Clinical Review

Botulism

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Clostridium botulinum is ubiquitous in the environment, yet symptoms of botulism occur in humans only if toxin A, B, or E is ingested, absorbed in the intestine, and bound and eventually internalized in the neuronal receptors, producing neuromuscular blockade. Clinically, botulism is divided into four types: food borne, infantile, wound, and unclassified. Systemic neurological symptoms occur within 72 hours of gastrointestinal symptoms and can progress rapidly to respiratory paralysis. Diagnosis depends on a high index of suspicion, but cultures and special tests may be helpful. Treatment remains mostly supportive with good respiratory care emphasized. Use of botulism antitoxin and guanidine may be helpful in some cases.

Botulism is an infrequent yet devastating disease. Most physicians will diagnose or miss all but a handful of cases throughout their professional career. Nevertheless, awareness of the clinical presentation and institution of prompt supportive treatment are the key elements in reducing the mortality and morbidity from this disease. It is therefore important to review the clinical aspects of botulism, with emphasis on some of the newer developments in diagnosis and treatment.

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Microbiology and Epidemiology

The word *botulism* derives from the Latin "botulus," or sausage, since blood sausage was known for centuries to be associated with the symptom complex now recognized as botulism. The first epidemiologic and microbiologic studies were performed by van Ermengen at the University of Ghent Medical School in 1895. He investigated a botulism outbreak among 24 people who dined on a brine-preserved uncooked ham at a wake. His efforts led to the identification of an

anaerobic gram-positive bacterium, which he named "bacillus botulinus." This was later changed to Clostridium botulinum.[1]

Cases of botulism remain infrequent, yet C botulinum has a ubiquitous distribution in the environment and has been identified in up to 18.5 percent of US soil surveys.[2,3] C botulinum spores are resistant to heat, light, drying, and radiation. They will germinate only under anaerobic and neutral or weakly acidic conditions if present for at least several days.[4,5] As a result, the ingestion of preformed toxin, not simply spores, is required in adult botulism. In infantile botulism, however, the toxin can be produced by incubation of the spores within the gut.[4]

Botulism toxin is the most dangerous toxin known, as only 0.5 g of toxin A is lethal for humans.[4] Although there are eight serologically distinct groups, the mechanism of action for all toxins is the same.[6,7] Only toxins A, B, and E cause human disease.[7] Type A toxin remains the predominant toxin associated with botulism in the United States, but there is a regional distribution of outbreaks by toxin type that parallels the distribution of spore types found in soil surveys.[8] Type A predominates west of the Rocky Mountains, type B east of the Rocky Mountains, and type E mainly in Alaska and along the borders of the Great Lakes.[7,8]

Three steps are necessary for toxin-induced neuromuscular blockade: (1) transport across the intestinal wall into the serum, (2) binding to neuronal receptors, and (3) internalization of bound toxin, an irreversible step leading to impairment of neurotransmitter release and resultant neuromuscular blockade.[6] Type A toxin may cause more severe disease than types B and E because of differences in amount of ingested toxin, absorption, or receptor affinity.[7,9]

Botulism outbreaks in the United States are usually food borne and associated with inadequate processing of nonacid foods, with home-canned products involved in 72 percent of cases and commercial products incriminated in only 8 percent.[5] Since the toxin is heat labile, the disease most commonly results from eating uncooked preserved foods. Vegetables, fish, fruits, and condiments lead the list as the most important vehicles of botulism.[10]

The Centers for Disease Control (CDC) reports that between 1899 and 1977 there were 766 recorded outbreaks of food-borne botulism in the United States. Outbreaks occur at a rate of approximately 10 per year and are clustered between June and December, probably because foods canned in the spring and summer are eaten during that time. The number of cases in any one outbreak is small, usually 2 cases with home-canned food and 3.3 cases with commercial food; 71 percent of reports involve only one case.[5,8] Although the number of outbreaks remains steady each year, the fatality rate has dropped from 60 percent to 16 percent, most likely a result of improvement in critical care management.[8,10]

Clinical Features

Clinically botulism can be classified into four types based on etiology and patient age: food-borne botulism, infantile botulism, wound botulism, and the unclassified cases.

