

Infant Botulism: Be Aware of this Rare Disease

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Infant botulism is a rare disease worldwide; in the United State the incidence is approximately 100 cases per year [1]. The mortality rate is low if the diagnosis is timely and followed immediately by efficient and supportive treatment. A high degree of suspicion must be maintained in order to diagnose this condition. Here we present a case of infant botulism that highlights the difficulties in the diagnosis.

Patient Description

A 4 month old previously healthy male infant was admitted to the hospital after 5 days of constipation, lethargy and unwillingness to eat. He was nourished only by breast milk but was given three homeopathic medications, one of which contains belladonna. He was also given chlorpheniramine maleate and phenylephrine for his runny nose over 5 days. The patient was never exposed to honey. Pregnancy, delivery, and development were normal. He is the third child in his family, and his siblings are healthy. He received all his vaccines on schedule.

On admission he was lethargic, with respiratory rate 36 breaths/min, mild hypertension 115/54 mmHg, pulse 135 beats/min, and fever 37.2°C. He was hypoxic and required oxygen. His limbs were hypotonic with weak reflexes. Gag and sucking reflexes were weak. His fontanel was normotensive, and he had dilated pupils. Complete blood count showed hemoglobin 12.9 g/dl, platelets 555,000/mm³, white blood cell count 16,180/mm³, with 53% neutrophils, 24% lymphocytes and 14% monocytes. Electrolytes, glucose, and renal and liver functions were all normal. Venous blood gases were pH 7.35, HCO₃

25.7, and pCO₂ 46.1. Thyroid functions, ammonia level, cholinesterase, creatine phosphokinase, and urine test were normal. Cerebrospinal fluid, taken twice with a 2 day interval, to rule out Guillian-Barré syndrome or infection showed normal protein, glucose, and 1 cell/mm. Imaging studies included abdominal ultrasound that showed an increased amount of feces in the colon. Brain computed tomography with contrast media to rule out sinus vein thrombosis and magnetic resonance imaging to rule out a structural pathology such as acute disseminated encephalomyelitis were both normal.

Electroencephalogram had a normal pattern. Electromyogram was normal and did not show the brief, small, abundant, motor-unit action potential pattern that is characteristic of infant botulism. A neostigmin test was performed, which was negative, to rule out belladonna intoxication and exclude myasthenia gravis or Lambert-Eaton myasthenic syndrome. At this stage, after exclusion of other diseases, infant botulism was suspected. Stool and blood samples were sent to a laboratory for cultures and toxin verification; the medications that he took were also sent.

Six days later, the mouse neutralization test from the stool was positive and indicated a type B botulinum toxin. In that test, mice are injected with a specimen taken from the patient's stool/serum that is incubated for several days; the mice are injected with this sample and test results are considered positive for toxin if the mice die of respiratory arrest within 24 hours. The exact type of toxin is determined by pretreating each mouse with a different type of antitoxin (A–G), then

injecting the incubated specimen. The mouse that is alive the next day is the one that was pretreated with the antitoxin to the toxin affecting the patient.

Our patient was treated with intravenous immunoglobulin on the day of admission for acute disseminated encephalomyelitis and for Guillian-Barré syndrome; those treatments were discontinued after 2 days as the possibility of infant botulism became more feasible. The patient did not receive an antitoxin against *Clostridium botulinum* because in Israel only the equine trivalent antitoxin is available and its efficacy in infant botulism is unknown and could produce severe allergic side effects. The human-derived botulinum antitoxin, which is the specific treatment for infant botulism, is not available. He was transferred to the pediatric intensive care unit after he became more hypoxic, where he was intubated for 3 weeks.

During his stay in the pediatric ICU he showed a slow progressive improvement: spontaneous movement and eye opening increased, his smile returned, and he was able to move all four limbs. He was eating well and his stool was soft and regular. On the day of his release, his 29th day in hospital, he was slightly hypotonic and still had a head lag. On follow-up 2 months later there were no neurological deficits.

Comment

Infant botulism usually occurs in children aged 2–6 months, and is caused by *C. botulinum*. *C. botulinum* is a gram-positive spore-forming anaerobe that naturally inhabits soil and dust. Infants can be

ICU = intensive care unit

exposed to the spores by eating honey, but in 85% of cases the cause and the means of exposure are unknown. Spores of *C. botulinum* germinate and multiply in the gut and produce the dangerous toxin in the large intestine. Botulinum toxins are zinc metalloproteases [2] that bind to membrane proteins which are involved in fusion of the synaptic vesicle to the pre-synaptic membrane and block the release of acetylcholine into the synaptic junction. There are seven kinds of botulinum toxins, classified as types A–G, but infant botulism is caused only by types A and B. Infant botulism normally affects children under 1 year of age owing to their relative lack of gastric acid, decreased levels of normal flora, and immature immune systems, especially the lack of secretory immunoglobulin A.

In Israel, only two cases of infant botulism have been reported to date [3]. As previously suggested [4], there may be a connection between sudden infant death syndrome and *Clostridium botulinum*. In this study it was found that 26% of SIDS cases could be explained by infant botulism. In one SIDS case [5], it was reported that the contamination route from *C. botulinum* was through a vacuum cleaner.

Treatment of infant botulism remains supportive. Recently, Arnon et al. [1] reported the success of intravenous human botulism immune globulin in shortening

the hospitalization period and reducing the number of admissions of infant botulism cases to the pediatric ICU. They showed a decrease in the mean length of hospital stay from 5.7 weeks to 2.6 weeks and a reduction in mean intensive care stay by 3.2 weeks. The greatest effect in reducing the period of hospitalization was seen when human BIG-IV was given during the first 3 days of hospitalization and no later than 1 week from admission. The antitoxin was not used in our patient because of its unavailability in our country, and because of the long period that had elapsed from the appearance of the symptoms to the suspicion of infant botulism.

We were misled by the possibility of belladonna poisoning and chlorpheniramine maleate and phenylephrine that the infant received: both of them can imitate some of the symptoms of infant botulism. Furthermore, the electromyography test, which is supposed to be an early disease diagnosis, was negative in our patient.

We considered several theories regarding the origin of botulism in our patient. First, the bottles of the medicines that he took could have contained the spores. Second, he was exposed to the spores during the Passover holiday, which is when most people in Israel undertake a

thorough spring cleaning, which includes the use of vacuum cleaners.

In summary, our case illustrates the problematic diagnosis of infant botulism. The key point to diagnosis is a high degree of suspicion by the physician, which should be raised in any child presenting with hypotonia and central nervous system depression.

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