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Botulism Beyond Radiologic Ileus

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Abstract

Botulism is a rare disease caused by *Clostridium botulinum* neurotoxin that irreversibly blocks releasing of acetylcholine on presynaptic cholinergic terminal of the autonomic nerves of the neuromuscular junction. Intoxication is most commonly reported in association with consumption of homemade canned or smoked products. Botulism is usually described as a potentially lethal disease, however, because the clinical presentation is dose-dependent, in some cases this disease can have a mild course and poorly defined symptoms. We present clinical findings of a 26 year old male patient who developed constipation, urine retention, blurred vision and weakness, after eating a homemade smoked ham. Our patient had mild form of botulism with no signs of respiratory distress and his treatment included only symptomatic measures. Laboratory diagnosis of botulism was obtained by the mouse bioassay (MBA) test which confirmed the presence of botulinum neurotoxin in the patient's serum. The diagnosis of botulism is frequently missed or delayed in patients with mild clinical presentations because of the sporadic nature of cases and general unfamiliarity with the syndrome.

Keywords: *Clostridium botulinum*; Food-borne botulism; Ileus

Introduction

Botulism is a rare but potentially life-threatening disease caused by accidental or intentional exposure to botulinum toxins. Botulinum neurotoxin (BoNT) is *single*-chain protein of 150 kD molecular weight. It is produced by bacteria of the clostridium genus. *Clostridium neurotoxins* can be distinguished in seven types (A-G). They have different toxicities, act through 3 different intracellular protein targets and exhibit different durations of the effect. Human botulism is primarily related to types A, B, E and rarely to type F. Type A is the most potent type of Botulinum neurotoxins [1]. The toxin acts on the nervous system by inhibiting release of acetylcholine, thus inducing flaccid paralysis. The cellular mechanism of action involves three main steps, binding to the neuron membrane, internalization and intracellular blockade of the release mechanism for neurotransmitters [2]. Toxin binding is noncompetitive and irreversible. Nerve terminals regenerate slowly, allowing for eventual full recovery in 95% of reported cases in the United States [3]. Botulism classically manifests as a distinct clinical syndrome of symmetrical cranial nerve palsies that may be followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death [4]. The most frequent clinical forms of botulism are: food borne botulism, wound botulism and infant botulism. Food borne botulism is caused by consumption of foods contaminated with botulinum neurotoxin (BoNT). *C. botulinum* grows and elaborates toxin only when the food is processed or cured in conditions that include an non-acidic and anaerobic environment. Home-canned foods and smoked meats have long constituted a major source of intoxication in Croatia. Between 2007 and 2011 only 12 cases of food borne botulism were reported to Croatian National Institute of Public Health. Most cases were sporadic and outbreaks were typically small, involving 2 or 3 persons. All patients had a mild clinical manifestation and there was no fatal outcomes [5]. Although rare, botulism outbreaks are considered to be public health emergencies that require rapid recognition to prevent additional cases and to effectively treat identified case-patients. The diagnosis in sporadic cases and even in small outbreaks is frequently missed, however, because botulism is a rare disease with which most clinicians are unfamiliar. The list of potential differential diagnoses is not extensive, and the combination of neurological findings and specific laboratory tests to rule out other toxins and infectious neurological diseases support a presumptive clinical diagnosis pending laboratory confirmation by MBA. Rapid diagnosis, provision of intensive care, and timely therapy with multivalent botulinum antitoxin are the cornerstones of the treatment.

