

Infant Botulism: Rare but very Dangerous Event: A Case Report

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Received: 25 Jun 2022

Accepted: 28 Jul 2022

Published: 05 Aug 2022

Citation: Milella L, Ficarella MT, Calabrese G, et al. Infant botulism: Rare but very dangerous event: A case report. *Int J Clin Invest Case Rep.* 2022; 1(2):29-32.



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Abstract: We report a case of infant botulism admitted to the Children's Hospital "Giovanni XXIII", Bari, Italy. After a week of constipation, hypotonia, lethargy, ptosis, reduction of suction and cry, a 2-month-old infant male, the first kid of unrelated parents was taken to the closest hospital, after being born normotrophic, at term, without a prenatal, perinatal, or postnatal medical history or neurodevelopmental delay. The patient was referred to the pediatric center for an undiagnosed progressive worsening of awareness and he was intubated for bradypnea and desaturation. The toxicologic panel, cerebrospinal fluid exam, radiological imaging, and laboratory results were negative. Only after neurological instrumental analysis, we found a normal EEG but a positive EMG that is associated with the history of raw honey intake (revealed only later by his mother). We were allowed to define the hypothesis of infant botulism earlier than the confirmation of the standard mouse bioassay. So, as a result, Botulism Immune Globulin-Intravenous IgG over 3 hours in a single recommended dose of 0.1 mL/kg/min was injected. The infant showed a gradual improvement and after 10 days he was extubated. The Preterm Oral Feeding Readiness Scale showed an improvement through the rehabilitation program with physiotherapy and parents' stimuli. After one month he was discharged. Frequently, infant botulism is not the first hypothesis but it is the result of a strict differentiation from other diseases characterized by hypotonia such as sepsis, infectious, genetic, autoimmune, or metabolic diseases through the use of history, and laboratory tests and radiological imaging. At first, toxin detection can be useful for early diagnosis. In the later stages, the neurological instrumental support can help the clinician to elucidate the cause of muscle weakness. In fact, the EEG and the EMG could be positive when toxins are unlikely to be detectable in the serum and other data are negative. A minimum of one arm and one leg should be examined for motor and sensory nerve conduction velocity along with two distal muscles for 2-Hz nerve stimulation and a needle EMG with an adequate sample. We suggest that the neurological instrumental support can help the clinician to elucidate the cause of muscle weakness, in particular in the later stages. Honey shouldn't be provided to infants under one-year-old children because the majority of instances still have a good history of exposure to it.

Keywords: Infant Botulism • Diagnosis • Hypotonia • Electromyography • Botulism Immune Globulin-Intravenous IgG • Preterm Oral Feeding Readiness Scale

INTRODUCTION

The first form of infant botulism was described in 1976 but in Italy, it was first recognized in 1986 [1]. Infant botulism is caused by the ingestion of *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium baratii* [2-4], and *Clostridium argentinense* spores found in food (usually raw honey with spores in the dust from the hive or carried by worker bees), the dust or the soil [5]. The source of *Clostridium botulinum* infection is typically unknown,

and it is assumed to result from ingesting dust [6]. Nearly 98% of the cases of infant botulism are about 2 week-6 month babies. We report a case of infant botulism in the Children's Hospital "Giovanni XXIII", Bari, Italy.

CASE PRESENTATION

A 6 kg-infant of 2 months and 2 weeks had a history of constipation, weakness, hypotonia, lethargy, ptosis, reduction of suction and cry, conjunctivitis (treated with cortisone and antibiotic in the eyedrops for five days), increased nasal and oral secretions, clubfoot, and normal Apgar scores at birth. He had a previous administration of industrial and raw honey for two weeks by his grandmother. After a week since the beginning of the signs, on 23/11/2020, the infant was accepted in the "Casa sollievo della sofferenza" hospital in San Giovanni Rotondo (Foggia), where he was intubated due to his neurologic status. A toxicological panel (negative) was performed here. On the same day, he was admitted to our ICU at Children's Hospital "Giovanni XXIII", Bari, where he appeared lethargic, hypotonic, and with moderate mydriasis. He was mechanically ventilated in PC mode and presented normal arterial blood gas analysis and stable hemodynamics. Chest X-ray was apparently normal. The parameters were SpO₂ 99% at FiO₂ of 0.4, HR 130 contractions/min, systemic BP 95/55 mmHg, and rectal temperature 38.5 °C. For this reason, a therapy with Vitamin B5, a prokinetic for constipation, and clarithromycin because of the fever (due to penicillin allergy) was administered. A cranial CT scan did not show any disease. A second Chest x-ray showed a diffuse opacity in the left lung treated with postural therapy. An evaluation for sepsis (PCR, PCT, blood culture, urine culture, Cerebrospinal Fluid (CSF) culture, virus PCR, and cytology) resulted to be negative. The neurological examination underlined generalized descendent hypotonia (floppy infant), weakness, reduction of deep reflexes, ophthalmoplegia, mydriasis, and the presence of pupillary light reflex.

