

## Antemortem Diagnosis of Human Rabies

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Human rabies is a rare but fatal disease. In the United States, the majority of people infected with rabies contract the disease by being bitten by a wild animal, most commonly bats. Because rabies is so rarely seen, it is often not diagnosed until after death, at which time exposed health care workers will require rabies prophylaxis. We describe a case for which the diagnosis was

made before death. The prompt consideration of this diagnosis allowed early isolation of the patient and prevented unnecessary risk to health care workers.

*Key words.* Rabies; infectious diseases; diagnosis; patient isolation; health care workers; fatal outcome.  
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Rabies, recognized since ancient times, continues to be a fatal disease. The incidence in the United States declined dramatically with the implementation of dog vaccination and stray animal control programs in the 1940s.<sup>1</sup> The incidence decreased from 50 to 60 cases per year prior to 1940 to two or fewer cases per year since 1960.<sup>2,3</sup> Because of the success of these programs, wild animals such as foxes, skunks, bats, and raccoons, rather than dogs, are now the primary means of rabies transmission to humans.<sup>4</sup>

Because of the low incidence of rabies and the absence of an animal bite history, physicians often do not consider a diagnosis of rabies in patients presenting with encephalopathy. The result has been failure to institute strict isolation early in the hospitalization, a delayed diagnosis, unnecessary exposure of health care workers to potentially infectious secretions, and excessive need for postexposure prophylaxis.<sup>5-13</sup>

We present a case for which the diagnosis was considered within 24 hours of admission to a regional hospital, which permitted early patient isolation and therefore

minimized postexposure prophylaxis to health care personnel. Early suspicion of rabies contributed to the antemortem diagnosis and an informed decision to withdraw intensive life support.

### Case Report

A 41-year-old man from West Virginia presented to a rural hospital with a 2-day history of nausea, headache, malaise, and tremors and a 1-day history of severe anxiety, hallucinations, vomiting, and an inability to bring liquids to his mouth. He denied fever and chills. His examination revealed good recall, a short attention span, severe agitation, and, in retrospect, early hydrophobia. He had a known history of substance abuse, and the preliminary diagnosis was acute psychotic reaction secondary to ethanol and marijuana toxicity. He became more agitated and left the emergency department. Over the next 24 hours, his condition worsened, and he was admitted to a regional hospital on day 3 of his illness.

The patient lived in a cabin in a rural forested area. He was a musician and an animal trapper. His history, obtained antemortem, revealed two episodes of animal exposure that were either too short or too long for the usual incubation period of rabies, but indicated that his activities may have placed him at risk for rabies exposure. Five days before the onset of symptoms, he had killed and skinned a muskrat. He kept two dogs outside his cabin but denied any animal bites. Questioning of his family and friends revealed that he had "brain-tanned" a fox pelt 15

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Figure 1. Unenhanced computed tomography scan of the brain shows decreased density involving the left temporal lobe (white arrows) with mass effect on the left temporal horn (black arrow). Courtesy of Dr Orlando A. Ortiz, West Virginia University.

months prior to onset. The brain tanning process involved holding the fox brain in his bare hands and rubbing it over the fox pelt.

A physical examination at admission revealed a temperature of 100.1°F. He was alert, coherent, diaphoretic, and agitated. He displayed tremors, spastic extremity movements, and hydrophobia. There were no mucocutaneous lesions. Frequent spitting of frothy saliva and withdrawal from objects placed near his mouth were noted. Laboratory studies revealed white blood cell (WBC) count, 18,100/mm<sup>3</sup>; creatinine phosphokinase, 1912 IU (normal, 5 to 50); serum ethanol, <10 mg/dL; and urine drug screen positive for cannabis. On day 4 of the illness, a lumbar puncture revealed the following cerebrospinal fluid findings: an opening pressure of 330 mm Hg; protein, 148 mg/dL; glucose, 128 mg/dL; WBC, 18/mm<sup>3</sup> (10% polymorphonuclear [PMN] cells; and 90% monocytes); red blood cell count, 725/mm<sup>3</sup>; and the cerebrospinal fluid culture showed no growth. On day 5 of the illness, he developed respiratory distress requiring mechanical ventilation and was transferred to the university hospital.

