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Wound Botulism in Black Tar Heroin Injecting Users: A Case Series

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Abstract

The incidence of wound botulism in injection drug users has increased since the introduction of black tar heroin. Many species of the *Clostridium* genus, most commonly *Clostridium botulinum, Clostridium baratii*, and *Clostridium butyricum*, have been associated with wound botulism. Patients often present with progressive bulbar weakness, including dysphagia, cranial nerve palsies, and loss of speech, in addition to symmetrical descending weakness of the upper extremities that may progress to the chest and lower extremities. In this article, we present 3 cases of wound botulism, in which the patients presented with bulbar weakness and were treated with botulism antitoxin heptavalent. The time to antitoxin administration and its effect on the patients' clinical courses is compared.

Keywords

wound botulism, botulism heptavalent antitoxin, *Clostridium botulinum*, injection drug users

Introduction

According to the Centers for Disease Control and Prevention (CDC), approximately 30 people are diagnosed with wound botulism every year in the United States. Wound botulism results from the introduction of *Clostridium* spores into a wound, leading to further multiplication, germination, in situ synthesis, and secretion of toxin under anaerobic conditions.[1] Wound botulism case associated with injection drugs was first reported in 1982 in New York City. Contamination of *Clostridium botulinum* into black tar heroin (BTH) could occur during several processes that include production, transportation, cross-contamination with chemicals and fillers, or during its preparation for use.[2] In 2017, 17 out of 19 laboratory-confirmed cases of wound botulism were associated with injection drug users (IDUs).[3] The majority of cases are associated with BTH and specific routes of injection, particularly subcutaneously known as "skin popping" or intramuscularly known as "muscle popping."[4] Botulinum neurotoxins (BoNTs) are considered to be one of the most toxic substances known, with only serotypes A, B, E, and F associated with human botulism. The toxins block the release of acetylcholine (ACh) at peripheral cholinergic nerve terminals of the skeletal and autonomic nervous systems and cause paralysis.[5] If left untreated, respiratory failure can lead to asphyxiation. Botulism heptavalent antitoxin (HBAT) has shown to be effective in all forms of botulism and should be promptly administered in clinically suspected patients. Prior studies reported 93% of all botulism-confirmed patients treated with HBAT survived.[6] According to the 2017 CDC National Botulism Surveillance Summary, there have been no deaths associated with confirmed and suspected cases of wound botulism. Wound botulism should be one of the top differential diagnoses in IDUs presenting with any associated symptoms.

Case Presentations

Case 1

A 29-year-old female with a history of hepatitis C and a history of heroin abuse presented to the emergency department with dysphagia, blurred vision, and generalized weakness. On presentation, the patient had multiple ophthalmic

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symptoms, including mydriasis, bilateral ptosis, ophthalmoplegia, and decreased visual acuity bilaterally with end-position eye nystagmus. Neurologic examination demonstrated reduced neck flexion and extension, facial and hypoglossal nerve weakness, and areflexia in upper extremities bilaterally with unremarkable motor examination. Cervical magnetic resonance imaging (MRI) and computed tomography (CT) of neck were negative for intracranial pathology. Lumbar puncture revealed white blood cell count 0 cells/mm^3, protein 26 mg/dL, glucose 43 mg/dL, negative oligoclonal bands, and myelin basic protein <2 ng/mL. Multiple sclerosis was ruled out in the patient given her reproductive age. The patient admitted to injecting BTH 12 to 18 hours prior to admission. A clinical diagnosis of wound botulism was made, and HBAT was administered within 36 hours of admission in addition to appropriate antibiotics. The patient did not require ventilation and had a full resolution of her symptoms within 10 days. Unfortunately, a laboratory confirmation of wound botulism could not be obtained as the specimen was rejected due to the inability to meet the CDC requirements.

Case 2

A 51-year-old homeless male with a history of hepatitis C, long-standing history of intravenous heroin use, and methamphetamine abuse presented to the emergency department with 1 day of dysarthria and left-sided weakness, numbness, and decreased sensation. The patient reported the onset of his symptoms after submuscular injection of heroin with the use of a dirty cotton ball. Given the patient's neurologic examination, the patient was initially treated for a suspected cerebral vascular accident. Within the first 48 hours of admission, the patient began to experience dysphagia and failed swallow evaluations. Imaging, including MRI of brain with and without contrast, CT scan of brain with and without contrast, and CT angiography of head and neck were negative for intracranial pathology. Approximately 36 hours after admission, the patient experienced continued dysphagia and dysarthria, in addition to the development of bilateral ptosis, hypophonic voice, and facial and hypoglossal nerve weakness. The patient had significant neck flexion and extension weakness and proximal arm and leg weakness with hypoactive reflexes. A lumbar puncture was unremarkable with protein and glucose levels in the normal range at 37 mg/dL and 51 mg/dL, respectively. The patient deteriorated rapidly and was intubated. After HBAT administration on hospital day 4, the patient underwent extensive wound debridement and received antibiotic therapy (Figure 1). Prior to discharge on hospital day 14, the patient reported intramuscular injection of BTH into his left lower extremity wounds before admission (Figure 2). Approximately 3 weeks later, the CDC confirmed the serologic diagnosis of botulism.

