenhard, J. MD, Robert T. Osteen, MD, Ted Gansler, MD)

17.10 Comprehensive Clinical Endocrinology G. Michael Besser MD, DSc, FRCP, Michael O. Thorner

Hypothalamus and Pituitary, Thyroid, Adrenal, Control of Blood glucose and its disturbance, gonad and growth, General conditions-basic, General conditions-clinical, Imaging, Patient Perspectives on endocrine Diseases

18.10 COMPREHENSIVE MANAGEMENT OF Chronic Obstructive Pulmonary Disease (Jean Bourbeau, MD, MSc, FRCP, Diane Nault, RN, MSc, Elizabet Borycki)

19.10 Core Curriculum in Primary Care Metabolic Diseases Section

20.10 Digestive Diseases Self-Education Program (A Core Curriculum and Self-Assessment in Gastroenterology and Hepatology)

21.10 Diseases of the Liver (8th Edition) (Lippincott Williams & Wilkins)
1.22 M. PracticePractical Review Anatomy – Create New Test – Open Existing Test

برنامه مور policie برای اطمینان از مطمئن شدن در این زمینه است. این برنامه شامل پیش از سال ۱۵۰۰۰ سوال احتمالی بوده که با توجه به پدیده و محتوای خاص در بر اشتهای CD در این قسمت می‌باشد. در این جمله، بسته به برنامه مور policie، مطالعه در دریچهoup شدی که از دستورالعمل‌ها، مطالب، مطالب و تصاویر احتمالی سوالات در این مورد سوال دارند. 2.12 مطلب‌یابی‌شده توسط دانش آموزان Rrelated images سنته سی در این زمینه و جلوگیری از احتمالات دیگر صورت است. اگر با دانستن CD در این زمینه و جلوگیری از احتمالات دیگر صورت است، با دندان کلید نهایی آرائشی می‌تواند جلوگیری از احتمالات دیگر صورت است. در نهایی آرائشی می‌تواند جلوگیری از احتمالات دیگر صورت است. در نهایی آرائشی می‌تواند جلوگیری از احتمالات دیگر صورت است. در نهایی آرائشی می‌تواند جلوگیری از احتمالات دیگر صورت است.
6.12 Clinical Examination

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7.12 CMDT CURREAT Medical Diagnosis & Treatment

8.12 Endoscopic Assessment of Esophagitis According to the Los Angeles Classification System

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2002

به کفته موفقیت، این CD برای پریشکان و متخصصین و دستی آنان برای روز سه‌رو می‌باشد در مورد بیماری‌های عمده داخلی، زنان، پوس، جراحی، جسم و ENT و گردونه‌های دستی است. پیش از آن برای مادران با تغییرات بیماران و ویژگی‌ها به جرم و درمان‌های، کمک‌هایی برای دیدار داده می‌شود. این CD شمار بیماری‌ها (بر زیر آورده شده است) و عکس‌های رنگی، نمونه و جدول‌های می‌باشد.

عنوان هزینه در 36 قسمت اصلی و 36 قسمت فرعی به تقلیل موضوع داده شده است. مشروب عناوین عبارات از:

- وعده برای یک صبحانه
Health Assessment

Gaylene Bouska Altman, RN, Ph.D., Karrin Johnson, RN, Robert W. Wallach, MD

10.12

MCCQE Review Notes and Lecture Series

Marcus Law & Brain Rotenberg

Section Menu:
- Anesthesia
- Cardiology
- Color Atlas
- Community Medicine
- Dermatology
- Diagnostic Imaging
- Emergency Medicine
- Endocrinology
- Family Medicine
- Gastroenterology
- General Surgery
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- Nephrology
- Neurology
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- Plastic Surgery
- Psychiatry
- Respilology
- Rheumatology
- Urology

11.12

Medical Dictionary

Dorland’s

12.12

MEDICAL Encyclopedia For Health Consumers

With Atlas

13.12

MedStudy™ The Best Internal Medicine Board Review

(Lara U. Pizzorno, Joseph E. Pizzorno, Jr, Michael T. Murray)

14.12

Patient Teaching Aids

Practical General Practice

(Guidelines for effective clinical management)

(Alex Khot, Andrew Polmear)

(RAPID REVIEW FOR USMLE STEP 1 (Mosby)

Sciences:
- Anatomy
- Behavioral Science
- Biochemistry
- Histology/Cell Biology
- Microbiology/Immunology
- Neurology
- Pathology
- Pharmacology
- Physiology
- Randomize All

SPSS 12.0 for Windows

Textbook of Physical Diagnosis

HISTORY AND EXAMINATION

Mark H. Swartz, M.D.

