Rabies Encephalomyelitis

Clinical, Neuroradiological, and Pathological Findings in 4 Transplant Recipients

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Background: Three patients received solid organ transplants from a common donor and were subsequently discharged from the hospital following an uneventful hospital course. Within 30 days, all 3 organ recipients returned to the hospital with varying symptoms that progressed to rapid neurological deterioration, coma, and death.

Objective: To describe the clinical, neuroradiological, and pathological findings of rabies virus infection in organ transplant recipients infected from a common donor.

Design: Case series involving a common donor and 3 organ recipients ascertained through review of clinical course and autopsy findings. A fourth case was determined by review of pending autopsy cases in which death occurred within the same time interval. Portions of postmortem central nervous system and organ tissues were frozen and formalin-fixed. Fluids and tissues were also collected for cultures, serology, and molecular studies. Postmortem fluids and tissues and antemortem fluids and tissues from all 4 transplant recipients and serum and banked lymphocyte or spleen cells from the donors were sent to the Centers for Disease Control and Prevention for further evaluation.

Setting: Transplant unit of an urban teaching hospital.

Results: Antemortem cerebrospinal fluid analysis for 3 of the 4 recipients was consistent with a viral etiology. Neuroimaging and electroencephalogram studies were suggestive of an infectious encephalitis or a toxic encephalopathy. Initial laboratory testing did not demonstrate an infectious etiology. Postmortem histologic analysis, immunohistochemistry, electron microscopy, and direct fluorescence antibody testing revealed rabies virus infection. Serological testing done postmortem confirmed rabies virus infection in the common donor.

Conclusions: These cases demonstrate a risk for transmitting rabies virus infection through solid organ and tissue transplantation, and this diagnosis should be considered in any rapidly progressing neurological disease.

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Rabies is one of the most feared diseases in human history, with reports of recognizable cases dating back to the 23rd century BC. Rabies is a zoonosis that can affect both wild and domesticated animals. Although many mammals may become infected, the prevalence of infection varies considerably from continent to continent. Increasingly, bats have been recognized as an important reservoir. Transmission in humans occurs primarily through the bite of an infected animal; in the United States, it most commonly comes from bats.1-3 Human-to-human transmission of rabies has been described.4 There have been 8 documented cases of rabies transmission through corneal transplants, of which 1 occurred in the United States.5-7 There have been no previously reported cases of rabies transmission through solid organ transplantation. Although human rabies cases in the United States are rare, the incidence is probably underestimated owing to the absence of a known animal exposure, lack of clinical suspicion, difficulty in making an antemortem diagnosis, and decreasing autopsy numbers.8 This report describes 4 cases in which transmission of the rabies virus occurred through solid organ transplantation and a vascular allograft. Postmortem examination permitted the diagnosis of transplant-associated rabies infection. Summaries of these cases have been previously reported by the Centers for Disease Control and Prevention (Atlanta, Ga).9-11

For editorial comment see page 855
METHODS

The donor case and first 3 organ recipient cases were discovered through contact with physicians of the transplant team, medical record review, and review of laboratory and imaging data and autopsy findings. A fourth case was determined by a review of pending transplant recipient autopsies that occurred within the same time interval. The transplant recipients developed an encephalopathy that progressed to coma and death and underwent a full postmortem examination. The donor did not undergo postmortem examination. Postmortem central nervous system (CNS) and organ tissues were frozen (−70°C) and formalin-fixed for 1 to 7 days. Tissue for histologic analysis was routinely processed, sectioned, and stained with hematoxylin-eosin. Various postmortem fluids and cerebrospinal fluid (CSF) and antemortem blood and CSF were held for further analysis. Postmortem cultures, serology, and molecular studies were conducted on site. Postmortem formalin-fixed tissues and paraffin-embedded tissues from all 4 patients, frozen CNS and organ tissue from 3 of the 4 patients, postmortem fluids and antemortem fluids from all 4 recipients, and serum and banked lymphocyte or spleen cells from the donors were sent to the Centers for Disease Control and Prevention for further evaluation.

RESULTS

Two males and 2 females, aged 18 to 55 years, received organs or vascular tissue from a common donor who developed rapid neurological deterioration and died with clinically unsuspected rabies infection. The lungs, kidneys, liver, and vascular allograft were harvested for transplantation after donor screening. The lungs were transplanted into a man who died at the time of operation of surgical complications. The 2 kidneys, the liver, and a vascular allograft were successfully transplanted into 4 recipients. All 4 transplant recipients developed rapidly progressive neurological disease and died within 48 days following transplantation.

