ANDES PEDIATRICA
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Andes pediatr. 2024;95(6):778-785
DOI: 10.32641/andespediatr.v95i6.5307

CLINICAL CASE

Respiratory failure due to acute muscle weakness and central nervous system involvement: severe infant botulism

Insuficiencia respiratoria por debilidad muscular aguda y compromiso del sistema nervioso central: botulismo grave del lactante

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Received: Jun 3, 2024; Approved: July 13, 2024

What do we know about the subject matter of this study?

Infant botulism is a rare but potentially lethal disease that produces neurotoxic effects (mainly flaccid paralysis) due to presynaptic blockade of acetylcholine transmission.

What does this study contribute to what is already known?

This report highlights the importance of considering botulism in infants as a cause of acute respiratory failure. Its progression can be severe and, in exceptional cases, may present an altered state of consciousness.

Abstract

Infant botulism is rare in Chile. This severe toxemia caused by the ingestion of *Clostridium botulinum* spores manifests as a descending flaccid paralysis, progressing from cranial neuropathy to ventilatory insufficiency. **Objective**: To report the case of a patient with ventilatory insufficiency caused by this neuroparalytic disease. **Clinical Case**: 7-month-old infant, who consulted due to a two-day history of difficulty feeding. On admission to the Intensive Care Unit, cranial nerve palsies, areflexic bilateral mydriasis, and compromised state of consciousness were observed. The imaging study did not show pathological findings. The stool sample was (+) for *Clostridium botulinum* with isolation of toxin A. Electromyography was discarded. The patient required invasive mechanical ventilation for 2 months. The patient presented motor recovery after a year of evolution. **Conclusion**: Infant botulism is a diagnostic challenge given its rarity, therefore a high index of suspicion is required.

Keywords:
Botulism;
Infant Botulism;
Clostridium botulinum;
Flaccid Paralysis

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Edited by:
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How to cite this article: Andes pediatr. 2024;95(6):778-785. DOI: 10.32641/andespediatr.v95i6.5307

Introduction

Infant botulism is a rare but potentially lethal neuroparalytic syndrome[1], which has been reported in Chile in recent decades[1-5], reporting 19 cases of infant botulism between 2012-2022, of which 57.8% were from the Metropolitan Region and predominantly male[6].

It is characterized by the development of acute descending flaccid paralysis (a presynaptic disorder of the neuromuscular junction), caused by the bacterium *Clostridium botulinum*, an anaerobic Gram-positive spore-forming bacillus, which can release various neurotoxins. It is classified into seven serotypes (A-G) based on the antigenic specificity of the toxin produced. A single strain usually produces only one toxin, but some strains can produce multiple toxins. Currently, eight different types of *Clostridium botulinum* toxins (A-H) have been described. The species that can cause infant botulism include types A, B, E, and F, but most are due to types A or B[7].

Since its first description in 1976 by Pickett et al.[8], infant botulism is the most frequently mentioned form in the infant population[1,7]. It occurs in children under one year of age due to the ingestion of *Clostridium botulinum* spores, which are widely distributed in nature or are found in certain contaminated foods (honey and herbal teas, among others). The spores can germinate and colonize the colon, which is more susceptible in this age group (less mature gut microbiome), with subsequent production of toxins *in vivo* (toxinogenesis) and, finally, after systemic absorption, reach the neuromuscular junction.

The botulinum neurotoxin (BoNT) exerts its effect on neurotransmission in the peripheral nervous system mediated by acetylcholine (ACh) through three mechanisms[9,10]: i) by irreversibly binding to presynaptic cholinergic receptors of voluntary and parasympathetic motor neurons, causing bulbar palsy and descending symmetrical flaccid paralysis; ii) by affecting the SNARE polypeptide complex, which consists of proteins necessary for the fusion of vesicles containing ACh with the presynaptic membrane; and iii) by blocking the presynaptic release of ACh, inhibiting neuromuscular and autonomic impulse transmission. (Figure 1).

Functional recovery requires the regeneration of nerve endings with the formation of new motor end plates, which will depend on the amount of toxin ingested, the number of affected axons, and the time it takes for them to recover[11].

The objective of this work is to report the case of a 7-month-old infant with severe botulism who required mechanical ventilation (MV) for two months. Among the existing symptomatology, the initial presence of an altered state of consciousness, a very infrequent finding, stood out. The patient recovered satisfactorily after one year.