(W.B. SAUNDERS COMPANY)

The Basics for Interns

(Lara U. Pizzorno, Joseph E. Pizzorno, Jr, Michael T. Murray)

16.12

Practical General Practice

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RAPID REVIEW FOR USMLE STEP 1 (Mosby)

18.12

SPSS 12.0 for Windows

20.12

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(W.B. SAUNDERS COMPANY)

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| 22.12 | Understanding Lung Sounds  (Audio CD) | — |
| 23.12 | UNDERSTANDING PATHOPHYSIOLOGY (Second Edition)  (Sue E. Huether, Kathryn L. McCance) | — |
| 24.12 | Virtual Medical Office CHALLENGE (to accompany Bonewit-West Clinical Procedures for Medical Assistants, 5th Edition)  (W.B. Saunders Company) | — |
|   | Case Study  | — |
|   | Clinical Skills  | — |
|   | Challenge Status  | — |
|   | Help  | — |

| 25.12 | Contemporary Nutrition  Food Wise (Food Wise, Weight Manager) | 2002 |
| 26.12 | Food Works  (College Edition) | — |
| 27.12 | INTRODUCTION TO NUTRITION AND METABOLISM (Third Edition)  (DAVID A Bender) | 2002 |
| 28.12 | Multimedia Workout  (Jeffrey S. Smith, Joseph D. Cook) | — |
| 29.12 | NUTRIENTS IN FOOD  (Elizabet S. Hands) | 2002 |
| 30.12 | THE FOOD LOVER'S ENCYCLOPEDIA  Culinary Techniques Recipes Nutrition Foods | — |

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<td>- Mathematics Review  - Introducing Drug Measures  - How to Read a Drug Label  - Calculatin Dosages  - Comprehensive Posttest</td>
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<td><strong>Patient Education Guide to Oncology Drugs</strong> Name Search – Categories – Comparisons <em>(Gail M. Wilkes, RNC, MS, AOCN, Terri B. Ades, RN, MS, AOCN)</em></td>
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| **19.13** | **THE MERCK INDEX on CD-ROM** *(Version 12:3)* | 2000 |

### CD عناصر

| **1.14** | **BUILDING A MEDICAL VOCABULARY** *(FIFTH EDITION)* *(FEGGY C. LEONARD)* *(W.B. Saunders Company)* | 2001 |
| **2.14** | **ELECTRONIC MEDICAL DICTIONARY** *(STEDMAN’S)* *(LIPPINCOTT WILLIAMS & WLKINS)* | 2001 |
| **3.14** | **English Family** *(Merriam-Webster)* | — |
| **4.14** | **Entertainment Collection** | — |
5.14 How to Prepare for TOEFL

6.14 Learn To Speak English Dictionary & Grammar (CD1-4)

7.14 Mad About English Spelling (Interactive Learning)


9.14 Preparation For the TOEFL (Dictionary Crossword Puzzle Matching Game)

10.14 Preparing for the GRE Writing Assessment

11.14 Studying a Study Texting a Test (Fourth Edition) (Richard K. Riegelman)

12.14 The AMERICAN HERITAGE® TALKING DICTIONARY (Daniel Finkel)

13.14 THE LANGUAGE OF MEDICINE (6TH EDITION) (W.B. Saunders Company)

14.14 TriplePlayPlus! ENGLISH (Syracuse Language Systems)

15.14 Users' Guides To The Medical Literature (A manual for Evidence-Based Clinical Practice) (Gordon Guyatt, MD, Drummond Rennie, MD, Robert Hayward, MD)

1.15 1. Reflux Disease and Nissen Fundoplication (Philip E. Donahue, MD) (VCD)

2.15 2. Supraceliac Aortic-Celiac Axix-Superior Mesenteric Artery Bypass (Gregorio A. Sicard, Charles B. Anderson)

2.15 Advanced Therapy in THORACIC SURGERY (Kenneth L. Franco, MD, Joe B. Putnam Jr., MD)

3.15 Aesthetic Department

ARTECOLL: Injectable micro-Implant, for long lasting levelling of facial wrinkles and folds

M-Implants By Rofil THE BEAUTY PHILOSOPHY: M-Implants by Rofil you and your patients with the highest quality mammary implants in every option possible.

4.15 Aspects of Electrosurgery (Dr. Anthony C. Easty, PhD PEng CCE) Department Medical Engineering

5.15 Atlas of RENAL TRANSPLANTATION (Prof. Legnade, Martin, Helenon, Lebranchu, Halloran, Nochy)
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<td>12.3</td>
<td>Core Curriculum in Primary Care Gynecology</td>
<td>(Michael, Isaac Schiff, Keith, Thomas, Annekathlon)</td>
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<td>22.15</td>
<td>External Ultrasonic Lipolysis</td>
<td>(Clinical Instructor, Division of Plastic Surgery University of Miami, Florida)</td>
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<td>23.15</td>
<td>Fundamental Techniques of Plastic Surgery and their Srgtical operations</td>
<td>(TENTH EDITION) (Alan D. McGregor, Ian A. Mc.Gregor) (Salekan E-BOOK)</td>
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</table>
GYNECOMASTIA CORRECTION THROUGH SUCTION LIPECTOMY ALONE (GARY J. ROSENBERG M.D.F.A.C.S.)

