BOTULINUM TOXICITY IN INFANT THE FIRST SUCESSFULLY TREATMENT CASE IN VIETNAM

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ABSTRACT

Overview: *Botulism infants is a potentially life-threatening disease caused by ingestion of Clostridium botulinum spores, which germinate, multiply in the large intestine and produce neurotoxins to the body [1]. The disease occur in children under 12 months [2]. This is a rare form of infection in Vietnamese infants. The key features of presentation were acute onset of bilateral cranial nerve palsies and symmetrical descending weakness in the absence of fever. But sometime, patients have vague symptoms such as decreased muscle tone, poor feeding. This report will present a case of a 10-month-old admitted to the hospital with acute generalized hypotonia and aspiration.*

Objectives: *Approach to diagnosis and treatment of botulism infants.*

Case study: *A 10-month-old female was admitted to the Vietnam National Childrens Hospital (VNCH) because of difficulty sucking and swallowing. These signs were acute onset 2 days before. The child had very little interaction, crying hoarsely, no tears and symmetrical descending weakness. The clinical diagnosis of botulism was confirmed through the identification of C. botulinumtoxin from the stool sample. The patient was given a single dose of botulinum antitoxin and she had fully recovered.*

Conclusion: *Due to its rarity, diagnosing botulism is a challenge, demanding high clinical suspicion. Successful outcomes depend upon early recognition and rapid initiation of specific treatment with botulinum antitoxin. There is a need to improve global access to antitoxin. These case, the first botulism infant in Viet Nam, serve as a reminder of the need to differential diagnosis with other acute peripheral paralysis.*

1. INTRODUCTION

Botulism is a neurotoxin-mediated illness caused by the gram positive, anaerobic, spore-forming bacillus Clostridium botulinum (C. botulinum), which occurs naturally in soil and sediments. Botulism infants are rare, unknown rick factor (sometimes follows the ingestion of anarerobicin honey, powdered milk, natural sweeteners, syrups, home-canned foods, fermented fish…), rapid progression, easily missed diagnosis [1]. Infant botulism occurs due to colonization of the gut by C. botulium, again resulting in endogenous toxin production.

Botulism is caused by C. botulinum through

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the action of botulinum neurotoxins (BoNTs). BoNTs are divided into several toxinotypes (A, B, C, D, E, F, G, H, and F/A) and each toxinotype is further divided into subtypes [2,3]. Only toxinotypes A, B, F often occurs in infant. Several observations suggest that type A was more severe than type B diasease [4]. The patient can be poisoned by one or multiple toxins at the same time.In contrast with the spores, the toxin is a heat-labile polypeptide readily denatured by heating above 80°C. The polypeptide toxin which composed of a light and heavy chain (150 to 165 kDa) is as a precursor polypeptide chain. Botulinum toxin is then cleaved by bacterial proteases into a fully active neurotoxin composed of a light chain and a heavy chain (50 to 100kDa) [5]. The botulinum toxin exerts its effects within neurons by inhibiting the fusion of acetyl choline containing pre-synaptic vesicles with the cell membrane, thus preventing the release of the neurotransmitter [4]. This presents clinically as a flaccid paralysis, and the classical manifestation of botulism is described as an acute onset of bilateral cranial neuropathies with a symmetrical descending paralysis. Fever is not a feature. Definitive diagnosis depends upon the detection of botulinum toxin, or isolation of C. botulinum, from both clinical and samples (food, stool). The diagnosis of possible botulism infants can be made based upon a typical presentation and a contact history.

