Original article

Arch Argent Pediatr 2023;121(3):e202202656

Infant botulism: a descriptive study in a pediatric intensive care unit

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ABSTRACT

Introduction. Infant botulism (IB) is the most common form of human botulism in Argentina. Our objective was to describe the main aspects of diagnosis and management of patients with IB admitted to the pediatric intensive care unit (PICU).

Methods. Observational, descriptive, and retrospective study. The PICU database with IB diagnosis in 2005–2020 period was used. Demographic variables, diagnostic methods, days of conventional mechanical ventilation (CMV), non-invasive ventilation (NIV), length of stay in the PICU and mortality upon hospital discharge were recorded.

Results. In total, 21 patients with IB were recorded; 14 were male, their median age was 5 months (IQR: 2–6 m). Diagnosis was made by bioassay, and the toxin was identified in the serum of 12 patients. Only 1 patient did not require CMV; 1 patient had a tracheostomy; 18 patients received antibiotics; 5 received NIV. No patient was administered antitoxin and no patient died. The median length of stay in the hospital was 66 days (IQR: 42–76); in the PICU, 48 days (IQR: 29–78); and the median use of CMV, 37 days (IQR: 26–64). The delay until diagnostic confirmation was 15.8 ± 4.8 days.

Conclusions. All patients were diagnosed using the bioassay technique, which resulted in a diagnostic delay that exceeds the recommended period for the administration of a specific treatment. No patient received a specific treatment. IB was related to a low mortality, but also to prolonged use of MV and length of hospital stay, which were associated with cross infections and frequent antibiotic use.

Key words: *botulism; infant; pediatric intensive care units; mechanical ventilation; diagnosis.*

doi: http://dx.doi.org/10.5546/aap.2022-02656.eng

To cite: Ávila CE, Cárdenas MM, Kaltenbach GH, Lazzarini L, Pierangeli N. Infant botulism: a descriptive study in a pediatric intensive care unit. *Arch Argent Pediatr* 2023;121(3):e202202656.

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Funding*: School of Medical Sciences of Universidad Nacional del Comahue.*

Conflict of interest*: None.*

Received*: 4-5-2022*
Accepted*: 8-27-2022*

INTRODUCTION

Infant botulism (IB) is an acute, reversible neuroparalytic infection resulting from the colonization of the intestinal tract by *Clostridium botulinum*, which subsequently produces botulinum toxin *in situ*, which is absorbed into the bloodstream and causes blockage of acetylcholine release at the neuromuscular junction and in the autonomic nervous system.[1] The severity of IB ranges from mild hypotonia to life-threatening sudden flaccid paralysis. Severe IB cases may require conventional mechanical ventilation (CMV). It has been estimated that IB may be the cause of death in 3–5% of children who die with a diagnosis of sudden death syndrome.[2] About 98% of babies with IB are 1 to 6 months old, although IB has been reported as early as 1 week of life and as late as 12 months of age.

IB has been documented in 4 continents, with the United States, Argentina, Australia, Italy, Canada, and Japan reporting the highest number of cases.[1,3] Argentina has an estimated incidence rate of 2.41 cases/100 000 live births, which is even higher than that of the USA.[2] Excluding the USA, our country accounts for 70% of the cases worldwide. In 1999, this disease was incorporated into the National Epidemiological Surveillance System as an immediately notifiable disease. By descending order, the highest incidence rates between 2013 and 2019 in Argentine provinces were reported in Neuquén, La Pampa, San Luis, Mendoza, and Río Negro.[2]

Most IB patients are breastfed infants residing in rural and/or peri-urban areas. A relationship has been established between the presence of *C. botulinum* spores in the soil and the incidence of IB in several regions of our country. Type A toxin has been the prevalent toxin found in soils and was detected in all cases of IB.[4,5] Some foods likely to be contaminated, such as honey, milk formulas, and some herbs (chamomile), have been reported as potential sources of spores responsible for IB cases in several publications.[6–8]

Laboratory criteria for the diagnosis of IB include the detection of toxins in stools or serum or the isolation of *C. botulinum* from stools.[8,9] The mouse bioassay (MBA) is considered the gold standard for diagnosis. This method is based on the injection of mice with samples obtained from suspected patients, with the subsequent development of botulism signs by the mice. The type of toxin is determined by neutralizing the toxin with specific antitoxins. This is the diagnostic approach implemented in Argentina and is currently carried out in 2 laboratories: in the City of Buenos Aires (Instituto Nacional De Enfermedades Infecciosas ANLIS Carlos G. Malbrán, Department of Health Bacteriology) and in the province of Mendoza (School of Medical Sciences, Department of Pathology, Area of Microbiology, Universidad Nacional de Cuyo).