Table 1 summarizes the demographic characteristics, immunosuppressant therapy, symptoms, and selected clinical laboratory findings for the donor and the 4 transplant recipients.

DONOR

The donor had twice visited an emergency department in the preceding 24 hours with complaints of nausea, vomiting, and abdominal pain. He then visited a different emergency department with worsening abdominal pain, nausea, hematemesis, throat pain, and intermittent periods of confusion and agitation and was noted to have ballistic movement of his trunk. When he first arrived, his vital signs were stable; however, within 6 hours he developed tachycardia and hypertension. Because of his agitation and inability to cooperate, he was sedated and intubated before technicians performed a computed tomography (CT) scan of the head that revealed a small subarachnoid hemorrhage (SAH). Over the next 8 hours, he became increasingly agitated (pulling at his restraints, biting the endotracheal tube, and attempting to self-extubate). He was admitted to the intensive care unit for acute cocaine-induced SAH, hypertensive crisis, and rhabdomyolysis (creatinine kinase, 8061 U/L). During the physical examination, his temperature was mildly elevated at 100.5° (oral), his pupils were equal and reactive, his neck was supple, his heart examination result was significant for tachycardia with a regular to irregular rhythm, and his breath sounds were significant for faint crackles and rales that cleared with suctioning. A repeat creatinine kinase level was 3404 U/L; creatinine kinase-MB fraction, 7.9%; and MB index, 0.2. A second troponin I level was 0.44 ng/mL (the initial troponin I level was within normal limits). He was weaned from the ventilator and extubated and continued to have episodes of coughing, retching, and vomiting. He developed generalized tonic-clonic seizures and was reintubated. He remained hypertensive (blood pressure, 199/110 mm Hg) and tachycardic (pulse, 187), and he was diaphoretic and febrile (101.8°). A third troponin I level was 3.61 ng/mL. He continued to have seizure activity, biting his endotracheal tube and tongue, and self-extubated. He soon became apneic and hypotensive and was reintubated. His seizure activity continued and his temperature increased to 106.5°. A neurology consult was obtained at which time he was noted to have absent motor and sensory responses, fixed dilated pupils, and decreased tone and flexor plantar responses. A repeat CT scan was now significant for a large SAH and evidence of herniation. Oculocephalic, gag, and cough reflexes were now absent. An electroencephalogram showed only muscle activity from agonal breaths. A perfusion study was negative for cerebral blood flow, and he was declared brain dead 92 hours after he arrived at the emergency department. Permission was granted for organ donation, and his lungs, kidneys, liver, and iliac vessels were harvested the following day.

TRANSPLANT RECIPIENTS

The 3 solid organ recipients were transplanted on the same day, and the vessel allograft was used for hepatic artery reconstruction in another liver-transplant recipient the following day. The 3 solid organ recipients were all discharged home following transplantation. By the 27th day following transplantation, the 3 organ recipients had been readmitted to the hospital with complex symptoms (Table 2) that rapidly progressed to coma and death. Patient 1 was the first to arrive (day 21) with symptoms of sleep deprivation, tremors, decreased appetite, and abdominal and back pain. Patient 2 was previously admitted 19 days posttransplantation with hydronephrosis and mild acute cellular rejection and was discharged with a nephrostomy tube in place. She was readmitted on posttransplantation day 27 with myalgia, worsening abdominal pain, right flank pain, and itching. She underwent an appendectomy for suspected appendicitis. Patient 3 was admitted to an outside hospital on posttransplantation day 27 with acute delirium, myoclonus, myalgia, and diaphoresis. A urine toxicology screen at the outside hospital was positive for methamphetamine. He was transferred...
to our hospital the same day and later underwent a transplant nephrectomy for a failed graft. The artery allograft recipient's hospital course was complicated by wound dehiscence, abdominal abscesses, and hepatic artery stenosis, necessitating 2 additional returns to the operating room. On posttransplant day 26, she developed mental status changes and suicidal ideations.

