Catastrophic Presentation of Infant Botulism May Obscure or Delay Diagnosis

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ABSTRACT. Three infants with infant botulism are presented to illustrate how atypical, early, and severe features may obscure or delay diagnosis. Two boys aged 6 weeks and 20 days, respectively, presented with rapid deterioration after brief periods of poor feeding, one with an apparent life-threatening event at home and the other with a full cardiopulmonary arrest. Initial abnormal laboratory findings of coagulopathy suggested sepsis in the first infant. In the second infant, severe acidosis and hypoglycemia suggested an underlying metabolic disorder. A third infant, aged 1 month, was hospitalized originally with an admitting diagnosis of "pharyngitis" resulting from his inability to take adequate feedings. He received intravenous fluids and antibiotics. One week later he suffered a respiratory arrest. Laboratory findings of severe hyponatremia and acidosis at the time of his arrest suggested a metabolic etiology. Even retrospectively, none of these infants had the typical initial complaint of constipation, and none were noted to have ptosis or facial weakness before catastrophic collapse. However, in each case, the parent had initially brought the child to the physician for "poor feeding" or "poor suck," which was not recognized by medical personnel as a result of bulbar weakness. Ultimately, all 3 infants were found to have infant botulism. All 3 had received antibiotics before catastrophic collapse, possibly contributing to the rapidity of the deterioration. Each recovered, although the delay in diagnosis made them ineligible for treatment with botulism immunoglobulin. *Pediatrics* 2005;116:e436–e438. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0297; *infant botulism, apparent life-threatening events, bulbar weakness.*

ABBREVIATIONS. SIDS, sudden infant death syndrome; Pco_2, partial pressure of carbon dioxide; CSF, cerebrospinal fluid.

The typical presentation of infant botulism is familiar to most pediatric neurologists and pediatric intensivists and thus is not likely to be missed. However, there are times when the presentation is so atypical or catastrophic that the diagnosis is not immediately obvious. This may then delay the diagnosis and treatment. We now report 3 infants with unusual presentations of catastrophic illness in whom the diagnosis of infant botulism was delayed.

Typically, infant botulism presents with acute or subacute onset of weakness and hypotonia. It first affects the bulbar musculature, manifesting as poor suck and hypophonic cry, facial weakness, ptosis, abnormal eye movements, and abnormal papillary reactions. It is then followed by neck and shoulder-girdle weakness and, finally, a progressive, descending pattern of weakness and hypotonia.[1–4] Onset is typically in the first 6 months, although cases have been reported as early as a few days through 12 months of age. Although "constipation" is a poorly defined complaint, parents typically report a change in stool pattern with decreased frequency of bowel movements before recognition of weakness. Early in the course, reflexes as well as distal strength tend to be preserved. Later, substantial weakness and incipient respiratory failure occur. The time course is highly variable, ranging from <24 hours to >1 week from time of first symptom to the nadir of strength. For the most part, infants maintain normal alertness and responsiveness to the environment. Substantially altered mental status is uncommon unless there are significant secondary complications of hypoxemia, dehydration or hypoglycemia, or incipient respiratory failure.

Shortly after infant botulism was recognized in 1976,[1,5] questions arose about whether it accounted for a proportion of sudden infant death syndrome (SIDS) cases.[6–8] Conflicting information initially suggested that botulism might account for as much as 10% to 15% of SIDS cases.[9,10] For example, Murrell et al found *Clostridium botulinum* spores in 6 (5%) of 120 SIDS cases compared with 0 of 53 healthy controls, but botulinum toxin was found in only 1 SIDS case compared with 0 of 49 samples from healthy infants.[11] Other studies failed to confirm an increased prevalence of *C botulinum* organisms and toxin in intestinal contents of deceased infants with SIDS compared with normal infants.[12–14] Exceptionally severe, early-onset infant botulism has been described, suggesting catastrophic metabolic or infectious disease, which may delay the diagnosis.[15]

With the development and approval of human botulism immunoglobulin (BabyBIG), prompt diagnosis is essential to end the toxemia associated with infant botulism as quickly as possible. To date, BabyBIG has only been available for use in those who are diagnosed within 7 days of hospital admission. We present 3 cases of atypical infantile botulism. Al-

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though all 3 infants ultimately recovered, none were eligible for treatment with botulism immunoglobulin because of a delay in diagnosis.

