Archives of Pediatrics
Primdahl D, et al. Arch Pediatr 8: 262
www.doi.org/10.29011/2575-825X.100262
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Opinion Article

A Case of Infant Botulism Caused by *Clostridium baratii* type F: Evaluation and Experience with Administration of Equine-derived Heptavalent Botulism Antitoxin

Ditte Primdahl[1*], Megan A. Derrer[2], Shawn Allen[1], Leslie Edwards[3], Farrell A Tobolowsky[3], Jessica Khouri[4], Andrew Waclawik[1], Lydia Wraight[2], Chrysanthy Ikonomidou[1]

[1]University of Wisconsin-Madison Department of Neurology, Wisconsin, Madison, USA

[2]University of Wisconsin-Madison Division of Neonatal-Perinatal Medicine, Wisconsin, Madison, USA

[3]Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

[4]Infant Botulism Treatment and Prevention Program, Center for Laboratory Sciences, California Department of Public Health, Richmond, California, USA

***Corresponding author:** Ditte Primdahl, Northwestern University Department of Neurology, 303 E Chicago Ave, Chicago IL 60611. Email: ditte.primdahl@nm.org

Citation: Primdahl D, Derrer MA, Allen S, Edwards L, Farrell A, et al. (2023) A case of Infant Botulism Caused by *Clostridium Baratii* type F: Evaluation and Experience with Administration of Equine-derived Heptavalent Botulism Antitoxin. Arch Pediatr 8: 262. DOI: 10.29011/2575-825X.100262

Received Date: 02 May 2023; **Accepted Date:** 10 May 2023; **Published Date:** 14 May 2023

Abstract

nfant botulism is the most common form of human botulism in the United States. Most cases are caused by toxin types A and B, which are treated with Human Botulism Immune Globulin Intravenous (BIG-IV; BabyBIG®). We present the case of a 10-day-old male with rapidly progressive paralysis and respiratory failure who was diagnosed with botulism caused by *Clostridium baratii* toxin type F, a rare form of botulism with poorly defined sources. BIG-IV has no demonstrated efficacy against this serotype of botulism. While the young age, rapid onset of symptoms, and severe presentation are consistent with other reported cases of toxin type F infant botulism, this case is interesting due to improvement with the administration of pyridostigmine and treatment with equine-derived heptavalent botulism antitoxin (HBAT), which has been rarely used in the treatment of infant botulism. This report adds to the literature on the efficacy and safety profile of HBAT administration in infants. Furthermore, this case report suggests that healthcare providers should be aware of the possibility of botulism caused by *Clostridium baratii* toxin type F in an infant presenting with sudden onset of paralysis and consider early treatment with equine-derived HBAT.

Keywords: Infant botulism; *Clostridium baratii*; Botulism toxin type F; Equine-derived heptavalent botulism antitoxin (HBAT); Pyridostigmine

Introduction

Infant botulism (IB), the intestinal toxemia form of the disease in a child aged less than one year, results when spores of the soil-dwelling anaerobic bacterium *Clostridium botulinum* or related neuro toxigenic clostridia temporarily colonize an infant's large intestine and produce botulinum neurotoxin (BoNT) [1]. BoNT then enters the systemic circulation and binds to presynaptic cholinergic synapses within the peripheral and autonomic nervous

system, blocking the release of acetylcholine which results in flaccid paralysis [2,3]. Most cases of infant botulism in the United States are caused by *C. botulinum* toxin type A and type B. Toxigenic strains of *Clostridium butyricum* and *C. baratii* produce botulinum neurotoxin type E and type F, respectively, and are rare causes of IB [2].

Although IB cases have been retrospectively identified in California as early as 1931[4], IB was first recognized as a novel form of human botulism in 1976 [2]. IB occurs globally and is the most common human form of botulism in the United States [5]. Approximately 40% of all IB cases in the United States have occurred in California. A forty-year longitudinal epidemiological study of California infant botulism cases found that 63.3 % of IB cases were attributed to toxin type A, 34.5% to type B, and only 0.2% to type F [3]. A 2018 review reported 18 IB cases caused by toxin type F in the United States from 1976-2016 including sporadic clusters [6]. According to the Centers for Disease Control and Prevention (CDC), in 2021 there were 214 laboratory-confirmed cases of botulism including 183 IB cases [7]. Toxin types A and B were identified in all 183 IB cases including 2 cases with rare dual-toxin-producing or "bivalent" strains, type Ba and type Bf.

