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The enemy at the gate: Botulism

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Abstract:

Botulism, caused by *Clostridium botulinum*, continues to pose a significant threat to public health. This review explores the historical context and contemporary relevance of botulism, emphasizing its potential lethality and evolving medical applications. In recent years, the use of botulinum toxin in medical procedures, particularly in cosmetic and therapeutic applications, has increased the risk of iatrogenic botulism. The rise in iatrogenic cases underscores the importance of vigilance among health-care providers, especially those in emergency departments, where prompt diagnosis and intervention are critical. This review underscores the necessity for health-care professionals to consider botulism in the differential diagnosis of patients presenting with relevant symptoms, given the potential severity of the condition.

Keywords:

Antitoxin, botulism, *Clostridium botulinum*, iatrogenic botulism

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Introduction

Clostridium botulinum is an anaerobic, spore-bearing, gram-positive staining bacillus. Wherever there is soil, *clostridium* bacteria can be isolated from fruits, vegetables, shellfish, and marine sediments.[1] Under favorable environmental conditions, the spores of these bacilli generate toxins, which enable the bacteria to proliferate.

Botulism is an infrequent yet potentially fatal medical condition caused by the bacteria *C. botulinum* and its neurotoxin. The study of this disease began in Europe in the 1800s when patients exhibited symptoms of food poisoning after consuming sausage, and it was further identified through the isolation of sporulated bacillus from ham and its connection to neuromuscular paralysis.[2] The disease arises from the ingestion of tainted homemade canned food that has been produced in unsuitable conditions and manifests as localized outbreaks in nations where traditional techniques of food preparation are prevalent. Nevertheless, the *C. botulinum* toxin is commonly employed in medical applications, particularly in the fields of cosmetic operations, bariatric surgery, urology, and neurology. The 2020 data report from the American Society of Plastic Surgery revealed that botulinum toxin applications were the most prevalent minimally invasive cosmetic operation performed on both males and females.[3] Recently, there has been a rise in instances of iatrogenic botulism, a condition that was previously considered less common than other clinical manifestations, and this increase is now being recognized as a significant public health concern.[4]

The purpose of this article is to analyze the clinical presentation, diagnosis, and treatment approaches for botulism based on current literature, to create awareness regarding the rise in iatrogenic botulism cases, and to contribute to the advancement of more efficient strategies in this domain.

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Epidemiology and Incidence

Clostridium botulinum has been phenotypically categorized into four groups (I–IV) and more often serologically classified into seven groups (A–G) based on their ability to produce toxins. Although the majority of strains typically create only one toxin, there are strains that have the ability to produce numerous toxins.[5] Botulism can be clinically observed in several forms. Historically, infant botulism, foodborne botulism, and wound botulism are frequently observed following the consumption of honey, although iatrogenic and adult intestinal colonization are less frequently observed. The European Center for Disease Prevention and Control recently published a paper indicating that the occurrence of botulism in Europe is fewer than 1 in 1,000,000 individuals. Among this population, children under the age of 1 have the highest occurrence rate.[6] According to the US Centers for Disease Prevention and Control reports around 200 cases of botulism annually.[7] Another region where botulism is a public health problem is the Far East. Fifty percent of the recorded cases in this region are attributed to foodborne botulism, which is caused by the excessive consumption of tofu, canned beans, and dried meat prepared using traditional techniques. Between 2004 and 2020, China witnessed a total of 80 instances of foodborne botulism outbreaks.[8]

Pathophysiology

The spores of *C. botulinum* are heat-resistant but can be destroyed by heating the spores at 120°C for 5 min. When the conditions in the environment are favorable, spores that are present in the atmosphere will develop into bacilli, which produce poisons. The germination of most spores occurs in an environment that lacks oxygen or has limited oxygen (anaerobic or semi-anaerobic), with pH levels around 7.0, and temperatures ranging from 25°C to 37°C.[9]

Up-to-date, eight types of *C. botulinum* toxin (A-H) have been identified. The toxins, excluding C and D cause disease in humans. Contrary to its spores, *C. botulinum* toxin consists of a heavy and light chain of 150–165 kDa, a polypeptide structure that can be denatured above 80°C.[10] Although the exact mechanism of action is not clearly understood, neurotoxins bind to receptors located on presynaptic nerve endings and can affect many tissues, such as striated muscle, smooth muscle, sweat glands, and salivary glands both as stimulants and blockers. It has been demonstrated to inhibit the release of many substances, such as dopamine, serotonin, and GABA.[10]

C. botulinum toxin is recognized as one of the most potent toxins in existence. It has no smell or taste. It is absorbed from the stomach and small and large intestines, and its durable structure is resistant to stomach acid. It is thought that 1 g of aerosolized toxin is capable of killing 1.5 million people. These attributes render it a significant prospective biological weapon.[11]

Foodborne botulism is caused by ingesting bacteria that have thrived in food under favorable conditions, while wound botulism occurs when bacteria develop in a wound. Infant botulism, on the other hand, occurs when spores are ingested orally.

