Cerebellar Ataxia and Central Nervous System Whipple Disease

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Background: Whipple disease (WD) is an infectious disease, which may affect the central nervous system. Central nervous system symptoms are eventually present in as many as 43% of the cases. To our knowledge, cerebellar ataxia in WD has never been formally studied in any large series.

Objective: To determine the prevalence of cerebellar ataxia in central nervous system WD.

Results: Between January 1974 and December 2003, we identified 11 patients who met criteria for definite central nervous system WD, the second largest series to date. Surprisingly, while oculomasticatory myorrhythmia was recorded in only 1 patient (9%), cerebellar ataxia had been documented in 5 cases (45%).

Conclusion: Our data suggest that cerebellar ataxia should be considered a more common feature of central nervous system WD.

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Whipple disease (WD) was first described by George H. Whipple in 1907 as “intestinal lipodystrophy” because of the lipid-laden histological appearance of the small bowel in a 36-year-old physician who had experienced 5 years of chronic gastrointestinal tract and constitutional symptoms.1 More than 50 years after the initial case description, the novel bacillus, Tropheryma whipplei, was identified as the causative agent.2,3 Clinically, the classic symptoms of WD include diarrhea, weight loss, and abdominal pain.4 Beyond these symptoms, central nervous system (CNS) involvement has been recognized in 6% to 43% of the reported cases.5-8 However, cases with asymptomatic CNS involvement have been identified post mortem,7 leading some researchers to postulate that all patients with WD have CNS involvement even in the absence of clinical, laboratory, or radiologic evidence.9 Isolated CNS involvement at the initial examination may occur in less than 5% of the cases,10 and WD may have no classic bowel involvement in up to 15% of the cases.11

Common signs and symptoms reported in case series of CNS WD include supranuclear ophthalmoplegia, memory loss, sleep disturbances, and movement disorders.3,7,12,14 From a clinico-anatomical standpoint, these signs and symptoms in CNS WD suggest functional or structural involvement of the brainstem, hippocampus, hypothalamus, and basal ganglia. However, there has not been any series that has specifically assessed cerebellar ataxia (CA) in WD.

METHOD

We identified and generated a list of all cases of WD seen at the Mayo Clinic, Rochester, Minn, between January 1974 and December 2003 using our electronic medical record review system. More than 100 cases were identified, and the medical records reviewed to determine who had CNS disease and had also been evaluated by at least 1 neurologist. Only patients who met diagnostic criteria for definite CNS WD1 were included in this study. Definite CNS WD was diagnosed if the patient had 1 of the following criteria: oculomasticatory myorrhythmia (OMM); CNS symptoms and/or signs and a positive tissue biopsy specimen; or CNS symptoms and/or signs and a positive result on polymerase chain reaction analysis. Neurological signs and symptoms were tabulated based on the dictated descriptions of the examiners, as well as abnormalities recorded on the standardized Neurological Examination Record. Ataxia, any disturbance in smooth performance of voluntary motor acts, was defined for review purposes by use of the word “ataxia” or “ataxic” in the neurological examination record and by pertinent recorded abnormalities in finger-to-nose-to-finger, heel-to-shin, gait, speech, and/or alternating motion and rate.

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RESULTS

DEMOGRAPHICS

All pertinent patient demographics for the 11 patients who met these criteria are summarized in Table 1. Nine (82%) of the 11 patients were male. The mean age of onset of WD symptoms was 49 years (age range, 28-64 years); mean age of CNS symptom onset was 55 years (age range, 38-73 years). Only 3 patients (Nos. 5, 8, and 9 [27%]) had CNS symptoms at the initial visit. The mean number of years from disease onset to the development of CNS symptoms was 6.3 years (range, 0-16 years).

Each patient was examined by a general neurologist. One patient (No. 9) was subsequently referred to a movement disorders subspecialty clinic.