The genetic analysis for type I spinal muscular atrophy did not confirm such a diagnostic hypothesis. It was carried out the measurement of serum electrolytes (Na⁺ 137 mmol/l, K⁺ 4.3 mmol/l, Ca²⁺ 9.5 mg/dl, Mg²⁺ 2.2 mg/dl), liver functions (AST 29 U/l, ALT 21 U/l, GGT 37 U/l and total bilirubin 0.26 mg/dl) and ammonia 84 µg/dl (for the differential diagnosis from Reye's syndrome), glucose 80 mg/dl, PCR 2 mg/dl and creatinine 0.29 mg/dl; a complete blood count (WBC 9 x 10³ /µL, RBC 2.81 x 10⁶ /µL, HGB 8.7 g/dl, HCT 25.03% and PLT 544 x 10³ /µL) (Table 1) and the physical-chemical analysis, the IgG, and the leukocyte count of the cerebrospinal fluid (CSF) (negative) from rachicentesis. A

fluorometric Dried Blood Spot (DBS)-based GAA activity assay and an echocardiogram were made for the Pompe disease hypothesis (both negative). The heart was normal in every function and anatomic relief. After two days, a head and spine MRI with and without contrast agent was done and resulted negative. A hereditary metabolic diseases screening that included the measurement of plasma and urinary amino acids (hyperaminoacidemia), urinary organic acids and bipterin (phenylketonuria), serum ammonia previous and after dietary protein intake, lactate and pyruvic acid (mitochondrial disease), creatine, homocysteine, uric acid, Vitamin B12 and B9 (demyelinating disease), and ceruloplasmin (Wilson's disease), and isoelectrofocusing of the sialotransferrin (type I and II Pompe disease) was negative. The EEG was normal, while the EMG underlined a reduction in the amplitude of the action potential velocity of two muscle groups in the right arm and leg. The EMG and clinical signs confirmed, by clinical exclusion, the suspect of infant botulism. On the 26/11/20, it was contacted the "Centro AntiVeleni (CAV)", a poison center in Foggia and Pavia that suggested, even in absence of diagnostic positive tests, the intravenous injection of the equine Botulism Antitoxin Heptavalent (A,B,C,D,E,F,G) IgGs over 3 hours in a single recommended dose of 0.1 mL/kg/min and then to start the administration of oral sulphamethoxazole-trimethoprim 24/120 mg every day and macrogol 5 g every 12 hours. A gradual improvement of the ptosis, mydriasis, and constipation, and then the hypotonia and the coordination of movements were observed during the next 48 hours. After 24 hours, since the neurologic status was fair, weaning from the mechanical ventilation changing the mode from PCV to PSV, and then to bubble-CPAP with decremental PEEP support from 8 to 5 cm H₂O was started. The rectal swab was carried out and then collected an effluent sample (25 ml) for *C. botulinum* culture and Botulin Neurotoxin (BoNT) investigation. The containers were sent to the "CNRB-Italian National Referral Center for Botulism Control", a specialized diagnostic center in Rome, to perform a standard and a toxin neutralization mouse bioassay. The second trial was positive after 2 days. On 30/11/20 there was an amelioration of the ophthalmoparesis and it was carried out a fundus oculi exam that excluded an optic neuritis. On 03/12/20 the infant was extubated. After 24 hours, the infant started a physiotherapy program that involved even the parents. The outcome was assessed via the Neonatal Behavioral Assessment Scale (NBAS) from Brazelton which seemed to be the best choice to assess the infant's (up to 60 days) global activity. It showed an improvement in listening, seeing, the attention/interaction attitude, head rotation, the movement of the four limbs, the asymmetrical tonic neck reflex, and the rooting reflex. Still, in presence

of dysphagia and coughing, it was started the logopedical rehabilitation through the Beckman Oral Motor intervention (BOMI) method (15 minutes of suction stimulation, lip stretching, and the massage of cheeks, lips, gum, tongue, and palate for 6 days) and respiratory exercises (assisted cough). It improved the coordination between suction and respiration and guaranteed its correct development, as well as avoided reintubation and tracheostomy. These endpoints were evaluated through the Preterm Oral Feeding Readiness Scale (POFRAS). He gradually showed reappearing of the Moro's, grasping, and rooting reflexes. On 06/12/20, he was transferred to the hospital neurological ward and kept on doing rehabilitation. One month after the admission to Hospital the infant was discharged home without any reliquate or specific therapy.