Clinical Symptoms and Diagnosis

The first requirement for a timely diagnosis is to suspect botulism. Clinical signs of botulism can develop within hours to days and last for several months. Botulism should be considered, especially in cases of sudden onset of cranial nerve abnormalities. The presence of a disease affecting the muscle-nerve junction (Myasthenia Gravis, Guillain–Barre syndrome, etc.) does not exclude the diagnosis of botulism. Botulism should be examined, particularly in neonates, when there is a fast development of sucking problems, ptosis, and immobility. The American Center for Disease Control and Prevention has established diagnostic criteria for botulism, which have been found in the majority of patients.[12] However, failure to fulfill the criteria in patients does not exclude the diagnosis of botulism. While the lack of fever is typically considered a characteristic of botulism, it is possible for a fever to occur in cases of wound botulism as a result of a simultaneous bacterial infection in the wound [Table 1].

Patients with botulism typically remain conscious and alert despite presenting with characteristic cranial nerve paralysis, leading to symmetrical descending muscular weakness, initially affecting proximal muscles before extending to distal ones. This paralysis can escalate to respiratory failure and potentially death if severe. The severity of paralysis correlates with the toxin dose. Clinically, patients may demonstrate ptosis, ophthalmoplegia, voice alterations, and gait difficulties, with sensory deficits and pain being rare, potentially complicating timely diagnosis. A detailed medical history is imperative on noting suggestive symptoms, accompanied by a comprehensive physical and neurological examination. Evaluation should also include assessment for tick bite paralysis and relevant exposure inquiries. Polyneuropathies, while similar, can usually be differentiated thorough physical exam. Reflexes in botulism typically remain intact unless there is complete paralysis of the involved muscles.[13] It is crucial to assess potential botulism exposure by querying about specific risk factors, including consumption of homemade canned foods, honey in infants, recent

Table 1: Findings suggestive of botulism*

Criteria	Symptoms and Findings
Presence of at least one of the symptoms of cranial neuropathy	Blurred vision
	Double vision
	Difficulty or impairment in speech
	Any change or hoarseness in the voice
	Dysphagia, secretion accumulation, drooling
	Swelling of the tongue
Presence of at least one of the neuropathy findings with cranial neuropathy findings	Ptosis
	Signs of extraocular neuropathy
	Extraocular palsy
	Decrease in eye tracking of objects
	Eye fatigue caused by shining light on the eye
	Signs of facial neuropathy
	Facial paralysis
	Loss of facial expressions
	Malnutrition or poor suction
	Fatigue while eating
	Fixed pupils
	Descending paralysis starting from the cranial nerves
Lack of fever	

*The diagnostic criteria's according to the American CDC. CDC: Center for disease control and prevention

trauma, parenteral therapies, and cosmetic procedures. In cases with multiple admissions, the potential for bioterrorism must also be considered. Laboratory tests and imaging are mainly used to rule out other conditions that could mimic botulism.

Types of Botulism

Foodborne botulism

Botulism is a potentially fatal kind of food poisoning caused by ingesting food contaminated with toxins. Type A, B, and E toxins most commonly cause foodborne botulism. Products such as homemade canned food, fruit, vegetables, and fish that have not been stored in proper conditions and homemade yogurt are infestation sources.[14] Implementing food safety procedures effectively is a crucial strategy to prevent foodborne botulism.

The incubation period varies between 18 and 36 h. Patients may initially report to hospitals exhibiting signs of food poisoning followed by nervous system symptoms. In advanced cases, death may occur as a result of respiratory failure and cardiac arrest.[12]

Wound botulism

C. botulinum has the ability to invade wounds and generate neurotoxins within the body. The presence of contaminated open fractures, particularly those exposed to soil, as well as areas where surgical procedures have been performed, increases the likelihood of developing wound botulism.[15] Similarly, there have been documented instances of localized outbreaks in various regions across the globe due to the usage of injectable drugs.[16] Addicted patients are at risk regarding this type. Isolation of *C. botulinum* as a result of intranasal cocaine use has been reported.[17]

Digestive symptoms do not occur in this type. The incubation period is much longer and varies between 7 and 21 days. Wound care is a key to the treatment.

