Bat Rabies Virus Variants Causing Human Rabies

To the Editors:

Willoughby and Hammarin[1] have recently discussed human rabies caused by bat rabies virus variants. They stated "the colonial species of bats found in very large numbers under bridges and in caves in central Texas have not transmitted rabies to humans." The main bat species they are referring to is the Brazilian (Mexican) free-tailed bat, *Tadarida brasiliensis*, and the rabies virus variant associated with this species is actually second only to the variant associated with *Lasionycteris noctivagans* (silver-haired bat) and *Pipistrellus subflavus* (eastern pipistrelle bat) as the most common cause of human rabies in the United States. Since 1990, there have been 7 well-documented fatal cases of human rabies resulting from infection with this variant in Texas (1990), Alabama (1994), California (1995, 2000 and 2002), Georgia (2000) and Arkansas (2004).[2,3] The latter case was an organ donor in Texas, and transmission occurred to 4 transplant recipients with fatal outcomes.[4] Although rabies is very common in big brown bats (*Eptesicus fuscus*), the variant associated with these bats is a rare cause of fatal human rabies, and a case occurred in Washington in 1997.[2] Little brown bats (*Myotis lucifugus*) belong to the *Myotis* species, and variants associated with this genus have also caused fatal human rabies in Washington in 1995[2] and in British Columbia in 2003.[5]

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Ptosis as a Presenting Feature of Bacterial Meningitis

To the Editors:

Involvement of the cranial nerves as a presenting feature of bacterial meningitis is rare.[1–3] We report a case presenting with total right oculomotor nerve palsy (OMP) caused by *Streptococcus pneumoniae* meningitis.

An 8-month-old boy was brought to the emergency department of the Children's Hospital Medical Center, Tehran, Iran, with abrupt onset of ptosis of the right eye. He had been well until 3 days earlier, when he developed fever and restlessness. The infant was diagnosed at that time as having otitis and managed as an outpatient with promethazine and oral antibiotics. On the day of admission, he was afebrile and alert but appeared ill. The anterior fontanel was flat. He had a complete right side ptosis with a dilated pupil that was unresponsive to light. The eyeball deviated laterally and inferiorly. A brain computerized tomographic scan revealed no pathologic findings. Lumbar puncture was done which showed turbid cerebrospinal fluid. The cerebrospinal fluid smear and culture were positive for *S. pneumoniae*, along with 110 white blood cells/mm^3 (85% polymorphonuclear cells, 15% lymphocytes), 1 mg/100 mL glucose and 290 mg/100 mL protein. Intravenous ceftriaxone, vancomycin and dexamethasone were started without further delay. He developed a low grade fever for 2 days coupled with left facial nerve palsy, poor feeding, several attacks of seizure along with ptosis and mydriasis on the left side and a gradual decrease in the level of consciousness leading to coma. A second brain computerized tomographic scan confirmed multiple hypodense regions in the basal ganglia, the thalamus and the internal capsule. A second lumbar puncture was performed which showed a good response to antibiotics with 23 white blood cells/mm^3, 52 mg /100 mL glucose, 97 mg/100 mL protein and a negative smear and culture. The clinical condition of the patient continued to deteriorate, leading to severe spasticity and apnea. The infant died 7 days after the day of admission. Postmortem study was not permitted by the parents.

OMP can result from intraorbital, intracranial or systemic infections,[2] including meningitis. Acute bacterial meningitis is a well-known cause of acute palsies of either the seventh or the eighth cranial nerve[4] but uncommonly produces acute onset palsy of oculomotor nerve, especially as a presenting symptom of the disease. In most of the reported cases for cranial nerve palsy, it has been a sequela of the infectious process and not a presenting feature.[1–3]

The mechanisms of oculomotor palsy in this patient could have been the inflammation around the nerve, but because of its acute nature a vascular mechanism (vasculitis or thrombosis of the small penetrating arteries) may be the likely cause of this unusual presentation.