Table 1: Result of meta-analysis for infant patient.

Na ⁺	137 mmol/l
K ⁺	4.3 mmol/l,
Ca ₂ ⁺	9.5 mg/dl
Mg ₂ ⁺	2.2 mg/dl
AST	29 U/l
ALT	21 U/l
GGT	37 U/l
Total Bilirubin	0.26 mg/dl
Ammonia	84 µg/dl
Glucose	80 mg/dl
PCR	2 mg/dl
Creatinine	0.29 mg/dl
WBC	9 x 10 ³ /µL
RBC	2.81 x 10 ⁶ /µL
HGB	8.7 g/dl,
HCT	25.03%
PLT	544 x 10 ³ /µL

DISCUSSION

The diagnosis of infant botulism is predominantly clinical. The clinical presentation is always acute (6 hours to 8 days) [7]. It includes constipation caused by the reduction of the bowel wall musculature contraction (differential diagnosis from congenital myasthenia gravis), which is followed by weakness of crying and sucking, the reduction of swallowing and vomit reflexes, ophthalmoparesis, blurred vision and diplopia, absence of the papillary light reflex, drooling, flat facial expression, ptosis, mydriasis, tongue weakness, gastroesophageal reflux, anhydrosis, the reduction in the tone of the anal sphincter and bladder wall, tachycardia

and hypotension from the palsy of the parasympathetic in cranial nerves (differential diagnosis from poisoning by organophosphorous amides or heavy metals and hepatic encephalopathy) and a progressive descendant flaccid paralysis of the head, the neck, the trunk, and bilateral limbs (floppy infant) (differential diagnosis from the ascendant palsy of the Guillain-Barrè syndrome [8-9], asymmetric

Table 2: Hypotonia differential diagnosis.

HYPOTONIA	
Central conditions	Peripheral conditions
<ul style="list-style-type: none"> Sepsis Meningoencephalitis Poliomyelitis Hepatic encephalopathy Hypoxic-ischemic encephalopathy Neuroblastoma stage III (presumptive Lambert-Eaton syndrome) Idiopathic central demyelinating disease, Cerebral atrophy from intrauterine drug exposure Metabolic congenital disorders (hypothyroidism, Reye's syndrome, type II Pompe disease, type I glutaric aciduria, maple syrup urine disease, Leigh's syndrome, and succinic semialdehyde dehydrogenase deficiency) Drugs like benzodiazepines, narcotics, and anticholinergics or poisoning by organophosphorous amides, carbon monoxide, or heavy metals 	<ul style="list-style-type: none"> Specifically, type I spinal muscular atrophy Porphyria Metabolic acidosis Hyponatremia Hypermagnesemia Hypomagnesemia Hypocalcemia Diphtheria Myasthenia gravis Guillain-Barrè syndrome Poliomyelitis Idiopathic spinal epidural hematomas Idiopathic diaphragmatic paralysis Congenital myopathies Congenital myotonic dystrophy

palsy of the poliomyelitis and from the existence at birth of the type I spinal muscular atrophy, the congenital myotonic dystrophy and myopathy), hypotonia, the reduction/absence of deep reflexes [10-13] and respiratory insufficiency from the palsy of motor nerves.

Since any nervous system dysfunction can result in hypotonia, the following conditions must be included in the differential diagnosis :

- Central conditions:** Sepsis, meningoencephalitis, poliomyelitis, hepatic encephalopathy, hypoxic-ischemic encephalopathy, neuroblastoma stage III

(presumptive Lambert-Eaton syndrome), idiopathic central demyelinating disease, cerebral atrophy from intrauterine drug exposure, metabolic congenital disorders (hypothyroidism, Reye's syndrome, type II Pompe disease, type I glutaric aciduria, maple syrup urine disease, Leigh's syndrome, and succinic semialdehyde dehydrogenase deficiency), drugs like benzodiazepines, narcotics, and anticholinergics or poisoning by organophosphorus amides, carbon monoxide or heavy metals.

- **Peripheral disorders:** Specifically type I spinal muscular atrophy, porphyria, metabolic acidosis, hyponatremia, hypermagnesemia, hypomagnesemia, hypocalcemia, diphtheria, myasthenia gravis, Guillain-Barré syndrome, poliomyelitis, idiopathic spinal epidural hematomas, idiopathic diaphragmatic paralysis, congenital myopathies, and congenital myotonic dystrophy [5, 10, 13] (Table 2).