Dr. Rosenberg VCD


Hypospadias Repair II: Onlay Flap Procedure (John W. Duckett Jr., MD) (VCD)

Laparoscopic Hepatic Cystectomy (Daniel J. Deziel, M.D.) (VCD)

MAMMARY AUGMENTATION (CLINICAL MIRASIERRA MADRID) (Ulrich T. Hinderer Dr. Juan L. Del Rio) (VCD)

NMS Surgery Tutor (Dereck Mooney, T. Mack Brown, Cristian Jansenson, Denise Riedlinger)

Open Repair of Abdominal Wall Hernias Using Prosthetic materials (Arthur I. Gilbert, M.D.)

Practical MINOR SURGERY

Single Puncture Laparoscopic Technique (Marco Pelosi, MD) (VCD)

Surgery of the Liver & Biliary Tract 3e: Selected Operative Procedures (L.H. BLUMGART, Y. FONG) (W.B. Saunders)

The Distal Splenorenal Shunt: Effective or Obsolete? (VIDEO JOURNAL OF GENERAL SURGERY) (Layton Fredrick Rikkers, M.D.) (VCD)
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<td>61</td>
<td>The Ileana Pull-through Operative Procedure of Ulcerative Colitis: Eliminating the Permanent Ileostomy</td>
<td>(Eric W. Fonkalseud, M.D.)</td>
<td>(VCD)</td>
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<td>42.15</td>
<td>The Massachusetts General Hospital Handbook of Pain Management (Second Edition)</td>
<td>(Jane Ballantyne, Scott M. Fishman, Salahadin Abdil)</td>
<td>(SALEKAN-E-book)</td>
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<td>44.15</td>
<td>TISSUE ADHESIVES In Wound Care</td>
<td>(James V. Quinn, M.D., FACEP)</td>
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<td>45.15</td>
<td>Video Journal General Surgery (VCD)</td>
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<td>46.15</td>
<td>Video Journal General Surgery (VCD)</td>
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### Additional Resources:

- **CD عللانا**
  - **1.16** Dental Implant System Fixed Implant Restorations (ITI Dental Implant System) (VCD)
  - **2.16** Esthetic Implant Dentistry (Daniel Buser, Hans Peter Hirt) (VCD)
  - **3.16** ESTHETICS IN DENTISTRY (Second Edition) PRINCIPLES COMMUNICATIONS TREATMENT METHODS
    - 1998
  - **4.16** Glossary of Orthodontic Terms (John Daskalogiannakis)
    - 1998
  - **5.16** Implant Medpor Mandibular A method to Restore Skeletal Support to the Lower Face (Oscar M. Ramirez M.D., F.A.C.S.) (POREX) (VCD)
    - 2000
  - **6.16** ITI TE Solution ITI TE Implant (DENTAL IMPLANT SYSTEM) (Daniel Buser) (Disk 1-3)
    - 2004
  - **7.16** LINGUAL ORTHODONTICS (Rafi Romano) (TO EXPLORE THE CD-ROM)
    - 1998
  - **8.16** Local Anesthesia in Dentistry (Dr. Markus D. W. Lipp Wolfgang Kelm) (VCD)
    - 2002
  - **9.16** PERIODONTAL MEDICINE (L.F. Rose, R.J.Genco, B.L. Mealey, D.W. Cohen)
    - 2003
  - **10.16** Saunders Dental Assisting (Multimedia Resource) (Second Edition) (Doni L. Bird, Debbie S. Robinson)
    - 2003
  - **11.16** The Center of Education, Teaching and Research for Oral Implant Reconstruction (Prof. Dr. Hns L. Grafelmann) (CD I, II)
    - 2002
  - **12.16** The Entegra Dental Implant System Entegra Surgical Videos (Robert Schroering)
    - 2002
  - **13.16** The IMZ Implant System (VCD) (Dr. Karl-Ludwig Ackermann, Dr. Axel Kirsch) (CD I, II)
    - 2002
  - **14.16** TOOTH-COLORED RESTORATIVES Ninth Edition (Principles and Techniques) (Harry F. Albers, DDS)
    - 2002
  - **15.16** Treatment Planning in Dentistry (Stephen Stefanac, D.D.S., M.S., Sam Nesbit, D.D.S., M.S.)
    - 2002