In comparison to toxin types A and B, infants infected with toxin type F typically have symptom onset at a younger age (median of 9 days compared to 1-6 months), with more rapid progression to severe paralysis, and a lower prevalence of constipation [6]. While common known risk factors for exposure to *Clostridium* spores include ingestion of honey [8] and environmental spores present in the soil, the source is not identified in the majority of infant botulism cases, including those caused by *Clostridium baratii* type toxin type F [5].

Following licensure in 2003 through 2015, human-derived botulism antitoxin, BIG-IV (BabyBIG) licensed for the treatment of infant botulism caused by toxin serotypes A or B, has been used to treat approximately 1,200 patients with infant botulism [9]. The equine-derived HBAT used to treat adult botulism patients is active against toxin types A,B,C,D,E,F,G; however, there is limited experience with its use for the treatment of infant botulism [10]. The article by Yu et al from 2017 [11] examined the use, clinical benefits, and safety of HBAT in patients younger than 17 years. The authors observed that those treated earlier in the disease course spent significantly fewer days in the hospital ($P < 0.1$) and intensive care unit ($P = 0.04$). They report one HBAT-related serious adverse event (< 1% of cases) where a 10-year-old child experienced hemodynamic instability characterized by tachycardia, bradycardia, and asystole during and following HBAT administration [10,12]. The article did, however, conclude that HBAT provided clinical benefits and was well-tolerated [11]. Given the limited safety data in the pediatric population, the short half-life of equine antitoxin, and concern for sensitization to equine proteins, there has been some hesitation for its use in infants. Notably, rapid recovery of infants with type F botulism without antitoxin treatment has also been reported [13].

Case presentation

In June 2020, a 10-day-old breastmilk and formula-fed male infant who was delivered post-dates was transferred to our level IV neonatal intensive care unit (NICU) for respiratory failure after a choking event. Oxygen saturations were noted to be in the 70 percent range upon arrival and the infant required positive pressure ventilation. He was described as lethargic and was intubated for airway protection. The examination was notable for generalized hypotonia with slightly dilated but reactive pupils and withdrawal of limbs to noxious stimuli. He had an intact gag reflex, palmar and plantar grasps, extensor plantar responses, and an incomplete Moro reflex. Within 12 hours, the infant became areflexic and paralyzed. He developed dilated and nonreactive pupils. Corneal, oculocephalic, and gag reflexes were absent. Muscle tone was diffusely flaccid with generalized areflexia and no spontaneous movements. There was no withdrawal to noxious stimuli despite cessation of sedative medications and administration of naloxone.

An electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain were performed to rule out anoxic brain injury or other processes, such as hemorrhage, infarction, encephalomyelitis, diffuse demyelination, or myelinolysis, that could affect the brainstem and both hemispheres and explain this clinical picture. EEG showed somewhat discontinuous activity with focal slowing, but normal amplitudes. MRI of the brain showed an incidental finding of a small frontal lobe calcification and scattered subdural blood products felt to be related to birth trauma. There was no evidence of structural lesions to explain the infant's symptoms. Screening metabolic and infectious laboratory analyses were negative. Cerebrospinal fluid (CSF) analysis for cells, protein, and glucose was normal for age. Screening for infectious etiologies including Gram stain, cultures, and BioFire FilmArray® (BioFire Diagnostics, Durham, NC) multiplex PCR molecular testing meningitis/encephalitis panel were negative. Brainstem auditory-evoked responses and visual-evoked potentials were present, though delayed and with altered waveforms.

Stool was collected for botulinum toxin testing, and the patient underwent nerve conduction studies (NCS) and needle electromyography (EMG). The NCS were abnormal and significant for absent motor responses from ulnar and peroneal nerves. Radial sensory nerve action potential was of normal latency and amplitude. Fast frequency (20 Hz) repetitive nerve stimulation elicited no motor responses. The needle EMG showed diffuse spontaneous activity (fibrillation potentials and positive waves without fasciculations) in all muscles tested. No motor unit

potentials were seen (Table 1). These findings were concerning for a process either affecting the anterior horn cells, peripheral nerves (severe motor axonal polyneuropathy), severe neuromuscular transmission defect, or possible severe myopathy.