All 4 recipients had rapid neurological deterioration with episodic periods of agitation, restlessness, delirium, and hallucinations. Three of the 4 patients had tremors or myoclonus (patients 1, 3, and 4) and 2 had seizures (patients 2 and 4). All 4 recipients developed respiratory failure requiring intubation, fever, excessive oral secretions, cardiac rhythm disturbances (2 patients required temporary pacemaker placement), hypotension, paralysis, coma, and progressive absence of brainstem reflexes and died within 7 to 23 days (median, 11.5 days) of the onset of neurological symptoms.

### Table 1. Characteristics of Donor and Transplant Recipients

<table>
<thead>
<tr>
<th>Patient/Sex/ Age, y</th>
<th>Transplant Type/Time to Readmission After Transplantation, d</th>
<th>Immunosuppressant Therapy</th>
<th>Symptoms and Duration</th>
<th>Elevated Immunosuppressant Levels (Reference Range)</th>
<th>CSF Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor/M/20</td>
<td>None</td>
<td>None</td>
<td>Nausea, vomiting, abdominal pain, throat pain for 2 d and hematemesis, mild confusion for 1 d</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patient 1/M/53</td>
<td>Liver/21</td>
<td>Tacrolimus, mycophenolate mofetil, prednisone</td>
<td>Loss of appetite, insomnia/sleep deprivation, tremors, anxiety, abdominal/back pain (indeterminate duration)</td>
<td>None</td>
<td>Posttransplant day 22</td>
</tr>
<tr>
<td>Patient 2/F/50</td>
<td>Kidney/27</td>
<td>CyA, sirolimus, prednisone</td>
<td>Diarrhea, abdominal pain and fullness, right flank pain, urinary urgency and frequency, low-grade fever (99.3°F) 10 d prior to current admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3/M/18</td>
<td>Kidney/27</td>
<td>Tacrolimus, mycophenolate mofetil, prednisone</td>
<td>Nausea, vomiting for 3 d</td>
<td>Posttransplant day 29</td>
<td></td>
</tr>
<tr>
<td>Patient 4/F/55</td>
<td>Iliac vessel conduit/27</td>
<td>Tacrolimus, mycophenolate mofetil, prednisone</td>
<td>Indeterminate</td>
<td>Posttransplant day 8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; CyA, cyclosporine A; RBC, red blood cells; WBC, white blood cells.
Laboratory Evaluation

Cerebrospinal fluid analysis was performed for patients 1, 3, and 4. All had increased nucleated cells (mean, 13; range, 7-32). 2 had increased protein (69 mg/dL and 227 mg/dL), and all had normal glucose levels (mean, 3.49 mmol/L [63 mg/dL]; range, 3.28-3.49 mmol/L [59-63 mg/dL]). Repeat CSF analysis was done on 2 of the recipients (patients 3 and 4), and the number of nucleated cells and protein levels increased. Viral culture results (CSF) were negative in all 3 recipients (Table 1). Aebovirus test results (West Nile, St Louis encephalitis, and dengue viruses) were negative in patients 1, 2, and 3. A West Nile virus IgG antibody test result was positive, and an IgM antibody test result was indeterminate in patient 4, results confirmed by the Texas Department of Health. Test results for cytomegalovirus infection by reverse-transcriptase polymerase chain reaction for all 4 recipients; herpes simplex virus test results for patients 1, 3, and 4; and the human herpesvirus-6 test result for patient 4 were negative. Immunosuppressant therapy was increased in patients 2 and 4 (Table 1), requiring dosage adjustments.

Neuroimaging and Electroencephalogram Evaluation

Cranial magnetic resonance imaging (MRI) and CT examinations were performed on all 4 transplant recipients. Routine protocol MRI brain studies were performed to include fluid-attenuated inversion recovery and diffusion weighted acquisitions.
The MRI result was significant for increased fluid-attenuated inversion recovery signal in the periventricular white matter (patient 2), leptomeninges (patients 1 and 3), medial temporal lobes (patients 1 and 3), inferior frontal lobes (patient 1), subinsular cortex (patient 4), precentral gyrus (patient 4), basal ganglia (patients 1, 3, and 4), thalami (patients 1 and 3), midbrain (patients 1 and 3), hippocampi (patient 3), cerebral peduncles (patient 1), and cerebellum (patient 1) (Figure 1 and Figure 2).

Initial CT scans in all 4 patients showed no intracranial abnormalities.

Repeat CT scans in 2 patients revealed marked interval changes. On posttransplant day 36, patient 2 had evidence of profound cerebral edema with herniation. On posttransplant day 40, patient 3 had CT findings of ischemic changes in the left fronto-occipital areas and vague signal attenuation in the superior posterior putamen.