Food-borne botulism is the most common and best studied. Symptoms occur 12 to 36 hours after ingestion of C botulinum toxin A, B, or E. The early symptoms, which are probably due to local effects on the gastrointestinal tract, include nausea, vomiting, abdominal cramps, and distention. A minority of patients will have diarrhea, whereas most will complain of constipation, which will often last throughout the illness. If the toxin is absorbed from the gastrointestinal tract into the bloodstream, it is then transported to the cholinergic neurons, where it appears to block the release of acetylcholine and cause neuromuscular dysfunction.

Systemic neurologic symptoms usually occur within 72 hours of gastrointestinal symptoms, but they may be delayed as long as eight days. Early neurologic symptoms probably indicate a more severe infection and worse prognosis.[4] Diplopia, dysphagia, dysarthria, and dry mouth are the most common symptoms. Weakness often spreads symmetrically and in a descending pattern involving both upper and lower extremities as well as respiratory muscles. Sensation is usually intact. Typically the patient remains mentally clear.[4]

A recent review of clinical symptoms made the

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point that some patients with botulism may have atypical neurological findings.[9] Fourteen percent had paresthesia, and depressed or absent deep tendon reflexes were found in 40 percent of patients. Although these clinical findings are more typical of Guillain-Barré syndrome, botulism should not be excluded. Pupillary abnormalities are found in a minority of patients.

The chief cause of mortality in these patients is respiratory or bulbar paralysis. Recovery from neurologic symptoms in the survivors is usually prolonged. In one review, resolution of 50 percent of the original symptoms took five months, and most patients had some persistent abnormalities as long as 13 months following the illness.[11]

Infantile botulism was first described in 1976 and is now known to present with a diverse clinical spectrum.[12,13] No clear food source can be implicated in most children with infant botulism; however, there have been reports of honey being the source of Clostridium.[14] Therefore, the CDC has recommended that honey not be given to infants less than one year of age.

The mere presence of C botulinum does not cause symptomatic disease. In fact, the organism can occasionally be cultured from the stools of normal asymptomatic children. Only when the bacteria produce toxin do symptoms occur. As described in adults, local toxin reaction causes gastrointestinal symptoms, most commonly constipation. Absorption of the toxin can lead to neurological symptoms that may be difficult to recognize in the infant. Most frequently noted are poor feeding, weak cry, loss of head control, floppiness, or failure to thrive. At the severe end of the clinical spectrum, the infant presents with a picture resembling sudden infant death syndrome (SIDS).[12,13] The peak age incidence of SIDS and infant botulism are similar, two to four months. It is estimated that about 5 percent of SIDS is actually due to botulism, and several infants have been found to have the bacteria and toxin present postmortem.[13] The true prevalence and outcome of infant botulism is unknown, since the diagnosis is often overlooked in mild cases; however, most infants do well and do not seem to have permanent sequelae.

Wound botulism is a rare disease, with only 27 cases having been reported to the CDC in a 40-year period (1943 to 1982).[15] It results from an infection of the wound by C botulinum, followed by the in vivo production and systemic absorption of the toxin. Gastrointestinal symptoms are absent. After an incubation period of 4 to 14 days, the patient presents with systemic neurological symptoms as described above. Manifestations include diplopia, dysarthria, and dysphagia, and a descending weakness that can involve the respiratory muscles. The wound can look benign, but the organism and toxin are usually present.[16] Wound botulism has been reported in parenteral drug abusers.[15] Thus botulism should be considered in any patient with typical neurological symptoms, even if gastrointestinal symptoms are not present.

