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A rare symptom of foodborne botulism: dysgeusia. Case report and clinical review

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Abstract

Clostridium botulinum has become one of the most well-known microorganisms in medical history, thanks to both fatal botulism epidemics and the recent medical use of botulinum neurotoxin. It is a Gram-positive, anaerobic, spore-forming bacterium that causes classic foodborne botulism, infant botulism, wound botulism, and intestinal colonization botulism, a serious neuroparalytic disease. The most common type of botulism is foodborne botulism, which is caused by eating botulinum toxin-contaminated foods. Just a few micrograms of toxin are enough to cause symptoms and, if untreated,
death. Rapid diagnosis of the condition is critical to avoiding fatal outcomes. This article describes a clinical case of a patient who presented to us in June with typical symptoms of botulism. Early clinical diagnosis is based on a thorough medical history, including a meticulous reconstruction of the patient's food history in the days preceding symptom onset, as well as a careful physical examination, which can be highly suggestive of botulinum intoxication. Botulism treatment consists of symptom control, mechanical respiratory support, and Botulinum Antitoxin (BAT) administered intravenously. Epidemiological investigation is critical for quickly identifying the food vehicle causing the intoxication.

Introduction

Clostridium botulinum is a Gram-positive, anaerobic, spore-forming bacterium responsible for classic foodborne botulism, infant botulism, wound botulism, and intestinal colonization botulism. Foodborne botulism is a severe neuro-paralytic syndrome caused by the ingestion of preformed botulinum toxins in contaminated foods. The consumption of minute quantities of food contaminated with botulinum toxins is sufficient to induce the disease and can even prove fatal. Botulism diagnosis is solely clinical; thus, a thorough medical history, including a meticulous reconstruction of the food history approximately 15 days before the onset of symptoms, and a careful physical examination of the patient can be highly suggestive of botulinum intoxication. In fact, in most cases/outbreaks of botulism where the food is later identified through laboratory analysis, its initial detection often occurs during the medical history phase. However, it should be noted that the literature reports incubation periods that can extend up to 30 days.

From 2001 to 2020, the Italian National Surveillance System of the Istituto Superiore di Sanità reported 1,039 suspected clinical cases, confirming 452 in the laboratory. Out of these, 412 (91%) were cases of foodborne botulism, 36 (8%) were related to infant botulism, and 4 (1%) were cases of wound botulism. The number of deaths was 14, with an average disease lethality rate of 3.1%. This lethality rate decreased from 3.8% in the period 2001-2011 to 2.6% in the period 2012-2020. The national average incidence in Italy from 2001 to 2020 was 0.39 cases per million inhabitants. Most botulism cases occurred in the male population (n. 272, 60%), with the age group 25-64 years having the highest number of laboratory-confirmed cases (n. 255, 56%). Despite no significant changes in the age distribution of the Italian population from 2001 to 2020, there was an increase in the number
of cases in the 25-64 age group from 2012 to 2020 compared to the period 2001-2011. The national surveillance system receives an average of about 50 reports of suspected cases per year and confirms about half of them in the laboratory. The average lethality rate from 2001 to 2020 was 3.1%, in line with international literature data.\textsuperscript{1-3} The highest incidence of laboratory-confirmed botulism cases occurred in the southern regions, attributed to the prevalent tradition of preparing homemade food preserves in these areas, especially in rural settings. Often, these preserves are made from self-produced raw materials and traditional recipes, frequently reducing the quantity of natural preservatives commonly used in homemade preserves (sugar, salt, vinegar, and lemon juice).\textsuperscript{4} Therefore, the prevention and control of foodborne botulism rely on meticulous adherence to food safety rules both at the industrial and domestic levels.

**Case Report**

In June 2023, a 34-year-old man came to our attention reporting symptoms such as profuse diarrhea, vomiting, syncope and sixth cranial nerve palsy, eyelid ptosis, diplopia, dysphagia, dysarthria, and xerostomia, which he had been presenting for a few days. In addition to the symptoms described previously, we encountered a further symptom: dysgeusia, a decrease in the perception of flavors. The symptom was constant, had arisen a few hours earlier, and continued for 3 months after the administration of the serum, and did not have dysosmia or parosmia. The patient mentioned consuming suspicious food at a restaurant approximately two days before the onset of symptoms. At that time, no other individuals exhibited similar symptoms. Therefore, the process for requesting serum, reporting food poisoning, and sending biological samples to the Istituto Superiore di Sanità was initiated. Urgent tests, including negative cerebrospinal fluid examination, high-frequency repetitive nerve stimulation, normal electrocardiogram (ECG), and vital signs, did not show significant abnormalities, except for an elevated C-reactive protein (CRP) level (15 mg/L). The serum reached our hospital within about an hour. The patient was admitted to the Neurology department, where an intravenous serum injection was administered antitoxin bivalent (7500 I.U. type A and 5500 I.U. type B). Approximately 5 hours after the administration, the patient reported a slight improvement in symptoms. Vital signs and ECG were within normal ranges. An objective examination conducted about 8 hours after serum administration already showed a slight improvement in the patient's dysphonia and dysarthria. Hematochemical tests remained essentially negative. About 10 days after serum administration, the patient developed a fever (with a maximum peak of 39°C) and diffuse joint pain. The fever spontaneously resolved in about two days with the sole administration of 1 gram of Paracetamol once a day. However, considering the possibility of a
“serum reaction,” the patient underwent additional tests, including complete blood count, PCR, erythrocyte sedimentation rate (ESR), serum protein electrophoresis, complement factors C3 and C4, serum cryoglobulins, creatinine, and urine analysis. All results were negative, and the aforementioned fever was attributed to a possible self-resolving influenza-like infection. In September, the patient sought our toxicology outpatient clinic, still mildly symptomatic. Despite an improvement in overall flaccid paralysis, diplopia and dysphagia persisted. Ophthalmologic and neurological visits were recommended. The total healing times are long and difficult to quantify. The patient is currently being followed by our outpatient clinic with biannual check-ups.