Electroencephalogram studies (Table 3) in all 4 patients showed moderate to severe generalized slowing in the theta to delta range. Patient 4’s EEG showed electroencephalographic seizures that were refractory to treatment. In both patient 2 and patient 4, moderate to large amplitude slowing progressed to attenuated delta slowing as their encephalopathy progressed. Prominent occipital slowing was seen in patient 2; it was thought to reflect cyclosporine-induced posterior reversible encephalopathy. A repeat EEG showed electrocerebral silence 5 days later when she developed signs of cerebral herniation.

Postmortem Evaluation

Available onsite testing of multiple postmortem samples was exhausted without demonstrating an infectious etiology to explain the neurological symptoms. Macroscopic examination of the CNS varied among all of the transplant recipients. Patient 1 had congestion; irregularly distributed discoloration of the cortical mantle; generalized softening and edema of the striatum, thalamic nuclei, midbrain, andpons; herniation of the left hippocampal gyrus and right cerebellar tonsil; and Duret hemorrhages involving the midbrain and pontine tegmentum. Patient 2 had congestion, generalized edema, and evidence of tonsillar herniation. Patient 3 had brainstem flattening; softening of the left insular cortex and inferolateral putamen most pronounced at the level of the rostral hippocampus; and petechial hemorrhages involving the insular cortex and pontine tegmentum. Patient 4 had mild generalized edema and congestion.

Histologic hematoxylin-eosin–stained sections in all 4 patients demonstrated widespread neuronal necrosis involving the cerebral cortex, hippocampus, and dentate nucleus of the cerebellum, accompanied by substantial Purkinje cell loss and Bergmann gliosis, which is con-

| Table 2. Known Symptoms Associated With Rabies Exhibited in Donor and Transplant Recipients* (cont) |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Rabies-Associated Symptoms      | Donor | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
| Hydrophobia                     | X     |             |             |             |             |
| Throat pain                     | X     |             |             |             |             |
| Difficulty swallowing          |       |             |             |             |             |
| Inspiratory muscle contractions|       |             |             |             |             |
| Epigastic pain                  | X     |             |             |             |             |
| Flexion/extension neck muscles  | X     |             |             |             |             |
| Opisthotonic posturing          | X     |             |             |             |             |
| Retching                        | X     |             |             |             |             |
| Vomiting                        | X     |             |             |             |             |
| Coughing                        |       |             |             |             |             |
| Aspiration                      |       |             |             |             |             |
| Grimacing                       | X     |             |             |             |             |
| Aerophobia                      |       |             |             |             |             |
| Hyperstimulation (sensory)      | X     |             |             |             |             |
| Sobbing respiration             |       |             |             |             |             |
| Fearful facial expressions      | X     |             |             |             |             |
| Apneustic or ataxic breathing   |       |             |             |             |             |
| Voice changes                   |       |             |             |             |             |
| Associated complications        |       |             |             |             |             |
| Hyperventilation                | X     |             |             |             |             |
| Hypoxemia                       | X     |             |             |             |             |
| Respiratory depression          | X     |             |             |             |             |
| Apnea                           |       |             |             |             |             |
| Atelectasis                     |       |             |             |             |             |
| Sinus tachycardia               | X     |             |             |             |             |
| Cardiac arrhythmias             | X     |             |             |             |             |
| Hypotension                     | X     |             |             |             |             |
| Heart failure                   |       |             |             |             |             |
| Cardiac arrest/asystole         | X     |             |             |             |             |
| Gastrointestinal hemorrhage     |       |             |             |             |             |
| Hematemesis                     | X     |             |             |             |             |

*X indicates the symptom was exhibited by the patient. No entry indicates the patient did not experience that symptom.
sistent with global hypoxic-ischemic injury. In addition to these changes, patient 1 had Duret hemorrhages in the brainstem. The brain of patient 3 showed innumerable punctuate hemorrhages and multiple acute and organizing infarcts involving the left frontoparietal and insular cortex, basal ganglia, hippocampi, and cervical spinal cord.

