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Botulism: An Overlooked Cause of Bulbar Weakness in Intensive Care – A Case Report

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Abstract
Introduction: Botulism is a rare but potentially life-threatening syndrome caused by botulinum neurotoxin. The classic presentation of botulism is the acute onset of bilateral cranial neuropathies associated with symmetric descending weakness. The antitoxin is the main therapeutic option for botulism, in addition to supportive care with intubation and mechanical ventilation when necessary. The outcome is usually favorable, with a slow but full neurological recovery. This case presents a difficult diagnosis of the sporadic form of adult intestinal toxemia, with a delayed diagnosis. ***Case Presentation:*** We report a 64-year-old patient who presented in a confused state with weakness in the limbs, bilateral ptosis, and dysarthria. Because of disease progression with respiratory compromise, the patient was transferred to the intensive care unit (ICU) and intubated. The diagnosis of botulism was eventually confirmed in the stool 46 days after presentation. By the end of follow-up, the patient still received rehabilitation. The outcome was good, except for the concomitant neurodegenerative disorder with the need for institutionalization at a residential care center. ***Conclusion:*** This case report illustrates the difficulties in diagnosing a patient with botulism in the ICU, especially if associated with comorbidities. Delayed diagnosis and misdiagnosis are common because of the rarity of the disease and overlapping signs and symptoms with other neurological diseases. Increasing the awareness of this disease is important to prevent mortality and morbidity.

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Introduction

Botulism is a rare neuroparalytic syndrome caused by botulinum neurotoxins (BoNTs) produced by BoNT-producing clostridia (mostly *Clostridium botulinum*) [1, 2]. Eight antigenically distinguishable exotoxins (A–H) have been described [2, 3]. The BoNT blocks the release of acetylcholine in the synaptic cleft by binding at the presynaptic membrane of the voluntary motor and autonomic nerves [1, 3–5]. Several forms of botulism have been described. The most frequent form in Europe is foodborne botulism, caused by the ingestion of BoNTs preformed in food products by contaminating BoNT-producing Clostridia. These food products are mostly home-canned food and traditional local food. Other forms are infant botulism, wound botulism, iatrogenic botulism, and adult intestinal toxemia botulism [6]. The sporadic form of adult intestinal toxemia botulism is believed to be very rare and is caused by colonization of *C. botulinum* in the intestine [1, 6]. Every type of botulism classically presents as a descending flaccid paralysis, with first the involvement of bulbar muscles. There is normal cognition and normal or depressed reflexes [1, 4]. Patients are at risk for life-threatening complications such as respiratory dysfunction and can have autonomic failure of the cardiovascular, urinary, and gastrointestinal system [1, 6]. If suspected, an electromyography with repetitive nerve stimulation can support the diagnosis. Diagnosis of botulism is confirmed in the laboratory by detecting BoNT in serum, stool and/or food and/or BoNT-producing clostridia in stool, a wound, food, or vomitus. The initial diagnosis and treatment of botulism is based on clinical suspicion since laboratory confirmation can take a few days to complete. Treatment of botulism is limited to administration of botulinum antiserum and supportive care. Gastrointestinal decontamination and the use of probiotics may be a useful [1, 4, 6].

Case Presentation

A 64-year-old man was brought to the emergency department after being found on the floor by his family, unable to stand up. Since he had not been seen for 2 days, he may have been lying there for a while. He was found in his urine and stool with small necrotic wounds on his buttocks. There was no tongue bite.

Since he was living alone and somewhat isolated, his family could not contribute much to the history either, but 4 days prior to admission, he had complained of headache and vertigo and had developed a cough. Family and personal history was negative for neurological diseases. However, he had slowly progressive cognitive problems in the past months. There was no suspicion of alcohol abuse or tabagism. He did not take medication.