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Septic Shock Complicating Acute Rotavirus-Associated Diarrhea

To the Editors:

Even though enteric Gram-negative rod (EGNR) bacteremia has been described as a possible complication of acute gastroenteritis,[1,2] very few reports of EGNR bacteremia as a complication of rotavirus-associated acute diarrhea have been published to date.[3] Herein we report 1 case of acute rotavirus-associated diarrheal disease complicated by enteric Gram-negative-induced sepsis and septic shock.

A previously healthy 10-month-old female infant was admitted after presenting watery diarrhea, heavy vomiting and low grade fever for <24 hours. At physical examination, lethargy, tented skin, dry mucous membranes, sunken eyes and delayed capillary refill were noted. White blood cells (WBC) count was normal except for mild lymphocytosis. Arterial blood gas, serum electrolytes, liver and renal function tests, urine and stool analysis and stool culture were normal. Enzyme immunoassay of stool samples was positive for rotavirus. Intravenous fluids were started, and the infant's condition improved on the following day.

On the third postadmission day, she appeared lethargic and presented fever (39.1°C), tachycardia (180 beats/min), tachypnea (50 respirations/min), poor peripheral perfusion, disseminated dark papulae in the skin and oliguria. Arterial hypotension (63/44 mm Hg) and severe metabolic acidosis (arterial blood pH, 7.24; bicarbonate, 9 mmol/L) ensued. A new WBC count revealed 10% band forms; platelets, 290,000/mm^3. She was admitted to the intensive care unit, and aggressive fluid resuscitation and norepinephrine were started. Cerebrospinal fluid analysis was normal. Empirical antimicrobial therapy was started with cefepime. She developed disseminated intravascular coagulation (DIC) (platelets, 51,000/mm^3; prothrombin activity, 20%; activated partial thromboplastin time, >180 s) and, despite the prophylactic use of omeprazole and the transfusion of platelets and fresh frozen plasma, she presented a self-limited upper gastrointestinal hemorrhage. No seizures occurred. A blood culture isolated a multidrug-resistant extended spectrum β-lactamase (ESBL)-producing *Escherichia coli* strain (resistant to ampicillin, ampicillin + sulbactam, aztreonam, cephalothin, cefazolin, cefepime, ceftazidime, ceftriaxone and cefuroxime). Antimicrobial therapy was then changed to meropenem. On the third day of intensive care unit stay, cellulitis was noted on her left leg. A new WBC count revealed 34,600 cells/mm^3, with 20% band forms and 2% metamyelocytes. Culture of the cellulitis purulent secretion yielded multidrug-resistant ESBL-producing *E. coli*. Antimicrobial therapy was maintained and the celullitis resolved in 5 days. She completed a 14-day regimen of meropenem and was discharged home. Liver and renal function tests remained normal throughout the hospital stay. She appeared to be in excellent health on the follow-up visit 1 month later.

Dehydration and hypovolemic shock are regarded as the most severe end of the spectrum of rotaviral disease. Our young infant was admitted because of a severe dehydrating typical rotaviral diarrhea that improved with supportive management; she deteriorated abruptly 3 days after the onset of the disease, developing lethargy and clinical and laboratory signs of systemic inflammatory response. A blood culture confirmed bloodstream infection, thus sealing the diagnosis of EGNR-induced sepsis. A multidrug-resistant ESBL-producing *E. coli* was isolated, and the empirical antimicrobial regimen adopted was ineffective. Consequently the patient deteriorated and developed severe complications of sepsis and shock, DIC and upper digestive bleeding.

Although severe sepsis, especially with Gram-negative bacteria, is the main cause of DIC in children, shock of any etiology can lead to DIC. DIC has been reported in infants with rotavirus diarrhea and negative blood cultures,[4] presumably as a consequence of hypovolemic shock and its metabolic derangements, but a direct effect of viremia cannot be excluded.

