A Case of Infant Botulism Treated with Human-Derived Antitoxin

Sara Jimeno Ruiz1,3,4 MD PhD, María Benedit Gómez1 MD, Paula Touza Pol1 MD PhD, Amaia García Arratibel2 MD and Alejandro López Escobar5* MD PhD

1Pediatrics Department, HM Hospitales, Madrid, Spain.
2Neurology Department, HM Hospitales, Madrid, Spain.
3HM Science Faculty, Camilo José Cela University, Madrid, Spain.
4Fundación de Investigación HM Hospitales, HM Hospitales.
5Pediatrics Department, Hospital Universitario General de Villalba, Madrid, Spain.

*Corresponding Author: Alejandro López Escobar MD PhD, Pediatrics Department, Hospital Universitario General de Villalba, Madrid, Spain. https://orcid.org/0000-0002-9052-1429 Email: alejandro.lopezefatjgvillalba.es

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Abstract

Background: Infant botulism is a severe and rare illness due to the ingestion of the neurotoxin secreted by Clostridium botulinum and is a neuroparalytic descendant acute disease which is reversible, treatable and preventable. Symptoms vary from mild hypotonia to respiratory failure and sudden death.

Clinical Observation: A four-months-old female baby taken to the Emergency Room because of hypoactivity and failure to eat. Parents reported constipation for the last 5 days. The physical examination showed a hypoactive baby with sleep tendency and mild axial hypotonia. During the next 48 hours there is a progressive worsening of the clinical condition with severe axial hypotonia, generalized weakness, weak cry, increasing difficulty in sucking and swallowing and increase of respiratory secretions together with weak cough reflex. An electromyogram was performed with normal results. Parents denied giving the baby honey, infusions or any other food other than milk or cereals. Although there was no clear epidemiological history, infant botulism was suspected, and contact was made with the local Health Department and a direct toxin analysis was requested from blood and fecal samples. She received treatment with human derived botulism antitoxin (BabyBIG®) with a favorable outcome. The diagnosis was confirmed by the detection of the botulism toxin B in the patient’s stools.

Comments: Infant botulism, although it is a rare disease in our environment, requires a high level of suspicion to make an early diagnosis and initiate a timely and specific treatment and thus reduce complications and the course of the disease.

Keywords: Botulism, Hypotonia, Antitoxin, BabyBIG

Abbreviations

FDA (Food and Drug Administration); PICU: Pediatrics Intensive Care Unit; CSF: Cerebrospinal Fluid; MRI: Magnetic Resonance Image; EEG: Electroencephalography; BAT: Heptavalent equine antitoxin
**Introduction**

Infant botulism is a severe and rare illness due to the ingestion of the neutotoxin secreted by *Clostridium botulinum*, an anaerobic bacillus capable of forming spores that are widely distributed in nature and can be transmitted to be transmitted through contaminated soil or through the consumption of contaminated food, such as honey and some medicinal herbs or infusions for babies (1).

Botulism is a neuroparalytic descendant acute disease which is reversible, treatable and preventable. Symptoms vary from mild hypotonia to respiratory failure and sudden death. Of all the clinical forms of botulism, infant botulism is the most frequent and should always be considered in a hypotonic infant. Early diagnosis and treatment are crucial, as it is to increase health education on this disease (2). In 2003 the FDA (Food and Drug Administration) approved the use of a human-derived antitoxin (BabyBIG®), a safe and effective drug for the treatment of infants in whom botulism is suspected (3). The first case of infant botulism treated with this drug in Europe was in Cordoba (Spain) in 2007 (4) and at the date of our diagnosis, no new case had been reported to the health authorities.

We describe a case of infant botulism in a four months old child admitted in our Hospital who received the human-derived antitoxin (BabyBIG®) with rapidly favorable clinical evolution.

**Case Report**

A four-months-old female baby taken to the Emergency Room because of hypoactivity and failure to eat. Parents reported constipation for the last 5 days. No fever or other symptoms were present.

Pregnancy, delivery and perinatal period had been normal. Newborn metabolic screening test yield no abnormalities. The baby had a normal psychomotor development and was correctly vaccinated. She received only breast milk until 6 days before admission when supplementary powder milk and gluten free cereals were added. In the last two months she received treatment with oral ranitidine to treat a gastroesophageal reflux which was substituted by oral omeprazole 6 days before hospitalization. From the age of three to four months the baby failed to gain weight (p10 to <p3). In the last 48 hours before consulting she had considerably reduced the food intake.