CLINICAL REPORTS

Patient 1

This 6-week-old boy was well until 4 days before admission when he had decreased oral intake and a weak cry. The next day he had a tactile fever and was treated with amoxicillin for ear infection by his pediatrician. On the day of admission, he stopped breathing immediately after nursing and became blue and limp. The father initiated cardiopulmonary resuscitation, and the paramedics were called. On arrival, paramedics noted that the patient had no spontaneous respiration and had a "weak" heart rate. Cardiopulmonary resuscitation was continued on route to emergency department, where he was intubated. Initial arterial blood gas analysis showed pH of 7.01, partial pressure of carbon dioxide (Pco_2) at 35 mm Hg, and partial pressure of oxygen at 305 mm Hg, while he was being ventilated with 100% oxygen. The initial examination demonstrated a lethargic and diffusely hypotonic infant, noted to have briskly reactive pupils and no facial asymmetry. He was noted to move all extremities to painful stimuli and had intact tendon reflexes. He was admitted to the pediatric intensive care unit (PICU). Initial abnormal laboratory values suggested sepsis with coagulopathy (prothrombin time: 15.6 seconds; partial thromboplastin time: >150 seconds). However, these values normalized over the first 2 days. All cultures (blood, urine, and cerebrospinal fluid [CSF]) were negative. He received intravenous antibiotics (ampicillin and ceftriaxone). The parents did not report any change in stool pattern. A neurology consultation was obtained on hospital day 2. On examination, he was somnolent, although briefly arousable. He had ptosis and sluggishly reactive pupils (3 to 2 mm), did not visually fix or follow, and had partial extraocular movements on dolls-head maneuver but no spontaneous eye movements. He had a poor gag reflex, poor cough, and no suck reflex. The face remained symmetric, and the tendon reflexes were present. The initial impression was sepsis with diffuse neurologic insult as a result of hypoxic-ischemic encephalopathy. A brain computed tomography scan was normal. He was extubated 3 days after admission but remained hypotonic, lethargic, and very weak. Stool sent for a botulinum toxin test 10 days after admission was positive for *C botulinum* type A toxin and organisms.

He had a biphasic course, initially improving and beginning to take oral feedings and then weakening again, with more typical features of infant botulism including infrequent bowel movements, ptosis, reduced gag, sluggish pupils, hypotonia, and weakness. Thirteen days after admission he had multiple episodes of apnea with CO_2 retention (Pco_2: 50–60 mm Hg). There were no obvious precipitants of the decline in strength. He was returned to the PICU for another 17 days but did not require reintubation. Total hospitalization was 57 days, requiring nasogastric tube feeding for 56 days. Follow-up in the neurology clinic 1 year after admission showed a complete resolution of all signs and symptoms with normal development.

Patient 2

This 34-day-old boy was well until 2 days before admission when he presented with poor oral intake. He was diagnosed with thrush and given mycostatin oral suspension. Two days later, he was admitted because of continued poor oral intake and weak cry and had an admission diagnosis of "pharyngitis." He was noted to be dehydrated, floppy, and lethargic. Change in frequency of bowel movements was denied, even later (retrospectively) in the course. Ampicillin and cefotaxime were started immediately on admission and continued throughout his stay at the referring hospital. All cultures (CSF, blood, urine) were negative. Cranial ultrasound, electroencephalography, and electrocardiography were all normal or negative. The patient worsened despite intravenous fluids and antibiotics and, on the eighth hospital day, became apneic with marked bradycardia, requiring intubation and respiratory support. He had severe metabolic acidosis and hyponatremia (serum sodium: 114 mEq/L.) He was transferred to the Childrens Hospital Los Angeles PICU for evaluation of respiratory failure and presumed metabolic encephalopathy. Neurologic consultation revealed a lethargic child who was diffusely hypotonic and weak, with nonreactive pupils, poor gag and suck, and absent tendon reflexes. His liver was slightly enlarged. Extensive evaluation of metabolic status was normal, including serum amino acids, urine organic acids, serum cortisol, and genetic testing for Prader-Willi syndrome, spinal muscular atrophy, and mitochondrial disorders. Neuroimaging (brain MRI) showed a punctate lesion in the right frontal white matter, ultimately thought to be insignificant. His metabolic acidosis recovered, but he remained severely hypotonic with poor gag and suck. Stool collected on the 14th day of illness was reported to contain toxin and spores of *C botulinum* type B. During his course, he developed transient bloody diarrhea, and his stool was positive for *Clostridium difficile* toxin. His diarrhea resolved without treatment.

He was intubated for a total of 13 days, unable to be orally fed for 17 days, and eventually discharged with minimal residual weakness 28 days after the original date of admission. On follow-up examination 2 months later, his neurologic examination was normal.

Patient 3

This 20-day-old boy had a diagnosis of suspected urinary tract infection at the age of 10 days and was treated with oral antibiotics for 5 days. He was well until 1 day before admission, when his mother noted that he was not eating well. Change in bowel movements was denied. On the morning of admission, he presented with poor oral intake, weak cry, lethargy, and floppiness. He had a full cardiopulmonary arrest in the emergency department requiring resuscitation including endotracheal intubation, 3 boluses of intravenous epinephrine, atropine, and bicarbonate. Immediately after resuscitation, arterial blood gas showed pH of 7.06, Pco_2 at 22 mm Hg, and partial pressure of oxygen at 569 mm Hg, while he was being ventilated with 100% oxygen. Initial blood glucose was 32 mg/dL. After resuscitation, cultures were collected, and he received intravenous ampicillin and gentamicin. The child was transported to the Childrens Hospital Los Angeles PICU.

