Clinical Reasoning: An unexpected diagnosis in a 4-month-old infant with lethargy and H1N1 influenza

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SECTION 1
A 4 month-old former full-term male infant presented with 4 days of lethargy, fussiness, low-grade fever, and dehydration, prompting hospital admission. His mother had tested positive for H1N1 influenza the week before, and treatment with oseltamivir was started. Oseltamivir treatment was started empirically in the infant, but he was brought in for emergency care for progressively worsening symptoms, including poor breastfeeding and decreased urine output. He was otherwise previously healthy and developmentally normal and lived with his parents and 4 siblings on a farm in rural Washington.

On admission, the patient was febrile, lethargic, and dehydrated. After an episode of emesis and subsequent increased respiratory effort, he was intubated and transferred to the intensive care unit. At the time of the initial neurology service consultation, on hospital day 2, he had recently received doses of morphine and fentanyl but was responsive to gentle physical stimulation. Although he did not track visual stimuli, he had intact horizontal eye movements on oculocephalic testing and 4-mm briskly reactive pupils bilaterally. His gag reflex was weak, and he appeared to have mild facial diplegia, but this was difficult to assess because of endotracheal tube taping. Spontaneous extremity movements were infrequent, and although his resting position was normal, appendicular tone was mildly low. His reflexes were 1+ at the brachioradialis, biceps, knees, and ankles. Plantar responses were upgoing.

Results of initial electrolyte analyses and complete blood count were normal, and C-reactive protein level was 3.7 mg/dL (normal <0.7 mg/dL). Results of a head CT scan and routine CSF studies were normal. Blood and CSF cultures remained negative. CSF herpes simplex virus 1 and 2, enterovirus, and parechovirus PCR assays yielded no detectable copies. Results of nasal wash fluorescent antibody testing and PCR were positive for influenza A, subtype H1N1. Brain MRI showed normal results. The serum creatine kinase level was 20 IU/L, and evaluation for metabolic disorders was unremarkable. His lethargy was attributed to an influenza-associated encephalopathy.

Questions for consideration:
1. What are the neurologic symptoms of H1N1 influenza in the pediatric population?
2. What aspects of the hospital care decrease the sensitivity of the neurologic examination?
SECTION 2
Fever, rhinorrhea, cough, sore throat, muscle aches, and gastrointestinal symptoms were common symptoms in patients with the novel H1N1 virus. Infants younger than 1 year had the highest hospitalization rates of any age group. Neurologic symptoms in pediatric patients typically began 1–5 days after disease onset, were similar to those seen with seasonal strains of influenza, and included altered mental status, irritability, headache, fatigue, seizures, weakness, dizziness, ataxia, movement disorders, cranial nerve palsies, and hallucinations. In some patients, neurologic symptoms were associated with MRI abnormalities.

The supportive care necessary for the comfort and safety of our patient, including opiate administration and endotracheal tube placement, may have compromised our initial neurologic examination. Opiates have a sedative effect, potentially causing decreased visual attentiveness, spontaneous movement, and tone, and can also produce pupillary miosis. The tapping required for endotracheal tube security often makes it more difficult to assess facial diplegia, symmetry, and movement.

By hospital day 4, our patient had not shown any signs of clinical improvement. Therefore, ceftriaxone was started for possible bacterial pneumonia, and antiviral coverage was changed to IV peramivir under emergency use authorization from the US Food and Drug Administration. On hospital day 5, the patient was found to have large, sluggishly reactive pupils and hypoactive reflexes in all 4 extremities. Extubation failed, and he had an absent gag reflex and weak cough. He had not produced stool since before admission, a symptom initially attributed to decreased oral intake.

Questions for consideration:
1. Could neuraminidase inhibitor administration adversely affect infants?
2. Should the differential diagnosis be broadened?
SECTION 3
Although there are no published trials of peramivir use in the pediatric population to date, retrospective reviews suggest that oseltamivir is safe and effective for infants younger than 1 year. Some have theorized that an iatrogenic reduction in human neuraminidase (also known as sialidase) activity by viral neuraminidase inhibitors can produce adverse neuropsychiatric effects. A recent study has shown that although recombinant human sialidases are not affected by oseltamivir, peramivir and zanamivir may inhibit these enzymes at high concentrations. To screen for a possible underlying mild neuraminidase deficiency (sialidosis) in our patient, we assayed urinary oligosaccharide excretion, which was normal.

Concerns for coexisting Guillain-Barré syndrome or infant botulism developed. Stool studies were ordered for botulinum toxin, botulism immunoglobulin was ordered, and peramivir was discontinued. On hospital day 6, motor and sensory nerve conduction studies with high-frequency tetanic repetitive nerve stimulation were done and provided no electrophysiologic evidence supportive of neuropathy or botulism.