In 2017, 182 laboratory-confirmed botulism cases were reported to CDC classified as: infant botulism (77%), foodborne (10%), wound (10%), and other (3%) [CDC]. Toxin types were A (37%), B (62%). The median age of infants was four months (range: 0–12 months); 72 (51%) were girls [1]. The first case of infant botulism was identified in France in 2004. During the period 2004–2016, 15 infant botulism cases and two botulism cases by intestinal colonization in 12 - and 18-months old infants were reported [2]. However, in Viet Nam, botulism infant has not previously been described. This may be genuine, the diagnosis may be missed due to low index of suspicion or overlap of symptoms with other neurological syndromes. Botulinum just have noticed since 2020, when 20 Vietnameses were hospitalized due to pate poisoning [6]. Importantly, the specific treatment for botulism - antitoxin - is not always available in Viet Nam. Delay in diagnosis and lack of specific treatment are likely to result in worse clinical outcomes. Here, we report the case who presented to our hospital with symptoms suggestive of botulism without infective foods identification. To our knowledge, these is the first cases of botulism infant reported from Viet Nam.

2. CASE PRESENTATION

On April 28, 2021, a female, 10 month olds, living in Hanoi, was hospitalized due to difficulty swallowing, symmetric descending weakness. The disease was onset 2 days, initially tired, eating poorly, sleeping a lot, crying weakly, limited movement in neck (neck tilted to the right), no localized mass in the neck, no fever. One day before admission, the child could not keep her head and neck steady, could not sit, drooped eyelids, hoarse voice, cried without tears, had difficulty feeding, choked and was admitted to the VNCH.

History: she is the second child, normal delivery, full term, birth weight 3,1 kg (now her current weight is 8 kg), fully vaccinated according to schedule, normal physical and mental development according to age. The child has no previous history of trauma and no history of constipation. No one in her family has neuromuscular disease.

In emergency room, she had spontaneous, regular breathing, SpO_2: 98% but profuse discharge,cry out hoarseness without tears. Her heat rate was 157 ppm, sinus rhythm, pulse clear, refill 2s. The child was alert, respond to noise. Her fontanelle was flat. She had palsies of cranial nerve III(pupil dilation (3x3mm, light

reflex (+), ptosis evenly on both sides,); palsies of cranial nerves IX, X, XII (hoarse voice,weak suck, dysphagia, soft neck). She was alsoinactivity, symmetric descending weakness, limb muscle strength 2/5, tendon reflexes are reduced (floppy baby syndrome). But she had no sensory disturbances. The patient had vague abdominal symptoms such as distention and constipation (7 days without defecation). She did not have fever, no vomiting, no facial paralysis, no convulsion, babinski (-) and bruise (-).

The primary diagnosis was peripheral paralysis. The causes which considered were myasthenia gravis, inherited metabolic disordes, mental intoxications, cervical spinal cord injury, Guillain-Barré syndrome. Laboratory evaluations for patient, including complete blood cell counts, and serum level of sodium, potassium, blood gas, blood glucose, blood trace elements (iron, copper, lead, asenic…), blood urea nitrogen, creatinine and creatinine kinase were normal. The patient was checked prostigmine test, but the result was negative. Cranial and cervical spine magnetic resonance imaging were normal. The patient underwent lumbar puncture; cerebrospinal fluid analyse was unremarkable. The patient underwent electromyography which showed low-voltage compound motor-units, consistent with axonal neuropathy. The possibility of Guillain-Barré syndrome was suggested in the differential diagnosis. Botulism infant was suspected and the dietary history re-explored from her relatives. The child was breastfed for the first 6 months (exclusively frozen breast milk). From 6 months of age, she was combined with frozen porridge (cook once in 3 days), add yogurt, unsalted butter, cakes (chewy junior). She did not use honey products. Tests for bacteria and C.botulinumtoxin genes from samples (stool, breast milk, porridge, yogurt, butter, cake) were performed at the anaerobic bacteria room in the National Institute of Hygiene and Epidemiology. The C.botulinum toxin gene type A, type B was detected in patient's sample stool but we couldn't find it in her foods. The patient received a single dose of botulinum antitoxin heptavalent in the tenth of illness. She also need oxygen support, laxative, digestive enzymes, nutrition through gastric tube. After 11 days intravenous botulinum antitoxin, the child could easy to swallow, muscle strength improved significantly. The child was discharged affter 22 days of hospitalization and continued rehabilitation at home.