Fernandez et al. reported 146 cases of IB in which *C. botulinum* was isolated by culture and type A toxin was detected in 100% of stool samples and in 63% of serum samples.[10]

Unlike other clinical forms of botulism, the mortality due to IB is less than 1%. In a 35-year series, Jackson et al. observed a mortality rate of 0.8% in 2352 patients.[11] However, IB is associated with significant morbidity, prolonged length of stay at the hospital, prolonged use of mechanical ventilation (MV) and of nasoenteral tube feeding.[12]

Currently, the treatment available for IB consists of supportive measures for the duration of the muscle condition and specific treatment with antitoxin. There is little evidence about ENT complications associated with prolonged MV or the frequency and eventual benefits of performing a tracheostomy in these patients.[13,14]

Despite the frequency of IB in Argentina, there are no studies describing the relevant aspects of diagnosis and clinical management. The objective of this study is to describe essential aspects of the diagnosis and treatment of IB during the hospitalization of a cohort of patients diagnosed with IB and admitted to the PICU of Hospital Provincial Neuquén (HPN).

POPULATION AND METHODS

This was an observational, descriptive, and retrospective study conducted between January 1st, 2005 and December 31st, 2020 in patients with a confirmed diagnosis of IB and admitted to the PICU of HPN. The PICU has 15 beds.

Data collection and analysis

The investigators used an instrument to collect data from the patients' medical records. The following data were recorded: population demographic characteristics (age and sex); variables related to patient management: diagnostic methods, use of non-invasive ventilation (NIV), performance of tracheostomy, administration of specific antitoxin treatment, days of delay between admission and sampling for diagnosis, and days of delay until confirmation

of diagnosis since admission; variables related to outcomes: mortality, days of MV, length of stay in the PICU, and length of stay in the hospital.

Ethical aspects

The study was approved by the hospital's Ethics Committee and the Teaching and Research Committee. Data were not used for other purposes than those described for their collection, and investigators protected the identity of data holders.

Statistical analysis

Descriptive statistics were used to describe the population statistics. Continuous variables were estimated as mean and standard deviation (SD) or as median and interquartile range (IQR), based on their distribution. Categorical variables were expressed as frequency and percentage.

Data were collected in Excel 2010 and processed using InfoStat and R.

RESULTS

Between January 1st, 2005 and December 31st, 2020, 21 patients diagnosed with IB and admitted to the PICU of HPN were identified; 14 patients (66.7%) were male, with a median age of 5 months (IQR: 2–6 m). All cases were caused by type A *C. botulinum*.

Diagnosis was confirmed in all cases by the MBA technique using samples sent to Instituto Carlos Malbrán. Type A toxin was isolated in the stools of all patients; in 12 patients (57%), the toxin was also isolated in serum.

An electromyography (EMG) was performed in 4 patients (19%); of these, 2 had a presumptive result of IB before receiving the confirmation. Additional diagnostic assessments were done in 2 patients: electroencephalogram (EEG), magnetic resonance imaging (MRI), and computed tomography (CT) of the brain.

Only 1 patient did not require MV nor NIV; 5 patients (24%) received NIV in addition to CMV for a mean of 6.6 ± 1.52 days. In all cases, initiation of NIV was elective immediately after weaning from CMV. Only 1 patient (5%) underwent tracheostomy due to subglottic stenosis. At some point during the course of their disease, 18 patients (85%) received antibiotics; no patient received specific treatment with human or equine antitoxin.

No patient in our series died. The median duration of CMV use was 37 days (IQR: 26–64), the median length of stay in the PICU was 48 days (IQR: 29–78), and the median length of hospital stay was 66 days (IQR: 42–76).

The average number of days between admission and sample shipment was 2.9 ± 2.7 days; however, the mean delay between admission and diagnostic confirmation was 15.8 ± 4.8 days (time to diagnostic confirmation); such delay was related to the logistics of sending the biological samples to diagnostic centers located at a great distance from our facility.

DISCUSSION

IB is a potentially severe disease and may require intensive care and CMV. In Argentina, 659 cases were reported between 1982 and 2011, all of them caused by serotype A. Neuquén is considered an endemic area due to the high number of cases reported.

Our study describes aspects related to the diagnosis, treatment, and outcome of patients with IB.

All cases were confirmed by the MBA technique at the Instituto Carlos Malbrán with a diagnostic confirmation delay that exceeds that recommended for the administration of a specific treatment. The data obtained here confirm that such delay is not related to difficulties in obtaining the samples (despite the fact that patients suffer from constipation), but to variables related to the logistics of shipping the samples.

With the diagnostic strategy used, it is difficult to consider the administration of a specific treatment in the time frame in which it is recommended, although such time may be optimized to obtain a preliminary result of typing tests. In addition to the delay, we may also consider cost-related issues and an ethical dilemma regarding the use of live animals.[15] Since the 2000s, a polymerase chain reaction (PCR) method with high sensitivity for the detection and determination of the type of toxin in stools has been under investigation, which would reduce the time to diagnosis to less than 24 hours and avoid the use of animals.[16] However, conventional PCR methods have certain limitations, such as the inability to distinguish between biologically active toxin genes and silent toxin genes. In the past decade, significant progress has been made in botulinum neurotoxin detection technologies, but none has been able to completely replace the MBA.[17] Several methods are being developed and investigated as valid and cost-effective, non-animal alternatives.[15]

In relation to treatment, the cohort described

here did not receive any specific treatment; only 1 patient did not require CMV and 5 patients required NIV, continuous positive airway pressure (CPAP) with elective nasal cannula after extubation.