Questions for consideration:
1. What is your differential diagnosis at this point?
2. Can electrophysiologic studies aid in the diagnosis of infant botulism?
The diagnosis of infant botulism is largely clinical. The most commonly reported symptom is constipation. On examination, infants have weakness of the face, neck, and shoulder girdle in the context of less affected extremity strength. Weak suck, decreased gag reflex, and respiratory distress are also common, but reports indicate that deep tendon reflexes are generally preserved and that pupillary reactivity is highly variable. A positive stool toxin neutralization mouse bioassay is supportive of the diagnosis, but because these results take a few days to return, clinical acumen in combination with electrodiagnostic testing may expedite a timely diagnosis. Published electrodiagnostic criteria for infant botulism require small evoked compound muscle action potentials (CMAPs) to supramaximal nerve stimulation, tetric facilitation of CMAPs in response to 20- to 50-Hz stimulation, and prolonged posttetanic facilitation of CMAPs. These studies were all normal in our patient.

Over the subsequent days, the patient remained intubated, with return and disappearance of the gag reflex, intermittently brisk pupillary reflexes, and variable spontaneous movement. On hospital day 10, results of the mouse bioassay returned positive for _Clostridium botulinum_ toxin, type A. The patient was given IV botulism immunoglobulin the same day and over the next 5 weeks made a gradual recovery, remaining intubated until hospital day 21. He was discharged on hospital day 35, still receiving the majority of his nutrition via nasogastric tube feedings and with persistent hypotonia and weakness in the neck, trunk, and extremities. Six months later, he had ongoing difficulties with constipation but was eating all age-appropriate table foods and had normal motor development.

**DISCUSSION**
The most prominent risk factor for infantile botulism is patient age, as most cases occur between 2 and 8 months. The infectious process begins with the germination and multiplication of _C. botulinum_ bacterial spores within the intestine. The bacteria produce a neurotoxin that inhibits acetylcholine release from neuromuscular terminals. Symptoms usually begin after a suspected incubation period of 3–30 days, and achievement of complete recovery is slow because it requires regeneration of terminal motor neurons and formation of new motor end plates. Administration of human botulism immunoglobulin IV (BIG-IV) has been shown to decrease the length of hospital stay, mechanical ventilation, and tube feedings and total hospitalization cost. The mean length of hospital stay for infants with type A infections is approximately 2.6 weeks for those receiving BIG-IV in the first week of illness, compared with 5.7 weeks for untreated infants. Because soil disruption is a risk factor, cases may be connected to infants’ exposure to spores found in soil and dust that surround farm-based homes. According to Washington State Department of Health statistics, a total of 15 infant botulism cases were reported in the state between 2005 and 2009, including 2 during the year of our patient’s presentation. Other areas of the United States with higher incidences of infantile botulism include California, Utah, and Pennsylvania. Although our breastfed infant was not transitioning to formula or exposed to honey, known risk factors for this infection, he was exposed to antibiotics. Theoretically, antibiotic administration may cause lysis of intestinal _C. botulinum_, leading to increased release and absorption of intraluminal neurotoxin. Most important, because host defenses probably play a significant role in disease manifestation, it is likely that our patient’s infection with H1N1 influenza decreased his natural, robust host response to colonization by _C. botulinum_ spores, causing emergence of the clinical manifestations of infant botulism. Conversely, a gradual neurologic deterioration from botulism could have already begun when he contracted H1N1 influenza.

With the diagnosis of a recently discovered viral influenza strain, our patient was quickly identified as having influenza-associated encephalopathy, and, in the context of growing reports of high infant hospitalization and mortality rates, this was not aggressively debated at the time of his admission. Given his laboratory-confirmed diagnosis of H1N1 influenza and nondiagnostic electrophysiologic studies, providers were hesitant to make the clinical diagnosis of infant botulism and initiate treatment before the return of stool study results. The high financial cost and potential risks (including flushing, anaphylaxis, and hypotension) of administering botulism immunoglobulin empirically to an uninfected infant were considered. In the end, the diagnosis was not made in time to administer treatment within the time period found to be most beneficial. This case highlights the importance of thorough history-taking techniques and meticulous serial neurologic examinations and the need for constant reevaluation of the differential diagnosis in young patients with nonspecific neurologic findings.

**ACKNOWLEDGMENT**
The authors thank Dr. Jessica M. Khouri and Jessica Payne, MPH, with the Infant Botulism Treatment and Prevention Program, California Department of Public Health, and Dr. Marcia Golofd, Deputy State Epidemiologist, Washington State Department of Health, for unpublished epidemiologic data and helpful discussions.

**DISCLOSURE**
Dr. Hyslop and Dr. Droker report no disclosures. Dr. Jansen has received research support from the NIH/NINDS and the Child Neurology Society.
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Neurology 2011;76:e88-e92
DOI 10.1212/WNL.0b013e3182190cf2

This information is current as of May 2, 2011