Australian Bat Lyssavirus in a Child: The First Reported Case

abstract

Human infection with Australian Bat Lyssavirus is extremely rare and has not previously been reported in a child. We describe a fatal case of Australian Bat Lyssavirus in an 8-year-old child, and review the literature pertaining to the diagnosis and management of lyssavirus infection with consideration of its applicability to this emerging strain.

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KEY WORDS
lyssavirus, rabies, child, Australia, bat

ABBREVIATIONS
ABLV—Australian Bat Lyssavirus
CSF—cerebrospinal fluid
MP—Milwaukee Protocol
PCR—polymerase chain reaction
PEP—post-exposure prophylaxis
RT-PCR—reverse transcription-polymerase chain reaction

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Australian Bat Lyssavirus (ABLV) was first identified in Australian pteropid fruit bats (flying foxes or *Megachiroptera*), insectivorous bats (*Microchiroptera*), and as a cause of human infection in 1996. Although low-level prevalence in Australian bats persists,1 human infection is extremely rare. Animal models and 2 previously reported cases of human infection suggest modes of transmission and clinical characteristics consistent with classic rabies.2,3 We describe the third reported case of confirmed human ABLV infection, and the first in a child.

**CLINICAL RECORD**

An 8-year-old boy from a regional island with a large fruit bat colony presented to hospital ~8 weeks after an unWitnessed scratch from a bat on his left forearm, an incident recollected by his sister only in the context of his illness. He presented with a 2-day history of fever, anorexia, and progressively worsening abdominal pain. Lipase was mildly elevated (560 IU/L) and a presumptive diagnosis of acute pancreatitis was made.

His pain and distress were severe, and worsened precipitously. Abnormal behavior and aggressive outbursts were prominent, in between periods of lucidity and cooperation. Extensor and flexor spasms of the lower limbs, abdomen, and face with associated pupillary dilation, tachycardia, and hypertension occurred. Reflexes were brisk globally. Hydrophobia was not described, but there were copious oral secretions and apparent difficulty swallowing.

Tracheal intubation was performed to permit adequate pain and spasm control. Sedation was difficult to achieve despite large doses of benzodiazepines, opiates, and ketamine. Spasms were only controlled with propofol sedation and muscle paralysis. Magnesium supplementation was beneficial. En-teral and intrathecal baclofen had little impact.

Many different diagnoses, including encephalitic rabies, were considered and investigated extensively. Blood tests revealed neutrophilia (16.24 × 10^9/L) and lactic acidosis (lactate 5.7 mmol/L), normal erythrocyte sedimentation rate, C-reactive protein, electrolytes, and liver function tests. Tests for metabolic and autoimmune diseases were negative. Cerebrospinal fluid (CSF) analysis demonstrated normal microscopy and biochemistry (leukocyte count 2 × 10^6/L, erythrocyte count 405 × 10^6/L, protein 0.3 g/L, and glucose 6.2 mmol/L). Serological and polymerase chain reaction (PCR) assays of blood and CSF were negative for Lyssavirus (heminested reverse transcription-PCR [RT-PCR] and real-time TaqMan), enterovirus, human herpes virus 1, 2, and 6, varicella zoster virus, parvovirus B19, Epstein-Barr virus, cytomegalovirus, dengue virus, and Murray Valley encephalitis virus. Serum Lyssavirus antibodies were not detected on enzyme immunoassay.

Computed tomography images of the chest demonstrated significant pneumomediastinum. Pancreatic appearance was normal on abdominal computed tomography and ultrasound scan, and magnetic resonance cholangiopancreatography was also normal. Upper gastrointestinal endoscopy was unremarkable. Neuroimaging was within normal limits, although several small foci (measuring up to 4 mm) within the periventricular white matter of the peririgional regions were seen on MRI of the brain. Electroencephalography was abnormal, with nonspecific features of encephalopathy.

Intravenous cefotaxime, vancomycin, acyclovir, and tetanus immunoglobulin were administered, although the child was fully immunized and subsequent results demonstrated pre-existing protective levels of tetanus immuno-globulin (0.67 IU/L). A 3-day course of methylprednisolone (30 mg/kg/day) and concomitant pooled intravenous immunoglobulin was given after bacterial and fungal infections were excluded.

The patient was extubated on day 5 of hospital admission. He was aware of his surroundings, but was clearly distressed. Ongoing severe spasms necessitated re-intubation, with recommencement of sedation and escalating analgesia requirements. Further clinical deterioration ensued, with progressive encephalopathy and decreased spontaneous movements. Dysautonomia was evidenced by temperature instability, diabetes insipidus, and atrial arrhythmias. Severe and progressive sinoatrial node dysfunction resulted in several episodes of sinus arrest, 2 of which required cardiac compressions.

Lyssavirus investigations were repeated on day 12 of hospital admission, and positive results obtained on day 14. Lyssavirus antibody titer increased to 0.17 IU/L on enzyme immunoassay using the Bio-Rad Platelia Rabies kit. Heminested RT-PCR (which detects several Lyssavirus genotypes) and a specific Pteropid-ABLV real-time TaqMan assay were both positive on saliva and CSF samples. Phylogenetic analysis of RT-PCR sequencing closely matched a 1999 Pteropid-ABLV sequence (99.1% concordance) and a 1998 human case (98.4% concordance) (Fig 1).

Supportive care aspects of the Milwaukee Protocol (MP), including fluid and electrolyte control to target euvolemia, euglycemia, and mild hypernatremia, and sedation using ketamine and benzodiazepines to manage dysautonomia, were in place before the diagnosis of ABLV infection was confirmed.5 Amantadine, recommended for its antiviral and neuroprotective effects, was subsequently commenced.