The patient's condition continued to deteriorate. He demonstrated severe spastic muscle activity, and his temperature rose to 102.7°F. Laboratory values revealed WBC, 18,999/mm<sup>3</sup> (87% PMN, 4% bands); erythrocyte

sedimentation rate, 58 mm/h; blood and urine cultures, no growth; and creatinine phosphokinase, 6000 IU. Computed tomography of the head revealed diffuse cerebral edema and low attenuation in the left temporal lobe (Figures 1 and 2). An electroencephalogram showed a possible left temporal abnormality. He was treated empirically with intravenous acyclovir, ceftriaxone sodium, penicillin G, and doxycycline hyclate. There was no improvement.

A skin biopsy of the posterior neck on day 6 was positive for rabies antigen by indirect fluorescent antibody test. These results were available after a temporal brain biopsy was performed on day 9, which revealed Negri bodies (Figure 3). The patient developed flaccid paralysis after being taken off paralytic agents and died on day 14 of the illness.

The Centers for Disease Control and Prevention (CDC) identified the specific viral ribonucleic acid (RNA) as a variant associated with the silver-haired bat, *Lasiurus noctivagans*. Postmortem interviews of additional friends of the patient revealed that 5 months before his terminal illness, he had killed a bat and examined its oral cavity. The description of the bat was consistent with *Lasiurus borealis*, the red bat. Inoculation of sites rich in innervation, such as the head and digits, is more likely to result in rabies infection.<sup>14,15</sup>

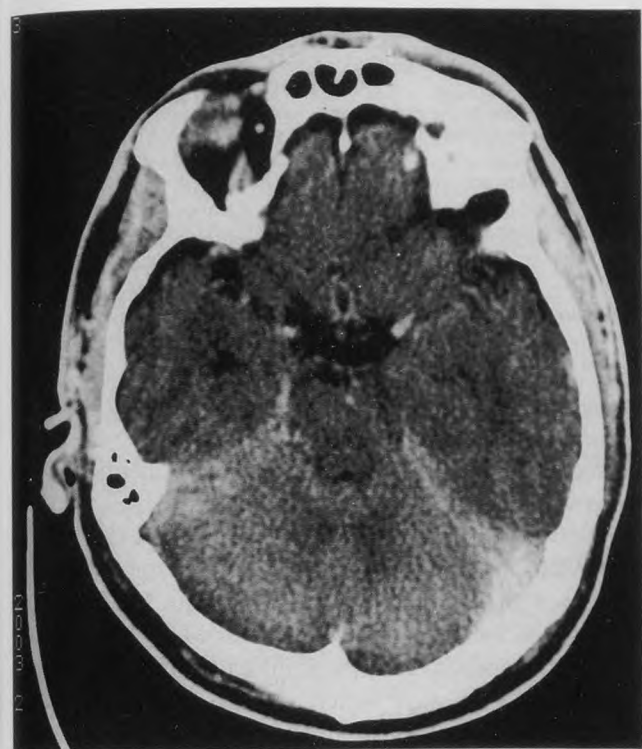


Figure 2. Enhanced computed tomography (CT) scan of the brain obtained 4 days after the first CT scan (Figure 1) shows persistent left temporal lobe swelling and no abnormal enhancement. Courtesy of Dr Orlando A. Ortiz, West Virginia University.

