Infant Botulism

A Review of the Literature

Jon M. Wigginton, M.D.[1]
Peter Thill, M.D.[2]

Introduction

Although adult-type botulism was recognized in the late 1800s,[1] infant botulism was not described until 1976.[2,3] Adult-type botulism results from the ingestion of preformed toxin in contaminated food, while infant botulism appears to occur when spores are ingested, with in vivo germination and elaboration of toxin.[2] The majority of cases have been reported in California, Utah, and Pennsylvania.[4,5] Many cases may go unrecognized due to the often insidious course and variable manifestations. These manifestations may range from constipation and self-limited weakness to respiratory failure and even sudden death. There has been some controversy regarding the association of the sudden infant death syndrome (SIDS) and *Clostridium botulinum* infection. Two previous series identified *C. botulinum* infection in 4.3%[6] and 15%[7] of SIDS cases, respectively. A recent prospective study, however, failed to confirm the presence of *C. botulinum* in 248 victims of SIDS,[8] although this study utilized culture alone, not toxin assay, for screening.

[1] Department of Pediatrics and Communicable Diseases
University of Michigan Medical School
Ann Arbor, Michigan
[2] University of Michigan Medical School
Ann Arbor, Michigan

Address correspondence to: Jon M. Wigginton, M.D., Pediatric Branch, National Cancer Institute, Building 10, Room 13N240, 9000 Rockville Pike, Bethesda, MD 20892

Pathogenesis

C. botulinum is a ubiquitous gram-positive spore-forming organism. It is found most commonly in soil and agricultural products, although honey has also been implicated as a significant reservoir for botulinum spores.[9,10] *C. botulinum* species are divided into four subgroups, all of which produce very powerful neurotoxins. These neurotoxins are assigned letters A through G. Infant botulism is caused primarily by organisms producing toxins A or B, although cases due to toxin C,[11] E,[12,13] F,[14,15] and G[7] have also been reported. Infant botulism results from the ingestion of spores with subsequent germination and production of toxin, which is then absorbed from the gut.[16] Animal studies suggest that the cecum is the primary site of multiplication and toxin production,[17] while others have demonstrated *C. botulinum* in equal amounts through all segments of the human colon.[18] Once released, toxin is absorbed from the gut and binds specifically and irreversibly to presynaptic cholinergic nerve terminals. It is then translocated intracellularly and disrupts calcium-dependent exocytosis of acetylcholine-containing presynaptic vesicles.[19,20] As a result, neurotransmission is blocked at all ganglionic and postganglionic synapses and the neuromuscular junction.

Epidemiology

Risk Factors

One of the most significant risk factors for the development of infant botulism is age. The median age of onset is approximately 2 to 4 months.[21-23] Infant botulism has been documented in adults, usually in the setting of disruption of the normal function of the gastrointestinal tract, such as after surgery, antibiotic therapy, or in the presence of gastric achlorhydria. This environment presumably permits colonization in a manner similar to that observed in infants.[24,25] The ingestion of honey and, to a lesser extent, of corn syrup has also been identified as a risk factor for the development of infant botulism.[22] Clearly, however, it is not the only source of spores, since the majority of children who develop the disease have not been exposed to honey or corn syrup.

The significance of breast-feeding as a risk factor remains somewhat controversial. It is clear that a disproportionate number of infants who are diagnosed with infant botulism have been primarily breast-fed.[23,26-28] When infants with botulism who died suddenly were compared with those who were

Table 1

SIGNS AND SYMPTOMS IN INFANTS WITH BOTULISM

Signs and symptoms	Schreiner et al (1991)[21] (N = 57)	Wilson (1982[illegible] (N = 99)	Thompson et al (1980)[28] (N = 12)
Weakness or hypotonia	50/57 (88%)	66/71 (93%)	12/12 (100%)
Weak suck, poor feeding	45/57 [illegible]	[illegible]3/76 (96%)	12/[illegible] (100%)
Constipation	37/57 (65%)	[illegible]3/76 (83%)	[illegible]
Lethargy, somnolence	34/57 (60%)	44/62 (71%)	
Weak cry	10/57 (18%		
Irritabil[illegible]	10/57 (18%)	4[illegible]	
Respiratory difficulty	5/57 (11%)[a]	[illegible](43%)[b]	9/12 [illegible]
Seizures	1/57 (2%)		
Poor head control	NR		
S[illegible] d	[illegible]		
F[illegible]			
H[illegible]	[illegible]		
S[illegible]	NR		
Ptosis	NR		
D[illegible] reflex	NR		
Mydriasis	NR	NR	[illegible]