3. DISCUSSION

This is the first case report of a botulism infant in Viet Nam. It demonstrates the need for a high index of suspicion in order to make the diagnosis in a timely manner, the severe associated morbidity, and the need to have rapid access to antitoxin.

Children are at risk of botulinum poisoning by ingesting spores which can survive 100°C at least 5 hours. In our patient, the child'habit of frozen foods feeding such as frozen breast milk, congee… that were reheated before eating was a risk factor. C.botulinum spores are less harmful to older children and adults if ingested because they easily pass through the intestinal tract without germinating. Whereas the immature enteric bacteria of infants from 6 days to 12 months of age (including our patient-10 months old), spores are capable of germinating and subsequently the bacteria can produce toxins [7].

Botulism infant is gradual, with incubation period (3 days-30 days) is longer than in adult [8]. In this patient, the incubation period is unknown, with sudden onset of hoarseness, weak crying without tears and limited neck mobility. Just 1 day after, the child was feeding difficulties, had to hospitalized. The earliest neurological symptoms tend to involve the eyes with ptosis, dilated pupils. On admission, it was difficult to determine whether a 10-month-old had cognitive disorder or not. These symptoms followed byprogressive weakness from the trunk, upper extremities to

the lower extremities muscles, atelectasisbut no signs of respiratory muscle paralysis. Neurologic deficits were bilateral. In addition, nonspecific gastrointestinal symptoms were anorexia, drooling and constipation. Around 68% of cases of botulism present with simultaneous neurological and gastrointestinal symptoms [8]. The patient need to support oxygen by mask, nourishing through gastric tube. Fortunatery, she could responde to sound, painful stimulianddid not autonomic dysfunction. Autonomic dysfunction as the leading symptom of botulism type B [9]. The patient was primary diagnosis of acute peripheral paralysis. After checking some her blood test, we excluded heavy metal intoxication, inherited metabolic disordes. Her tendon reflexes were reduced and prostigmine test was negative, except myasthenic syndrome. 95% cases of myasthenia have positive prostigmine test [10]. She did not have any signs of infection so we excluded tick paralysis, Japanese encephalitis [10]. Guillain-Barre syndrome usually involves an ascending rather than descending paralysis, associated sensory findings, and an elevated cerebrospinal fluid protein. Her cranial and cervical spine magnetic resonance imaging were normal, excluding cervical spinal cord injury. Electromyography in peripheral paralysis is supportive [10]. Reduction in compound muscle action potential and M-wave amplitudes, excessive action potentials, and frequency-varying response to repetitive nerve stimulation often occur in botulism, but it is difficult to do in infants.

Table 1. Differential diagnosis of acute weakness [10]

Disease	Signs/symptoms	Diagnosis
Guillain-Barré syndrome (GBS)	Symmetric ascending weakness and paralysis with loss of deep tendon reflexes +/– autonomic dysfunction	CSF studies, EMG
Miller-Fisher variant GBS	Triad of opthalmoplegia, ataxia, and areflexia	CSF studies, EMG
Myasthenia gravis	Proximal muscle and bulbar muscle weakness with cranial nerve deficits that worsen with exertion	Ice-pack test, edrophonium stimulation test, acetylcholine receptor antibodies
Tick paralysis	Symmetric ascending flaccid paralysis with loss of deep tendon reflexes	Clinical diagnosis with resolution of symptoms on tick removal

