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Infantile botulism in British Columbia: A case report

The clinical progress of two infants admitted to Victoria General Hospital in 2017 and 2018 illustrates the typical presentation of *Clostridium botulinum* infection and the approach to managing this infection.

ABSTRACT: Infantile botulism is a rare condition in children under 1 year of age caused by ingestion of *Clostridium botulinum* spores. The growing organism colonizes the intestinal tract and releases toxins that cause an acute flaccid paralysis. Many of the complications that occur in infantile botulism are respiratory in nature and include aspiration, acute respiratory distress syndrome, recurrent atelectasis, and pneumothorax. Gastrointestinal complications such as *Clostridium difficile* colitis can also occur. Two infants admitted to our pediatric centre approximately 2 months apart in 2017 and 2018 were both eventually diagnosed with infantile botulism. These cases illustrate the presentation, clinical course, and management approach typically seen in infantile botulism. Each patient presented with constipation and poor oral intake followed by diminishing strength and flaccid paralysis with respiratory compromise. In both cases the patients were treated with botulism immune globulin in the form of a product called BabyBIG that had to be ordered from the supplier in California. Diagnosis of infantile botulism is challenging because of the low prevalence of the disease in Canada and the large number of possible conditions that must be considered when generating a differential diagnosis for a hypotonic infant. A high index of suspicion is required to detect infantile botulism and treat affected patients early in the clinical course of the infection. The cost of BabyBIG and the need to order the antitoxin product from an out-of-country supplier must be taken into account when treating infantile botulism.

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Infantile botulism is a rare condition in children under 1 year of age that begins with ingestion of *Clostridium botulinum* spores.[1] The growing organism colonizes the intestinal tract and then releases toxins that bind to acetylcholine receptors, causing muscle weakness and leading to flaccid paralysis.[2] In contrast, foodborne botulism and wound botulism are caused by isolated toxin exposure, not colonization of the gut.[2]

C. botulinum infection is one of several conditions to include in the differential diagnosis when infants present with acute hypotonia. The cases of two infants admitted to Victoria General Hospital in 2017 and 2018 illustrate the typical presentation of infant botulism and the clinical course and approach to managing the infection.

Case 1 data

A previously healthy 2-month-old female presented to a smaller hospital in our region with a 4-day history of constipation and 1 day of decreased oral intake, lethargy, and a hoarse cry. Her father had a mild upper respiratory tract infection, but no other infectious contacts were identified. The patient was breastfed and formula fed and had no exposure to honey or solid foods. The week before presentation she had been switched to a new formula.

On examination the patient had no fever or symptoms of focal infection but did require treatment for dehydration. Her infectious disease workup included a nasopharyngeal swab and urine, blood, and cerebrospinal fluid cultures. The nasopharyngeal specimen was found positive for human metapneumovirus and a chest X-ray indicated pneumonia. The patient was started on ampicillin, cefotaxime, and oseltamivir. On day 1 she was placed on high-flow nasal cannula oxygen to treat apnea and bradycardias. On day 2 she was transferred from the smaller hospital to the pediatric intensive care unit at our centre because of her decreased respiratory effort and progressively worsening hypotonia. Shortly after arrival, the patient was intubated for respiratory failure with hypoxia and hypercapnia. She was profoundly hypotonic with shallow breathing, areflexia, no motor response to stimulation, minimal eye opening, and no cough or suck reflex. Results from an EEG and head imaging (ultrasound and CT scan) were normal. With flaccid paralysis making infantile botulism a possibility, a stool sample was

collected and sent for botulinum toxin testing.

On day 6 of hospitalization the patient was transferred to the provincial pediatric centre for neurological assessment and further workup. MRI results showed no lesions or other cause for hypotonia. The patient remained intubated and ventilated and exhibited little change in neurological status. With the clinical picture still suspicious for infantile botulism, botulism immune globulin (BIG) was ordered from the supplier in California. The antitoxin product BabyBIG arrived and was administered on day 8. Stool culture results confirmed the presence of botulinum toxin A on day 12.

Once the patient received BabyBIG her neurological function improved. However, due to ventilator-associated pneumonia she had a prolonged recovery and required extensive rehabilitation. After 40 days of hospitalization the patient was discharged with mildly decreased muscle tone, neurological function close to baseline, normal respiratory function, and full oral feeding.

No source of botulism in the patient's home was ever identified. The family used a formula-making machine and followed proper sterilization techniques. Public health was involved in testing the formula, the formula-making machine, and other possible sources of exposure.