Clinical Case

A 7-month-old male infant, exclusively breastfed for 6 months, with no history of morbidities, and normal psychomotor development, consulted due to decay and progressive difficulty in feeding, associated with 2 days of weak crying and "noisy" breathing. The patient had been examined on an outpatient basis, assuming a viral respiratory infection, and symptomatic treatment with inhaled β2 agonists and paracetamol was indicated. On admission to the Emergency Department, the patient was hypoactive with mild dehydration and breath sounds. Urine drug screening was negative. Therefore, it was decided to admit him to the intensive care unit (ICU).

During the physical examination in the ICU, his vital signs were as follows: heart rate: 158 bpm, blood pressure: 99/58 mmHg, mean arterial pressure (MAP) 72 mmHg, respiratory rate: 34 bpm, and Sat O_2 100% with 1 bpm. On physical examination, the patient was responsive only to painful stimuli, with generalized muscle weakness, tetraparesis with preserved osteotendinous reflexes, ophthalmoplegia with bilateral non-reactive mydriasis, and cranial nerve paralysis (III, V, VI, VII, IX, XI).

During the following six hours, the patient persisted with altered consciousness, stridor, and arterial desaturation, so endotracheal intubation was performed and MV was started.

During the directed interview, the mother reported constipation for approximately 5 days without any associated symptoms. There was no intake of honey or medicinal herbs. Additionally, there was no regular habit of dipping the pacifier in sweet liquids.

During the first 12 hours of ICU stay and due to the presence of a possible encephalopathy in a patient with no known hypoxic event or associated electrolyte imbalance and with acute hypotonia, a brain CT scan, and lumbar puncture were performed, both with normal results. An electroencephalogram (EEG) was performed, which showed generalized continuous slowing; however, the patient was under sedative analgesia (fentanyl 1 µcg/kg/h + midazolam 0.05 mg/kg/h), which was discontinued on day 2 of admission due to the suspicion of a neuromuscular disease.

Given the signs of ophthalmoparesis, ptosis, and bulbar involvement, the following initial differential diagnoses were considered: i) Myasthenia *gravis*, for which a therapeutic test with pyridostigmine (0.04 mg/kg) was performed, with negative results, and ii) Guil-