Laboratory criteria for the diagnosis of botulism are the detection of toxin/C.botulinum in the stool [1]. Her foods, gastric aspirate and stool sample were collected, cultured and PCR reaction in absolute anaerobic environment. The C.botulinum toxin gene type A, type B was detected in patient's sample stool. Identifying the food source of botulism is crucial in confirming the diagnosis and managing the risk to public health [6]. Improper food storage and preservation can provide specific conditions such as the anaerobic, low salt, low acid environments which facilitate the growth and development of the toxin producing C. botulinum. Identification of the food source should lead to an examination of food handling practices with education and remediation as needed. However, in this case, we could not find the rick factor because C. botulinumwere unable to isolate from almost foods involved and family's stool sample.In France, two infant botulism cases exposure to dust containing C. botulinum spores was the only risk factor possibly involved. A 2-month old girl living close to a thermal power station

that intermittently releases sprays of vapor and smoke/dust, developed several relapses of botulism. C. botulinum A2 resistant to β-lactams was isolated on stools up to 110 days after onset. In the second outbreak, a 5-month old male infant exclusively breastfed was living close to a construction site. He presented clinical symptoms of botulism and BoNT/B was detected in his stools. C. botulinum B was isolated from stool as well as from three soil samples of the active construction site [2].

The complexity of the diagnosis botulism infantdepends in the first instance upon clinical suspicion based upon the history and clinical signs. There are no rapid tests available to aid diagnosis at the time of presentation. Confirmation of diagnosis comes through epidemiological investigation to identify potential exposure, with microbiological confirmation of the presence of the organism or toxins in the source +/- patient samples [3]. As seen in our case, identifying the organism in human clinical samples has low sensitivity and requires 1-4 days for the result. The decision to administer antitoxin should be based on the presumptive clinical diagnosis of botulism, not be delayed while awaiting results of confirmatory diagnostic studies. The diagnosis of botulism in this case report was refer to previous foodborne botulism case series consumed vegetarian paté in Vietnam which was the presentation of multiple patients with consistent syndromes in 2020 [6].

As for any cause of acute weakness in the ED, our focus should be on initial airway management, either for prevention of aspiration or impending respiratory failure. Monitoring of vital signs and respiratory parameters, such as negative inspiratory force and vital capacity, are crucial in identifying the patient's trajectory and those that require early intubation. Thereafter, early initiation of treatment with botulinum antitoxin might decrease mortality and reduce duration of mechanical ventilation [11]. The benefit of antitoxin depends on neutralization of that toxin which is unbound to neuromuscular junctions, and this requires administration within the first 24 hours of presentation [11]. However, it must be noted that there is no constraint for the latest time of effective antitoxin administration (see WHO botulism factsheet), with benefit having been reported in patients treated with antitoxin up to 8 days after the onset of symptoms [1,11].

There are two botulism antitoxin therapies available: equine serum heptavalent botulism antitoxin treated for children over 1 year old and adults; human derived botulism immune globulin (BIG-IV) used for infants less than one year of age [1]. The review of randomized controlled trials (RCTs) and quasi-RCTs examining the medical treatment of infant intestinal botulismshows that BIG-IV probably shortens hospitalization; may shorten time spent on a ventilator; and probably reduces the duration of tube feeding compared to placebo [18]. The risk of harmful effects of the treatment was probably no greater with BIG-IV than with the inactive treatment. The evidence was mostly of moderate certainty (low certainty for time spent on a ventilator)[11]. Unfortunately, human derived botulism immune globulinwas not available in Vietnam when we received the case reported here, so we use a singer dose (1/10 vial) of equine serum heptavalent botulism antitoxin for the baby.

4. CONCLUSSION

We report the first recognized botulism infant in Viet Nam. It is important to consider botulism in the differential diagnosis of acute weakness. The syndrome should be considered in patient presenting with absence of fever, a normal conscious level, and an acute descending paralysis. Detailed exposure history is essential to identify sources that may be continuing to put the wider community at risk. Although a rare illness, it is important to keep botulism in the differential for patients presenting with weakness, as timely diagnosis and appropriate treatment are critical to the patient's outcome.

Consent

Written informed consent for publication of their clinical details was obtained from the patients.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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