Case 2 data

A previously healthy 3-month-old female presented to our centre after 4 days of constipation, 2 days of decreased oral intake and low energy, and 1 day of increased fussiness, poor head control, lethargy, and weak cry. She had no fever and no symptoms of focal infection. Both parents had upper respiratory tract infections. A few days earlier the patient had been seen by a family physician who recommended applesauce for her constipation. Other than the applesauce, the patient had no solid food or honey exposures and was breastfed and formula fed. In the month leading up to admission she had tried multiple premade and powdered formulas.

An examination of the patient revealed nonvigorous spontaneous movement in all four limbs, weak cry, no head movement, moderate peripheral and central hypotonia, and intact reflexes. The symptoms were considered suspicious for infectious causes. Nasopharyngeal swabs were taken along with urine and blood samples for culture. A metabolic workup, chest X-ray, and head ultrasound were all completed. The nasopharyngeal specimen was found positive for human metapneumovirus. Broad spectrum antibiotics were initiated at first presentation.

On day 1 the patient developed bilateral ptosis and a stool sample was sent for botulinum toxin testing. On day 2 she developed desaturation and increased secretions requiring high-flow oxygen and transfer to the pediatric intensive care unit.

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On day 3 the patient was transferred to the provincial pediatric centre for neurological assessment and further workup. On arrival her paralysis was seen to be progressing in a descending fashion. Given the possibility of *C. botulinum* infection, antibiotics were discontinued on day 4 to prevent the exacerbation of toxin release and BabyBIG was ordered. On day 5 the antitoxin product arrived and was administered. The patient was intubated for an MRI and was unable to be extubated after the procedure because of hypoventilation. Her MRI results were normal and no EMG or nerve conduction study was done. On day 7 her stool sample was found positive for botulinum toxin A.

The patient's hypotonia improved slowly after she received BabyBIG. She was extubated on day 10 and continued to recover with the help of extensive physical therapy. The patient was discharged after 22 days of hospitalization. She was back to her baseline for strength and muscle tone at follow-up shortly after discharge. She had mild weakness, but no respiratory distress.

No source of botulism exposure was found, even after public health tested the patient's formula and applesauce. There was also no *C. botulinum* source found that connected Case 2 with Case 1.

Discussion

Diagnosing and managing an acutely hypotonic infant requires investigating many possible causes. The differential diagnosis for acute hypotonia differs from the differential diagnosis for chronic hypotonia.

Primary neurological causes of acute hypotonia are rare but important to consider and include Guillain-Barré syndrome, myasthenia gravis, encephalitis, and spinal muscular atrophy type 1.[3] Infectious conditions other than infantile botulism that can cause acute hypotonia include poliomyelitis, acute flaccid myelitis, sepsis, and meningitis.[4] Metabolic disorders can cause hypotonia as well and should be considered along with toxic ingestions and nonaccidental injuries.[4] Disorders such as hypothyroidism and electrolyte disturbances can cause milder hypotonia and present in a way similar to the early stages of infantile botulism.[4]

Diagnosis

Hypotonia investigations should include a full neurological examination and detailed history of symptom progression to narrow down the number of possible causes for the differential diagnosis.[5] There should be careful documentation of muscle tone, strength, head lag, ptosis, hand grip, spontaneous and resisted limb movement, cry, reflexes, gag, suck, ocular movements, pupillary response to light, resting posture and leg positioning, and Babinski reflex.[3,5] An infectious disease workup and metabolic workup should be completed as well.[5] The infectious disease workup in hypotonic infants usually includes lumbar punctures.[5] Other investigations to consider include head imaging, chest X-rays if respiratory symptoms are involved, EEG, and stool testing for botulinum toxins.[6] Nerve conduction studies and EMGs can be useful when trying to rule out a primary neurological cause such as Guillain-Barré or myasthenia gravis.