Figure 1. Postoperative wound debridement of the left lower extremity.

Case 3

A 53-year-old male with a history of hepatitis C, polysubstance abuse, chronic obstructive pulmonary disease, and recent diagnosis of nasopharyngeal carcinoma presented to the emergency department with approximately 3 days of upper and lower extremities weakness, fatigue, dysphagia, and dysarthria. On presentation, he was unable to walk and lift his upper extremities above the shoulder level. Brain MRI and CT scan of the spine, brain, chest, abdomen, and pelvis were unremarkable. Neurological examination revealed bilateral mydriasis and hypoglossal nerve weakness. The patient experienced neck flexion and extension weakness in addition to bilateral upper and lower extremity weakness and upper extremity areflexia. Lumbar puncture revealed glucose 78 mg/dL and a normal level protein of 54 mg/dL. Given his recent diagnosis of nasopharyngeal carcinoma, paraneoplastic syndrome and dermatomyositis was also considered. However, lack of elevated creatine kinase and associated skin findings made the diagnosis less likely. He ultimately admitted to injection of BTH in his left proximal lower extremity 5 days prior to admission. The patient experienced progressive neurologic deficit and within 24 hours of admission developed respiratory failure, requiring intubation. A clinical diagnosis of wound botulism was made, and on day 5 of admission, HBAT was administered. The patient also underwent incision and drainage of the left thigh abscesses, most likely the source of botulism (Figure 3). Unfortunately, a wound botulism laboratory confirmation could not be established since the initial

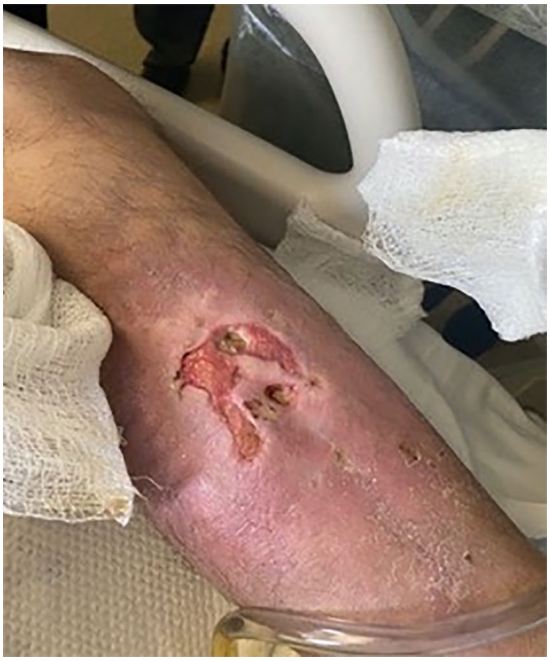

Figure 2. Site of intramuscular heroin injection. Chronic ulcerative lesion on the medial aspect of the patient's left lower extremity with surrounding erythema.

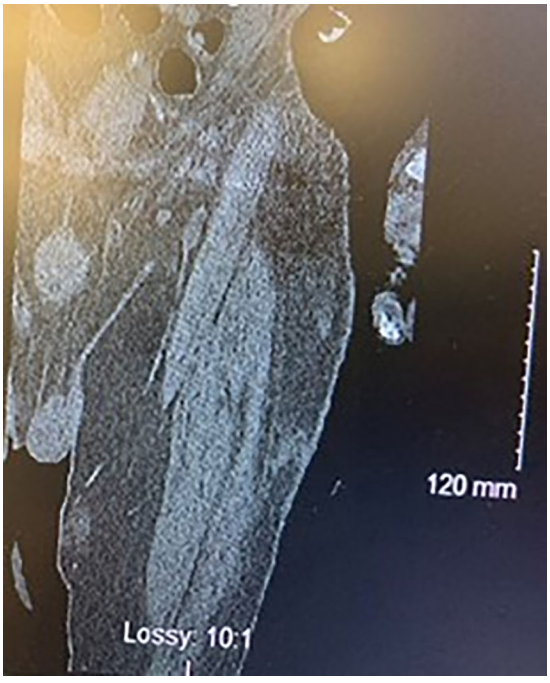

Figure 3. Computed tomography scan of lower extremity showing left lateral thigh abscesses.

specimen was accidentally discarded by the laboratory and it was already late to obtain the second sample. The patient required prolonged intubation ultimately requiring a tracheostomy. After a 19-day hospital stay, the patient was discharged to a long-term acute care facility for long-term weaning of ventilation and rehabilitation.