NR = status of feature not reported
[a]respiratory difficulty at presentation
[b]respiratory compromise at any time during course

hospitalized and who subsequently recovered, however, the formula-fed infants were overrepresented in the sudden death group, while more breast-fed infants were among the hospitalized survivors.[27] The intestinal flora differs significantly in breast-fed and non-breast-fed infants.[29-33] The composition of the intestinal microflora may play a critical role in determining susceptibility to colonization and subsequent germination of *C. botulinum* spores. Dramatic changes in the intestinal flora occur during the transition from breast-feeding to nonhuman food.[33] It has been suggested that the most susceptible period for the development of infant botulism may be during this transition period.[34] In one large series, the majority of cases were reported within four weeks of the introduction of food other than breast milk to infants who had previously been exclusively breast-fed.[23]

Outbreaks: Geography

While cases of infant botulism have been reported throughout the United States, the incidence is significantly greater in certain regions of the country. More than half the cases reported in the U.S. have come from California, Utah, and Pennsylvania,[4,5] states in which levels of botulinal spores in the soil are high.[35] It also appears that there are occasional outbreaks in which the incidence of disease rises significantly above its baseline in a limited geographic area. Only six cases of botulism have been reported between 1977 and 1985 in Colorado. Three of them were from the same town of 800 people. Two of the three infants shared a crib, and all samples from their environments yielded *C. botulinum*, producing type A toxin.[36] A cluster of 12 cases occurring over two years was reported in Utah.[28] A unique situation exists in Pennsylvania, where nearly all of the cases of infant botulism come from counties immediately surrounding Philadelphia, but almost none come from the city itself or from the western part of the state.[26] No explanation for this phenomenon has been identified.

Clinical Features

The infant with botulism is typically afebrile and may present with constipation, weakness, poor suck, and a weak cry.[4,10,21,28] Constipation may precede the onset of other symptoms by several weeks.[10,37] There is no apparent sex predilec-

Table 2

ASSOCIATED COMPLICATIONS IN INFANTS WITH BOTULISM

Complication	Schreiner et al (1991)[21] (N = 57)	Johnson et al (1979)[42] (N= 10)
SIADH		
Autonomic instability		
Apn		
Uri		
Pne		2/10 (20%)
Sepsis		
Seiz		NR
Res		3/10 (30%
Int		
An		
Tu		
SIA		
NR	eported	

tion.[21] Infants typically range from 6 weeks to 6 months of age at presentation. One study of 57 infants found an average age at diagnosis of 102 days (range 18 to 219 days).[21]

Autonomic nervous system involvement generally occurs initially, followed by motor deficits, which often progress in a descending fashion, with early cranial nerve involvement preceding trunk and limb muscle weakness.[34,37] Autonomic impairment may cause dry mucous membranes (which can be misinterpreted as dehydration), urinary retention, gastrointestinal (GI) dysmotility, cardiac arrhythmias, alternating skin flushing and pallor, and blood pressure instability. Cranial nerve palsies may be manifested as impaired ocular motility, ptosis, mydriasis, loss of head control, facial weakness, or an impaired gag reflex and suck. Infants may experience pharyngeal pooling of secretions or poor feeding. If airway protective mechanisms are sufficiently impaired, they may be susceptible to aspiration. Peripheral neuromuscular involvement may produce hypotonia as well as diminished spontaneous movements and reflexes. Diaphragmatic involvement may lead to progressive respiratory failure.

The relative frequency of symptoms reported in three previous series of patients is shown in Table 1.[4,21,28] The most common symptoms include weakness, swallowing difficulties with diminished suck and poor feeding, constipation, weak cry, and diminished gag reflexes. Although a relatively small number of infants have respiratory difficulty at presentation,[21] a large number (77% to 89%) develop respiratory failure and/or impaired airway protective reflexes and require intubation and mechanical ventilation during their course.[21,23] The presence of weakness suggests blockade of approximately 75% or more of the receptors at the neuromuscular junction,[38] but diaphragmatic function may not be compromised until 90% to 95% of the receptors are blocked.[39-41] Thus, respiratory failure may be a relatively late sign of disease progression. Intubation is often required for airway protection and to avoid the complications of sudden respiratory compromise.

It is important to remain aware of the variable severity and rates of disease progression in infants with botulism and to ensure close cardiorespiratory monitoring. Manifestations may vary from benign subclinical infection to fulminant progression and death within hours. The symptoms may wax and wane significantly as gradual improvement occurs. The pattern of resolution generally reverses the sequence of the appearance of symptoms. Symptoms often peak by two or three weeks and begin to resolve, although full resolution may take up to several months. Hospitalizations range from two to 201 days, with an average of approximately one to 1.5 months.[4,21]

Table 2 compares the associated complications in two previous series of patients.[21,42] A majority of the complications reflect the high frequency of respiratory compromise and mechanical ventilation of these patients. Other complications include syndrome of inappropriate antidiuretic hormone production (SIADH), particularly in mechanically ventilated patients, and urinary tract infections, presumably secondary to urinary retention with autonomic dysfunction. Seizures may occur in a small number of patients, although the mechanism is not well understood. Aminoglycoside use may precipitate rapid progression and respiratory failure via potentiation of neuromuscular blockade by the botulinum toxin.