As the cases described above illustrate, seemingly benign and mild symptoms are often seen early in infantile botulism.[7] Constipation, poor feeding, and hoarse cry commonly precede manifestation of muscle weakness, including ptosis, hypotonia, cranial nerve palsies, drooling, and respiratory distress.[7] The bulbar

functions are often impaired first, causing the initial weak cry, poor feeding, poor gag reflex, and poor head control seen early on in these cases.[7] The somatic musculature weakness and respiratory distress usually develop later on.[7] Eventually deep tendon reflexes are lost as well.[7] Neither of our patients displayed urinary retention, although this should be monitored since retention occurs in some cases.[8] Sensation remains intact in affected patients, since the botulinum toxin cannot cross the blood-brain barrier.[7] In terms of age, our patients were the age of peak incidence (2 to 3 months), but it is important to remember infantile botulism can occur in any child under 1 year.[1] The relative gut immaturity of infants is thought to allow for colonization with *C. botulinum*, and gut maturation with age precludes older children and adults from developing botulism in the infantile form.[2] Although both of our patients were female, the incidence of botulism is the same in males and females.[2]

Often no source of infection is identified, as was the case for both our patients.[2] *C. botulinum* is known to be present in soil, fruit, vegetables, and honey.[1] The incubation period is between 3 and 30 days, making it difficult to isolate a source of exposure.[2] A lack of possible sources should not be seen as reassuring. If infantile botulism is suspected, stool samples should be sent immediately for culture and toxin detection.[2] This is far more challenging than it sounds because an almost universal early symptom of infantile botulism is constipation.[7] A formal bowel irrigation protocol should be used when collecting stool to ensure the laboratory can process the sample.[9]

Management

Since infantile botulism causes gut colonization with *C. botulinum*, the patient can excrete toxin in the stool for weeks to months after the infection.[8] This means that caregivers must dispose of stools appropriately and avoid exposing other infants to the infected child's stool for many months.[8] Anyone with open lacerations should also wear gloves while handling stool to prevent development of wound botulism.[8]

The natural course of the disease involves the progression of weakness over 1 to 2 weeks until the patient reaches a nadir.[8] The infant then remains in this weakened state for 2 to 3 weeks before symptoms improve.[8] If the infant is supported through this nadir of respiratory failure and flaccid paralysis, the symptoms can resolve even without administration of BabyBIG.[8]

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Although infantile botulism should resolve with proper supportive care, complications can increase morbidity and mortality. As the ventilator-associated pneumonia developed by our Case 1 patient illustrates, many of the complications that occur in infantile botulism are respiratory in nature. These complications include aspiration, acute respiratory distress syndrome, recurrent atelectasis, pneumothorax, tracheal granuloma, tracheal stenosis, tracheitis, tracheomalacia, and respiratory arrest.[8] Gastrointestinal complications such as *Clostridium difficile* colitis are also possible.[6] Other complications are those seen in many critically ill children, including but not limited to anemia, inappropriate antidiuretic hormone secretion, urinary tract infection, and secondary bacterial infections.[8]

BabyBIG contains antibodies for both botulinum toxin A and toxin B.[6] The antitoxin works by binding to the toxin and thus neutralizing it, and acts only on the toxin, not the organism itself.[6] The use of BabyBIG reduces the recovery time to 2 or 3 weeks of symptoms in total.[8] Although BabyBIG is an effective treatment, the cost is high—US$45 000 per dose at the time our patients were treated and US$57 000 per dose as of January 2019. The medication is also produced and stored exclusively in California and is not available immediately. Delivery takes 1 to 2 days after an order is submitted.[10] As we learned in our cases, deciding when to order and administer BabyBIG is one of hardest parts of treating infantile botulism. We had to consider not only the cost and lack of immediate access, but the need to order the product before we had results from the stool tests. Rather than waiting the 1 week that stool test results typically take, we needed to administer BabyBIG once infantile botulism was suspected to stop the progression of the disease.[11]

Both of our patients left hospital with normal respiratory function and oral intake but decreased strength. In cases like ours, discharge home can occur before full recovery of strength as long as feeding and respiratory status are good. This is because there is no relapsing or recurring pattern with infantile botulism. Symptoms are unlikely to return after resolution and a full recovery to developmentally normal muscle tone and strength can be anticipated.[8]

After discharge, infantile botulism patients require multiple community supports and long-term follow-up. Many patients have residual weakness at the time of discharge and require physiotherapy or occupational therapy until they return to baseline. Although infantile botulism does not have any direct developmental effects, the critically ill period does create a pause in the affected infant's development.[8] Assessment and support from an infant development program will be needed. The vaccination schedule of these patients may also need to be adjusted.[8] Because BabyBIG is made from human plasma,[6] infants treated with the product cannot receive live vaccines within 6 months of antitoxin administration due to the impaired immune response the antibodies may cause.[8] Rotavirus vaccine should be deferred until gut function returns to normal.[8]

Infantile botulism in Canada

Infantile botulism is a rare but reportable disease in Canada and engagement with public health is required in all suspected cases.[10] Between 2011 and 2016 only 11 cases were reported in Canada.[12] The source of botulism is often unknown, but the disease tends to cluster in certain regions, with California having the greatest number of cases in North America.[1]