Infant botulism

Infant botulism is the most common form of botulism in the US, usually affecting children under 1 year of age, caused by ingestion of *C. botulinum* spores. Typically observed in newborns between the ages of 2 and 4 months.[18] Infant botulism is characterized by decreased muscle tone and weakness in the muscles responsible for controlling swallowing and speaking. However, the symptoms can vary greatly among affected individuals. The cranial nerves are initially impacted, subsequently followed by the trunk, extremities, and diaphragm. Infants suffering from infant botulism commonly exhibit symptoms of constipation and malnutrition when they seek medical attention. This is followed by progressive hypotonia. Examination may uncover malfunctioning of the cranial nerves, reduced ability to gag and suck, limited range of eye movement, paralysis of the pupils, and drooping of the eyelids. In advanced cases, respiratory failure may occur.[19]

Infant botulism has a large list of differential diagnoses. A study carried out by the California Department of Public Health examined children diagnosed with infant botulism from 2005 to 2015. Out of the 76 children who did not have laboratory confirmation but were treated for botulism, 44 of them were later diagnosed with a different condition.[20]

Infant botulism is a serious medical issue that necessitates early diagnosis and appropriate treatment to reduce the risk of complications and ensure a healthy recovery for patients.

Adult intestinal botulism

It is a clinical condition caused by ingestion of spores of the bacterium through contaminated food and *in vivo* toxin production. It is an extremely rare condition after the neonatal period, as the intestines are resistant to *C. botulinum* colonization. It was reported in a 2018 article that only 33 patients were reported after 1980.[21] Most of the reported patients had predisposing factors such as inflammatory bowel disease and previous gastrointestinal surgery.

Inhalation botulism

Inhalation botulism is extremely rare and does not occur naturally. It is caused by accidental or intentional inhalation of toxins in aerosol form. This can be witnessed in laboratory accidents or acts of bioterrorism. Symptoms occur 1–3 days after ingestion; the clinical picture is similar to that of the foodborne type. If inhalation botulism is suspected, further exposure of the patient should be prevented, and the patient should be decontaminated.[11]

Iatrogenic botulism

Botulinum toxin products are commonly recognized as safe agents for both therapeutic and cosmetic use, and side effects are very rare in appropriately selected patients with the correct dosage and injection technique.[13] Due to its dissemination, botulinum toxin can affect the muscles and glands around the injection site. Effects and complications differ depending on the application site. Cases of iatrogenic botulism as a result of such injections are quite rare, but the number of cases has been increasing with the increasing use in cosmetic and bariatric fields. In fact, 87 cases of iatrogenic botulism were reported in 2023 after botulinum toxin injection into the gastric antrum by endoscopy in Türkiye for weight loss.[4] Although less common, iatrogenic botulism can also be seen after facial and other injection sites.[22] If applied appropriately and in the right amount, side effects are very rare. Cases of iatrogenic botulism are usually those who have received high doses of toxin. Practitioners should be trained in careful patient selection and injection techniques. The restricted availability of botulinum toxin in most countries paves the way for the illicit supply of toxin preparations in the form of drugs used for cosmetic purposes. More stringent regulations and controls on these practices are needed worldwide.

Laboratory

Patients with botulism typically present with normal laboratory results. Cerebrospinal fluid (CSF) analysis generally shows normal findings, though elevated CSF protein may be observed in a minority of cases, as evidenced by a study by Rao *et al*. in 2017, which found increased CSF protein in 13% of 332 patients aged over 1 year, assessed over 13 years in the US. The Tensilon test, used primarily to diagnose Myasthenia Gravis, typically does not support a diagnosis of botulism, often yielding negative results.[23]

Electrodiagnostic studies can help support the diagnosis. Repetitive nerve stimulation, electromyography, and nerve conduction studies are used to elucidate the etiology of muscle weakness. The results of these tests may be normal in the early stages but may give positive results as the disease progresses and can help differentiate it from other neuromuscular diseases.[12]

Confirmation of botulism requires detecting neurotoxin in serum, stool, or gastric fluids, isolating neurotoxin-producing *Clostridium* species from stool or wound cultures, and identifying neurotoxin in ingested food. It is advisable to collect these samples before administering antitoxin, and blood samples should be drawn into tubes without anticoagulants. Negative laboratory tests can occur later in the disease course when serum toxin levels decrease below detectable limits or, in cases like wound botulism, when neurotoxin-producing *Clostridium* species are not always detectable in wound samples. In such instances, clinical judgment may suffice for diagnosis, with treatment decisions based on clinical presentation and symptoms. A positive response to treatment can help confirm the diagnosis but repeated clinical evaluations and symptom monitoring are crucial for definitive confirmation of botulism.