A longer median CMV use, length of PICU stay, and length of hospital stay were observed than those reported in other studies. In their study conducted in Mendoza, Vanella et al.,[18] reported a significantly shorter median CMV use (25 ± 4.5 days), length of stay in the PICU (28 ± 4.3 days), and length of hospital stay (52 ± 6.8 days) in patients who did not receive a specific treatment. That retrospective study reported a statistically significant reduction in duration of CMV use and length of stay in the PICU and in the hospital in the group that received a specific treatment with equine botulinum antitoxin (EqBA). The authors emphasized the importance of a rapid diagnostic test, since only patients with a confirmed diagnosis of IB (performed at the School of Medical Sciences of Universidad Nacional de Cuyo) received the EqBA.

The antitoxin is beneficial when administered early, while the toxin is in the plasma and before it is internalized to the cholinergic presynaptic terminal. The USA has been producing since 2003 a human derivative of botulinum antitoxin (BabyBIG®), which has been approved by the US Food and Drug Administration (FDA) for the treatment of IB. A 5-year safety and efficacy study conducted in California showed that its early use reduced the mean length of hospital stay and the duration of MV use.[19–21]

EqBA is widely used in foodborne botulism and is considered a valid alternative to BabyBIG® for IB.[22]

Vanella de Cuetos et al., in a retrospective cohort study, observed that the administration of EqBA reduced the length of hospital stay, the length of stay in the intensive care unit, MV duration, and artificial feeding compared to supportive therapy alone. Only 1 of 31 infants treated with EqBA developed mild adverse effects (transient rash).[18] Griese et al., in a systematic review of the use of EqBA in pediatric patients, reported common severe adverse events in patients with other forms of botulism, but not IB.[23] Anaphylaxis has been reported in 1–2% of patients receiving EqBA.[18,24]

In addition, Arnon et al., reported, in patients who did not receive a specific treatment, a mean length of hospital stay of 5.7 weeks (40 days) and a mean CMV duration of 4.4 weeks (31 days), and demonstrated a statistically significant reduction of both variables with the use of human antitoxin. In that study, patients received the antitoxin due to diagnostic suspicion and had to be admitted to the hospital for at least 3 days. That study included patients with type B IB, whose course is milder than that of type A.[19] Although BabyBIG® is considered the gold standard treatment, it is expensive and difficult to access, and the studies that support its effectiveness were carried out in California, where it is produced.[22]

In our study, 12 patients showed toxin in serum (similar to other reports of type A IB). Unlike other reports, this finding did not have an impact on the duration of MV use or the length of hospital stay.

No patient died in our series, which is to be expected given that the overall mortality rate reported in these patients is less than 1%.[2,19,25] One patient required tracheostomy due to subglottic stenosis as a complication of prolonged MV.

This study has limitations. Given its retrospective, observational design with a sample of patients with IB from a single center, it is not possible to extrapolate the findings to all children with this disease. Notwithstanding this, some findings are relevant, such as objectively establishing the difficulties in access to the gold standard diagnostic method for IB.

It may be assumed that such difficulties are common to many facilities that care for these patients, so that the development of strategies that allow an early diagnosis could be promoted at the local level.

In many cases, antitoxin is administered based on clinical suspicion, without a diagnostic confirmation of IB. A study conducted by the California Department of Public Health, which analyzed 1226 patients who received human antitoxin for 10 years, reported that 6.2% of them did not have a laboratory confirmation of IB and established alternative diagnoses in 58% of these patients (spinal muscular atrophy type 1, metabolic disorders, infectious diseases).[25]

Electrodiagnostic techniques, such as electromyoneurography (EMNG), may be useful while waiting for the diagnostic confirmation,[26,27] although its sensitivity is variable and, moreover, it is not always available in all facilities.[28,29] In the early years of the study, patients were assessed using an EMNG, but this technique is not currently performed in our hospital.

Since Neuquén is an endemic area, it is important to implement strategies for an early diagnosis –by optimizing the logistics of sample shipment or achieving preliminary typing– and to safely administer the specific treatment.

CONCLUSIONS

In the series described here, all patients were diagnosed using the MBA technique, which resulted in important diagnostic delays that exceed the recommended period for the administration of a specific treatment. IB is related to a low mortality, but also to prolonged use of MV and length of hospital stay, which are associated with cross infections and frequent antibiotic use, as well as potential associated complications, such as subglottic stenosis. It is important to have access to available diagnostic methods that allow the early confirmation of IB cases in order to administer a specific treatment in a safe manner. ■

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