

Botulism in Bioterrorism

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Abstract

Botulism, a potential lethal disease related to neurologic complications caused by neurotoxins most of them were produced by *Clostridium botulinum*. Food related botulism, infant botulism and wound botulism were reported all over the world after the first published by Kerner in 1820, botulism of adult with unknown was distributed in recent year which may due to colonization in gastrointestinal tract or toxin produced in vitro. The botulinal neurotoxin is the most lethal biological substance known, and it can be purified in laboratory. Bioterrorism is discussed after the terrier attack of United State in 2001 and botulism is one of the most possible agents. Prevention to the attack of biological weapons is impossible, it is emergent that clinicians should learn to recognize, diagnose and manage this rare but lethal disease, include the possibility of large outbreak due to terrorism. (*Ann Disaster Med* 2002;1 Suppl 1:S17-S25)

Keyword: Botulism; Bioterrorism; *Clostridium botulinum*

Introduction

Botulism, caused by *Clostridium botulinum*; neurotoxin produced by this organism related to food borne disease and outbreak occasionally all over the world. Botulism is a life-threatening neuromuscular disease caused by neurotoxins produced from *Clostridium* strains. *C. botulinum* causes most of the cases and a few other clostridial strains accounting for the others. The clinical infections of botulism include food borne botulism, infant botulism, wound botulism and botulism of undetermined etiology. The neurotoxins of botulism are designed types A through G based

on antigens.

The term of botulism derives from the Latin word botulus, means sausage. It was recognized since the early 19th century in Europe.¹ In 1897, Van Ermengen reported the description of botulism and the affected animals.² Botulinal toxin, the paralytic agent that causes the clinical symptoms of botulism poisoning, had been used to achieve controlled paralysis of the extraocular muscles.³ Advances in the clinical use of botulinal neurotoxins continue in recent years, it is the advanced practice in the treatment of movement disorders, spasticity,

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neuromuscular disorders, pain control, pharyngeal disorders, laryngeal disorders, and cosmetic applications.^{4,5} Even more, it is believed the use of botulinal toxin, as a weapon in bioterrorism is possible.⁶

The organism

C. botulinum is a large, gram-positive, strictly anaerobic, spore-forming bacillus widely distributed throughout the world in soil and marine sediments. *C. botulinum* is classified as a single species but consists of at least four genetically distinguishable groups of organisms. Most of the botulism cases caused by *C. botulinum*, and rare cases of infant botulism have been reported due to *C. baratii*⁷ or *C. butyricum*.⁸ Spores of *C. botulinum* were found throughout the world in soil samples and marine sediment, and the spores are heat resistant requiring temperatures above 100°C more than several hours for destruction, and they may germinate at room or body temperature under anaerobic condition.⁹ Proper preparation of foods in a pressure cooker can kill bacterial and spores.

Toxins

Botulism is one of the most lethal toxins known. Although seven types of neurotoxins (toxin types A, B, C, D, E, F, and G) are produced by different strains of *C. botulinum*;¹⁰ Clostridium botulism produces toxin types A, B and E which cause most of the human infections.

Neurotoxins type F (produced by *C. butyricum*) cause human botulism occasionally. Toxin types C and D produced by strains of Clostridium botulism are known to associate with infections in birds and mammals, but not in humans. Toxin type G has not been associated with naturally acquired disease. The seven types of neurotoxin are distinguished by neutralization of biological activity with specific serologic reagents.¹¹

The botulinal toxin consist a small light chain approximately one third of the total mass, and the heavy chain. The molecular weight of toxins range from 150 to 165 kD depending on the type of toxin. The botulinal toxin binds irreversibly to the presynaptic nerve endings of cranial and peripheral nerves, and then prevents the release of acetylcholine. The following symptoms characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Blurred vision, dysphagia, and dysarthria are also associated initial complaints.

Botulinal toxin type A has been found to be effective in the treatment of various spastic disorders of smooth muscle in the upper and lower gastrointestinal tract.¹² Botulinal neurotoxin is considered the most potent lethal substance known. It is 15000 to 100000 times more toxic than sarin, the organophosphate nerve agent used in the terrorist attack of subway in Tokyo.¹³

The botulinal toxin has the lethal dose as low as 0.00625 ng in mouse; it is the lowest lethal dosage in clostridial strains.¹⁴

Clinical Manifestations

Four clinical forms of botulism are recognized as food borne botulism, infant botulism, wound botulism and botulism of undetermined etiology. Food borne botulism is the most frequent botulism in outbreaks, and the others usually cause sporadic cases. The clinical manifestations of botulism is dependent on toxin type rather than the site of infection.