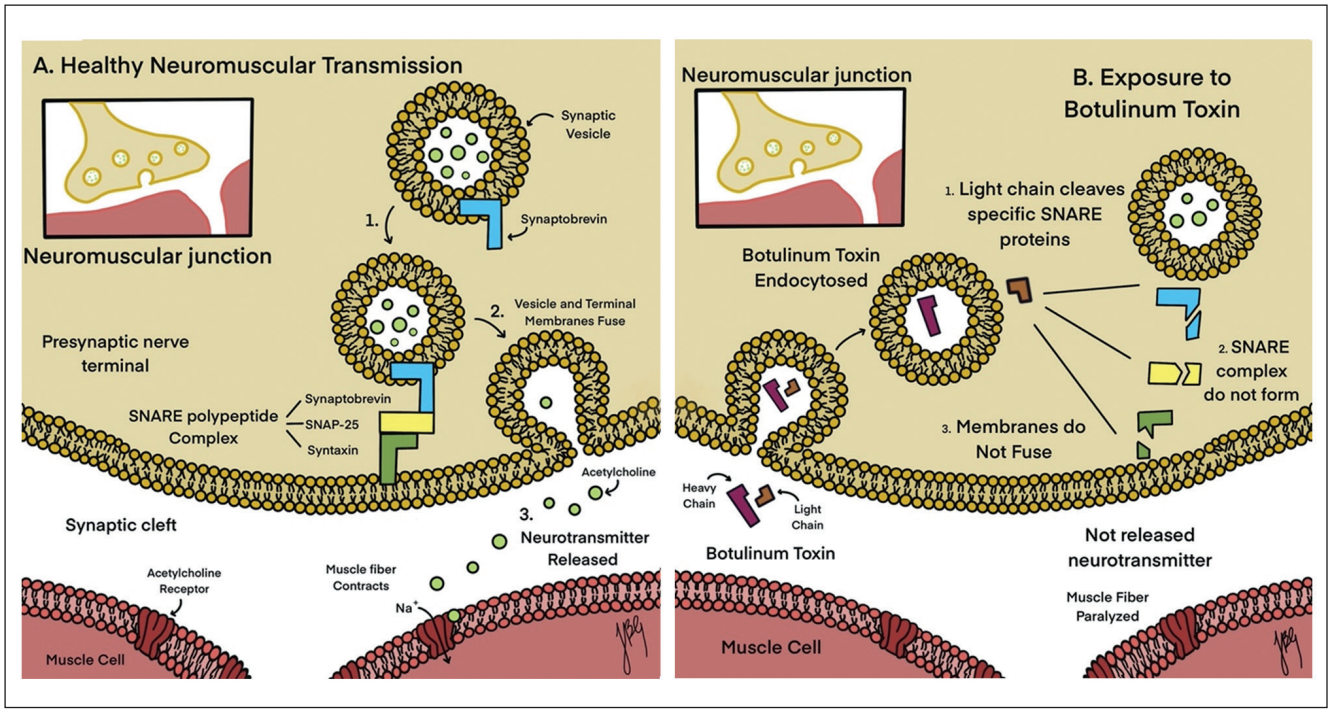

Figure 1. Mechanism of Action of Botulinum Toxin (Original Creation). Botulinum toxin interferes with the neuromuscular junction, blocking the release of acetylcholine (ACh) from presynaptic motor neurons, causing muscle paralysis. This action occurs in three steps: It irreversibly binds to presynaptic cholinergic receptors on motor and parasympathetic nerve endings. The toxin, or part of it, is endocytosed and, through its peptidase action, acts on one or more of the three SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) and prevents the fusion of the vesicle containing acetylcholine with the nerve terminal membrane, thereby blocking acetylcholine release and inhibiting neuromuscular and autonomic impulse transmission.

lain-Barré syndrome, Miller-Fisher variant, therefore deciding to initiate therapy with intravenous human immunoglobulin (0.4 g/kg/day for 5 days), with no clinical response. Further investigation was conducted with brain and spinal cord MRI, which showed no alterations. The expanded neonatal screening was normal.

Given the clinical experience of the treating team in another case of infant botulism, a new interview was conducted with the patient's mother. It was revealed that the patient had been playing with soil repeatedly in the days before the onset of symptoms. Therefore, along with the administration of immunoglobulin, a stool sample was sent to the Public Health Institute (ISP) in search of *Clostridium botulinum*. The results were positive with the isolation of toxin A (day 15), confirming the diagnosis of type A infant botulism. Given the clinical manifestations and the confirmatory microbiological findings, an electrophysiological study was ruled out.

Regarding his encephalopathy, the patient showed clinical compromise for a week. A new EEG (day 7) still showed signs of generalized continuous slowing. The third EEG (day 10) was reported as normal.

The patient remained on MV while awaiting the spontaneous resolution of his condition. On day 15 of hospitalization, he began to move his limbs at the same level, achieving spontaneous eye-opening on day 25. Extubation was attempted on day 35, but it failed due to the absence of airway protection reflexes, leading to the decision to perform a tracheostomy (day 38).

On day 60, the patient still presents a slow motor recovery, but with spontaneous ventilation and without the need for MV. Therefore, it was decided to refer him to a specialized center to continue with his neurorehabilitation program. One year later, the patient is asymptomatic in terms of motor function. However, he has not been decannulated yet as he developed airway stenosis, with periodic dilatations being performed while awaiting definitive surgical resolution.

Discussion

In Chile, the first confirmed case of infant botulism was forty years ago[2], and since 2000, it has been classified as an event requiring immediate mandatory notification.

Age is a determining factor in the susceptibility of infants to this disease, with a maximum incidence between 2 and 8 months of age. In this age group, the richness and diversity of the gut microbiota are still developing, which creates vulnerability to colonization by *Clostridium botulinum*[12].

Recent studies have characterized the microbiota of infected infants to determine its role in colonization, toxinogenesis, and recovery from the disease. Shirey et al.[13] found a different quantitative profile of the fecal microbiota in cases of infants with botulism; however, it could not be determined whether this was a predisposing factor or a direct result of botulism. Additionally, they noted that botulinum toxin-producing *Clostridium* was present in very low numbers, indicating that botulism may manifest from a relatively limited presence of these organisms in the gut.

Likewise, Wang et al.[14] sequenced stool samples from 20 infants infected with *Clostridium botulinum* over 3 months, finding a higher prevalence of the *Enterobacteriaceae* family. They highlighted the abundance of *Enterococcus* in the infected group, which decreased over time, while *Bifidobacterium* was abundant in the group of healthy infants and increased over time in the infected group, suggesting that *Bifidobacterium* may play a role in the recovery of this disease.

In recent decades, some interesting epidemiological changes have been described. It has been pointed out that the history of ingestion of honey, corn syrup, or medicinal herbs is becoming less frequent (20% of cases in part) due to the increased education of the population[15,16]. Exposure to soil is another known risk factor, as it can contain *C. botulinum* spores[17]. Transmission can occur through household environmental dust, agricultural work, nearby construction sites, and similar sources[17].