Figure 1. Images from magnetic resonance examination of patient 1, posttransplant days 22 and 28 (GE 1.5T Signa system; General Electric, Fairfield, Conn). Axial fluid-attenuated inversion recovery image sequences of posttransplant day 22 demonstrate subtle leptomeningeal enhancement (A) and signal elevation within the pontomesencephalic junction (B); those of posttransplant day 28 reveal marked, nearly symmetric signal change within the anterior temporal lobes, hippocampi, basal ganglia, and brainstem (C, D). A coronal fast spin-echo inversion recovery image of posttransplant day 28 shows profound hyperintense signal changes throughout the undersurface of the frontal lobes and head of the caudate nuclei (E).

Figure 2. For patient 4, axial fluid-attenuated inversion recovery image sequences of posttransplant day 34 demonstrate considerable signal elevation within the caudate, putamina, thalami, and dorsal midbrain without associated hemorrhage (A, B). An axial diffusion weighted image shows ischemic changes within the bilateral perirolandic area (C).
An acute encephalomyelitis characterized by a brisk lymphohistiocytic infiltrate, perivascular lymphocytic infiltration, glial nodules, and neuronophagia was present in the cortical gray matter, deep gray structures, and inferior olivary nuclei; it was accompanied by patchy, less severe inflammatory changes in the white matter in all 4 recipients (Figure 3A and C). Although the extensive hypoxic ischemic changes obscured much of the neuronal morphology, eosinophilic intracytoplasmic viral inclusion bodies of varying sizes consistent with Negri bodies were present in multiple neurons, most prominently within residual Purkinje cells, and larger neurons of the brainstem (Figure 3B and D). A patchy lymphocytic leptomeningeal inflammatory infiltrate was present in all 4 recipients. Ganglionitis was present in the thoracic dorsal root ganglia of patients 2 and 3 with occasional Negri inclusions seen in the ganglion cells. Mononuclear inflammatory infiltrates were also present in the neurohypophysis in patient 3, in the nerves of the transplanted kidneys in patients 2 and 3, in the liver in patient 1, surrounding the iliac artery conduit in patient 4, and within epicardial nerves in patient 3. In addition to the epicardial infiltrates, patient 3 also had a significant myocarditis characterized by multifocal dense mononuclear inflammatory infiltrates involving the myocardium with associated myocardial necrosis. There were mild chronic inflammatory infiltrates seen in postmortem sural nerve segments from patients 2 and 3.

Rabies virus infection was confirmed by multiple methods (Centers for Disease Control and Prevention), including immunohistochemistry, direct antibody fluorescence, cell cultures, mouse inoculations, and electron microscopy. Serological testing was positive for IgG antibodies to rabies in patient 4, positive for IgG and IgM antibodies in patients 1 and 3 and the common donor, and negative for IgG and IgM antibodies in patient 3. Preliminary antigenic characterization of the rabies virus was consistent with a rabies virus variant associated with insectivorous bats.

**Table 3. Summary of Electroencephalogram Findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time After Transplantation, d</th>
<th>Clinical State at Time of Electroencephalogram</th>
<th>Findings</th>
<th>Impression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>Mixed, posterior dominant delta/theta activity; anterior dominant beta activity</td>
<td>Generalized encephalopathy, medication effect</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>Posterior dominant theta, with occasional delta activity; vertex sharp transients and sleep spindles centrally</td>
<td>Generalized encephalopathy</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>Attenuated, mixed delta/theta continuous slowing</td>
<td>Moderate to severe generalized encephalopathy</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Prominent occipital theta slowing</td>
<td>Possible cyclosporine-induced reversible posterior encephalopathy</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Witnessed tonic-clonic generalized seizure, comatose with absent pupillary response and brainstem reflexes</td>
<td>Severe attenuated recording with occasional brief low-amplitude activity</td>
<td>Electroencephalographic silence vs severely attenuated cerebral activity</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>Large amplitude delta slowing, abundant beta activity</td>
<td>Generalized encephalopathy, beta activity, likely medication effect (Diprivan)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Delirium, agitation, generalized myoclonus, and posturing</td>
<td>Technically limited study due to movement artifact; nonreactive large amplitude continuous delta slowing</td>
<td>Generalized encephalopathy</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Encephalopathic with generalized myoclonic activity</td>
<td>Limited study due to movement; attenuated delta/theta slowing, 2-5 Hz delta activity</td>
<td>Generalized encephalopathy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Moderate posterior slowing, frontal beta activity, abundant muscle and movement artifacts</td>
<td>Moderate generalized encephalopathy, no epileptic activity</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Altered mental status and generalized “twitching”</td>
<td>Semirhythmic, bifrontal 2-3 Hz activity with intermittent spike- and polyspike-wave complexes that resolved with 2 mg lorazepam IV; semirhythmic frontal activity persisted</td>
<td>Electroencephalographic status epilepticus</td>
<td></td>
</tr>
<tr>
<td>34-37 Strip electroencephalogram monitoring</td>
<td>Unresponsive, intubated; receiving lorazepam and Diprivan drip, phenytoin, phenobarbital, valproic acid, and levetiracetam</td>
<td>Semirhythmic delta slowing with frequent sharp-slow wave complexes</td>
<td>Refractory electroencephalographic status epilepticus</td>
<td></td>
</tr>
</tbody>
</table>