Food borne botulism is typically seen in adults resulting from the ingestion of toxins within contaminated food. The most frequent source is canned foods or decayed meats, in which botulinal spores survive, germinate, reproduce and produce toxins in anaerobic environment. In food borne botulism, symptoms generally begin from 18 to 36 hours after eating a contaminated food, but they can occur as early as 6 hours or as late as 10 days. The clinical syndrome of food borne botulism resulted from a toxin-induced blockade of the voluntary motor and autonomic cholinergic junction; including gastrointestinal, neurologic and some miscellaneous symptoms (Table)

Infant botulism is due to ingestion of botulinal toxin or intestinal colonization of *C. botulinum*. The

disease commonly occurs in the first year of life, especially during the first two months. Infant botulism can be caused by toxin A, B and F. The clinical features including constipation, poor feeding, lethargy, weak cry, decreased sucking, lack of muscle tone and floppy head.¹⁵ The onset of this disease is ranging from constipation to sudden death, and the recovery ranges from weeks to months. Most of the source is unknown (85%), and in up to 15% of the cases is thought to relating to ingesting of honey.^{16,17} Because honey can contain spores of *C. botulinum* and this has been a source of infection for infants, children less than 12 months old should not be fed honey. Honey is safe for persons 1 year of age and older.

Wound botulism occurs when the wound within anaerobic condition allow germination of spore, replication of the microorganism and producing of neurotoxins. The incubation time of wound botulism is longer than foodborne botulism, as long as seven to fourteen days. Wound botulism is often caused by toxin A and B. Clinical features of wound botulism including all the symptoms of the foodborne botulism except gastrointestinal manifestations.

Botulism of undetermined etiology may occur in adult as a result of intestinal colonization of *C. botulinum* or in vivo toxin production. The production of toxins may be as a source of bioterrorism. The cases of intestinal colonization may have a history of

abdominal surgery, gastrointestinal tract abnormalities, or disrupt of normal flora due to recent treatment of antibiotics.^{18,19}

Diagnosis

Diagnosed cases of botulism are under estimate because the symptoms can be mistaken for more common clinical diseases, such as stroke, Guillain-Barre syndrome and myasthenia gravis.¹⁴ The diagnosis is not difficult in most of the cases once it has been considered, the history of patient is important in the suspect of this disease. Because early diagnosis and treatment can reduce the mortality of botulism, initial diagnosis should be based on the history and physical examination before toxin testing and the result of culture could be noted. The diagnosis of botulism is based on compatible clinical findings; history of exposure to suspect foods or toxins; and supportive ancillary of suspected cases testing to rule out other cause of neurologic entities, such as stroke, the Guillain-Barre syndrome, and myasthenia gravis. Laboratory confirmation should be performed for suspected cases.

Clinical diagnosis of botulism requires demonstration of botulinal toxins in serum or feces, or isolation of *C. botulinum*. Isolation and identification of this organism is by conventional cultural biochemical procedures and the toxin neutralization test.¹⁰

The confirmation of suspected botulinal case is based on toxin and cultures of stool or food. The most reliable test of toxin is the mouse inoculation test; this can be done at some laboratories. The type of botulinal toxin is determined by neutralizing of bioactivity of toxin by injected type-specific antitoxin into the mice. Cultures should be done to stool and food of suspected foodborne botulism, wound of suspected wound botulism, and stool to suspected infant botulism. Toxin testing in stool should be performed in such suspected patients. If an outbreak is suspected, stool samples and toxin testing should be performed.

Treatment

The mortality rate of severe botulism could be improved by supportive care, especially in intensive care unit and ventilatory support. Respiratory arrest may be rapid, intensive care and ventilatory monitor should be considered in severe and progressive cases.