At presentation, the patient was confused and lethargic and could not contribute to the history. Vital signs were normal, with the exception of slightly elevated body temperature (37.3°C). On neurologic exam, he had a stiff neck, normal reactive pupils, unconjugated eye movements, bilateral ptosis, facial weakness, bulbar weakness with dysarthria, severe swallowing issues, and weakness in both arms and legs, which was more pronounced on the right. Due to his confusion, it was difficult to determine the exact MRC score of weakness [7]. Reflexes were brisk, without being pathological. There was no obvious autonomic dysfunction, except maybe from the reported vertigo and diarrhea.

Because of respiratory compromise, the patient was transferred to the intensive care unit. There, an epileptic seizure was witnessed with nystagmus, upward eye deviation, and loss of consciousness, for which levetiracetam was started. The seizure was most likely triggered by the infectious state and metabolic dysregulation.

The blood analysis on admission showed leukocytosis and a highly elevated C-reactive protein up to 228.9 mg/L (<0.5). Creatine kinase was elevated up to 5,324 U/L (10–195) with normal renal function. The liver enzymes were slightly increased. Vitamin B12 and folic acid were below detection levels (respectively, <150 ng/L and <2 μg/L) and were substituted. Lactate was 3 mmol/L (0.36–1.25), and glucose was slightly elevated. Chest X-ray showed an infiltrate in the left lower lobe of the lung, which explained the inflammatory parameters in the blood. A CT of the brain and neck with angiography was normal. On electrocardiogram, there was atrial fibrillation. Thiamine and antibiotics were started intravenously.

Further investigations included a lumbar puncture, which showed no cells, normal glucose and slightly elevated protein (56 mg/dL, 15–50), one oligoclonal band (not present in the serum), and a negative polymerase chain reaction. During the first week of hospitalization, he worsened. The patient was not able to move his muscles except for minimal eye opening and horizontal movements of the eyes. The reflexes remained brisk. His respiratory function declined, requiring intubation, and a nasogastric feeding tube was placed because of swallowing issues.

At first, the differential diagnosis for the bulbar and limb weakness was Guillain-Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, or a paraneoplastic/autoimmune syndrome, although none were fitting very well. The concomitant confusion, difficulties to determine the exact pattern of limb weakness (proximal versus distal) and brisk reflexes, made the differential diagnosis challenging. Dual pathology, such as a neurodegenerative disease or vitamin deficiency plus a neuromuscular disease, was considered. Nerve conduction studies and electromyography were performed during his stay in the intensive care unit: nerve conduction studies showed low left distal ulnar nerve compound muscle action potential and absent ulnar sensory action potential, with evidence of conduction slowing across the elbow, but other compound muscle action potentials (of the median, peroneal, and tibial nerve) were normal. Electromyography showed active denervation, and some reduced recruitment in the masseter muscles [8]. Repetitive nerve stimulation (at 3 Hz for 10 stimulations) was normal, and a trial of neostigmine did not alleviate the symptoms. In the second week, the patient slowly showed some improvement in strength and could be extubated. In the third week, when the respiratory infection had resolved, the patient could be transferred to the neurology ward, where rehab was started. He further improved, both physically and mentally, albeit very slowly.

Further investigations during his stay in the hospital included extended serological testing and autoimmune and onconeural antibodies in serum and CSF; all were negative. Metabolic screening, including screening for heavy metals, was normal, but zinc was decreased. Gastroscopy showed ulcerative bulbitis, and colonoscopy was normal. MRI of the brain with gadolinium and MRI full spine showed no abnormalities. FDG-PET scan of the brain revealed mild hypometabolism bilateral frontoparietotemporal. Electroencephalography showed bilateral slowing. Neurofilaments in the CSF were slightly elevated (CSF pNfH 443 pg/mL, <1,038 and CSF NfL 1,414 pg/mL, <1,682), and biomarkers for Alzheimer's disease were normal.