- **1.17** ANATOMY & PHYSIOLOGY (5th Edition) (Gary A. Thibodeau, Kevin T. Patton)
  - 2002
- **2.17** BODY WORKS 6.0 A 3D Journey Through The Human Anatomy
  - 2002
## Interactive Guide to Human Neuroanatomy

**Author:** Mark F. Bear, Barry W. Connors, Michael A. Paradiso

**Publication:** 2002

### Contents

- Surface Anatomy of Brain
- Cross-Sectional Anatomy of Brain
- The Spinal Cord
- The Anatomy Nervous System
- The Cranial Nerves
- The Blood Supply to the Brain

### Additional Information

- Exam I:
  - Surface Anatomy of the Brain
  - Cross-Sectional Anatomy of the Brain
  - Comprehensive Exam

## Interactive Physiology

**Author:** A. D. A. M. Benjamin/Cummings

**Publication:** (Marvin J. Branstrom, Ph.D.)

### Contents

- Anatomy Review: Skeletal Muscle Tissue
- The Neuromuscular Junction
- Sliding Filament Theory
- Muscle Metabolism
- Contraction of Motor Units
- Contraction of Whole Muscle

### Additional Information

- Cardiovascular System
  - The Heart
  - Blood Vessels
  - Anatomy Review: The Heart
  - Intrinsic Conduction System
  - Anatomy Review: Blood
  - Blood Pressure Regulation
  - Cardiac Action Potential
  - Vessel Structure and Function
  - Autoregulation and Capillary Dynamics
  - Cardiac Cycle
  - Measuring Blood Pressure
  - Cardiac Output
  - Factors that Affect Blood Pressure

## Interactive Physiology for Windows

**Author:** Andrea K. Salmi

**Publication:** (Eleventh Edition)

### Contents

- Anatomy Review: Respiratory Structures
- Pulmonary Ventilation
- Gas Exchange
- Gas Transport
- Control of Respiration

### Additional Information

- MedWorks Anatomy & Physiology
  - Overview Cells and Tissues
  - The Integumentary System
  - Body Chemistry
  - The Skeletal System
  - The Muscular System
  - The Nervous System
  - The Endocrine System
  - Cardiovascular System: The Blood
  - Cardiovascular System, The Heart
  - Lymphatic and Immune System
  - The Respiratory System
  - The Digestive System
  - The Urinary System
  - The Reproductive System

## Student Companion CD-ROM for Principles of Anatomy & Physiology

**Author:** Gary A. Thibodeau, Kevin T. Patton

**Publication:** (Tenth Edition)

### Contents

- Panorama of Anatomy & Physiology Structure & Function of the Body
- Measurement and Documentation
- The Interactive Skeleton Tutorial
- The Sensory Organs
- Somatic and Autonomic Systems
- The Peripheral Nervous Systems
- Inheritance
- The Central Nervous System
- The Reproductive System

### Additional Information

- World of SPORT examined

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مرکز فنیات فرهنگی شانگکن : ارائه کلیدهای کتاب و سریع‌های تخصصی گزینه

شناختی، انتقالات، در کارگری، پذیرش گزینه، پذیرش گزینه، پذیرش گزینه، پذیرش گزینه.
| 1.18 | The Oncology Nursing Society presents THE ADVANCED PRACTICE ONCOLOGY NURSING REVIEW |  
| 3.18 | Focus on Nursing Pharmacology (Lippincott Williams & Wilkins) | 2000 |
| 4.18 | Wongs ESSENTIALS OF Pediatric Nursing (Mosby) A Harcoun Health Sciences Company | 2001 |
| 5.18 | Maternal, Neonatal and Women's Health Nursing | By Delmar, a division of Thomson Learning | 2002 |
| 6.18 | Nursing Care of Infants and Children (Seven Edition) | 2003 |

| 2.18 | Textbook of MEDICAL SURGICAL NURSING (Ninth Edition) (Katherine H. Dimmock) Student Self Study Disk to Accompany BRUNNER & SUDDARTH'S Textbook of MEDICAL SURGICAL NURSING |  
| 7.18 | McMinn's Interactive Clinical Anatomy |  
| 8.18 | INRERACTVE ATLAS OF CLINICAL ANATOMY (Illustrations by Frank H. Netter, M.D.) |  