The hypotonia examination anticipates family and prior medical history analysis (prenatal, perinatal, and neonatal assessment) and differential diagnosis from myotonic dystrophy and benign congenital hypotonia. About central causes, they usually worsen with time and develop a depressed level of consciousness, normal strength, and hyperactive or normal reflexes. Although type II Pompe disease often develops in the second postnatal month, it may be present during pregnancy. A mixed central and peripheral clinical picture results from aberrant glycogen deposition in the skeletal (feeding abnormalities, hypotonia, weakness, and respiratory insufficiency), cardiac (hypertrophic cardiomyopathy, which is usually invariably diagnostic), and smooth muscles, and CNS (hypotonia). Cervical trauma from a breech delivery or cervical presentation, as well as maternal exposure to chemicals or infections, are other major causes [10].

About peripheral causes, the disorders of the anterior horn cell show an acute onset and do not affect mentation, generalized weakness, absent reflexes, or feeding difficulties (as in infant botulism since BoNTs do not cross the blood-brain barrier) unless there are significant secondary complications (hypoxemia or cardiorespiratory failure, hypoglycemia, or profound dehydration and electrolyte abnormalities) [7]. Low Apgar scores may suggest floppiness from birth (differential diagnosis from congenital myasthenia gravis) [14]. The classic infantile form of type I spinal muscular atrophy presents fasciculations of the tongue, an intention tremor, a history of progressive weakness, the absence of ophthalmoparesis, and normal anal sphincter tone (differential diagnosis from infant botulism) [8]. Routine studies include an evaluation

for sepsis (blood culture, urine culture, Cerebrospinal Fluid (CSF) culture, virus PCR, and cytology) since a hypotonic newborn should be considered septic until proven otherwise; the measurement of serum electrolytes, liver functions, and ammonia (for the differential diagnosis from Reye's syndrome) [8], glucose, calcium, magnesium, and creatinine; a complete blood count; a urine drug screen and Cerebrospinal Fluid (CSF) IgGs (differential diagnosis from Guillain-Barré disease) and leukocyte count (leukocyte > 10/mm³ can differentiate poliomyelitis) [8-9]. The MRI may delineate hypoxic-ischemic encephalopathy, neuronal migrational defects, abnormal signals in the basal ganglia (mitochondrial diseases), cerebellar vermis defects (Joubert syndrome), white matter signal changes (Lowe syndrome), malformation in the corpus callosum (Smith-Lemli-Opitz syndrome), and heterotopias (congenital muscular dystrophy) [10].

The electromyography from an infant with botulism syndrome must show:

- Compound muscular action potentials in at least two different muscle groups that have the decreasing amplitude.
- Tetanic and post-tetanic facilitation with amplitude greater than 120% of baseline.
- Prolonged post-tetanic facilitation lasting more than 120 seconds without post-tetanic exhaustion [15].

Infants should be held at a 30° angle to prevent aspiration if they are not intubated [16-17]. They should also be regularly watched for lack of breathing brought on by secretions and poor upper airway tone [18]. Early intubation is frequently thought of as a preventative approach [11,19]. Ventilator Associated Pneumonia (VAP) and the requirement for a tracheostomy are complications that are frequently brought on by the emergence of a severe subglottic stenotic granuloma [20]. Botulism Antitoxin Heptavalent (BAT) IgG injections and physical therapy make up the unique "life-saving" treatment [10]. The BAT eliminates all circulating botulinum antitoxins (BoNT) right away and stays in the bloodstream for several months, enabling nerve-ending regeneration [11]. Aminoglycosides can cause lysis of the bacteria in the gut and additional toxins released [9,21-22]. If treatment is started within three days of the first illness's onset, it is believed that response will be best [23-26].

CONCLUSION

Infant botulism probably is underdiagnosed in Europe, because of the wide range of possible diagnoses, including myasthenia gravis, acute inflammatory demyelinating

polyneuropathy, and metabolic inborn errors. Frequently, infant botulism is not the first hypothesis but it is the result of a strict differentiation from other diseases characterized by hypotonia such as sepsis, infectious, genetic, autoimmune, or metabolic diseases through the use of history, and laboratory tests and radiological imaging. At first, toxin detection can be useful for early diagnosis. In the later stages, the neurological instrumental support can help the clinician to elucidate the cause of muscle weakness. In fact the EEG and the EMG could be positive when toxins

are unlikely to be detectable in the serum and other data are negative. A minimum of one arm and one leg should be examined for motor and sensory nerve conduction velocity, two distal muscles should be stimulated at a frequency of 2 Hz, and a needle EMG with enough sampling should also be performed.

Clinicians should be aware that baby botulism could occur if honey is added to water, food, or formula fed to infants younger than 12 months old. So early treatment with IgGs could be performed for the outcome best results.

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