Because of the lack of explanation on the performed investigations and the clear (spontaneous) improvement after a few weeks, the possibility of botulism was considered, with the potential combination with nutritional deficiencies and a neurodegenerative problem. High-frequency repetitive nerve stimulation was performed at 20 Hz for about 100 stimulations since he was not cooperative enough for a short, appropriate voluntary contraction. Longer stimulation was not tolerated by the patient. This showed an increment of >100% (from 0.5 to 1.2 mV) in the musculus abductor digiti minimi and of 40% (from 2.2 to 3.2 mV) in the musculus nasalis. There was no significant increment (from 5.1 to 6 mV) in the musculus trapezius. Since these findings could fit a diagnosis of botulism or Lambert-Eaton

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syndrome, CT chest and laboratory tests for botulism were performed [8]. The first was normal. Serum and fecal samples were both sent to the National Reference Center for Clostridium botulinum, Clostridium perfringens and Clostridium tetani for the detection of BoNT and/or BoNT-producing clostridia. Samples were analyzed using the in vivo reference method and the RT-PCR method (see Discussion). The in vivo reference method confirmed the presence of BoNT in the feces sample, which was taken 46 days after his first presentation to our emergency department. No BoNT was detected in the serum sample, and no BoNT-producing clostridia could be detected in the feces sample. The sample quantity was too low to determine the BoNT type. Based on these results, the diagnosis of botulism was confirmed. A follow-up feces sample taken 74 days after the first day of hospitalization was negative. At that time, he was still experiencing mild swallowing difficulties.

The patient was in the hospital for 2 months, after which he went to a retirement home with physiotherapy once per week. At 3 months of follow-up, the patient had further improved, but some facial weakness persisted. He could walk a couple of kilometers unaided. Neuropsychological testing after discharge showed dementia but without a specific pattern. Articulation normalized, but naming words remained difficult.

Discussion

This case illustrates that the diagnosis of botulism can be challenging when an adequate history or typical clues are lacking. It is nevertheless important to think of this condition and diagnose it as soon as possible since misdiagnosis can compromise appropriate care for the patient.

Botulism is probably underdiagnosed due to its rarity [1]. The incidence of botulism is very low: in Belgium, only 24 laboratory-confirmed cases were reported from 1988 to 2022 based on NRC data. Having a low threshold to suspect botulism is essential for timely diagnosis. It is important to consider botulism in the differential diagnosis when clinical signs are present, such as bulbar weakness and descending weakness of the limbs. However, these signs are not pathognomonic [1]. Other typical features of botulism are nausea, diarrhea or constipation, vomiting, abdominal pain, respiratory difficulty and dizziness, with slight differences between the different forms [9]. The duration of paralysis depends on the toxin type, varying from a few days to several months, with the longest duration seen for types A and B [10]. In the literature, no cases of an affected central nervous system due to botulism have been found. The possibility of botulism should be considered in any patient with acute onset of cranial (motor) nerve palsies [11]. It should thus be considered in patients with suspected myasthenia gravis, Guillain-Barre syndrome, Lambert-Eaton syndrome, and organophosphate exposure [9]. In this case, the lack of a good patient and family history, along with the brisk reflexes, the epileptic seizure, and concomitant cognitive failure, made the diagnosis difficult and delayed the analysis of samples for detection of BoNT and/or BoNT-producing bacteria. The brisk reflexes and cognitive decline might (in part) be explained by the vitamin B12 deficiency, although a clear picture of combined degeneration was lacking clinically and radiologically.

Most often, the diagnosis can be made with the typical clinical presentation and additional technical investigations. During high-frequency RNS, which is usually only done in comatose patients, there is typically an increment after 10–20 s of stimulation at 20–50 Hz. However, this is not pathognomonic for botulism [8, 12]. In Lambert-Eaton syndrome, another presynaptic disorder, an increment is also observed but is often more than 200%, compared to botulism, where it is less than 200% [8]. In botulism, there is no post-activation exhaustion [8].