**COMMENT**

Rabies has been described as an unpredictable disease with the only consistent feature being its uncharacteristic symptoms.12 We have described a unique and uncharacteristic...
transmission of rabies virus infection through the transplantation of multiple organs and an arterial allograft. Rabies virus is transmitted through a bite (via saliva) in the classic form or can be transmitted through a scratch, in bat-variant rabies. The virus then incubates at the inoculation site for a period ranging from 5 days up to several years (average, 30-60 days), depending on the size of the inoculum and the severity and location of the wound. During the incubation period, the virus then replicates locally in muscle cells (classic form) or in the epidermis and dermis (bat-variant rabies), whereby replication has been shown to occur at lower temperatures and with higher infectivity in nonneuronal cells, including fibroblasts, macrophages, and epithelial cells.13-16 The virus then attaches to nerve endings and moves centripetally from the periphery to dorsal root ganglia and then on to the CNS by fast axonal transport. In the CNS, the virus has a predilection for the brainstem, thalamus, basal ganglia, and spinal cord, where it selectively replicates intraneuronally, producing an encephalomyelitis, and eventually spreads centrifugally along neural pathways to multiple organ and tissue sites.17,18 Approximately 80% of patients develop an encephalitic (furious) form, and the remaining patients develop a paralytic (dumb) form of the disease.19 In classic rabies, a multitude of nonspecific symptoms can occur during the prodromal phase; they generally last only a few days, up to 1 week, and signify movement of the virus from the periphery to the CNS. Central nervous system infection results in an acute neurological phase, in which initial symptoms commonly include fever and hyperactivity. Patients may have intermittent periods of hyperactivity, disorientation, confusion, bizarre behavior, agitation, aggression, or hallucinations, either occurring spontaneously or precipitated by sensory stimuli. During this stage, patients may also develop autonomic dysfunction (eg, excessive salivation, piloerection, lacrimation, sweating), cranial nerve signs, muscle fasciculations, tremor, myoclonus, nuchal rigidity, or paralysis.20 Classic hydrophobia is only seen in approximately 30% to 50% of patients, although most patients have some difficulty in swallowing or throat pain.15 Although biting behavior in humans is unusual, it has been reported to occur.21,22 The cardinal signs of classic rabies (encephalitic form) include fluctuating consciousness, phobic spasms, and autonomic dysfunction.20 Patients with bat rabies virus infection can have clinical features different from those of classic rabies. Patients infected with the bat-variant ra-

Figure 3. Hematoxylin-eosin–stained sections demonstrate multiple glial nodules within the midbrain (A) and an eosinophilic intracytoplasmic inclusion body (Negri body) within one of the preserved neurons of the inferior olivary nucleus from patient 1 (B). A brisk lymphohistiocytic inflammatory infiltrate and perivascular inflammation involving the inferior olivary nucleus (C) and a preserved Purkinje cell containing a Negri body from patient 2 (D). Original magnification was ×10 for A and C; ×40 for B and D.
butes more commonly have local symptoms or neuro-
pathic pain at the inoculation site described as burning,
numbness, tingling, or itching. A history of an anteced-
ent bite may be lacking. Anisocoria, bilateral ptosis, dip-
loria, nystagmus, pinpoint pupils, intermittent facial nerve
palsy, and tremor have also been reported. During the
acute neurological stage, nerve conduction abnor-
malities and weakness in the bitten limb, myoclonus, hemi-
paresis, hemisensory loss, asymmetry of deep tendon re-
flexes, and cranial nerve and brainstem involvement have
been reported to occur. Seizures are generally rare but
are also more often seen in patients infected with bat
rabies.14