The gold standard for diagnosis is the rat biological test using experimental animals. This is the only method approved by the US Food and Drug Administration to laboratory confirm the diagnosis. Polymerase chain reaction test detects A-G genes and can identify the species produced in cultures. Since this method detects DNA and not the toxin, another method, such as a mouse bioassay, should be used to confirm the toxin. Sensitive and specific tests such as mass spectrometry can differentiate between serotypes of neurotoxin within a few hours, but access is limited.[5,12]

Treatment

Emergency department

Patients often present to the emergency departments (EDs) due to rapidly progressive signs and severity of symptoms. Following the patient history and examination, the initial intervention in a patient with suspecting botulism is classically securing the airway, breathing, and circulation. Respiratory failure is the leading cause of death in such patients. Therefore, it is essential to continuously monitor the respiration of patients with suspected botulism in EDs and to intubate and mechanically ventilate patients with respiratory failure. Other interventions in the ED consist of supportive treatments. Patients should be hospitalized in appropriate clinics as recovery times will be long. Antitoxin administration to appropriate patients should be performed in EDs in cases where patient admission may be delayed.

Antitoxin

Antitoxin is the primary treatment option and should be administered as soon as clinically diagnosed. Antitoxin binds to circulating neurotoxins and prevents them from binding to the nerve-muscle junction. Early administration potentially prevents respiratory failure. Since the antitoxin cannot reverse paralysis, it should be administered to patients as soon as possible to prevent paralysis.

Although studies on antitoxin are scarce, a meta-analysis of cases between 1923 and 2016 found that it reduced mortality.[24] The same study also reported that earlier administration was associated with lower mortality. Antitoxin administration is recommended in pregnant patients.[25]

Antitoxin is not available in many hospitals but can be obtained from antidote centers. It is, therefore, essential to report patients to health authorities to request antitoxins.

Among the two types of antitoxins, immune globulin produced from humans is used for infant botulism, while antitoxin produced from horse serum is used for other types. The dose varies by age. One vial of antitoxin is administered intravenously (IV) for adults. There are not enough studies to determine the efficacy of additional dosing. Children aged 1–17 years are administered 20% to all of one vial depending on the weight of the child. However, the amount of toxins in circulation has no relation to weight. Patients whose symptoms do not resolve despite treatment may receive an additional dose of antitoxin. Children under the age of 1 year should be administered 10% of the adult dose of antitoxin obtained from horse serum.[26] Human immune globulin should also be administered to this age group. It should be administered IV as soon as possible.

Wound care

In cases with wound botulism, debridement may be performed to remove toxin-contaminated tissue and reduce the bacterial load.

Antibiotics

Routine antibiotherapy is not recommended in patients with wound botulism unless there are signs of infection in the wound itself or in the area where it is located. However, antibiotics could theoretically increase bacterial lysis, leading to the release of more toxins. Antibiotic treatment may be useful after antitoxin administration in the presence of conditions such as wound infection and cellulitis.[27]

Intestinal regulators

Laxatives, enemas, and other bowel-regulating agents may be used in cases of ileus. However, there is no evidence that it is effective on botulism.

Vaccinations

Studies indicate that recombinant subunit vaccines exist that provide safe and effective protection against botulinum neurotoxins. These vaccines have been developed and tested in different formats for BoNT types A and B and for toxins derived from other subtypes.[28] Mucosal vaccination is the first line of defense of the mucosal immune system against such pathogens, with botulinum neurotoxins considered a bioterrorism threat. Considering that current injection-type vaccines provide protective immunity only in the systemic compartment, it is crucial to develop an effective mucosal vaccine against botulinum poisoning.[29]

Conclusion

Botulism is a serious health problem that still remains relevant today. Currently, botulinum toxin applications, which are frequently performed for various purposes, pose a risk for iatrogenic botulism. Especially physicians working in emergency wards should definitely consider the diagnosis of botulism in suspected patients, as they will almost always be the first ones to be consulted by these patients.

Author contributions statement

ÖT: Conceptualization, methodology, investigation, resources, data curation, and writing – original draft. AAA: Conceptualization, methodology, investigation, resources, data curation, and writing – original draft, review, and editing, supervision. All authors approved the last version of the manuscript.

Conflicts of interest

None Declared.

Ethical approval

The study does not require ethical approval.

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