Case Report: A Case of Fatal Serotonin Syndrome–Like Human Rabies Caused by Tricolored Bat–Associated Rabies Virus

Hariharan Regunath,* Bhavana Chinnakotla, Christian Rojas-Moreno, William Salzer, Natalie J. Hughes, and Harbaksh Sangha

Division of Pulmonary, Critical Care and Environmental Medicine, Department of Medicine, University of Missouri, Columbia, Missouri; Division of Infectious Diseases, Department of Medicine, University of Missouri, Columbia, Missouri; Department of Medicine, University of Florida, Gainesville, Florida

Abstract. Human rabies is a fatal disease, transmitted by saliva of infected animals, and the diagnosis requires a high index of suspicion. Very few cases are reported annually in the United States. We present a case of human rabies without a clear exposure history that masqueraded as serotonin syndrome.

INTRODUCTION

Human rabies is a zoonotic encephalitis that is almost universally fatal except for a few cases.^{1,2} Canine rabies is common in most of the world, but in the United States and Canada most human rabies is acquired from bats and less frequently from raccoons, skunks, coyotes, and foxes.^{3–5} The Centers for Disease Control and Prevention (CDC) conducts annual surveillance for animal and human rabies in the United States.⁵ Despite the decline in the total number of human rabies cases, the number of bat-associated human rabies have tripled from 1950 to 2007.^{3,5} Of the 50 cases of human rabies reported since 1995, 70% were caused by bat variants of rabies virus.⁶ Clinical manifestations of human rabies are classified as encephalitic, paralytic, and atypical forms. Bat-associated rabies is notable for atypical presentations.^{7,8} In 56% of human rabies cases reported to the CDC from 1995 to 2011, there was no history of animal bite or exposure, and of those, 85.7% were bat-associated rabies.^{6,7} We present a case of bat-related human rabies with unknown exposure that masqueraded as serotonin syndrome.

CASE REPORT

A 52-year-old male presented in September 2014 to an emergency department (ED) with severe radicular cervical pain and paresthesia in his left upper extremity for a few days. He was prescribed cyclobenzaprine for musculoskeletal pain and was discharged. The next day diffuse tremors, fever, and sweats woke him from sleep, and he presented to ED again after taking two doses of cyclobenzaprine in the interval period. Examination findings were as follows: temperature 37.1°C, heart rate (HR) 65/minute, blood pressure (BP) 140/78 mm Hg, respiratory rate (RR) 24/minute, and oxygen saturation (SpO₂) 96% on room air. He was anxious, diaphoretic, and hypertonic with coarse tremors noted in bilateral upper and lower extremities. He was treated with cyproheptadine and benzodiazepines for suspected serotonin syndrome and was transferred to our facility the next day. Past medical history was notable for obesity, hypertension, type 2 diabetes mellitus, and hyperlipidemia. He was single, nonsmoker, and never consumed alcohol or illicit drugs.

At our facility, he was alert, oriented, diaphoretic, temperature 39.8°C, HR 113/minute, BP 153/105 mmHg, RR 37/minute,

and SpO₂ 98% on room air. Exam was only remarkable for significant rigidity in bilateral upper and lower extremities, hyperreflexia, and clonus. Cranial nerve, motor and sensory, exam was normal. Admission blood counts were normal, abnormal laboratory results included serum sodium 149 mM/L, bicarbonate 18 mM/L, anion gap 22 mM/L, blood urea nitrogen 32 mg/dL, creatinine 1.29 mg/dL, creatine kinase (CK) 1,475 units/L, and lactate dehydrogenase 244 units/L. Urine drug screen was positive for benzodiazepine. Serotonin syndrome and neuroleptic malignant syndrome were high on the differential. Intravenous dantrolene and lorazepam were given without clinical improvement. He refused all oral liquids and nasal oxygen for fear of aspiration. Within 24 hours, he developed hypoxia and was transferred to the intensive care unit where he was intubated and placed on mechanical ventilation.

On hospital day 2, temperature 40.5°C, rigidity and tremors persisted and progressed to myoclonic jerks. Serum CK and creatinine progressively increased. Because of rhabdomyolysis, he was sedated and paralyzed. Cyproheptadine and continuous infusion of lorazepam were given. A magnetic resonance imaging (MRI) of the brain was unremarkable. An electroencephalogram (EEG) with photic stimulation was performed, during which he had several random jerks involving upper and lower extremities without corresponding epileptiform abnormalities.

On hospital day 3, the cerebrospinal fluid (CSF) was obtained and showed protein 72 mg/dL, glucose 119 mg/dL, white blood cells (WBCs) 8 cells/ μ L (neutrophils 42%, lymphocytes 55%, and monocytes 3%), red blood cells (RBCs) 7 cells/ μ L. Other CSF studies including Venereal Disease Research Laboratory (VDRL) test, herpes simplex virus (HSV) type 1/2 real-time DNA polymerase chain reaction (PCR), West Nile virus IgM, and St. Louis encephalitis virus IgM were negative. Serologic tests for ehrlichiosis, Rocky Mountain spotted fever, syphilis, and West Nile virus were also negative. Gram stain and bacterial culture were negative.