Eight of 11 patients receiving aminoglycosides in one study experienced rapid clinical deterioration.[39]

Differential Diagnosis

Several disorders may mimic infant botulism and must be considered in the evaluation of the infant presenting with poor feeding, lethargy, and diffuse progressive weakness. These include sepsis, meningitis/encephalitis, dehydration, electrolyte imbalance, myasthenia gravis, polio, Reye syndrome, hypothyroidism, tick paralysis, Guillain-Barré syndrome, heavy metal ingestion, carbon monoxide poisoning, snakebite, cerebrovascular accidents, and various metabolic disorders. Not uncommonly, infants with botulism are initially presumed to be septic or dehydrated at presentation. Other diagnoses may be entertained only after symptoms fail to improve or progress despite rehydration and empiric broad-spectrum antibiotic therapy. Misdiagnosis is common and may have catastrophic consequences if cardiorespiratory function is not monitored closely.

The characteristic presence of constipation, often preceding the onset of other symptoms, and the absence of fever are useful historical characteristics to help differentiate botulism from other infectious disorders. The descending progression of motor neurologic signs in botulism contrasts with the ascending progression with sensory changes found in Guillain-Barré syndrome and other demyelinating processes. Although clinical improvement with empiric neostigmine or edrophonium may suggest myasthenia gravis, clinical improvement may also occur in other disorders. Some researchers have reported equivocal responses to edrophonium in infants with botulism.[43]

Diagnosis

Definitive diagnosis requires the isolation of organism and/or toxin from stool specimens. *C. botulinum* has been isolated from the stool of affected infants as late as 158 days after the onset of symptoms, and toxin, up to 138 days.[10] Stool specimens should be refrigerated after collection, but no specific preparation is required before processing. Laboratory procedures for the culture of *C. botulinum*, as well as toxin isolation and identification, have been described previously in detail.[44] Culture of the organism utilizes both enrichment and selective media. Briefly, this involves incubation of specimen in chopped-meat-glucose-starch medium for four days, followed by selective culture on egg yolk agar plates for two days.[45] Toxin isolation and identification is accomplished via mouse lethality testing, with typing confirmed by neutralization of toxin with specific antisera.[44] Detection of toxin can take anywhere from one to four days, with specific typing often taking an additional four days.[46] Testing is typically performed at state health departments or the Centers for Disease Control and Prevention.

Given the time often required to obtain stool and isolate organism and/or toxin, many investigators have advocated clinical features and electromyography (EMG) as means of establishing a presumptive diagnosis, with stool studies providing confirmation. The functional denervation of the muscle, which occurs as a result of impaired acetylcholine release at the neuromuscular junction, gives rise to abnormal spontaneous activity at the motor end-plate and the brief-duration, small-amplitude, overly abundant motor unit potentials (BSAPs) seen on EMG. Additionally, analogous to posttetanic potentiation, a marked incremental response to high-frequency (20 to 50 Hz) repetitive stimulation may be seen, as repetitive stimulation enhances acetylcholine release by unaffected presynaptic nerve terminals.[47] Nerve conduction studies are normal.[47] Although not pathognomonic, these findings in the appropriate clinical setting may strongly support the diagnosis of botulism. A recent retrospective review, however, found that four of 11 microbiologically confirmed cases of infant botulism did not display the characteristic EMG changes.[48] It appears, then, that normal electrodiagnostic studies may not exclude the presence of *C. botulinum* infection. Clinical history and physical exam findings consistent with botulism should be evaluated thoroughly and include EMG as well as stool studies.

Treatment and Outcome

The cornerstone of management of the infant with botulism is meticulous supportive care. There is no current evidence to support the use of antibiotics or botulinum antitoxin. A trial of human-derived botulism immune globulin is planned.[49] The use of gentamicin or tobramycin may potentiate neuromuscular blockade[39,50] and is thus contraindicated. Adequate pulmonary toilet and monitoring of cardiorespiratory function are essential. Intubation may be required for airway protection or respiratory failure. Tube feeding may be necessary if swallowing mechanisms are impaired, although parenteral hyperalimentation may be required if significant GI dysmotility is also present. As noted previously, the duration of hospitalization is approximately

one to 1.5 months, on average.[4,21] A review of the experience at Children's Hospital of Philadelphia found that three of 63 infants (5%) with botulism experienced recurrence of symptoms after their initial recovery and hospital discharge.[51] There were no identifiable predictors of relapse. These infants also ultimately returned to normal function after relapse. Overall, the mortality rate of infants with botulism has been estimated at less than 5% in hospitalized patients.[4] With close monitoring and supportive care, gradual improvement and return to baseline function may be expected.

Conclusion

Infant botulism may present with a variety of manifestations and may be difficult to differentiate from other disorders solely on clinical grounds. It should be considered in the evaluation of infants presenting with constipation, poor feeding, and hypotonia. Definitive diagnosis requires the isolation of organism or its toxin from stool specimens, although the presumptive diagnosis may be established by the characteristic EMG pattern. With meticulous supportive care measures, virtually all infants may be expected to have a gradual but full recovery.

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