**Review**

Consulting the following scientific search engines PubMed, MedlinePlus, and Cochrane Library, we read 437 titles of scientific articles using the keyword: Food Health and Botulism. We excluded duplicate articles and selected the articles of greatest interest for our work; we read abstracts and selected 159 articles, of which 86 were read in full; 40 had scientific material suitable for review.

**Clostridium botulinum and mechanism of action**

*Clostridium botulinum* is a Gram-positive, anaerobic bacterium that forms endospores and is responsible for botulism, a severe neuroparalytic disease affecting humans and vertebrate animals. The etiology of botulism lies in the neurotoxin produced by Clostridium. It is a metalloprotease capable of cleaving the proteins of the receptor for the N-ethylmaleimide-sensitive factor (SNARE) attachment protein in nerve terminals, preventing neurotransmitter release and blocking neural transmission to effector muscles. Botulinum neurotoxin (BoNT) is one of the most potent biological agents with the lowest lethal dose of any known natural substance. The lethal dose for humans (LD50) depends on the absorbed quantity. Botulinum toxin falls under biological weapons used for bioterrorism, raising global concerns. *C. botulinum* spores usually pose no threat to people unless they germinate into neurotoxin-producing vegetative cells. Since the healthy human digestive system does not favor spore germination, they normally pass through the body and are excreted without causing harm, except in cases of infant and adult botulism. *Clostridium botulinum* has become one of the most well-known organisms in medical history, not only due to fatal botulism outbreaks but also for the development of pharmaceutical applications of botulinum neurotoxin and its use in cosmetics. The toxicology and pharmacology of Botulinum Neurotoxins (BoNT) are well-studied, but less is known about the physiology of the bacteria responsible for their production.
**Botulism**

Botulinum toxin causes botulism, a severe and potentially fatal neuromuscular disease in humans and animals. The signs and symptoms of botulism evolve over a period ranging from a few hours to several days. Initially, symptoms include mild visual disturbances, and abdominal discomfort, followed by progressive cranial paralysis, which may then be accompanied by bilateral descending flaccid paralysis. In some patients, the maximum extension of neurological signs can range from ptosis alone or mild findings of cranial nerves to bilateral descending flaccid paralysis, involving the respiratory muscles and axial extremities of the cranial nerves. Gastrointestinal symptoms such as nausea and vomiting are more common in individuals affected by foodborne botulism compared to other types of botulism.\(^{19-22}\) Human botulism is characterized by bilateral descending muscle weakness, with symptoms generally starting in the cranial nerves, presenting as blurred or double vision, dry mouth, and difficulty speaking.\(^4\) The classic early physical presentation of botulism can be remembered using the "four Ds": dysarthria, diplopia, dysphonia, and dysphagia. As the neurotoxin spreads, muscle weakness occurs, which if left untreated, can reach the respiratory muscles, causing respiratory failure and death.\(^{23}\) The frequent and infrequent symptoms are summarized in Table 1.

Foodborne botulism is the most common form, caused by the ingestion of food contaminated with preformed Botulinum Neurotoxin (BoNT). Just a few milligrams of contaminated food are sufficient to induce symptoms and cause the patient's death if left untreated.\(^{15}\) Symptoms typically begin within 12-72 hours after consuming contaminated food, depending on the ingested quantity.\(^{12}\) Foodborne botulism is associated with the consumption of inadequately prepared homemade foods and in food factories not adhering to proper procedures, such as preservation techniques like fermentation, canning, or bottling without prior heat treatments. These conditions create the anaerobic environment necessary for spore germination and bacterial growth.\(^4\) The proper implementation of food control measures such as "botulinum cook" (heat treatment at 121 °C for 3 minutes), freezing, and refrigeration (below 4 °C) has significantly reduced the incidence of cases.\(^{25}\)

**Diagnosis and treatment**

Rapid diagnosis of the condition is essential to prevent fatal consequences. When diagnosing botulism, in addition to observing clinical symptoms and patient history, laboratory confirmation is also essential. Samples used in the laboratory include serum, feces, gastric fluid, and food consumed by the symptomatic individual.
The "gold standard" method for identifying botulinum neurotoxin is the mouse bioassay. This method involves inoculating infected serum into mice, with subsequent manifestation of typical botulism symptoms. The mouse bioassay is the only method approved by the FDA for laboratory confirmation of botulism. Real-time PCR is essential for detecting the presence of Clostridium, and identifying the bont A-G genes of toxin-producing species. The neurotoxin is detected using mass spectrometry (Endopep-MS), a highly sensitive and specific method capable of differentiating between serotypes A, B, E, and F of botulinum neurotoxin within hours.