Many methods have been developed for the detection of BoNTs [13, 14]. In Belgium, the NRC for *C. botulinum*, *C. perfringens*, and *C. tetani* performs laboratory confirmation of botulism using different methods: the mouse bioassay and the PCR method. The detection and typing of BoNT and BoNT-producing clostridia is performed by using a mouse bioassay, which is considered the gold standard method and very sensitive for detection of botulinum toxin [15]. Stool extract, serum, or culture extract is injected intraperitoneally into 2 mice, after which the mice are observed for 4 days for botulism symptoms [13]. Typing can be performed by injecting a mixture of extract together with antitoxin(s). The analysis is considered positive only if no symptoms are observed in mice injected with the sample-antitoxin mixture and symptoms are observed in mice injected with sample only. Additionally, the BoNT-encoding genes can be detected by performing PCR on an enrichment culture.

The time of sampling is critical for successful detection of BoNT in human serum and stool [6]. The sooner the analysis of the toxin can be performed, the lower the chance of false-negative results. In this case, neurotoxins were detected only in the fecal sample 46 days after first presentation. This could hint toward the rare form of adult intestinal toxemia, which has already been reported in previously healthy individuals without a history of gastrointestinal problems. Further indications for adult intestinal toxemia are the persistence of symptoms and the presence of detectable BoNT in stool, which is undetectable in serum [6]. Nonetheless, the lack of detection of BoNT-producing clostridia in the stool sample is surprising. Because of the cognitive dysfunction, the patient was not able to recollect any memory of suspicious food. The differentiation between foodborne botulism and the rare form of adult intestinal toxemia remains a challenge [6]. Even though the patient was found to have necrotizing wounds, wound botulism can be ruled out since BoNT was detected in the stool.

Any patient with clinical signs, symptoms, or a history suspicious for botulism should be hospitalized and monitored for progressive weakness and signs of respiratory failure that warrant intubation. If diagnosis is made early after ingestion, there are two approaches for treatment. One is gastrointestinal decontamination to remove the spores and toxins and to prevent the uptake of the toxins into the blood and the binding to the presynaptic receptors of the neuromuscular junction in foodborne botulism. Another type of treatment is the administration of the antitoxin (trivalent, pentavalent, or heptavalent antitoxin) to neutralize the freely circulating toxins and thus inhibit binding of the toxin to neuronal receptors. Treatment with decontamination of the toxin is proven effective when given early, resulting in a shorter hospitalization duration [1]. In the case of adult intestinal toxemia, the use of probiotics to promote the return of a healthy gut microbiome can be eligible [6]. There are no current guidelines in the literature on this topic. In this case, the antitoxin or probiotics were not given since diagnosis was only made when the patient had already significantly improved. Further treatment is supportive, such as ventilation or antibiotics if needed [1, 4]. The prognosis is highly variable. In the literature, with early administration of the antitoxin (within the first 24–72 h), the mortality rate is reduced, as well as the disease progression, the need for ventilatory support, and the duration of hospitalization [9].

In summary, by publishing this case of hidden botulism, we want to raise awareness about the possible diagnosis of botulism in any patient presenting with subacute, fast progressing bulbar or descending weakness, even in the absence of clear indications such as suspicious food, and especially when typical electroneuromyography findings for other differential diagnoses are lacking. High-frequency repetitive nerve stimulation and testing of the BoNT in both stool and serum and BoNT-producing clostridia in stool can lead to a timely diagnosis, which is of therapeutic and prognostic importance to the patient. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541500).

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case. A copy of the written consent is available for review in the patient's medical documents. Ethical approval is not required for the description of this case report in accordance with local or national guidelines. All animal experiments were approved by the Ethics Commission of Sciensano (ethical file number 20190708-01).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.A. was responsible for drafting the manuscript, supported by S.L. and H.P. S.H. was responsible for evaluation of the manuscript and the intellectual clinical content. J.L., A.V., M.M., and T.V.N. were responsible for the evaluation of the manuscript and intellectual content focusing on the tests for laboratory confirmation of botulism. All authors have read and approved the manuscript. S.H. is a member of the European Reference Network for Neuromuscular Diseases.

Data Availability Statement

All data generated or analyzed during the writing of this case report are included in this article. Further inquiries can be directed to the corresponding author.

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