### CD 

- Family-Centered Care of the Newborn
- Family-Centered Care of the Adolescent
- Family-Centered Care of the Child with Special Needs
- The Child With a Problem that Interferes with Physical Mobility
- Childre, Their Families, and the Nurse
- Assessment of the Child and Family
- Family-Centered Care of the School-Age Child
- The Child who is Hospitalized
- The Child with Disturbance of Fluid and Electrolytes
- The Child with Problems Related to Transfer of Oxygen and Nutrients
- The Child with Problems Related to Production & Circulation of Blood
- The Child with Disturbance of Regulatory Mechanisms
- The Child who is Hospitalized
- Childre, Their Families, and the Nurse
- Assessment of the Child and Family
- Family-Centered Care of the School-Age Child
- The Child who is Hospitalized
- The Child with Disturbance of Fluid and Electrolytes
- The Child with Problems Related to Transfer of Oxygen and Nutrients
- The Child with Problems Related to Production & Circulation of Blood
- The Child with Disturbance of Regulatory Mechanisms
- The Child who is Hospitalized

### Fibromyalgia Syndrome Bodywork Management Strategies

**Assessment Methods**

- Manual Thermal Diagnosis
- Skin on Fascia Adherence
- Hypersensitive Skin Zones reduced Skin elasticity
- Drag palpation for increased hydrosis
- Neuro muscular Technique Evaluation (NMT)

**Fibromyalgia Syndrome Bodywork Management Strategies**

- Program Lifecycle Software Group: set up your software to run in your computer system Lifestyle software Group

**Set-Up:**

1. Run setup.exe on your computer.
2. Follow the on-screen instructions.
3. Select the language you want to use.
4. Choose the location where you want to install the software.
5. Click "Next" to start the installation.
6. Follow the instructions on the screen to complete the installation.
7. Click "Finish" to exit the setup program.

**Additional Information:**

- The installation will take some time to complete.
- You may need to restart your computer after the installation.
- If you encounter any problems during the installation, contact the software support team.

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**Digital Shiatsu**

- program installer install.exe contains the executable file for the software.
- place the installer file on your desktop and click the setup icon to start the installation.
- Follow the on-screen instructions to complete the installation.
- Click the finish button to complete the installation.
- The software will be installed on your computer.

**Digital Shiatsu**

- therapist can use the software to perform digital shiatsu on their patients.
- the software is easy to use and provides a wide range of features.
- the software is compatible with Windows operating systems.

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**Jurassic Park Entertainment**

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- The software is free to download.
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- The software is compatible with Windows operating systems.
- The software is free to download.
- The software is easy to use and provides a wide range of features.
Fundamentale of Sensation ad Perception (3rd Edition) (M.W. Levine)

### 3.19 Introduction and instructions
- Threshold experiment or Signal Detection
- Specializations of the Vertebrate eye
- Retinal Cells responding to light
- Brain anatomy, Blink Suppression, or Cortical Cell responses
- Cortical columns or Equiluminant demos
- Demonstrations of Fourier components
- Depth from motion of random dots
- Optical Illusions and Constancies
- Motion demonstrations
- Color mixing or Opponent cells
- Pitch and Loudness of tones
- Speech sounds of Mystery phrase
- Muscle spindles feedback
- Motions from form of Impossible figures
- Mechanics of the middle and inner ear
- Taste-influenced by vision

Health & Fitness (DataSel Software, Inc)

#### 4.19
- Getting Started
- The Exercise Demonstration Screen
- Strength
- Stretch
- Equipment
- Muscles
- Workouts
- Setup
- Technical Support

Manipulation of the Spine, Thorax and Pelvis

- An Osteopathic Perspective
- HVLA thrust techniques-spine and thorax
  - Cervical and cervicothoracic spine
  - Thoracic spine and rib cage
  - Lumbar and thora Columbar spine
- HVLA thrust techniques-pelvis

Massage Therapy Review (Interactive Edition) (Mosby)

#### 6.19
- Cervical and cervicothoracic spine
- Thoracic spine and rib cage
- Lumbar and thora Columbar spine

Muscle Energy Techniques (Second Edition)

#### 7.19
- HVLA thrust techniques
- Cervical and cervicothoracic spine
- Thoracic spine and rib cage
- Lumbar and thora Columbar spine

Palpation Skills for Muscles and Joints

#### 8.19
- HVLA thrust techniques
- Cervical and cervicothoracic spine
- Thoracic spine and rib cage
- Lumbar and thora Columbar spine

Physical Education and the Study of Sport (Bob Davis, Ros Bull, Jan Roscoe, Dennis Roscoe) (Mosby)

#### 9.19
- Physical Education and the Study of Sport
- Synoptic Questions Harcourt Health Sciences
- The Project Personal Performance Profile

Positional Release Techniques

#### 10.19
- HVLA thrust techniques
- Cervical and cervicothoracic spine
- Thoracic spine and rib cage
- Lumbar and thora Columbar spine