At the time of initial presentation, infant botulism is often mistaken for other pathologies, with the most commonly misattributed alternative diagnoses being Guillain-Barré syndrome, myasthenia *gravis*, brainstem stroke, inborn errors of metabolism, spinal muscular atrophy, heavy metal poisoning, and Eaton-Lambert syndrome[18].

The clinical presentation typically begins after a variable incubation period of 10 to 30 days, with constipation appearing 3 to 5 days before consultation, along with urinary retention. These clinical signs often precede muscle weakness and hypotonia[5,7].

Flaccid paralysis progresses cephalo-caudally, from proximal to distal, starting with cranial nerves involvement, which is usually bilateral and symmetrical, in addition to feeding difficulty or decreased sucking, weak cry, and sialorrhea (bulbar muscle involvement). Non-reactive mydriasis, a sign present in about half of the affected patients[7,16,19], ptosis, and facial paresis that progress to symmetrical weakness of the trunk and limbs (somatic muscle involvement) may be observed. In the most severe cases, paralysis may affect the diaphragmatic muscles, this being the main cause of respiratory failure. Osteotendinous reflexes are usually preserved[7], and there is no sensory deficit except for blurred vision. Finally, the patient remains afebrile, except in the presence of infectious complications.

During the course of the disease, three typical phases are classically described: i) Signs of disease progression (1-2 weeks), ii) nadir of muscle dysfunction (2-3 weeks), and iii) motor recovery phase (about 1 month or longer)[20].

Nerve conduction and electromyography studies are painful and are rarely performed to establish the diagnosis. They usually show characteristic but not diagnostic patterns, whose absence does not rule out the diagnosis of infant botulism, especially at the onset of symptoms[7,20].

The patient is usually alert, but the presence of facial weakness, ptosis, poor feeding, and limited activity due to muscle weakness can sometimes mimic an impaired state of consciousness. Complementary tests are needed to differentiate between true encephalopathy and weakness of bulbar origin.

Since BoNT is large (~150 kDa, light chain 50 kDa, heavy chain 100 kDa), it does not cross the blood-brain barrier (BBB); therefore, infant botulism is a disease that does not affect the central nervous system (CNS). However, it is interesting to note that in some previous reports[4,21,22], the presence of encephalopathy of varying intensity has been described, being more evident at the onset of the disease[15], similar to what was observed in our patient. The causative mechanism has not been explained, although it has been suggested that the BoNT could reach the CNS through retrograde axonal transport[23,24].

In the United States, in the early 1970s, 17% of botulism cases presented ataxia, and 10% developed lethargy and confusion[25]. In adult patients, complications with symptoms compatible with encephalitis have been reported after injection of type A BoNT as a treatment for dystonia[23].

Regarding infant botulism, few reports have mentioned brain involvement. Gautier et al.[26] reported a male infant with type A BoNT isolation who presented an altered EEG and abnormal response in evoked potentials. Smith et al.[27] reported the case of an infant with type B and F BoNT who presented with an EEG showing generalized high-amplitude slow wave activity, which increased a week later to later normalize, an event similar to what occurred in our patient. Likewise, two cases with unusual findings in neuroimaging have been described. One of them was an infant with botulism (type B BoNT) who presented persistent neu-

Table 1. Epidemiological, Clinical, Laboratory, and Therapeutic Characteristics of Reported Cases of Infant Botulism in Chile

	1987 Erazo et al.[2]	1995 Bavestrello et al.[3]	1996 Moline et al.[4]	2008 Córdova et al.[5]	2009 Arriagada et al.[1]	2022 Current Report
Age (months)	2 ½	2	2	2	7	7
Sex	Male	Female	Female	Male	Male	Male
Source of Contamination	Unknown	Unknown	Unknown	Oregano infusion (*Origanum vulgare*)	Homemade honey	Unknown (soil?)
Neurotoxin Type	No refiere	A	A	A	A	A
Pupillary Reflex	Areflexic	Slow	Areflexic	Areflexic	Slow	Areflexic
Sensory Involvement	Not reported	Not reported	Not reported	Not reported	Not reported	Yes
EEG Electroencephalography	Not performed	Not performed	Diffuse slowing	Normal	Not performed	Generalized slow dysfunction
EMG Electromyography	Narrow low-voltage potentials and non-decremental response with repetitive stimulation	Multiple brief low-amplitude potentials	Low-amplitude, short-duration potentials. 35% increase in response area with repetitive stimulation	With a 50 Hz stimulus, it showed the classical response of pathological increase due to presynaptic blockade	Abnormal increase in motor potentials from 20 Hz	Not performed
Mechanical Ventilation/ Days	No	Yes/30	Yes /37	Yes /150	No	Yes/ 109
Hospitalization Duration (days)		50	98	180	30	150
Alive/Deceased	Alive	Alive	Alive	Alive	Alive	Alive