The final category, unclassified botulism, is essentially a "wastebasket" diagnosis to include all cases of botulism confirmed by diagnostic studies that do not fall into the three categories mentioned. One theory of the etiology of unclassified botulism is that adults have the same disease mechanism as do the infants described above.[4] A small percentage of adults may have C botulinum in the gastrointestinal tract from an unknown source. If the C botulinum form toxin in vivo that is then absorbed, the patient will manifest gastrointestinal and neurologic symptoms of botulism poisoning. Although this model is consistent with known facts, the hypothesis has yet to be proved. The symptoms, clinical course, and prognosis are the same for unclassified botulism as for the food-borne type.

Diagnosis

The initial diagnosis of botulism is clinical, based on history and physical examination. As a majority of cases originate in food, a careful history of exposure to home-canned or home-prepared food should be sought in anyone presenting with a gastroenteritis or in anyone with new onset of neurologic symptoms.

The differential diagnosis of neuromuscular junction pathologies with or without gastrointestinal symptoms is formidable. Table 1 lists the most common diagnoses. The conditions that most commonly must be differentiated from botulism are Guillain-Barré syndrome, Eaton-Lambert syn-

Table 1. Differential Diagnosis of Neuromuscular Pathology

Botulism
Diphtheria
Guillain-Barré syndrome
Eaton-Lambert syndrome
Acute intermittent porphyria
Myasthenia gravis
Tick paralysis
Organophosphate insecticide
Saxitoxin
Poliomyelitis
Carcinomatosis of cranial nerves
Atropine
Phenothiazines (idiopathic reaction)
Antibiotics (aminoglycosides, polymyxin)

Table 2. Differential Diagnosis of Infant Weakness

Botulism
Failure to thrive
Sepsis
Dehydration
Viral infection
Idiopathic hypotonia
Myasthenia gravis
Poliomyelitis
Meningitis
Brain stem encephalitis
Neoplasm
Acute infantile polyneuropathy
Hereditary metabolic diseases

drome, and myasthenia gravis in adults[4] and sepsis, dehydration, myasthenia gravis, meningitis, SIDS, failure to thrive, and various hereditary and metabolic diseases in infants (Table 2).[13,17]

Definitive diagnosis can be made by demonstration of preformed toxin in the serum or stool by the mouse inoculation test in which a patient's specimen is injected into the peritoneal cavity of a mouse. If death is prevented by the preadministration of C botulinum antitoxin, the diagnosis is established.[4,18,19] The toxin may routinely be found in the serum 7 to 9 days after exposure[20] and can be found up to a month later.[18] Forty-five percent of suspected cases will be thus confirmed.[18] In infant botulism the toxin may be found in stool weeks to months after the patient has recovered.[13]

Finding the organism in the stool or toxin in the suspected food is strong confirmatory evidence. The organism is found in the stool in over 50 percent of proven cases compared with 4.5 percent in normal individuals.[18] Using the combination of serum and stool toxin tests with stool culture, the diagnosis can be confirmed in 72.9 percent of cases. This can be improved to 87.5 percent if food analysis for toxin is added.[18]

History and to a larger extent physical exam-

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Table 3. Changes in Evoked Potential in Response to Repetitive Nerve Stimulation and Exercise

Differential Diagnosis	2/sec (low rate)	50/sec (high rate)	Post-exercise
Normal	±	±	±
Myasthenia gravis	↓	↓ to ↑ or ±	±
Eaton-Lambert syndrome	↓	↑↑	↑
Botulism	↓	↑↑	↑

±No potentiation
↑Potentiation of response
↑↑Greater potentiation of response
↓Decremental response

ination will help differentiate some of the other possible diagnoses. The pharyngeal membrane of diphtheria should be easily seen. A tick may be found on the body in tick paralysis. A history of exposure to insecticides, shellfish, phenothiazines, or antibiotic use may also be obtained to pinpoint or eliminate these possibilities.[4]

Although the classical picture of Guillain-Barré is one of an ascending paralysis (with late, if any, involvement of bulbar muscles) following a viral infection, a descending paralysis or one that involves primarily bulbar muscles may be seen.[4] Cerebrospinal fluid protein is often elevated,[4] although it may also be elevated in botulism.[9]

