Pediatric Neurology 52 (2015) 487–492

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Infant Botulism: Review and Clinical Update

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ABSTRACT

Botulism is a rare neuromuscular condition, and multiple clinical forms are recognized. Infant botulism was first identified in the 1970s, and it typically occurs in infants younger than 1 year of age who ingest *Clostridium botulinum* spores. A specific treatment for infant botulism, intravenous botulism immunoglobulin (BIG-IV or BabyBIG®), was developed in 2003, and this treatment has substantially decreased both morbidity and hospital costs associated with this illness. This article will review the pathogenesis of infant botulism as well as the epidemiology, clinical manifestations, diagnosis, and treatment of this condition.

Keywords: botulism, infant, review, *Clostridium*, botulinum, infantile, paralysis

Pediatr Neurol 2015; 52: 487-492

Introduction

Botulism is a rare neuromuscular disorder resulting from toxins produced by *Clostridium botulinum* bacteria. Infant botulism, first recognized in 1976, typically affects children younger than 1 year of age.[1] It is the most common clinical form of botulism in the United States, with between 70 and 100 cases recognized annually.[2] Infant botulism usually presents as a combination of hypotonia, bulbar weakness, and flaccid paralysis of the skeletal muscles, although a broad range of clinical presentations is possible.

Etiology and pathogenesis

C. botulinum is a sporulating, obligate anaerobic, gram-positive bacillus present in soil and aquatic sediment. Seven distinct subtypes exist, depending upon the neurotoxin produced, and these are arbitrarily named A-G. Only subtypes A, B, E, and F cause disease in humans, and almost all cases of infant botulism in the United States are caused by subtypes A and B.[3-5] Botulinum-like toxins E and F are produced by *Clostridium baratii* and *Clostridium butyricum* and are only rarely implicated in infant botulism.[4,6,7]

Infant botulism occurs when the clostridial spores of *C. botulinum* are ingested, then germinate and multiply in the gastrointestinal tract, allowing the release of botulinum neurotoxin (BoNT) into the bloodstream. BoNT then irreversibly binds cholinergic receptors in the presynaptic cell membrane of voluntary motor and autonomic neuromuscular junctions. Normally, neuromuscular transmission occurs when vesicles containing acetylcholine fuse with the presynaptic terminal membrane via formation of a fusion complex, releasing acetylcholine into the synaptic cleft. This fusion complex is made up of three soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins: vesicle-associated membrane protein (VAMP, also known as synaptobrevin); syntaxin; and synaptosomal-associated protein 25 (SNAP-25). After BoNT is taken up into the presynaptic terminal, it cleaves one of these SNARE proteins, thereby disrupting formation of the fusion complex and preventing acetylcholine release into the cleft. This causes failed neuromuscular transmission and flaccid paralysis. The particular components of the SNARE complex that are targeted vary depending on BoNT subtype: BoNT subtypes A, C, and E target SNAP-25; subtypes B, D, F, and G target VAMP/synaptobrevin; and subtype C additionally targets syntaxin (Fig 1).[8] Botulism is the most potent poison known, with a

Article History:
Received October 6, 2014; Accepted in final form January 13, 2015
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http://dx.doi.org/10.1016/j.pediatrneurol.2015.01.006