## Discussion

Twenty-six cases of human rabies have been reported to the CDC from 1980 to 1994.<sup>5-13,16-27</sup> Of the 14 cases with indigenous sources, only three were diagnosed before death.<sup>8,13,16</sup> Eighty-six percent (12/14) had no

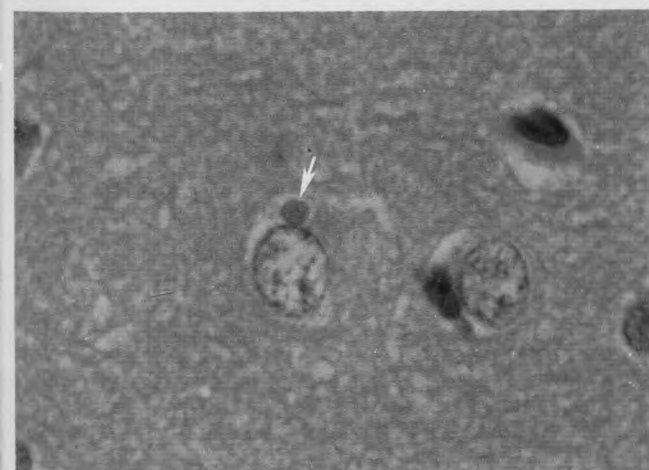


Figure 3. Round eosinophilic inclusion (Negri body) stained with hematoxylin-eosin. Courtesy of Dr Sydney S. Schochet, West Virginia University.

known prior animal exposure.<sup>5-13,16-27</sup> In two cases, the source was identified after the virus was isolated.<sup>13,16</sup>

From 1980 to 1989, the majority (9/11) of cases of human rabies were imported. From 1990 to 1994, however, the majority (11 of 14) of cases were indigenous.<sup>5-14</sup> Of the indigenous cases documented in this decade, 82% (9 of 11) were associated with bats.<sup>5,7,9-13,16</sup> Bat rabies is enzootic throughout the continental United States.<sup>28,29</sup> The most common bat strain identified is *L. noctivagans*,<sup>6,9-13</sup> followed by *Tardarida brasiliensis*.<sup>7,11,13</sup> In our patient, the viral RNA was identified as a variant associated with *L. noctivagans*, although the descriptions of the bat were consistent with the red bat, *L. borealis*. Two cases diagnosed in the early 1980s have not been serotyped.<sup>6,8</sup>

Rabies, caused by the bullet-shaped RNA-containing virus of the family Rhabdoviridae, presents as acute encephalomyelitis. Rabies virions, introduced by animal bites or scratches, have an affinity for nicotinic acetylcholine receptors, where they replicate and reach the central nervous system by retrograde axoplasmic transport, and then return to the periphery by intra-axonal transport to highly innervated extraneural sites. Aerosol transmission has been documented in laboratory workers during rabies research and in spelunkers visiting bat-infested caves. Six unusual cases of rabies were associated with infected corneal transplants.<sup>30,31</sup> The average incubation period in humans is 10 to 90 days, but it may vary from a few days to more than 1 year, depending on the anatomic distance between the inoculation site and the brain. In our patient, the estimated incubation period was approximately 20 weeks.

There are two clinical types of rabies: classic (furious) and paralytic. Classic rabies is divided into three phases. During the prodromal phase, the patient feels nonspecific influenza-like symptoms. The second phase is the acute neurologic phase, characterized by hyperactivity, disorientation, bizarre behavior, and hallucinations, followed by episodes of dysphagia and hydrophobia. Hydrophobia, pathognomonic of rabies, is characterized by violent jerky contractions of the muscles of inspiration in response to attempts to swallow. It is associated with laryngeal and pharyngeal muscle spasms, facial grimacing, opisthotonos, and seizures. The differential diagnosis of classic rabies includes tetanus, delirium tremens, psychiatric disorders, hysteria, and other viral encephalitides. In the paralytic form of rabies, patients have a prodrome similar to the classic form, except that it includes an ascending paralysis. The clinical course of this type of rabies is slower, and the differential diagnosis includes Guillain-Barré syndrome, poliomyelitis, postvaccine neuroparalytic reactions, herpes simplex virus encephalitis, and acute immune-mediated polyneuritis.<sup>32</sup>