Certain special laboratory tests may also help. The Schick test (diphtheria), urinary porphyrins (acute intermittent porphyria), serum cholinesterase (insecticide poisoning), and a lumbar puncture (meningitis) may all help to determine the diagnosis.[4,17] Physical examination and routine laboratory tests are of little value in differentiating the remainder of possibilities.[20]

The edrophonium chloride test for myasthenia gravis may be positive in botulism in 15 to 26 percent of cases.[9,21] If the test is performed improperly, patients with myasthenia gravis may have a negative response.[2]

Electromyography can help in differentiating Eaton-Lambert syndrome and myasthenia gravis from botulism (Table 3).[4,21] Myasthenia gravis can be differentiated by the smaller increment in response to high-frequency repetitive stimulation and lesser postexercise facilitation. Eaton-Lambert syndrome and botulism may have similar electrophysiologic findings, although with Eaton-Lambert syndrome these findings are uniform in any muscle group tested, but the changes found in botulism will be more prominent in certain muscle groups or limbs and tend to evolve over time.[4] Up to 15 percent of patients with botulism may have normal electromyography.[9]

Treatment

Over the years the fatality rate in adult botulism has decreased from 60 percent to 16 percent, probably as a result of improved respiratory management in the intensive care unit setting.[4] Treatment remains mostly supportive, and early intervention is indicated. In one study 9 of 13 patients intubated after respiratory arrest died, whereas only 1 of 15 electively intubated patients died.[9] Patients who died within two weeks after the onset of illness usually did so because the physician failed to correctly diagnose the disease and failed to recognize the gravity of the situation, or they died from pulmonary or systemic infections. Death after two weeks usually occurs from respiratory malfunction, which indicates the importance of meticulous respiratory management.[9]

The usefulness of antitoxin is still subject to de-

bate. It appears that antitoxin has relatively little effect with types A and B and a greater effect with type E toxin poisoning. A trivalent equine-derived antitoxin against types A, B, and E is currently available from the CDC. The knowledge that free toxin can be found in the serum so late after exposure suggests that antitoxin should be given as long as complete paralysis has not yet occurred.[4,20] Current efforts are focusing on developing type-specific antitoxin of human origin.[22]

Because guanidine enhances release of acetylcholine from nerve terminals, its use has been suggested, and it appears to help in mild cases; however, it is less effective in overcoming respiratory muscle paralysis.[21]

The picture in infant botulism is similar. Twenty percent of patients experience a respiratory arrest, often secondary to paralysis of respiratory muscles, but also as the result of mechanical factors such as pooled secretions or improper neck position.[13] Treatment is again primarily supportive, with special attention to pulmonary hygiene and nutrition.[4] There is a lower fatality rate in this group (3.1 percent), and antitoxin is not considered necessary for recovery. Antitoxin administration in children is associated with a 7.4 percent incidence of serum sickness, a 2.9 percent incidence of anaphylaxis, and it is of unproven therapeutic value.[13] The use of guanidine has not yet been studied in children. Antibiotics, enemas, and cathartics have not proven effective.[13]

In both adult and infant botulism, aminoglycosides and polymyxins will cause further blockade of the neuromuscular junction and are contraindicated.[4]

In summary, clinical suspicion must be aroused if the diagnosis is to be made. Diagnosis depends upon recognition of the classic features of the disease as well as of the wide variability of presenting signs and symptoms. Definitive diagnosis is based on finding the preformed toxin in the serum or stool and supported by finding the toxin in the suspected food and culturing the organism from stool culture. Various other diagnostic tests, including edrophonium chloride, cerebrospinal fluid protein, and electrophysiologic studies, can help distinguish botulism from other neuromuscular junction pathologies.

Treatment is primarily supportive with particular attention to respiratory care. Consideration should be given to early or elective intubation. Antitoxin is generally used in adult cases, and guanidine may have some value in mild cases. Further advances lie in three areas: better food preparation awareness, a high index of suspicion resulting in the recognition of the illness and its seriousness in the early stages, and the development of a monovalent human-derived antitoxin.

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