NERVE CONDUCTION STUDIES (NCS)						
SIDE	**NERVE**	**STIM SITE**	**LATENCY ms (normal)**	**AMPLITUDE mV (normal)**	**F-WAVE ms (normal)**	**F-EST ms**
(L)	Peroneal	ankle	NR*		absent	
	Peroneal	Fibula head Knee	NR*		absent	
	2Hertz and 20 Hertz repetitive stimulation at rest: No CMAPs recorded					
	Radial (s)	forearm	1.5 (<2.8)	0.021 (>0.019)		
	Ulnar (m)	wrist	NR*		absent	
		b elbow				
		a elbow				

Comment NCS: Absent CMAPs, normal left radial response. NR: non-reactive. CMAP: compound muscle action potential.

ELECTROMYOGRAPHY (EMG)							
SIDE MUSCLE	**INS**	**SPONTANEOUS**	**REC**	**MOTOR**	**UNIT**	**POTENTIALS**	**OTHER**
		+Spikes+WAVES FASC		**DURATION**	**AMPLITUDE PHASE HIGH LOW % #**		
(L)Ant Tib		3+ 3+ 0					No MUPs
Med Gast		2+ 2+ 0					No MUPs
Vast Lat		2+ 3+ 0					No MUPs
(L) Deltoid		2+ 2+ 0					No MUPs
(R)Vast Lat		2+ 3+ 0					No MUPs

Comment EMG: Diffuse spontaneous activity (fibrillation potentials and positive waves). No motor unit potentials (MUPs) were observed in any of the muscles tested.

Table 1: Neurophysiology results.

The infant was empirically started on pyridostigmine while awaiting results of stool cultures, due to concern for a neuromuscular junction disorder. Shortly after pyridostigmine administration, the patient had spontaneous movements of his toes and intermittent breathing over the ventilator which strengthened the suspicion for a neuromuscular junction disorder. His stool culture was ultimately positive for *C. baratii* type F. Powdered infant formula fed to the patient and the mother's lanolin breast ointment were tested at the CDC National Botulism Laboratory and found to be negative for C. baratii.

The decision to treat with antitoxin was made late in the course because our patient demonstrated no signs of spontaneous improvement for over 2 weeks. HBAT was administered on hospital day 16 (e.g.,17 days following symptom onset) and was tolerated without adverse reactions. Pyridostigmine was slowly weaned after administration of the antitoxin, and the infant was successfully extubated on hospital day 19. His muscle strength gradually improved. The week prior to discharge he was able to keep his eyes open, grimace, and feed orally the majority of his formula. He was able to move his limbs proximally and distally against gravity. His deep tendon reflexes returned. He continued to demonstrate profound head lag and proximal hypotonia at discharge, on hospital day 34.

Discussion

Here we present a case of IB caused by *C. baratii* toxin type F in a 10-day-old neonate. Previously reported toxin type F cases also occurred at an early age and presented with more fulminant onset and progression compared to botulism caused by toxin types A or B. Our patient is one of the few infants who received equine-derived HBAT and experienced rapid recovery. Furthermore, at a time when there was still diagnostic uncertainty, the administration of pyridostigmine appeared to provide transient improvement in symptoms, consistent with a neuromuscular junction disorder. We hypothesize that pyridostigmine permitted whatever small amount of acetylcholine was released from the presynaptic axons to remain within the synaptic cleft for a longer period of time.

It is unclear whether the administration of succinylcholine for intubation precipitated the patient's rapid symptom progression. Succinylcholine is contraindicated in patients with underlying or undiagnosed neuromuscular disorders, such as myasthenic syndromes, due to the risk of exacerbating paralysis [14].