The precise mechanisms by which normal intestinal flora bacteria reach the bloodstream and spread throughout the body remain unclear. Although it is tempting to believe that normal intestinal flora disseminate through a damaged mucosa during rotaviral disease, rotavirus has never been shown to cause substantial cell death or mucosal inflammation.[5,6] On the other hand, rotavirus is known to cause intestinal epithelium dysfunction, and rotavirus-infected enterocytes are more vulnerable to bacterial invasion.[7] The impact of these findings on intestinal permeability to bacteria from normal intestinal flora is unknown.

The case herein presented documents a life-threatening complication of rotavirus-associated diarrhea that is rarely reported. Although it may indeed be a rare event, it may also be frequently overlooked and confused with a severe picture caused by rotavirus alone. The possibility of sepsis should be promptly considered in severely ill patients and in those who develop lethargy, poor peripheral perfusion or signs of systemic inflammatory response after a few days with proven or suspected rotaviral diarrhea.

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Oseltamivir and Delirious Behavior in Children With Influenza

To the Editors:

Influenza virus sometimes causes severe disease including pneumonia, bronchiolitis and encephalopathy. A substantial number of influenza-associated deaths occur even in advanced countries. In addition, there is an increasing threat of pandemic avian influenza virus disease that can have a high case fatality rate.[1] The neuraminidase inhibitor oseltamivir constitutes an important treatment option for influenza. Moreover many countries have begun to stockpile oseltamivir as a part of their pandemic planning. Oseltamivir has few adverse effects when administered for either treatment or prophylaxis,[2] although the safety of oseltamivir in infants has not been established.[3] Moreover some pediatric deaths after the use of oseltamivir were recently reported in Japan. Among them, the concern arose that abnormal behavior in relation to oseltamivir may have resulted in accidental deaths of 2 juvenile patients (reported by Hama).[4]

We studied retrospectively the occurrence of delirious behavior after the use of oseltamivir in pediatric patients. The records of patients younger than 15 years of age who were prescribed oseltamivir between January 2004 and March 2005 were reviewed in 6 Nagoya University-affiliated hospitals. We included all patients with documented influenza who had delirious behavior during this period whether or not they were treated with oseltamivir.

Oseltamivir was prescribed to 6121 patients in the 6 hospitals. Nine patients with delirious behavior were identified, of whom 4 patients (2 boys and 2 girls) had delirious behavior after the use of oseltamivir. The average age of these 4 patients was 5.9 years (range, 3.7–10.1 years). Delirious behavior was observed 1 day after the onset of fever in all patients. Its duration was 30 minutes or less in 2 patients, but it lasted intermittently for several hours in the other 2. Their delirious behavior included meaningless speech, disorientation, fearful response and running around the room. No patient had neurologic sequelae.

From the review of their medical records, we believe that oseltamivir was not responsible for delirious behavior in these 4 patients. All patients received other drugs including antipyretics and antihistamine drugs that can cause adverse effects with neurologic findings. All patients received additional doses of oseltamivir despite the delirious behavior, which did not recur in any of them.

The result of our review is consistent with the statement of the United States Food and Drug Administration on the safety of oseltamivir.[5] We totally agree with the comment from United States Food and Drug Administration that the increased reports of neuropsychiatric events in Japanese children are most likely caused by an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir and a coincident period of intensive monitoring of adverse events.

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Anthrax Meningoencephalitis Secondary to Oral Infection

To the Editors:

Meningeal involvement is an extremely rare manifestation of anthrax, and most cases are secondary to gastrointestinal and mediastinal infection.[1] We report fatal anthrax meningitis that developed following oral anthrax disease.

An 11-year-old boy from a highland village of eastern Turkey had a few small, itchy papules on the oral surface of his lips with high fever, headache and sore throat on January 22, 2006. Within ~4–6 hours, his lips and tongue became swollen, and dysphonia developed. When he was admitted to our pediatric emergency clinic, he was unconscious with shallow breathing caused by oropharyngeal edema. The patient had 3 generalized seizures and was mechanically ventilated because of apnea episodes.