The treatment of botulism includes supportive care, antimicrobial therapy, surgical debridement and use of trivalent antitoxin. Gastric lavage and enema should be attempted in cases with foodborne botulism and suspected food exposure for removing unabsorbed toxin from the intestinal tract. Cathartic agents were not suggested because of the containing of magnesium may enhance the action of botulinal toxin. Surgical

debridement should be performed accompanied with antimicrobial therapy to wound botulism.

The trivalent antitoxin had been proved with beneficial effect on survival and shortens the course of patients with type A botulism.²⁰

Bioterrorism

Biological weapons have recently attracted the attention of the world. Infectious disease or toxin is an effective step toward averting the suffering that could be wrought by a terrorist's use of a biological agent.

Bioterrorism is the use of biologic agents against people to create fear or illnesses for purposes of intimidation, gaining an advantage, or interruption of normal activities. In possible bioterroristic agents, the agent is considered to cause morbidity, possible mortality, and perhaps a disease difficult to diagnosis and to treat. The best characters of these agents include accessibility, reproducibility, stability, and dispersibility.

The bioterroristic agents that are considered to be the most pathogenic include *Variola major* (smallpox), *B. anthracis* (anthrax), *Yersinia pestis* (plague), *C. botulinum* (botulism), *Francisella tularensis* (tularemia), and some hemorrhagic fever viruses such as Ebola, Lassa, and Marburg. The next level of agents includes *Coxiella burnetii* (Q fever), *Brucella* species (brucellosis), *Pseudomonas mallei*

(glanders), and some encephalitis-causing viruses. Additionally, there are some other microorganisms of lesser toxicity that have been used in bioterroristic events such as *Vibrio cholera*, *Salmonella*, *Shigella*, and *Staphylococcus*.²¹

The event of large outbreak of botulism caused by an enteric or aerosolized route or exposure is possible, because the purified toxins could be performed in laboratory. The primary treating of the victims is supportive care and rapid respiratory care including early intubation with ventilatory support. Rapid administration of antitoxin is the only useful pharmacologic treatment in these non-infected victims. If the administration of antitoxin is delayed until the signs occurred, the toxin will be lethal in non-ventilator victims.²² Asymptomatic persons in outbreak can be monitored closely without specific therapy, and injected with antitoxin should be initiated if there were any symptoms or signs found.

Prevention of bioterrorism is impossible, rapid and adequate history taking and early diagnosis are the most important to stop the progressing of large outbreak. Clinicians especially those in emergent department are the first to treat patients with any type of botulinal infection and in outbreak, they must know how to recognize, diagnose, and treat this rare but potentially lethal disease.

Table. Common symptoms and Neurologic Signs of Botulism

Symptoms	Signs
Neurologic	Neurologic findings
Blurred vision	Ptosis
Dry mouth	Diminished gag reflex
Diplopia	Ophthalmoparesis
Dysarthria	Facial paresis
Dysphagia	Tongue weakness
Dyspnea	Pupils fixed or dilatation
Extremity weakness	Nystagmus
Paresthesia	Extremity weakness
	Ataxia
	DTRs diminished or absent
	DTRs hyperactive
	Changed mental status
Gastrointestinal	
Abdominal cramping	
Constipation	
Diarrhea	
Nausea	
Vomiting	
Miscellaneous	
Dizziness	
Fatigue	
Sore throat	

DTRs: deep tendon reflexes

Data from reference 10, 15, 16 and 20.

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肉毒桿菌之於生化戰

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摘要

肉毒桿菌中毒,一個因肉毒桿菌神經毒素引起的致命疾病。自 1820 年 Kerner 發現第一個病例起,全世界都有食物肉毒桿菌中毒,傷口肉毒桿菌中毒,嬰兒肉毒桿菌中毒的報告,近年來更有因腸胃道移生菌及體外製造毒素所引起的成人肉毒桿菌中毒。肉毒桿菌神經毒素是世界上已之最致命的毒素,而且它可以在體外被純化。自美國在 2001 年被恐怖攻擊以來,生化戰就一直被討論,肉毒桿菌中毒也是其中一個可能的致病源,預防生化武器的攻擊是不可能的,因此如何去了解,診斷並處理少見但致命的肉毒桿菌神經毒素中毒及因恐怖攻擊所引起的群突發,是現在臨床醫師的一重要課題。(Ann Disaster Med 2002;1 Suppl 1: S17-S25)

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