Admittedly, treatment with HBAT was pursued late during the course of the disease in this infant. Contributing factors were delays in confirming the diagnosis, the uncertainty as to whether treatment with HBAT would be beneficial at that stage, concerns about the potential risks of treatment with HBAT, and the lack of experience with its use in infants and children. Our patient did not demonstrate any spontaneous clinical improvement, therefore it was decided to proceed with HBAT treatment which was tolerated well. Given that little is known about the natural history of IB due to *C. baratii* toxin type F, uncertainty remains as to what extent the administration of HBAT facilitated recovery. Similar to previously reported cases, the source of C. baratii for our patient remains unknown.

Conclusion

IB is the most common type of human botulism in the U.S. Honey is the one, identified, avoidable source of botulinum spores. However, most cases are likely due to swallowing airborne spores of neuro toxigenic clostridia, which are ubiquitous in soils and dust worldwide, and IB should therefore be considered in the differential diagnosis in infants even without identifiable risk factors. The vast majority of IB cases (> 98%) are caused by toxin types A and B. Infant botulism caused by *C. baratii* type F is rare, occurs at younger age and has a very fulminant course. As aptly stated in the report, an environmental source of toxigenic C. baratii spores has not been identified.

The human-derived antitoxin, BabyBIG® is indicated for the treatment of IB caused by toxin types A and B, but has not demonstrated efficacy against toxin type F. Timely treatment with equine-derived HBAT in infants with botulism caused by toxin type F should be considered. Our case adds data to support the safety and probable efficacy of HBAT in infants with botulism.

References

1. Centers for Disease Control and Prevention (2011) Botulism (Clostridium botulinum) 2011 Case Definition.
2. Arnon S (2009) Ed. Infant botulism. In: Feigin and Cherry's Textbook of Pediatric Infectious Disease. 6th Ed. Philadelphia, Pennsylvania: Elsevier, 2009. Accessed via the Infant Botulism Treatment and Prevention Program.
3. Panditrao MV, Dabritz HA, Kazerouni NN, Damus KH, Meissinger JK, et al. (2020) Descriptive Epidemiology of Infant Botulism in California: The First 40 Years. J Pediatr 227: 247-257.
4. Arnon SS, Werner SB, Faber HK, Farr WH (1979) Infant botulism in 1931. Discovery of a misclassified case. Am J Dis Child 133: 580-582.
5. CfDC and Prevention (2017) National Botulism Surveillance Summary. Atlanta.
6. Halpin AL, Khouri JM, Payne JR, Nakao JH, Cronquist A, et al. (2017)Type F Infant Botulism: Investigation of Recent Clusters and Overview of This Exceedingly Rare Disease," (in eng), Clin Infect Dis 66: S92-S94.
7. Centers for Disease Control and Prevention (CDC) (2021) Botulism Annual Summary [Unpublished manuscript]. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC.
8. Arnon SS, Midura TF, Damus K, Thompson B, Wood RM, et al.(1979) Honey and other environmental risk factors for infant botulism 1. J Pediatr 94: 331-336.
9. Payne JR, Khouri JM, Jewell NP, Arnon SS (2018) Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure J Pediatr 193: 172-177.

10. Richardson JS, Parrera GS, Astacio H, Sahota H, Anderson DM, et al. (2020) Safety and Clinical Outcomes of an Equine-derived Heptavalent Botulinum Antitoxin Treatment for Confirmed or Suspected Botulism in the United States. Clin Infect Dis 70: 1950-1957.

11. Yu PA, Lin NH, Mahon BE, Sobel J, Yon Yu, et al. (2017) Safety and Improved Clinical Outcomes in Patients Treated With New Equine-Derived Heptavalent Botulinum Antitoxin. Clin Infect Dis 66: S57-S64.

12. Griese SE, Kisselburgh HM, Bartenfeld MT, Thomas E, Rao AK, et al. (2017) Pediatric Botulism and Use of Equine Botulinum Antitoxin in Children: A Systematic Review. Clin Infect Dis 66: S17-S29.

13. Keet CA, Fox CK, Margeta M, Marco E, Shane AL, et al. (2005) Infant botulism, type F, presenting at 54 hours of life. Pediatr Neurol 32: 193-196.

14. Burns B, Hager HH (2020) Succinylcholine Chloride. In: StatPearls [Internet]. Treasure Island (FL): StatPearls.