rological changes (muscle weakness in the left upper extremity) and whose brain CT scan during the recovery phase showed attenuation of the frontotemporal cortical thickness[21]. Before this report, Black et al.[28], reported the existence of cholinergic receptors for type A BoNT in rat brains, mainly in the temporal horn, the same site as in the patient reported by Jones et al.[21]. The second case was a 5-month-old infant with botulism (type A BoNT) whose complementary examinations included a brain and spinal cord MRI revealing diffusion restriction in the corpus callosum, splenium, bilateral optic radiations, and pons. In the spinal cord, symmetric enhancement of the cervical nerve root was observed, with no abnormality of the spinal cord signal[24].

Regarding retrograde axonal transport, it is based on the specificity of BoNT, which derives from its binding to specific gangliosides and other receptors on the presynaptic nerve terminal[29]. Once endocytosis occurs, retrograde transport can produce direct effects in the CNS. Studies have suggested that BoNT may inhibit neurotransmitters other than ACh. Also, several animal studies[30,31] have shown that BoNT does not remain confined to the injection site (muscle, intraperitoneal, or retina) since physiologically significant amounts were located in retrograde synapses.

The diagnostic confirmation of infant botulism consists of toxin isolation in serum (which is usually negative) or spores isolation in stool since this microorganism is not considered part of the normal flora[20]. In Chile, identification is performed at the ISP through toxin neutralization testing in mice, which is the gold standard. Although the results may take days, it has the advantage of allowing the determination of the type of toxin. Finally, there is a PCR test that allows for toxin identification within 24 hours, but it does not distinguish whether the toxin is biologically active or not[32].

Treatment of the patient with botulism is mainly supportive and the prognosis is generally favorable. The binding of BoNT to nerve endings is irreversible, and neurological recovery occurs given the motor neuron regeneration over weeks or months[7]. The need for

MV is highly variable and in different series in the U.S. ranges from 40 to 80% of admitted patients[16,33]. In the National Pediatric Critical Care Database in the U.S., in 8 years (2009-2016), the average IMV was 6.2 days (0.2 - 81 days)[34]. In contrast, in a recent report[32], 21 cases of infant botulism were reported, and 20 of them required MV, with a median duration of 37 days. In the Chilean casuistry published (1987-2009), three of the five patients required MV (Table 1)[1-5].

Antibiotics should not be used unless concurrent infection is demonstrated; there is a theoretical risk that *C. botulinum* intraluminal lysis could increase the amount of toxin available for absorption[20]. Also, antibiotic therapy does not affect the duration of fecal bacterial excretion, which reaches 6 weeks in the case of type A BoNT[35].

The use of intravenous botulism immune globulin (BIG-IV; BabyBIG®) is useful in reducing the duration of MV and ICU and hospital stays[34,36], recommending its early use since its administration before 48 hours has been shown to reduce both mortality and the need for ventilatory support[36].

Its mechanism of action is based on binding to circulating neurotoxins, thus preventing their binding to the neuromuscular junction, potentially preventing progression to respiratory failure. Since it cannot reverse paralysis, early administration in the course of the disease is essential.

A recent report[37] evaluated the efficacy of treatment with BIG-IV after more than a decade of use, showing convincing beneficial results regarding economic and hospital management aspects. However, it is not currently available in Chile and is very expensive.

The Infant Botulism Treatment and Prevention Program (IBTPP) of the California Department of Public Health provides online support (ibtpp@infantbotulism.org) and has facilitated the shipment of specific immunoglobulin to several countries in Europe and Asia[38].

Conclusion

Infant botulism is a rare disease, requiring a high index of suspicion, which is essential for a timely diagnosis.

Our case's particularity was the altered state of consciousness presented by the patient, although uncommon as an initial presentation of botulism, should be considered within the spectrum of manifestations of this disease, given the clinical evidence mentioned above. Likewise, its non-assessment could lead to a delay in diagnosis and, therefore, to inadequate therapeutic and supportive measures.

Once this entity is confirmed, the use of specific immunoglobulin at an early stage is crucial. Unfortunately, it is not available in our country. Public health strategies should be oriented toward the prevention of this disease through education.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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