The acute neurological phase generally lasts between
2 and 7 days and then, as the virus disseminates more
widely throughout the CNS, progresses to paralysis and
coma. Death generally occurs from failure of basic cen-
tral vegetative functions or can be due to myocarditis.
Hematemesis is seen in 30% to 60% of the patients 6 to
12 hours before death.15

It is during the acute neurological phase that most pa-
tients come to the hospital. The differential diagnosis is
quite broad during this phase, and making a diagnosis is
particularly difficult in the absence of a history of an
animal bite or exposure. This was the case for the donor
and the 3 organ recipients. Prior to donation, the do-
nor’s family denied a history of animal exposure when
asked by the organ bank whether the donor had experi-
enced animal bites. However, after a diagnosis of rabies
was made, further investigation revealed that the donor
had been bitten by a bat, as recalled by his friends. The
case of the fourth patient was even more perplexing in
that she had never left the hospital because of postop-
erative complications, including abdominal abscesses, sep-
sis, and hepatic artery stenosis. Although the possibility
of a primary CNS infection was considered in the differen-
tial for the transplant recipients, it was not consid-
ered for the donor. The donor’s habits, symptoms, clini-
cal course, laboratory data, and imaging findings all were
reasonably attributed to acute cocaine toxicity at the time
of his death.22 Similarly, in the case of 1 of the kidney
recipients (patient 3), a recent history of drug use re-
sulted in suspicion of methamphetamine toxicity.

Imaging studies of the brain in the donor and 4 re-
cipients varied. The donor had CT evidence of an SAH,
and although this has not previously been described in
rabies virus infection, there are reports of SAH associ-
ated with other types of vector-borne24 and viral25,26 en-
cephalitides. In patient 1, marked MRI signal abnor-
malities were seen by day 28, and profound CT and MRI
abnormalities were apparent in patients 2, 3, and 4 be-
tween posttransplant days 34 and 36. Not unlike other
reported cases, these patients showed preferential in-
volvement of the basal ganglia, thalami, and brain-
stem.27,30 The sizable left middle cerebral artery infarct in
patient 3 and restricted diffusion surrounding the motor
strip in patient 4 are atypical features for rabies virus
infection. Interpretation of the imaging findings was chal-
lenging in that the abnormalities seen were nonspecific
and prospectively raised concerns for other, more com-
mon encephalitic diseases, including any number of toxic/
metabolic insults, herpes simplex virus infection, and West
Nile virus infection. Similar imaging abnormalities have
been described in transplant recipients with proven West
Nile virus encephalitis.31,32

The differential was further clouded by other infec-
tious and noninfectious complications known to occur
in the early transplantation period. Most of the com-
mon infections seen in the early transplantation period
were considered in all 4 of the recipients and essentially
ruled out in all but 1 (patient 4), resulting in further con-
sideration of a toxic/metabolic encephalopathic pro-
cess. Patient 2 had elevated cyclosporine levels, and pa-
tient 4 had a mildly elevated tacrolimus level, requiring
dosage adjustments.

Although antemortem diagnosis of rabies is possible
by demonstrating rabies virus ribonucleic acid, antigen,
and antibodies in skin and brain biopsies, CSF, saliva,
and blood, the possibility of rabies is often not consid-
ered, particularly in the absence of a known exposure.
In the cases discussed here, a definitive diagnosis of ra-ies was not made until after death, similar to previous
reports in which more than one third of cases were not
diagnosed antemortem primarily because of lack of clini-
cal suspicion.1 Human-to-human transmission of ra-ies, although rare, has been described to occur through
corneal transplants.6,33-36 Although the risk for rabies trans-
mission through solid organ transplantation has always
existed,22 transmission through solid organ transplantation
has not been previously described. This series of cases
along with a subsequent case25 brings the number of re-
ported human rabies cases since 1980 in the United States
to 55.1,4,27 Even if the number of US rabies cases in-
creased by 100-fold, given the population and known or-
gan donation rate, a conservative estimated risk of ra-
bies infection through solid organ transplantation is less
than 1:1 000 000 000 000. However, these cases demon-
strate that the risk for transmission of rabies infection
through solid organ and tissue transplantation exists, and
the diagnosis should be considered in any rapidly pro-
gressing neurological disease. Moreover, although ra-
bies infection is almost always fatal once symptoms oc-
cur, prompt antemortem or postmortem diagnosis remains
necessary to implement appropriate infection-control mea-
sures and prophylaxis to decrease the risk of disease.

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