Power Touch

#### 11.19
- Spontaneous Positional release variations
- The evolution of dysfunction
- Unloading and Proprioceptive taping
- Modified strain/counterstrain technique
- Learning SCS
- SCS for muscle pain (plus INTT and self-treatment)
- Goodheart and Morrison’s Positional release variations and lift techniques
- SCS (and SCS variations) in hospital settings
- The Mulligan concept: NAGs, SNAGs, MMWs, etc.
- Functional technique
- Facilitated Positional release (FPR)
- Cranial and TMJ Positional release methods
| 12.19 | Surface and Living Anatomy (Gordon Joslin SOtJ) | 2002 |
| 13.19 | The Complete Acupuncture | |
| 14.19 | The Principles of Harmonic Techniques (Eyal Lederman) (VCD) | |
| 15.19 | YOGA for YOU (Anatomy) | |

| 1.20 | Advanced Pediatric Life Support: The Critical First Hour CPR and ACLS Review (David G. Nichols, MD) | |
| 2.20 | ANESTHESIA (Ronald D. Miller, MD) (Fifth Edition) | 2000 |
| 5.20 | Emergency Medical Training (MedEMT) Victory Technology, Inc. Presents (DISC ONE, TWO) | |
| 7.20 | Peripheral Regional Anaesthesia Tutorial in the Ulm Rehabilitation hospital (Prof. Dr. Med. M. Mehrkens) (VCD) (CD I, II) | |
| 8.20 | The American Academy of Pediatric (David G. Nichols, MD Associate Professor of Anesthesiology and Clinical Care Medicine) | |
| 9.20 | The Lipponcott-Raven Interactive Anesthesia Library on CD-ROM (Version 2.0) (Paul G. Barash, MD) | |
| 10.20 | The Massachusetts General Hospital Handbook of Pain Management (Salekan E-Book) | |
| 48.9 | New Analgesic Options: Overcoming Obstacles to Pain Relief | 2002 |

**CD**

من کامل آناتومی سطحی قسمت‌های مختلف بدن وجود دارد و پیاپادند. 224 منطقه آناتومی را مرحله به مرحله توضیح می‌دهد. در کتاب هر یک از منطقه‌های مختلف عکس‌های زیبا و چشم‌گیر وجود دارند که به وسیله مراکز‌های مختلف در این مرحله رونمایی می‌شود.

În tehnica gândirii, predominăocuparea cu următoarele categorii de informații:
- Dimensiuni fizice: mărimea, greutate, lungime, etc.
- Costumul: tricouri, pantaloni, etc.
- Obiectiva: modul în care s-a dat utilitate unei idei sau a unor informații.
- Interessența: cunoștințe sau interes pentru o anumită subiect.
- Profesionalitate: cunoștințe sau experiență într-un anumit domeniu.

În concluzie, în literatura disponibilă, există mai multe studii care susțin că tehnica gândirii, în special tehnica gândirii figurative, poate avea o influență semnificativă asupra performanței și calității comunicării.
Adult and Pediatric Urology (Jay Y. Gillenwater, John T. Grayhack, Stuart S. Howards, Michael E. Mitchell) 2002

Advanced Therapy of Prostate Disease (Martin I. Resnick, MD, Ian M. Thompson, MD) 2000

Atlas of RENAL TRANSPLANTATION (Prof. Legendre, Martin, Helenon, Lebranchu, Halloran, Nochy) ___

AUA Vide Digest The American Urogical association (AUA) Impotence and Infertility ___

BLADDER BIOPSY INTERPRETATIONS (Jonathan I. Epstein, M.D., Mahul B. Amin, M.D., Victor E. Reuter, M.D.) (CD I, II) (SALEKAN E-BOOK) 2004

Bristol Urological Institute (Computer Aided Learning Program) ___
Core Curriculum in Primary Care Patient Evaluation for Non-Cardiac Surgery and Gynecology and Urology (Michael K. Rees, MD, MPH)

- 1. How to eradicate Renal mass/Tumor
- 2. Drugs vs Diet in Modifying Renal failure
- 3. Treatment of Hypertension-Special Case
- 4. Clinical Application of Renal Physiology

Core Curriculum in Primary Care Nephrology (Michael K. Rees, MD, MPH)

- 1. How to eradicate Renal mass/Tumor
- 2. Drugs vs Diet in Modifying Renal failure
- 3. Treatment of Hypertension-Special Case
- 4. Clinical Application of Renal Physiology

Core Curriculum in Primary Care Gynecology (Michael, Isaac Schiff, Keith, Thomas, Annekathryn)

- 1. How to eradicate Renal mass/Tumor
- 2. Drugs vs Diet in Modifying Renal failure
- 3. Treatment of Hypertension-Special Case
- 4. Clinical Application of Renal Physiology

Hot Topics in UROLOGY (Roger S Kirby, Michael P O’Leary) (SALEKAN E-BOOK)
11.21 PRIMER ON KIDNEY DISEASES (Second Edition) (NATIONAL KINDEY FOUNDATION SCIENTIFIC ADVISORY BOARD)