Hospital days 4 and 5 were remarkable for persistent fever, episodic bradycardia (lowest HR 20/minute), and further rises in serum CK (13,555 units/L on day 5) and creatinine. Attempts at weaning sedation or paralysis resulted in appearance of myoclonic jerks. Suspicion for rabies arose when worsening encephalitis was coupled with autonomic instability, hydrophobia, and aerophobia. His family then revealed that patient lived in a trailer and wildlife photography was a hobby. Infectious diseases consultation was obtained on day 5.

On day 6, CSF, serum, saliva, and skin biopsy from the nape of neck were sent to the CDC. CSF on that day showed

*Address correspondence to Hariharan Regunath, Department of Medicine, University of Missouri, 1 Hospital Drive, CE 334, Columbia, MO 65212. E-mail: regunathh@health.missouri.edu

protein 109 mg/dL, glucose 97 mg/dL, WBCs 30 cells/ μ L (neutrophils 27%, lymphocytes 55%, and monocytes 3%), and RBCs 321 cells/ μ L.

By days 7 and 8, serum CK peaked at 25,914 units/L, he developed refractory shock and needed norepinephrine infusion. Hemodialysis was instituted for anuric renal failure. Multiple blood cultures were negative.

On day 9, he became unresponsive with absent brain stem reflexes while off sedation and paralytics. Repeat CSF showed xanthochromia, protein > 600 mg/dL, glucose 92 mg/dL, WBCs 129 cells/ μ L (neutrophils 48%, lymphocytes 33%, and monocytes 19%), and RBCs 4,000 cells/ μ L. Repeat MRI of brain revealed subdural fluid collections. Repeat EEG had generalized low voltage delta activity with minimal reactivity to noxious stimulation. A cerebral perfusion study showed normal perfusion and was reported as negative for brain death.

On day 11, CDC reported that reverse transcription PCR (RT-PCR) from skin biopsy and saliva were positive for rabies virus genome associated with the small insectivorous bats of the common name "tricolored bats" (*Perimyotis subflavus* formerly *Pipistrellus subflavus*). By day 13, refractory hypotension developed, and because of poor prognosis and medical futility, family opted for comfort measures. Life support was discontinued. Antirabies IgG and IgM were negative on day 6 but positive on day 13 (IgG > 1:128 and IgM > 1:32 by indirect fluorescent antibody test; neutralizing antibody titer by rapid fluorescent focus inhibition test was positive at 0.9 IU/mL).

DISCUSSION

Rabies virus is a neurotropic bullet-shaped *Lyssavirus* of the family *Rhabdoviridae*. Infection results from virus inoculation through breaks in skin or mucosa caused by a bite from an infected animal or may rarely be transmitted by aerosols in laboratory accidents.^{8–11} Aerosol exposure in natural conditions were suspected in a few human rabies cases, who had entered caves inhabited with thousands of bats, but unrecognized bat bites were rather believed to be a more likely explanation.¹¹ After inoculation, rabies virus invades nerves and by retrograde axoplasmic transmission reaches the central nervous system.^{8,12–14} Progressive significant neural dysfunction, notably of brain-stem function, occurs in rabies resulting in cerebral death.¹⁵ In 2008, a case of fatal rabies was reported from Missouri, in a man who sustained a bite in his left ear from a bat that flew into his house 4–6 weeks prior and was sheltered in his house for 2 days. The rabies virus for this case was typed as a variant associated with silver-haired bats (*Lasiurus noctivagans*).¹⁶

In 2010, a case of rabies was reported from Wisconsin, involving a man presenting with progressive shoulder pain, tremulousness, abnormal behavior, and dysphagia. Benzodiazepines and haloperidol were given for presumed alcohol withdrawal syndrome, and the next day, rhabdomyolysis, fever, and rigidity ensued. Neuroleptic malignant syndrome was suspected. Later encephalopathy, respiratory failure, acute renal failure requiring hemodialysis, and episodes of cardiac arrest developed. On day 9, rabies was suspected and on day 11, nucleic acid amplification and sequencing of the nuchal skin biopsy and saliva samples, confirmed infection with silver-haired bat rabies virus variant. On day 12, rabies virus antigens related to silver-haired and tricolored bats

were detected in postmortem brain tissue analysis by antigen typing with monoclonal antibody. However, there was no report of a bat bite. He died on hospital day 13.¹⁷ In our case, there was no clear evidence of exposure except that he lived in a trailer in the woods, wildlife photography was a hobby, and the RT-PCR of skin and saliva samples detected the rabies virus genome associated with the tricolored bats (*P. subflavus*). Autopsy was refused by his family.