ATAXIA

The frequencies and descriptions of cerebellar dysfunction are summarized in Table 1. Ataxia was reported in the neurological examination of 6 patients (55%). Of these, 5 had features consistent with CA. Patients 2 and 4 were described as having an ataxic gait, with patient 2 actually having pancerebellar ataxia, with ataxic gait, and dysmetric finger-to-nose-to-finger and heel-to-shin testing. Patient 3 had ataxia on finger-to-nose-to-finger testing. Patient 6 had dysmetric heel-to-shin maneuver, and patient 7 was noted to have “irregular” alternating motion and rate and “mild limb ataxia,” in addition to deficits in tandem walking. Patient 5 was only described as having an ataxic gait; however, no specific cerebellar feature was described.

OTHER NEUROLOGICAL FINDINGS

The frequency of specific neurological symptoms and signs are detailed in Table 2. Memory loss was the most common report and finding, occurring in 7 patients while hypothalamic dysfunction occurred in 5, being manifest as hyperpersomnolence, insomnia, hypothermia, and weight gain or weight loss. Involuntary chewing movements were present in 1 patient (No. 7), while only 1 patient displayed OMM (No. 11). The most common systemic reports in these patients included fever, diarrhea, and arthritis and arthralgias.

TREATMENT AND RESPONSE

Almost all patients in our series received intravenous ceftriaxone sodium, 2 g, twice daily for 2 weeks, followed by oral trimethoprim-sulfamethoxazole, double strength, 1 tablet twice daily, for from 1 year to an indefinite duration. In general, patients had significant improvement of their neurological impairment in cases with documented follow-up.
Movement disorders had been described as early as 1963.16 However, OMM occurred in only 9% of the patients. The high prevalence of CA in this series is important, and when present on neurological examination together with gastrointestinal tract symptoms, arthritis and arthralgias, and fever of unknown origin, CNS WD should be considered in the differential diagnosis.

Table 2. Frequency of Neurological Signs and Symptoms

<table>
<thead>
<tr>
<th>Neurological Signs and Symptoms</th>
<th>No. of Patients With Sign or Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic memory loss</td>
<td>7</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6</td>
</tr>
<tr>
<td>Corticospinal tract signs (spasticity or hyperreflexia)</td>
<td>4</td>
</tr>
<tr>
<td>Visual complaints (blurred or diplopic)</td>
<td>4</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>4</td>
</tr>
<tr>
<td>Supranuclear gaze palsy (vertical and/or horizontal)</td>
<td>3</td>
</tr>
<tr>
<td>Hallucinations (visual or olfactory)</td>
<td>3</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>2</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>1</td>
</tr>
<tr>
<td>Dystonia</td>
<td>1</td>
</tr>
<tr>
<td>Involuntary chewing movements</td>
<td>1</td>
</tr>
<tr>
<td>Oculomasticatory myorrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>1</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>1</td>
</tr>
<tr>
<td>Myopathy (muscle biopsy specimen positive)</td>
<td>1</td>
</tr>
<tr>
<td>Proximal extremity weakness (muscle biopsy specimen negative)</td>
<td>1</td>
</tr>
<tr>
<td>Behavioral dyscontrol</td>
<td>1</td>
</tr>
</tbody>
</table>

Based on our review, CNS WD is uncommon. More than 100 cases treated at the Mayo Clinic had well-documented WD, yet only about 10% had CNS manifestations. No patients had pure CNS symptoms before being diagnosed with WD, suggesting that WD is an unlikely diagnosis for CNS syndromes manifesting in patients without gastrointestinal tract or other systemic symptoms.

The high prevalence of CA in this series is important, as prior reviews have reported a prevalence of only 10% to 20%, similar to the frequency of OMM.5,7 In our series, however, OMM occurred in only 9% of the patients. The difference in prevalence between our series and others may be because we limited our cases to patients having a diagnosis of definite CNS WD. Also, OMM was not reported to be specific to WD until 1986,13 although such movement disorders had been described as early as 1963.16

The use of intravenous ceftriaxone therapy followed by oral trimethoprim-sulfamethoxazole treatment resulted in significant improvement in our patients. Therefore, we recommend this combination treatment in patients with CNS WD.

This series and those reported previously have been small, making it difficult to draw firm conclusions. However, therapy for WD is available, and WD is fatal if untreated17; thus, it is invaluable to recognize common manifesting signs and symptoms. As such, this study dem-

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Additional Information: Case 3 may have been reported with a prior Mayo Clinic series.

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REFERENCES