Case Details

A male patient aged 26 was admitted to the hospital with 20-day history of blurry vision, diplopia and constipation. His medical history was uneventful and he was in previously excellent health condition. In the clinical status bilateral ptosis was prominent, the pupils were symmetrically enlarged and a lack of the pupillary light reflex and the accommodation reflex were found, along with a terminal horizontal bilateral nystagmus. He had visited an ophthalmologist three times complaining of vision disturbances without the diagnosis of botulism being considered. His oral mucous membranes were extremely dry and he complained of severe dryness of the mouth and the throat, accompanied by difficult swallowing, which was interpreted as symptomatic of anhydrosis, a clinical manifestation of autonomic nervous system dysfunction. Postural hypotension - another typical symptom of autonomic dysfunction was also present. Blood pressure in the supine position was 140/90 mmHg while in the orthostasis it was 110/60 mmHg. Assessment of the mouth revealed a symmetrical rise of the soft palate during phonation with slight deviation of the uvula from the midline to the right. The function of other cranial nerves was preserved. The sensory system was unaffected and no lack of skeletal muscle strength was found. Deep tendon reflexes were symmetrically diminished and pathological reflexes were not present. Our patient complained of gastrointestinal disturbances, including heartburn,

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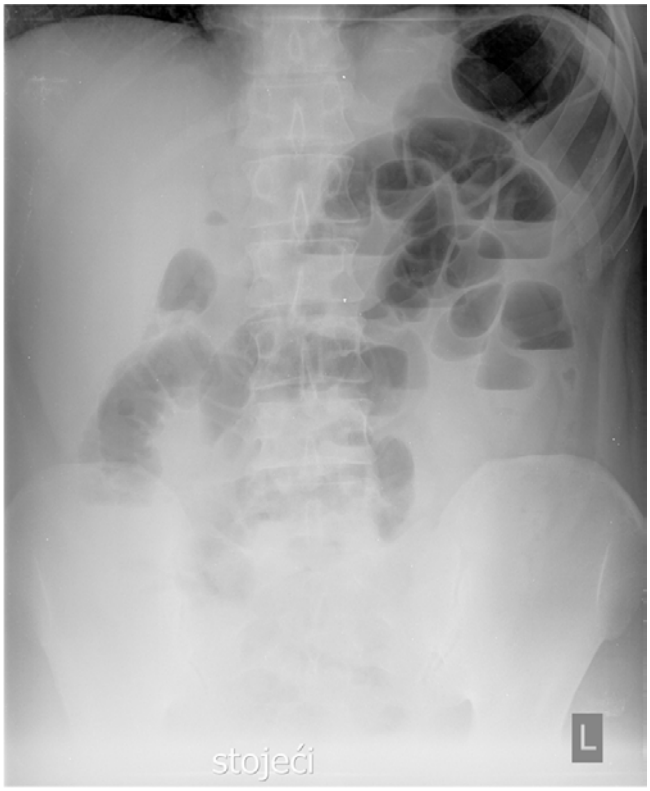

Figure 1: Plain abdominal X-ray.

dyspepsia, vomiting and constipation. He was given proton pump inhibitor and metoclopramid without clinical improvement. Several days before the hospitalization the patient was examined at a surgery department. Plain abdominal radiographs demonstrated numerous air-filled loops of bowel, suggesting ileus (Figure 1). The patient was adminstered enemas, but radiological signs of ileus persisted. Urinary retention symptoms were present and the patient was conscious of suprapubic pressure.

Clinical signs guided us to consider the possibility of botulism. When a detailed case history was taken, the patient recalled that he had eaten home prepared smoked ham 3 weeks ago. The ham reportedly had a specific smell and a strange taste. Three other members of his family were reported to be mildly affected with similar symptoms. Routine laboratory tests were not useful for diagnosis of botulism; in this case revealed only slightly increased C-Reactive Protein (CRP) 16.54 mg/L (normal range less than 5). The suspected food was no longer available to submit for analysis and we were unable to demonstrate BoNT in the specimens of patient's stool. The mouse bioassay (MBA) was used to confirm the tentative clinical diagnosis of botulism by intraperitoneal injection of the patient's serum into mice unprotected and protected with polyvalent botulinum antitoxin, followed by observation of the development of botulism-specific symptoms in the animals. In our patient the disease was related to the serotype B of botulism neurotoxin.