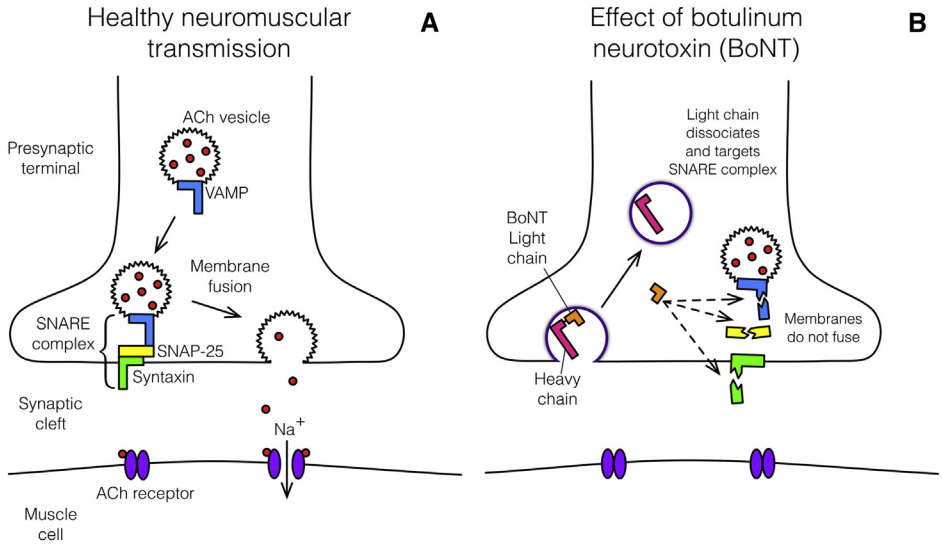

FIGURE 1.
(A) Healthy neuromuscular transmission. Acetylcholine (ACh)-containing vesicles bind to the presynaptic terminal membrane via formation of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) complex, leading to membrane fusion and release of ACh into the synaptic cleft. ACh molecules then bind to receptors on the muscle cell, allowing influx of sodium and muscle contraction. (B) Effect of botulinum neurotoxin (BoNT). BoNT binds receptors on the presynaptic terminal and is endocytosed. The light chain is dissociated from the heavy chain and translocates into the cytoplasm, where it cleaves specific SNARE proteins according to BoNT subtype. Subtypes A, C, and E target SNAP-25; subtypes B, D, F, and G target vesicle-associated membrane protein (VAMP); and subtype C further targets syntaxin. (The color version of this figure is available in the online edition.)

lethal dose of only 10^{-9} mg/kg of body weight. The incubation period of botulism is hypothesized to range between 3 and 30 days.[9]

There are multiple other recognized clinical forms of botulism, including wound botulism, in which wounds become contaminated with *C. botulinum* spores, and foodborne botulism, in which preformed toxin is ingested from contaminated food sources. Adult intestinal toxemia is an uncommon presentation of botulism that is similar in pathogenesis to infant botulism, occurring via ingestion of clostridial spores. Rarely, cases of botulism have also been reported from inhalational or iatrogenic exposure.[10,11] In the United States, infant botulism is by far the most common form, constituting approximately 65% of reported botulism cases per year.[12] Outside the United States, infant botulism is less common.[3]

Epidemiology and risk factors

The first diagnosis of infant botulism was made in 1976, although the first known case (diagnosed retrospectively) is believed to have occurred in California as far back as 1931.[1,13] Botulism affects infants ranging from less than 1 week to 1 year of age, with a median age of 10 weeks. Up to 95% of infant botulism cases occur in children younger than 6 months of age.[14,15] Geographically, the prevalence of infant botulism in the United States is highest in California, Utah, and the eastern Pennsylvania-New Jersey-Delaware area.[16,17] Type A disease tends to be more prevalent in the Western United States, whereas type B disease is more prevalent in the Eastern United States.[5,16] Infants living in rural/farm environments appear to be at higher risk for contracting botulism than those living in more urban environments, presumably because of higher exposure to dust particles.[18] It has been suggested that exposure to soil from active construction sites may also increase the risk of contracting botulism, whether by living near a construction site or by having a parent who works in construction; however, this link has not been conclusively established.[19-21]

Infants are felt to be particularly susceptible to intestinal colonization by *C. botulinum* because of the immaturity of their gut flora. This concept is supported by animal studies demonstrating that infant mice experience age-related susceptibility to botulism colonization of the gastrointestinal tract. Additionally, human infants that experience transient perturbations in gut flora, such as after weaning from breast milk, appear to have further increased risk of intestinal colonization by *C. botulinum*.[16] The risks and benefits conferred by breastfeeding itself are less clear: although infants hospitalized for botulism are more likely to have been breastfed than formula-fed, some studies suggest that breastfeeding delays the progression of botulism and is therefore protective.[18,22] Formula-fed infants, on the other hand, tend to develop botulism at earlier ages and may have a more fulminant presentation.[22] Given the relatively rare occurrence of botulism, current recommendations support breastfeeding, even in patients who have developed botulism.[23]

Ingestion of contaminated honey has been implicated in a number of cases of infant botulism; however, it is worth noting that in the majority of cases, a definitive source of *C. botulinum* spores is never identified.[1,24] In many patients in whom no source is found, infection is presumed to result from swallowing spores that adhere to microscopic dust particles in the air.[4] Corn syrup was previously found to contain *C. botulinum* spores, but changes in production practices have apparently eliminated this problem, and no cases of infant botulism to date have been definitively attributed to contaminated corn syrup.[16,24] Nonetheless, the American Academy of Pediatrics continues to recommend