On admission physical examination, the child was intubated and found to be minimally responsive, with some grimacing to pain, poor cough, and minimal gag. Initial blood lactate was elevated markedly (54 mg/dL [normal: 6–16 mg/dL]). All cultures (blood, CSF, urine) were negative. Because of initial severe acidosis and hypoglycemia, admission diagnoses included metabolic disorder, cortisol deficiency, or sepsis. He received multiple intravenous antibiotics (ampicillin, ceftriaxone, and acyclovir). Neurologic consultation on hospital day 3 documented a poorly arousable infant with minimal eye movements, unreactive pupils, no spontaneous facial movements, and minimal responses to pain. The initial neurologic impression was severe hypoxic-ischemic encephalopathy, with a possible underlying inborn error of metabolism. Cranial computed tomography, electroencephalography, and renal ultrasound were all within normal limits. On hospital day 8, he was somewhat arousable, with partial extraocular movements on doll's-head maneuver, ptosis, slowly reactive but fatigable pupils, and some spontaneous movement of fingers and toes. Tendon jerks were equivocally present. Because of the specificity of the finding of fatigable pupils for infant botulism, stool for *C botulinum* was sent on day 14 of the illness. Stool was reported positive for *C botulinum* toxin B.

He required intubation with respiratory support for a total of 19 days, PICU care for 21 days, nasogastric tube feeding for 24 days, and hospitalization for 25 days. Follow-up examinations 2 months after admission showed minimal neck extensor weakness, which was resolved at the next visit.

DISCUSSION

These 3 infants each presented with acute onset of weakness, culminating rapidly in respiratory and/or cardiorespiratory arrest in 2. None had the typical prodrome of constipation. Although each infant presented with similar bulbar weakness manifested by poor suck and weak cry, none were recognized as having facial weakness, ptosis, or abnormal eye movements. The poor suck and feeding difficulties were not initially recognized as resulting from bulbar weakness. They were attributed to other causes in-

cluding "pharyngitis," an unlikely diagnosis in the first few months of life. Two of the 3 were noted to have normally reactive pupils on admission, although poor pupillary reactivity or fatigable pupil reaction was noted later in the course. Fatigable papillary reaction is a finding relatively specific to infant botulism. In each case, severe infection and metabolic abnormalities were considered the likely etiology because of the severe metabolic acidosis. In 1 case, severe coagulopathy suggested sepsis. In another, marked hypoglycemia, hyponatremia, and an enlarged liver seemed to point to a metabolic etiology. Initial neurologic diagnoses were diffuse encephalopathy caused by hypoxic-ischemic insult, possibly complicating an underlying metabolic etiology in cases 2 and 3. As a consequence, stool samples for *C botulinum* toxin testing and cultures were not sent immediately. Delay in diagnosis made each of these patients ineligible for treatment with botulism immunoglobulin. Ultimately, metabolic and coagulation abnormalities present on admission were likely attributable to poor intake, dehydration, and the acute effects of the respiratory arrest. The hyponatremia present in patient 2 at the time of transfer was probably caused by secretion of antidiuretic hormone, known to occur in infant botulism.[16] All 3 children received multiple doses of broad-spectrum antibiotics. One received an aminoglycoside briefly, which could have worsened or prolonged the course of the infant's botulism.[17] One child (patient 2) developed transient bloody diarrhea, apparently caused by *C difficile*, a previously reported complication of infant botulism.[18,19]

We report these cases to illustrate that infant botulism can occasionally present as a catastrophic illness, which can lead to a delay in diagnosis while other etiologies are sought and presumptively treated. Over the last 20 years, 48 cases of infant botulism have been diagnosed at Childrens Hospital Los Angeles. Twenty-six of these cases have been diagnosed and treated in the last 10 years, the same period in which these 3 infants were admitted. These 3 cases stand in contrast to the rest in that diagnosis was delayed because of atypical and catastrophic presentation. We know of no other delayed diagnoses. However, atypical or catastrophic presentation may account for up to 12% (3 of 26) cases of infant botulism at this institution.

Even retrospectively, it was appropriate to initially evaluate and treat each of these infants for presumed sepsis and to consider possible inborn errors of metabolism in patients 2 and 3. Unfortunately, the use of broad-spectrum or clostridiacidal antibiotics may contribute to the abrupt worsening that each infant experienced, with the abrupt lysis of intestinal clostridia causing a massive release of toxin. This may have contributed to the severe toxemia in each infant, evidenced by unreactive or fatigable pupils. However, we urge that when infants are admitted for unexplained respiratory or cardiac arrest or with apparent life-threatening events in the presence of hypotonia and weakness, infant botulism should also be included in the differential diagnoses even if laboratory abnormalities initially suggest infection or metabolic abnormalities. Poor feeding is an extremely nonspecific complaint in young infants and may be seen in a variety of systemic illnesses. However, the possibility that bulbar weakness may account for poor feeding should be considered, and a careful neurologic examination should be performed. Bulbar weakness, as evidenced by poor feeding and weak cry, should raise the question of infant botulism.

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