13.21 Urogynecology: Evaluation and Treatment of Urinary Incontinence (Bruce Rosenzweig, MD, Jeffrey S. Levy, MD, Donald R. Ostergard, MD)

Consideration for the OB/GYN Generalist → won surgical & surgical Management → Evaluation → Introduction & Defining Incontinence (1)

Types of incontinence • incontinence awareness

Patient misconceptions • affected women • incontinence • post void residual • voiding diary • Cystoscopy • uroflowmetry • behavioral modification • Multi-Channel urodynamics • Pessary test • Complication

Urogynecology as a subspecialty

Complication: Consideration for the OB/GYN Generalist (4) • incontinence • uroflowmetry • urological survey • device cost • setup requirement • professional consideration

CD I: - Clinical Urology - Pediatric Urology - Investigative Urology - Urological Survey

CD II: - Clinical Urology - Pediatric Urology - Investigative Urology - Urological Survey - CME Participant Assessment Test and Course Evaluation

CD I, II: - Clinical Urology - Pediatric Urology - Investigative Urology - Urological Survey - CME Participant Assessment Test and Course Evaluation

- Clinical Urology - Pediatric Urology - Investigative Urology - Urological Survey - CME Participant Assessment Test and Course Evaluation
طريقة مشاهده فیلم های VCD توسط کامپیوتر:

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<td>1. Pediatric Radiology (The Requestions) (Hans Blickman)</td>
<td>نقش جلدی</td>
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<tr>
<td>2. Differential Diagnosis in Conventional Gastrointestinal Radiology (Francis A. Burgener, Marti Konnano)</td>
<td>نقش جلدی</td>
<td>240,000</td>
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<tr>
<td>3. DUKE Radiology Case Review (James M. Provenzale Rendon C. Nelson)</td>
<td>نقش جلدی</td>
<td>300,000</td>
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<tr>
<td>5. Primary Care Radiology (Mettker, Guibert EAU. VO.SS', URBINA)</td>
<td>نقش جلدی</td>
<td>250,000</td>
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<tr>
<td>6. A-Z of Orthopaedic Radiology (Sarah Burnett, Andrew Taylor, Martin Watson)</td>
<td>نقش جلدی</td>
<td>200,000</td>
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<tr>
<td>7. FUNDAMENTALS OF Uroradiology (Williamson, Smith)</td>
<td>نقش جلدی</td>
<td>180,000</td>
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<tr>
<td>8. Textbook of Uroradiology (N. Reed Dunnick, MD, Carl M. Sandler, Md, Jeffrey H. Newhouse, MD, Estephen Amis’, JR., MD)</td>
<td>نقش جلدی</td>
<td>400,000</td>
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<tr>
<td>9. Head and Neck Radiology a Teaching File (Anthony a Mancusd, Hiroya Ojiri, Ronald G. Quisling)(Lippincott Williams &amp; Wilkins)</td>
<td>نقش جلدی</td>
<td>400,000</td>
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| 25. Gastrointestinal Radiology  
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**CT**

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81. Atlas of Musculoskeletal Imaging (Thomas Lee Pope, Jr. Stephen Loehr)(Thieme)

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84. Atlas of Musculoskeletal Imaging

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Aids Imaging

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Modern Head and Neck Imaging

Variants and Pitfalls in Body Imaging

Diagnostic Imaging Brain

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The Radiologic Clinics of North America

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Imaging of the newborn, infant, and young child
(LEONARD E. SWISCHUK, M. D.)
(FIFTH EDITION) (2004)

Borderlands of Normal and Early Pathological Finding in Skeletal Radiography
(Fifth revised edition)
(Juergen Freyschmidt, Joachim Brossmann, Juergen Wiens, Andreas Sternberg)
(Thieme)

Clinical Imaging
(Ronald L. Eisenberg, Amelia County)
(an atlas of differential diagnosis)
(Lippincott Williams & Wilkins)

این کتاب شامل مباحثی در مورد تشخیص‌های افتراقی مربوط به نماهای گوناگون رادیولوژی و تصویربرداری می‌باشد و در مورد تشخیص‌های افتراقی مختلف مربوط به هر نماهای رادیولوژیک (عنوان) توصیف شده است. این کتاب نمونه‌ای شامل تشخیص‌های افتراقی مربوط به نماهای رادیولوژی و تصویربرداری یک دسته موضوعاتی (درباره multiple Pulmonary nodules مثال) در نمایش گذاشت. در نگاه‌گیری‌های مختلف تشخیص‌های افتراقی مربوط به نماهای رادیولوژی و تصویربرداری کل یک بهره و کتاب‌های مختلف Imaging، Plain film و ... در انجام نمایش شده است.