Among the rabies virus variants identified by CDC, those associated with these two insectivorous bats, *L. noctivagans* and *P. subflavus* caused ~60% of human cases.¹⁸ Tricolored bats are the smallest bat species in North America, hence their bites are often undetected.^{19–21} Along with bats, terrestrial animals—foxes, coyotes, skunks, raccoons, etc.—also serve as major animal reservoirs in the United States.²²

Serotonin (5-HT), a prominent neurotransmitter in the midbrain raphe nucleus, has been linked to control aggressive behavior.²³ Serotonin syndrome is a life-threatening condition characterized by increased serotonergic activity in brain. It is diagnosed clinically and suspected in patients with a history of intake of serotonergic drug and manifesting or presenting with clonus, hyperreflexia, hypertonia, agitation, diaphoresis, or hyperthermia.²⁴ Cyclobenzaprine, a muscle relaxant that inhibits serotonin receptors, may provoke serotonin syndrome.^{25,26} In addition to stopping the culprit drug and treatment with benzodiazepine, cyproheptadine, a non-specific 5HT receptor antagonist, can be used in severe cases. Although initially, our case was suspected to have serotonin syndrome based on anxiety, diaphoresis, hyperthermia, and myoclonic jerks after a few doses of cyclobenzaprine, the lack of response to sedation and cyproheptadine, the progression of symptoms, and the development of bradycardia and hypotension suggesting autonomic instability elicited a suspicion for rabies. Although there is lack of evidence to support increased brain serotonin activity in rabies, there is evidence for the contrary. On the basis of the studies in rabid skunks, low brain serotonin levels were associated with aggressive behavior in encephalitic rabies.²⁷ One study found that 5 days after inoculation of rats with a laboratory strain of rabies virus into their masseter, there was a significant decrease in 5HT binding to 5HT-1 receptors in cerebral cortex; another study, which measured hippocampal levels of neurotransmitters, observed that serotonin and other neurotransmitter levels increased from day 1 to day 3 (peak) after intranasal rabies virus inoculation and by day 7 declined to preinfection levels, which is when clinical manifestations commenced.¹⁵ CSF studies in three human rabies cases had low levels of tetrahydrobiopterin, an essential cofactor for tryptophan hydroxylase (key enzyme in serotonin synthesis), postulating that low serotonin neurotransmission has a pathophysiologic role in encephalitic human rabies.²⁸

Given the above experimental evidences that low serotonin levels were associated with encephalitic rabies, the constellation of serotonin syndrome-like manifestations in our rabies case was probably just a red herring. CSF serotonin and other neurotransmitter levels were not measured, autopsy and brain biopsy was declined by family, which limits proof of this hypothesis, but nevertheless, the clinical manifestations of our case raise questions regarding the neuro-pathophysiology of encephalitic rabies. Interestingly, patients who develop withdrawal symptoms from cessation of long-term selective serotonin reuptake inhibitors can also develop

neuromotor features akin to serotonin syndrome (muscle rigidity, tremor, and myoclonus).²⁹ On the basis of this, whether a serotonin excess occurs early in the disease process of human encephalitic rabies, followed by a decline in levels and manifesting as withdrawal symptoms, remains a speculation. Tremor, hypertonia, and myoclonus have been associated more often with bat-associated rabies due to involvement of peripheral nerves, spinal cord, brain stem, thalamus, basal ganglia, cerebellum, cortex, and subcortical regions.^{7,30,31} Bat-associated rabies cases have also been associated with other presentations such as cranial nerve palsies, focal brain stem signs, hemichorea, and Horner's syndrome.^{7,8,32} Rhabdomyolysis was likely secondary to refractory myoclonic jerks and rigidity and has been reported in other human rabies cases.^{33–37}

The Milwaukee protocol (sedation with ketamine and midazolam and antiviral therapy with ribavirin) was associated with survival of one patient in whom protective antibodies were noted within a week, but subsequent reports of failure with the same protocol have also been published.³⁸ Our patient was sedated with lorazepam infusion and was paralyzed but when protective antibodies appeared on day 13, his clinical condition had progressed to medical futility.

In conclusion, this was the second case of human rabies reported in Missouri over the past 50 years and stands next only to the Wisconsin case presenting as a hyperthermia syndrome. Clinicians must not only exercise increased vigilance and high index of suspicion to diagnose rabies in patients presenting with clinical findings suggestive of encephalitis and autonomic instability, but also consider to include rabies in the differential diagnosis of hyperthermia syndromes such as serotonin syndrome.

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Authors' addresses: Hariharan Regunath Division of Pulmonary Critical Care and Environmental Medicine, Department of Medicine, University of Missouri, Columbia, MO, and Division of Infectious Diseases, Department of Medicine, University of Missouri, Columbia, MO, E-mail: regunathh@health.missouri.edu. Bhavana Chinnakotla, Department of Medicine, University of Missouri, Columbia, MO, E-mail: bhavana611@gmail.com. Christian Rojas-Moreno and William Salzer, Division of Infectious Diseases, Department of Medicine, University of Missouri, Columbia, MO, E-mails: rojasch@health.missouri.edu and salzerw@health.missouri.edu. Natalie J. Hughes, Department of Medicine, University of Florida, Gainesville, FL, E-mail: natalie.hughes@medicine.ufl.edu. Harbaksh Sangha, Division of Pulmonary Critical Care and Environmental Medicine, Department of Medicine, University of Missouri, Columbia, MO, E-mail: sanghah@health.missouri.edu.

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