The diagnosis of ABLV infection was confirmed coincident with ongoing neurologic deterioration. Pituitary
dysfunction progressed; vasopressin was required for diabetes insipidus and hydrocortisone for low cortisol levels and hypoglycemia. Repeat EEG identified seizure activity, and phenytoin was commenced. Serial neuroimaging demonstrated progressive changes with uniform T2 and Flair hyperintensities originating in the basal ganglia and bilateral thalami (Fig 2), and CSF protein increased dramatically to $>36.0$ g/L.

 Serum Lyssavirus antibody titer increased to 1.58 IU/L. Repeat PCR testing of CSF and saliva remained positive for Lyssavirus. Pupils became fixed and dilated, spasms resolved, spontaneous movements ceased, and reflexes were absent, despite weaning sedation. By day 26 of hospital admission the EEG was isoelectric in the absence of sedating medication. The child was extubated on day 28 of hospital admission, and died shortly thereafter.

**DISCUSSION**

Human ABLV infection is extremely rare, but has proved fatal in all 3 confirmed cases. The clinical presentations and subsequent poor outcomes of the 2 previously reported cases in adults and the child here described are consistent with what is known of other Lyssaviruses, including classic rabies. Although indigenous cases of classic rabies have never been identified in Australia, ABLV is enzootic in Australian pteropid fruit bats and insectivorous bats. Prevalence of ABLV is low in the wild bat population (<1%), but is between 5% and 10% in sick, injured, or orphaned bats. Transmission to humans is believed to occur through direct inoculation of saliva from an infected primary host, typically via a bite or scratch. Wide variation in incubation periods have been observed in human rabies, from 5 days to 7 years. The 3 confirmed cases of human ABLV infection presented 4 weeks, 27 months, and ∼8 weeks, respectively, after the encounter with a bat.

Classic rabies presents in 1 of 2 forms. The encephalitic or “furious” form of the disease is most common, but a paralytic presentation with “dumb” rabies is also well described. All 3 cases of ABLV have followed the pattern of encephalitic rabies. In such cases, the acute neurologic phase manifests after a short prodrome of fever, malaise, and occasionally localized paraesthesia or pruritis at the site of inoculation. Cerebral and autonomic dysfunction develops, manifested by pathognomonic symptoms of hydrophobia and aerophobia, and less specific findings of agitation, confusion, hyperventilation, and hypersalivation. Hyperactivity is typically episodic, interspersed with periods of calm during which the patient may be cooperative and oriented. Spasms are nearly always present in encephalitic rabies, and may be associated with facial grimacing and expressions of fear. Pneumomediastinum is a rarely reported complication. Seizures are rarely part of the initial presentation, but may be seen late in the illness.

Antemortem diagnosis of rabies and other Lyssaviruses is challenging. Neuroimaging may be normal at time of presentation. A mild CSF pleocytosis is seen in ∼60% of patients. Serum and CSF Lyssavirus antibodies are frequently negative initially, with antibody response a late feature in patients who have longer survival. ABLV has close phylogenetic similarity to rabies, and can be identified using rabies RT-PCR assays. Rabies is not always detectable on CSF analysis, but RT-PCR is reliably positive on nuchal skin biopsy (sensitivity 98.3%). Sensitivity of saliva RT-PCR is ∼70%, but is improved by repeated testing. Nuchal biopsy has not been studied specifically for the diagnosis of ABLV, but it is likely that it would facilitate earlier diagnosis, as it does with rabies. ABLV was detected by Taqman RT-PCR on saliva and nuchal skin biopsy in a previous case of human infection, 14 and 12 days before...
death, respectively. Serum and CSF samples tested negative. There are no established treatment guidelines for ABLV infection, and therapeutic options for Lyssaviruses as a group are limited. Palliation remains the appropriate course in most cases. Corticosteroids are thought to precipitate progression of disease and should be avoided. Administration of rabies vaccine or immunoglobulin has not proven effective after onset of symptoms, and may be harmful. Activity against rabies virus has been identified in vitro or in animal models for amantadine, ribavirin, interferon-α, and ketamine, but these have not demonstrated efficacy in human infection. The MP was established after the first recorded survival of rabies in the absence of post-exposure prophylaxis (PEP). Further successes have followed, but failures have also been reported. A causative link between use of the MP and survival has not been established, and its use remains controversial. The MP is based on general intensive care principles such as aggressive sedation and supportive measures, with amantadine incorporated for its antiviral capability. These elements, including strict glycemic and intravascular control, treatment of dysautonomia, ketamine for sedation, and the addition of amantadine, were all used in the case we describe.

On notification of the case, Infection Control and Public Health Unit staff coordinated identification, assessment, and PEP of potential contacts (household

FIGURE 2
MRI brain T2 Flair images on A, day 7; B, day 11; C, day 19; and D, day 28 of admission, demonstrating progressive changes in the basal ganglia and thalami.
members and healthcare workers) in accordance with national and international guidelines. PEP, using a regimen of 4 doses of rabies vaccine and a single administration of human rabies immunoglobulin, is safe and provides effective protection against all Lyssaviruses known to cause human infection, including ABLV. It should be offered to any person who has had mucous membrane or broken skin contact with the saliva or neural tissue of a potentially infected animal, including any bat or flying fox from Australia. Awareness among clinicians and the population of the importance of even minor exposures remains an ongoing concern.

CONCLUSIONS
ABLV has proved fatal in all 3 human cases reported to date. As with classic rabies, it presents a diagnostic challenge, and therapeutic options are limited. The pathophysiology of the disease remains poorly understood, and further research is required to develop effective therapies. PEP prevents disease, and should be considered in all cases that constitute a potentially significant exposure. There is a need for increased public and clinician awareness of the risk associated with bat contact, and the fact that timely PEP can effectively avert further devastating cases such as the one we describe.

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