It can be appreciated that our patient had mild form of botulism with no signs of respiratory distress. Because of the significantly delayed diagnosis and relatively minor clinical effects experienced by the patient at the time of referral, therapy with botulinum antitoxin was not indicated. Treatment consisted symptomatic measures and a period of in-hospital monitoring; after seven days he was discharged in good health. At follow-up 3 and 6 months later his neurological examinations were completely normal.

Discussion

Botulism is a rare disease and the diagnosis is easily missed by health care providers who are unfamiliar with its clinical manifestations. In our case correct diagnosis was delayed for about three weeks. Specialty physicians need to be familiar with the symptoms of botulism because its signs concern the nervous system, the organs of sight, and the gastrointestinal system. The differential diagnosis includes Guillain–Barré syndrome, myasthenia gravis, stroke syndromes, Eaton-Lambert syndrome, tick paralysis and intoxication with central nervous system depressants [6]. Infectious diseases should be considered include the viral meningoencephalitis viruses such as West Nile Virus, rabies, etc. Less likely conditions include tetrodotoxin and shellfish poisoning, antimicrobial-associated paralysis, and a host of conditions due to even rarer poisons. A thorough history and meticulous physical examination can effectively eliminate most competing diagnoses.

In our case the disturbances in the autonomic nervous system presented primarily as ocular and visual complaints (bilateral ptosis, mydriasis, absence of direct and consensual pupillary light reflexes, and terminal horizontal bilateral nystagmus), concurrent with extreme dryness of mucous membranes, orthostatic hypotension, urine retention, and gastrointestinal discomfort. In food borne botulism, the gastrointestinal symptoms nausea and vomiting may precede neurological symptoms. Constipation is a nearly universal symptom and radiologic signs of ileus could be seen. Usually, blood pressure in botulism patients is in the normal range, possibly representing equilibrium between vagal blockade and extensive peripheral vasodilatation, both caused by the toxin.

The confirmation of a botulism diagnosis requires demonstration of the neurotoxin in specimens of the patient's serum, gastric secretions, stool or in a food sample. We were unable to demonstrate the toxin in the specimens of the patient's stool, probably because of the time elapsed between the symptoms onset and the sample collection. The gold standard of botulism diagnosis is the mouse bioassay test, the results of which may not be available for 24-48 hours. Toxin serotype can be determined by injecting the patient's serum into mice unprotected and protected with polyvalent botulinum antitoxin and by observing which antitoxin confers protection on the mice. A mouse-bioassay testing of our patient's serum was positive for type B toxin, which is the most frequent botulism serotype seen in the Croatian patients [5]. Because symptoms of botulism toxicity are dose-dependent and may progress rapidly, sometimes waiting for results is not possible or acceptable; in such cases initiation of medical treatment with multivalent botulism antiserum is indicated upon reaching a presumptive clinical diagnosis.

Botulism antitoxin should be given early in the course of illness [7], because it neutralizes only toxin molecules that are yet unbound to nerve endings. Botulism antiserum is of equine origin and use of the antitoxin may be associated with adverse effects including anaphylaxis, other hypersensitivity reactions, and serum sickness [8]. Hyperimmune monovalent antitoxins fail to cross-neutralize other botulinum neurotoxin serotypes indicating a high degree of specificity of each antitoxin for the toxin serotype used during immunization [9]. Trivalent botulinum antitoxin is usually administered in adult patients with botulism and human-derived botulinum immune globulin for the treatment of infant botulism [10]. Because of the patient's stable

condition and the time elapsed between the estimated date of exposure to the contaminated food items and the time of the diagnosis, the administration of antitoxin was not a consideration in this case.

Conclusion

Clinicians should consider botulism as part of their differential diagnosis list for patients presenting with gastrointestinal and neurological symptoms. In botulism cases, diagnosis and appropriate case management depend primarily on history and physical examination, rather than routine laboratory results or rapid specific assays. The definitive diagnosis requires the mouse bioassay test to confirm the clinical diagnosis. The diagnosis in mild form of the disease is frequently missed.

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