فهرست کلی مربوط به فصول مختلف این کتاب به شرح ذیل می‌باشد:

| 1 | گره‌های رادیولوژیک گردش | Chest |
| 2 | گره‌های رادیولوژیک قلب و عروق |
| 3 | گره‌های رادیولوژیک گردن | Gastrointestinal |
| 4 | گره‌های رادیولوژیک بیماری‌های و مامو‌گرافی | Genitourinary |
| 5 | گره‌های رادیولوژیک سونوگرافی | |
| 6 | گره‌های رادیولوژیک سونوگرافی ستون فقرات |
| 7 | گره‌های رادیولوژیک و عروق |

همچنین به میزان افزایش و کاهش باعث می‌شود تا در تماشای و سریع‌تر استفاده از این کتاب بسیار مؤثر شود.

مشابه در مورد هر گونه چشم‌پوشی که دارد، در انتخاب هر چیز، فهرست کدکار و پژوهش در انتخاب با نشان‌های رادیولوژیک مربوط به میحت مذکر آورده شده است که در تسهیل و تسهیل استفاده از این کتاب بسیار مؤثر خواهد بود.

مطالعه این کتاب از شرکت در امتحانات بر در تخصص رادیولوژی و همچنین کار عملی در مؤسسات رادیولوژی بسیار مفید خواهد بود.

فهرست کلی مربوط به فصول مختلف این کتاب به شرح ذیل می‌باشد:
Atlas Of Normal Roentgen Variants that may Simulate Disease (Mosby Inc.) (2001) (Seventh Edition)

Theodore E. Keats M.D., Mark W. Anderson M.d.

Chair, Radiology Department, London, Ontario, Canada

Over diagnosis of normal roentgen variants that may simulate disease is a common problem in radiology. This text is designed to help radiologists avoid over diagnosis by presenting normal roentgen variants that may simulate disease.

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Ingolf P. Arlt, Ph.D., M.D.

Professor of Radiology and Director, Ophthalmic Radiology, University of Leuven, Belgium

Magnetic resonance angiography (MRA) is a non-invasive imaging technique that uses magnetic resonance imaging (MRI) to visualize blood vessels. MRA is used to visualize the brain, heart, and other blood vessels to diagnose and treat various medical conditions.

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John R. Haaga, MD, FACR
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Note: The above table is a simplified representation of the imaging modalities used in CT and MR imaging. The actual number of modalities and their specific applications may vary depending on the specific needs and conditions being examined.
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**Section 1: MRI and CT Scan of Head and Spine**

(C. Barrie Grossman, M.D., Indiana University)

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HIGHLIGHTS OF OPHTHALMOLOGY INTERNATIONAL

WAVEFRONT ANALYSIS, ABERROMETERS and CORNEAL TOPOGRAPHY

B. BYOD, A. AGARWAL (2003) 1100,000R

گرچه هنوز هم در بیماری از نقاط کشورمان امکان عمل جراحی کاتاراکت حتی به روشهای نسبتاً قدیمی نیز وجود نداشت، عدسی‌های زیادی به پاس خدمات دائمی، مورگانی نام می‌گیرد. (Morgagnian Cataract) است. در سال‌های اخیر با ورود تکنیکs، افق تازه‌ای به نام Customized LASIK پیداگشته است. سپس بسیار سریع این پیشرفت باعث شده که کتاب کاربود، لازم به ذکر است که در کتاب پژوهش‌هایی مربوط به ورود برتری‌های جدید، زیادی از طراحی‌های جدید در هنوز در حال در حال به‌کارگیری است.

WAVEFRONT ANALYSIS, ABERROMETERS and CORNEAL TOPOGRAPHY

آرایش گردیده، پاسخی است در جهت فروشنندگان علی‌الخصوص این زمینه. این کتاب با عنوان "Super Vision"، "Wavefront Analysis, Orbscan, Topography" و "Highlights Of Ophthalmology" کتاب‌هایی از امیدی است که تکنیک‌شناسی شده‌اند که ممکن است به دوره‌های تخصصی و کاربردی کتاب در آن جهت انتشار آن در خارج از کشور تهیه بر روی کاغذ، در کتاب کتاب‌ها، آنگاهی که در سایر WAVEFRONT ANALYSIS, ABERROMETERS and CORNEAL TOPOGRAPHY و دسترسی به صورت تمام رنگی بر روی کاغذ، کتاب‌های جدیدی در این زمینه به‌کارگیری خواهد گرفت.

Cataract Surgery, Customized LASIK, Standard LASIK

تویستگان این کتاب استاندارد برجسته‌ای از کشورهای آمریکا، آسیا، اروپا و هند و هند را تهیه که به سرپرستی Benjamin F. Boyd, M.D., FACS جامعه‌های جهانی چشم‌پزشکان آن‌ها کرده‌اند.

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