Table 1. Rabies Postexposure Prophylaxis

Vaccination Status	Treatment	Regimen
Not previously immunized	Local wound cleansing	Thorough washing with soap and water
	Human rabies hyperimmune globulin	20 IU/kg body weight One-half dose infiltrated around the wound(s), the rest to be given IM in the gluteal area
	Vaccine	HDCV or RVA, 1.0 mL (deltoid area) IM, one each on days 0, 3, 7, 14, and 28
Previously immunized	Local wound cleansing	Immediate thorough cleansing with soap and water
	Human rabies hyperimmune globulin	Should not be administered
	Vaccine	HDCV or RVA, 1.0 mL (deltoid area) IM, one each on days 0 and 3

IM denotes intramuscularly; HDCV, human diploid cell vaccine; RVA, rabies vaccine, adsorbed.

Definitive laboratory diagnosis includes detection of the rabies antigen or antibody or isolation of the virus. Antemortem diagnosis may be made by using corneal impressions, viral isolation from saliva and cerebrospinal fluid, serum and cerebrospinal fluid for rabies antibody titers, and skin biopsy of the highly innervated hair-covered area of the neck for rabies fluorescent antibody testing for the rabies antigen.<sup>33</sup> Findings from neck skin biopsies are positive in 50% to 60% of patients with rabies.<sup>1,34,35</sup> The Negri bodies are eosinophilic intracytoplasmic viral inclusion bodies in infected neurons. They are absent in up to 20% of proven rabies.

There is no successful treatment for rabies once the disease occurs. Clinical rabies infection is virtually always fatal in nonimmunized humans. Until there are advances in the therapy of rabies, suspicion and early diagnosis are most beneficial for those in contact with the patient. Successful prophylactic treatment depends on preventing clinical illness by means of thorough wound cleansing, active immunization with the human diploid cell vaccine, and passive immunization with the human rabies hyperimmune globulin. Prophylaxis should be started immediately after the exposure and within 72 hours for the best results. Recommendations for rabies prophylaxis are given in Table 1. Guidelines for preexposure immunization for rabies are listed in Table 2.

Several factors contributed to the early presumptive diagnosis of rabies in our patient. The patient's preference for hunting, his exposure to a wildlife environment, and his history of skinning a muskrat 5 days before the onset of

Table 2. Rabies Pre-exposure Prophylaxis Schedule

Type of Vaccination	Route	Regimen
Primary	Intramuscular	HDCV or RVA, 1.0 mL (deltoid area) on days 0, 7, and 21 or 28
	Intradermal	HDCV, 0.1 mL, on days 0, 7, and 21 or 28
Booster	Intramuscular	HDCV or RVA, 1.0 mL (deltoid area), on day 0 only
	Intradermal	HDCV, 0.1 mL, on day 0 only

HDCV denotes human diploid cell vaccine; RVA, rabies vaccine, adsorbed.

the encephalitic picture alerted the family physician and the infectious diseases specialist to consider rabies. The subsequent development of agitation, hydrophobia, and hypersalivation suggested the diagnosis, which was confirmed by biopsies of the skin and brain. The availability of the Medical Access and Referral System (MARS) prompted the family physician to consult the infectious diseases specialist. MARS was established in 1986 by West Virginia University Health Sciences Center in Morgantown, West Virginia,<sup>36</sup> which provides a 24-hour, 7-day-a-week telephone consultation service to physicians located in rural areas.

The epidemiology of human rabies in the United States has changed. A majority of cases are now caused by bats, and an increase in indigenous rabies occurred during the early half of this decade. Programs that facilitate communication and interaction between university and community-based physicians can aid in the diagnosis and management of rare diseases such as rabies. Early consideration of the diagnosis of rabies allows for early institution of proper isolation of the patient and avoids unnecessary prophylaxis to hospital personnel.

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