The treatment of botulism is based on symptom control, mechanical respiratory support, and intravenous administration of Botulinum Antitoxin (BAT). There are two types of intravenously administrable botulinum antitoxin: bivalent botulinum antitoxin (7500 I.U. type A and 5500 I.U. type B) or monovalent (8500 I.U. type E). In adults, the dosage is one vial intravenously, potentially repeatable according to clinical evolution. In mild cases, it is possible to survive botulinum poisoning without antidote therapy through supportive patient care, such as mechanical ventilation; however, recovery and hospitalization duration will be prolonged. General laboratory and instrumental tests are useful for differential diagnosis.

There are concerns about clindamycin's ability to block acetylcholine release, and its action may work together with aminoglycosides. Theoretical concerns exist regarding penicillins increasing toxin load through cell lysis and tetracyclines through calcium chelation. However, avoiding the use of these agents in a patient with a comorbid infection must be evaluated against the benefits of treating the comorbid condition. Patients with botulism treated with antimicrobial agents should be observed for any clinical worsening related to antibiotic administration.

**Discussion**

The treatment involves supportive therapy, intubation, and mechanical ventilation when necessary, and the administration of equine-derived botulinum antitoxin. Botulism produces prolonged flaccid paralysis lasting from weeks to months. Death in the acute state is typically the result of early respiratory failure. Timely administration of botulinum antitoxin (within 48 hours of symptom onset and ideally within 24 hours) mitigates the extent and severity of paralysis and the progression to respiratory compromise while also reducing the duration of mechanical ventilation, length of hospital stay in intensive care and mortality. However, it cannot reverse the existing paralysis.

It is a preparation of equine-derived antibodies that bind and neutralize botulinum toxin in the blood that has not yet irreversibly bound to synaptic receptors; the resulting antitoxin-toxin complex is
eliminated from circulation. Botulinum antitoxin is type-specific for the toxin (e.g., antitoxin against type A toxin neutralizes only type A toxin). Botulinum antitoxin is a mixture of antibodies against botulinum toxin types A, B, C, D, E, F, and G, authorized for the treatment of symptomatic botulism in adults and children. The standard dose for adults is one vial, administered by intravenous infusion, repeatable if symptoms persist. The pediatric dose is weight-based. Concentrated protein preparations may provoke immune reactions, including anaphylaxis, in human recipients. BAT data indicate an anaphylaxis rate below 2%; a similar frequency has been calculated for previously used formulations. Other allergic reactions, such as rash, have been observed in six patients and had no consequences. Serum sickness has been reported among subjects receiving antitoxins; the frequency is unknown. Crucial decisions about initial treatment and management of patients with suspected botulism must be made based on the clinical picture. Laboratory confirmation can take several days.

Conclusions

Italy is one of the European countries with the highest incidence of food-borne botulism. This is due to the tradition of preparing canned food nationwide. Foodborne botulism remains a public health problem in Italy, especially in the southern regions. The case described is a clear example of the use of altered food preserves in which the classic symptoms of botulism were observed, characterized by the 4 Ds (Dysarthria, Diplopia, Dysphonia, Dysphagia). In particular, in the specific case the 5th D, dysgeusia, is present, which although not frequently found in the literature, we have detected this further symptom. The patient was treated with both supportive therapy and botulinum antitoxin, which proved to be effective. The case examined highlighted that early anamnestic and clinical assessments remain the main focus in the diagnostic field. In recent years, despite considerable progress in the prevention and early diagnosis of botulism, the rate of intoxication remains high in European countries, especially in Italy.

References


Table 1. Summary of frequent and infrequent symptoms of foodborne botulism.

<table>
<thead>
<tr>
<th>Frequent symptoms</th>
<th>Infrequent symptom</th>
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<tbody>
<tr>
<td>Dysarthria</td>
<td>Asthenia</td>
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<tr>
<td>Dysphagia</td>
<td>General malaise</td>
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<tr>
<td>Diplopia</td>
<td>Constipation</td>
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<tr>
<td>Dysphonia</td>
<td>Headache</td>
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<tr>
<td>Symmetric descending paralysis</td>
<td>Dysgeusia</td>
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<tr>
<td>Eyelid ptosis</td>
<td>Xerostomia</td>
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<tr>
<td></td>
<td>Paresthesias</td>
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<td></td>
<td>Nausea and vomiting</td>
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