The physical examination showed a hypoactive baby with sleep tendency and mild axial hypotonia. Blood test were normal except for a mild microcytic hypochromic anaemia. She was admitted to hospital with intravenous fluids. 48 hours after admission there was a clinical worsening with hypotonia, lethargy and pallor. Rest of the neurological examination, including knee and plantar osteotendinoseus reflexes, was normal. She was reffered to PICU and due to the suspicion of sepsis with encephalitis, empirical intravenous treatment with cefazoline and acyclovir was started. Blood test did not show elevated acute phase reactants or acidosis. Liver and thyroid function test were normal as well as creatine kinase, ammonium and lactic level. Urine test and CSF test showed no abnormalities. Metabolic blood, CSF and urine screening test were normal. Transfontanellar ultrasound and brain and spinal MRI evidenced no alteration. EEG showed normal brain activity with no seizure activity, asymetries or paroxistic episodes. Blood karyotype test proved 46 XY normal chromosomes. Fluorescence in situ hybridization (FISH) analysis for Prader Willi syndrome showed no microdeletion within 15q11-q13.

During the next 48 hours there is a progressive worsening of the clinical condition with severe axial hypotonia, generalized weakness, weak cry, increasing difficulty in sucking and swallowing and increase of respiratory secretions together with weak cough reflex. Also, a mild right palpebral ptosis is detected. Pupils were mildly dilated, and sluggishly reactive and tendon reflexes started to be decreased (Figures 1-4). The baby required supplementary oxygen with nasal canula and suffered some episodes of choking due to respiratory secretions, but had not apnea breaks or respiratory failure. Temperature was always normal and there were no symptoms or signs of infection. Constipation had persisted for 12 days.

An electromyogram was performed with repetitive nerve stimulation test at low (3 Hz) and high frequencies (30 and 50 Hz), with normal results. Nerve conduction speed was also normal.
Parents denied giving the baby honey, infusions, or any other food other than milk or cereals. The family home is a detached house with garden in a town near Madrid. They reported spending some days in a rural environment in 2 weeks before admission.

Although there was no clear epidemiological history, infant botulism was suspected, and contact was made with the local Health Department and a direct toxin analysis was requested from blood and fecal samples. Fecal samples were also sent to cultivate. Samples of the formula milk, cereals and omeprazole taken by the baby at home were sent to be analysed. At the same time, we started the procedures to get the human-derived antitoxin (BabyBIG®) from the Infant Botulism Treatment and Prevention Program (IBTPP) in California.

While we waited for results, we maintained respiratory and nutritional support. We received the antitoxin on the 13th day of hospitalization, and it was administered without any side effect during the infusion. Clinical improvement of hypotonia, level of activity, ptosis, mydriasis, pupillary reactivity, respiratory secretions, and the sucking-swallowing was evident and allowed oral feeding. Deep reflexes became normal. Three days after the administration of the antitoxin the nasogastric tube was removed, and the patient was dismissed from the PICU to the paediatrics floor.

On the 16th day, we received the laboratory results from the Centro Nacional de Microbiología del Instituto Carlos III. The neurotoxin was detected both on the patient's faeces and on the mouse lethality assay. Also, Clostridium botulinum was isolated from the patient stools. During her stay at the paediatric floor the patient continued the gradual improvement in the muscle tone, limbs movement, level of activity, sucking and swallowing. Vojta therapy was started.

Considering the positive clinical course the patient is discharged home and continued follow up in the paediatrics, neuropaediatrics and rehabilitation outpatient clinics. The patient continued with Vojta therapy as well as sensorial motor stimulation (Le Metayer and Bobath method). At this moment the patient is fully recovered and has an average physical and psychomotor development.
Discussion and Conclusion

Infant botulism is a potential severe illness, which courses as a descendant symmetric flaccid motor paralysis followed by a slowly recovery of the muscular function. It affects infants below 12 months of age being more prevalent between two weeks and six months of age (5). It results from the colonisation of the bacterium Clostridium botulinum in the intestine (and other less frequent species such as C. baratti and C. butyricum) and the further absorption of the botulinum toxin in the systemic circulation (5-7). The first case of infant botulism was reported by Pickett in the USA in 1976 (8). At this moment it is the most frequent form of botulism ahead of foodborne botulism or botulism due to wounds infections (2, 8-10).