The low incidence of infantile botulism in Canada means that access to BabyBIG is limited. The product must be shipped from California and takes 1 or 2 days to arrive. BabyBIG should be ordered as soon as infantile botulism is suspected, even if stool test results are not

yet available. Giving the product early in the disease course is important.[11]

Although BabyBIG was used in our cases, another antitoxin is available in Canada: botulism antitoxin heptavalent (BAT) for botulinum toxins A to G, available within 24 hours of ordering.[10] However, efficacy of BAT in infants has not been proven and studies have reported complications of anaphylaxis and serum sickness in some adults.[10] BabyBIG is the recommended treatment for infantile botulism in UK and US guidelines.[2] In our cases BabyBIG was also the choice of the infectious disease team at the provincial pediatric centre.

The diagnosis and management of infantile botulism is challenging because of the low prevalence of the disease in Canada and the large number of possible conditions that must be considered when an infant has acute hypotonia.

Summary

Our cases show the importance of a high index of suspicion for infantile botulism when patients under 1 year of age present with mild symptoms such as constipation, head lag, and poor feeding. The two females treated at our centre within 2 months of each other in 2017 and 2018 received support for hypotonia and respiratory complications. As well, they underwent infectious disease, neurological, and metabolic investigations. Eventually both patients were transferred to the provincial pediatric centre. Because infantile botulism was the likely diagnosis based on the workups completed at our centre and the provincial centre, the antitoxin product BabyBIG was administered to both patients before stool test results confirmed the presence of botulinum toxin. The diagnosis and management of infantile botulism is challenging because of the low prevalence of the disease in Canada and the large number of possible conditions that must be considered when an infant has acute hypotonia. Management is also challenging because of the high cost of BabyBIG and the need to order the product from an out-of-country supplier. ■

Competing interests

None declared.

References

1. Arnon SS. Infant botulism. In: Feigin RD, Cherry J, Kaplan SL, Demmler-Harrison GJ, editors. Feigin and Cherry's textbook of pediatrics infectious diseases. 6th ed. Philadelphia, PA: Elsevier; 2009. p. 1862-1869.
2. American Academy of Pediatrics Committee on Infectious Diseases. Botulism and infant botulism (Clostridium botulinum). In: Kimberlin DW, Brady MT, Jackson MA, editors. Red book. 31st ed. Itasca, IL: AAP; 2018. p. 283-286.
3. Piña-Garza JE. The hypotonic infant. In: Fenichel's clinical pediatric neurology. 7th ed. Philadelphia, PA: Elsevier; 2013. p. 147-169.
4. Neuromuscular disorders. In: Kliegman RM, Stanton B, St. Geme J, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. Philadelphia, PA: Elsevier; 2016. p. 1428-1431.
5. Ahmed MI, Iqbal M, Hussain N. A structured approach to the assessment of a floppy neonate. J Pediatr Neurosci 2016;11:2-6.
6. Arnon SS, Schechter R, Maslanka SE, et al. Human botulism immune globulin for the treatment of infant botulism. N Engl J Med 2006;354:462-471.
7. Division of Communicable Disease Control, California Department of Public Health. Infant Botulism Treatment and Prevention Program: Clinical diagnosis. Posted 2010. Accessed 15 February 2019. www.infantbotulism.org/physician/clinical.php.
8. Division of Communicable Disease Control, California Department of Public Health. Infant Botulism Treatment and Prevention Program: Patient management. Posted 2010. Accessed 15 February 2019. www.infantbotulism.org/physician/patient.php.
9. Division of Communicable Disease Control, California Department of Public Health. Infant Botulism Treatment and Prevention Program: Specimen collection. Posted 2010. Accessed 15 February 2019. www.infantbotulism.org/laboratorian/collection.php.
10. BC Centre for Disease Control. Communicable disease control manual. Botulism. Published November 2018. Accessed 15 February 2019. www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/Botulism_Guidelines.pdf.
11. Division of Communicable Disease Control, California Department of Public Health. Infant Botulism Treatment and Prevention Program: How to obtain BabyBIG. Posted 2010. Accessed 15 February 2019. www.infantbotulism.org/physician/obtain.php.
12. Public Health Agency of Canada. Notifiable diseases online. Reported cases by age group in Canada. 2016. Accessed 15 February 2019. http://diseases.canada.ca/ndis/charts.php?c=gbt.