Edema of his tongue and lips with widespread, small, necrotic vesicular lesions, chills, nuchal rigidity and a positive Kernig-Brudzinski sign were the most significant findings. Vital signs were: fever 36°C (rectal), blood pressure 88/60 mm Hg and heart rate 92/min.

Hematologic findings included white blood cell count of 18,700/mL with 85% neutrophils and 9% lymphocytes. Erythrocyte sedimentation rate was 3 mm/h. The cerebrospinal fluid (CSF) findings were glucose 117 mg/dL (simultaneous serum 155 mg/dL), protein 439 mg/L and chloride 102 mg/L. Many erythrocytes, 3000 neutrophil/mm^3 and 1000 mononuclear leukocytes/mm^3 were present, and Gram

staining of the CSF also showed the presence of large (1.5–2 × 6–8 μm in size) and square-ending Gram-positive bacilli that appeared single or as chains of 2–3 organisms.

Computerized tomography scan and radiograph of the chest were normal. Cranial computerized tomography scan demonstrated 5 × 8 mm of hemorrhagic focus in the left supratentorial area and diffuse cerebral edema. Magnetic resonance scan of the brain revealed findings consistent with meningoencephalitis in both cerebral hemispheres, cerebellum and basal ganglions. Therapy was commenced empirically with acyclovir, cefotaxime and dexamethasone. For consideration of anthrax, ciprofloxacin was also added to the therapy (20 mg/kg/d, in 2 equally divided doses).

After an overnight culture of the CSF sample, white, wavy and nonhemolytic R-form colonies 3–4 mm in diameter grew on sheep blood agar. Bacterial growth with similar morphology was observed from an aerobic blood culture and from the aspirate of an oral mucosal vesicle. The organism did not grow in 6% NaCl containing nutrient agar; was urease-negative; reduced nitrate; used glucose, maltose and sucrose; and hydrolyzed gelatin. The organism was susceptible to penicillin, azithromycin, rifampin, clindamycin, ciprofloxacin and vancomycin by disk diffusion testing. Minimal inhibitory concentrations of penicillin and ciprofloxacin were 0.032 and 0.023 μg/mL, respectively. The organism was identified as *Bacillus anthracis* based on growth characteristics, morphologic features, biochemical reactions and antimicrobial susceptibility pattern.

The patient's fevers gradually decreased to 34–34.5°C. Disseminated intravascular coagulation developed, and fresh plasma was given 3 times. Phenytoin was commenced for continuing seizures. Pupillary reflexes in both eyes disappeared, and electroencephalograpy confirmed brain death 32 hours after admission. The patient could not be resuscitated from a cardiac arrest at 40 hours, and he died on January 25.

Polymerase chain reactions were conducted for the CSF, blood and vesicular aspirate samples. The pathogen was confirmed as anthrax bacillus. Polymerase chain reaction testing for herpesvirus was negative for these 3 samples.

There are a few well-documented case reports of anthrax meningitis in pediatric patients.[2–4] The infections developed secondary to pneumonia[2] or gastroenteritis[3,4] caused by *B. anthracis*. Acquisitions of the organism by these patients resulted from inhalation of the spores or from ingestion of contaminated food. Family infections were also encountered.[3] Hemorrhagic and edematous meningitis and sepsis developed in all the cases, and only 1 patient recovered from the infection.[2–4]

A detailed interview was conducted with the patient's family. They heard that 4 cattle in their neighbor's farm died due to anthrax in the previous summer. The patient assisted his father and his neighbors when they processed the meat during the Muslim Festival of Sacrifices on January 10–14. The patient's oral lesions emerged within 4 or 5 days.

Anthrax is prevalent in the Middle East. Though the developed countries have reduced the prevalence of anthrax with vaccination practices and industrial hygiene,[5] it is still prevalent in the eastern part of the Turkey.

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