Infant botulism is spread all over the world and cases have been documented in many countries on all continents. The variability in incidence between different countries may be the result of several factors: the heterogeneous environmental distribution of spores, the different ability to detect the disease and the documentation of cases, cultural practices (such as the administration of honey or infusions to infants), exposure to dust or soil and perhaps the different susceptibility of patients to the disease (11). Botulism is a notifiable disease in Spain since 1969 and the first cases of Infant Botulism were reported in Cádiz (1997) and Ciudad Real (1998) (4, 12). In the event of an outbreak an urgent declaration must be made. In 2015, the National Epidemiological Surveillance Network (RENAVE) emerged to facilitate the notification of cases (13). From 2015 to 2022 inclusive, a total of 88 cases of botulism were reported. Epidemiological information on the botulism situation in Spain can be consulted here (14): https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/Resultados_Vigilancia_Botulismo.aspx

Clostridium botulinum is an anaerobic bacterium, capable of forming spores and whose natural habitat is the ground, which makes it an inexhaustible source of contamination, especially considering it is not a bacterium with demanding growth conditions. Spores can be often found in the dust, and they have been also identified in bed line, clothes, dust from hoovers as well as in bee honey, cane honey and some type of medicinal herbal infusions (1-5). However in 85% of the cases the source of contamination is unknown (7). Spores get to the infant’s gut when the baby eats contaminated food or by swallowing respiratory secretions contaminated by dust or soil. It occurs when infants ingest C. botulinum spores, which germinate into bacteria that colonize in the gut and release toxins. In most cases the intestinal flora could prevent the colonization of the spores. However, a transient decreased in the flora, an impaired motility or an alteration pH could promote the proliferation of the ingested spores. Infant intestine immaturity makes it more susceptible to contamination. It has also been related to weaning in babies exclusively fed with breast milk (1, 7, 9, 10). The influence of the type of milk on infant botulism has no yet been clearly established; according to some studies, breast milk could increase the risk of suffering it, but could, at the same time, slow the onset of illness (2, 7, 9). Botulinum toxin is the most potent neurotoxin known. There are 7 types of neurotoxins (from A to G) but type A, B, E and F are the neurotoxins involved in human botulism (1, 7, 9, 10). Botulinum toxin impedes the normal release of acetylcholine from presynaptic motor neurons blocking the transmission of neuromuscular and autonomic impulses. This blockage of neurotransmitter release is irreversible. Function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; this usually begins after 2-3 weeks but can take up to 6-9 months. Botulinum toxin never passes through the blood-brain barrier so the central nervous system is not affected (1, 9).

Usually, the course of the illness is mild and self-limited with a favourable outcome. Clinical course may vary between a mild paralysis to a moderate or severe course. On rare occasions the history and clinical findings are indistinguishable from typical cases of sudden infant death syndrome and diagnosed by autopsy (2, 9). The severity of the symptoms depends on the amount of toxin ingested. The incubation period is unknown because it is usually impossible to determine the exact moment when the spores get into de intestine. Some authors mention a duration of 12 to 36 hours after the toxin ingestion (1, 10).

Often the parents consult for the first time when hypotonia, weakness, decrease of limbs movements and poor head control appear. Symptoms progress to a flaccid symmetric descending motor paralysis that can sometimes affect the respiratory muscles producing a respiratory failure that requires admission to the PICU and respiratory support. Deep tendon reflexes are usually decreased or abolished. Constipation almost always precedes hypotonia although it is often overlooked (2, 7). It is the main clinical characteristic and occurs in 97% of the cases. It is also a risk factor as it disrupts intestinal flora and favours the development of spores and the toxin absorption (7, 9). Cranial nerves are typically affected: there is an impairment of the suck, swallow and cough reflex, a hoarse and feeble cry, palpebral ptosis, ophthamoplegia and, sluggishly reactive pupils.
Patients appear lethargic and expressionless. Due to autonomic dysfunction, patients can have decreased salivation or tearing, tachycardia, bradycardia, hyper or hypotension and urinary retention.

The hospital course of untreated infant botulism is variable, but typically symptoms progress for 1 to 2 weeks, then remain stable for about another 2 to 3 weeks before beginning to show signs of improvement in strength and movement. This improvement is slow and steady and can last for months. During this period, patients are especially vulnerable to events that affect neuromuscular transmission (7).

The diagnosis of botulism can be complicated as it shares clinical features with other illness such as Miastenia gravis, Eaton-Lambert syndrome, Werndig Hoffman syndrome, poliomyelitis, Reye syndrome, Guillain-Barré syndrome, sepsis, meningitis, pathology affecting the spine, metabolopathies, hypothyroidism, myotonic dystrophy disease and congenital myopathies, tick borne paralysis and other flaccid paralysis (7).

In case of clinical and/or epidemiological suspicion of infant botulism, diagnosis is established by identification of 
*C. botulinum* organisms in the faeces and/or its toxin in faeces and/or serum. In infant botulism the toxin is almost always detected in faeces but seldom in serum.

Electromyography can be helpful although it is not diagnostic by itself and can be normal at early stages of the illness (15) and there are several confirmed cases of infant botulism with normal electromyogram (16, 17). Electromyography often discloses a pattern of brief, small and abundant motor unit potentials. Nerve conduction velocity test is normal and the test with edrophonium o neostigmine will show no response (7, 9, 18, 19).

Management of infant botulism depends on supportive nutritional and respiratory care, thus early clinical suspicion is crucial. To maintain an adequate caloric intake the early use of a nasogastric or nasojejune tube is recommended. Intravenous feeding is only necessary when the enteral via cannot be use. On clinical respiratory worsening of the patient early admission to the PICU for close monitoring and potential need for mechanical ventilation. Constipation can be initially handled with enemas that help eliminate botulinum spores and toxin and allow to get the faeces sample for confirmatory diagnostic testing (saline solution should be used). Hydration and stool softeners can be useful although laxatives are not recommended. We must keep in mind that these patients may continue to excrete spores and toxins in stools for up to 4-5 months after the onset of symptoms (7, 9).

Studies agree that antibiotics should not be administered. Some of them, like the aminoglycosides, can potentiate the action of botulinum toxin at the neuromuscular junction or increased the liberation of intracellular neurotoxin into the gut lumen by lysis of intraintestinal *C. botulinum*, like penicillin. Also, antibiotics could disrupt the intestinal flora which would favour the growth of *C. Botulinum*. Antibiotic is indicated only for the treatment of complications such as pneumonia or sepsis (4, 16).

Specific treatment of botulism is based on the administration of intravenous botulinum antitoxin as soon as possible, preferably within the first 48 hours (13). The antitoxin neutralizes the circulating toxin before it reaches the presynaptic cholinergic nerve endings at the motor endplate. It is ineffective to discharge the toxin already bound to nerves. There are two types of antitoxins: human-derived antitoxin and equine antitoxin.

There is very little experience using equine antitoxin in the treatment of infant botulism. Its use in most countries is not approved due to the limited evidence of its efficacy and the possibility of serious side effects including anaphylactic reactions (5-7). Heptavalent equine antitoxin (BAT) is available in Spain and its use is authorized for all age groups, including those under 1 year of age (11). It can be requested through this computer application of the Spanish Agency for Medicines and Health Products: https://sede.aemps.gob.es/usoHum/otros/medicamentos-situaciones especial-es.html#andlaTop.

In intestinal botulism, support measures are essential, but since 2003 there has also been a specific human-derived immunoglobulin (BabyBIG®) for the treatment of infants in whom this disease is suspected (4, 11). These are human antibodies obtained from the plasma of immunized adults with the ability to neutralize the botulinum toxin circulating in the blood. This drug is approved in children under 1 year of age, has a longer half-life than BAT and its dose is lower than the recommended dose in children under 1 year of age with BAT (10% of the dose in adults).

Human-derived antitoxin (BabyBIG®) is produced in the USA, and is approved by the FDA (Food and Drug Administration) since 2003 (3, 20). At the time of our diagnosis, this treatment was only available in at the Infant Botulism Treatment and Prevention Program (IBTPP) from the California Department of Public Health (Figure 5) (21).
At present, BabyBIG® is available, upon request through the computer application of the Spanish Agency for Medicines and Health Products (13).

Use of human-derived antitoxin reduces mean hospital stay per case an average of 3.1 weeks, PICU stay 3.2 weeks, mechanical ventilation 3.2 weeks and nasogastric feeding 6.4 weeks (22). Treatment with human-derived antitoxin should be started as early in the illness as possible, during the first 3 to 7 days in suspected cases in a single dose of 50 mg per kilogram (Figure 5) (23). Treatment should not be delayed for laboratory confirmation of the clinical diagnosis.

Immediate side effects are usually minor like erythema, but, just as any other gamma globulin, can cause anaphylaxis and hypotension (20). It has a half-life of 28 days, and it can neutralize the toxin during a period of 6 months (3). The economic cost of the human-derived antitoxin is very high hence not every country can afford it (5, 16).

Epidemiological surveillance is essential to implement preventive measures, reduce the incidence of the disease, improve the precocity of diagnosis and treatment of cases and identification of the agent. The distribution of infant botulism is worldwide, and most of the cases occur in a rural environment, in areas with low rainfall and strong winds, factors that would facilitate a greater load and spread of spores in the environment (5, 9, 10). The growth of C. botulinum in food products can be prevented controlling the water acidity, refrigerating and applicating chemical conservatives. Honey should not be given during the first year of life (24, 25).

Infant botulism, although it is a rare disease in our environment, requires a high level of suspicion to make an early diagnosis and initiate a timely and specific treatment and thus reduce complications and the course of the disease (Figures 6 and 7).
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Conflict of Interest
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All the authors drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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