Discussion

Wound botulism is clinically defined as acute descending paralysis with cranial nerve palsies, including diplopia, ptosis, dysarthria, or dysphagia, and a visible wound on physical examination or a recent history of injection drug use.[7] Wound botulism is the fifth most common form of botulism after foodborne, childhood, enteric infectious, and inhaled botulism.[8] In wound botulism, BoNT enters the bloodstream and targets the SNARE polypeptide complex (SNAP-25, VAMP, or syntaxin). SNARE proteins are required for fusion of ACh-containing vesicles with the presynaptic membrane. The release of ACh into the neuromuscular junctions is inhibited when the SNARE proteins are blocked by BoNT, resulting in flaccid paralysis.[9] However, various factors including spore exposure time, time to germination, and how quickly the resulting colonies elaborate sufficient BoNT govern the onset of wound botulism after the toxin reaches the bloodstream. Additionally, presentations vary widely with bacterial species, toxin serotype, and the patient's age and immunological status.[9] BTH is a dark, gummy form of drug primarily produced in Mexico. BTH has a high possibility of contamination since it often contains adulterants. Unsanitary conditions during both production and transportation can expose the drug to soil and other contaminants containing *Clostridium botulinum* spores. During preparation, the spores in BTH are not destroyed with heat.[10] Skin popping or muscle popping, the acts of subcutaneous and intramuscular drug injection, can also create a nidus of necrotic tissue where anaerobic BoNT can easily germinate.[10] Homeless IDUs may have a higher likelihood of coming in direct contact with the environmental soil and therefore a higher likelihood of developing wound botulism.

Heptavalent botulism antitoxin is an equine-derived antitoxin approved for the treatment of symptomatic botulism following documented or suspected botulism exposure.[5] However, it is important to note that the administration of HBAT does not result in immediate cessation in the clinical progression. The probable explanation for this phenomenon is that the duration of the recovery phase can range from several days to many months depending on the severity of the disease, serotype involved, and timing of treatment.[5] Antitoxin/toxin ratios of at least 30:1 is required for the successful toxin neutralization.[11] On administration, HBAT binds to BoNT and sequesters it in the liver and spleen, eventually enhancing the elimination and limiting the total number of SNARE complexes affected by the toxin.[9] Administration of HBAT is imperative to prevent respiratory failure.[12] Wound debridement is recommended after

antitoxin administration in an attempt to neutralize toxin entering the bloodstream.[12] Early HBAT administration and wound debridement is recommended to decrease the length of stay in intensive care units.[4]

While there are confounding variables such as age, sex, and immunological status, all 3 patients presented with similar symptoms of bulbar weakness and a history of BTH injection. The time interval between the last BTH injection and the presentation to the hospital should also be considered. According to the CDC, symptoms of wound botulism are not immediate and usually appear several days after injection causing diagnostic delays. The patient in Case 1 reported the last injection less than 20 hours prior to presentation, whereas the patients in Case 2 and Case 3 reported the last injection approximately 24 hours and 120 hours prior, respectively. The patient in Case 3, who had the longest time interval between the last BTH injection and the hospital presentation, had more progressive neurologic symptoms on presentation compared with the patients in Case 1 and Case 2.

As a notifiable disease, all suspected botulism cases require an emergent consultation with the state health department and a formal request for HBAT from CDC Quarantine Stations located at 20 ports of entry and land-border crossings across the United States. A diagnosis of botulism requires mandatory specialized testing by the state public health department's laboratory prior to submitting specimens to the CDC. However, confirmation can take days to result and should not delay treatment. Acceptable samples to diagnose wound botulism include debrided tissue, wound swab, at least 10 g feces, and at least 5 mL of serum without anticoagulant obtained prior to antitoxin treatment. Specimens should be refrigerated between 2 and 8 °C immediately following collection and shipped with cold packs. Labeling should include 2 patient identifiers in addition to biological hazard labeling (UN3373 biological substance, Category B). The clinician should be aware of delicacy and timeliness of the collection and process. We lost the opportunity in 2 of our cases. After shipping the specimen, an email should be sent to the CDC Point of Care with appropriate tracking information. Final written reports are available within approximately 12 weeks.

The timely administration of HBAT is critical in determining the clinical progression and recovery time of patients with wound botulism. Delayed treatment results in toxins entering the increasing numbers of neuronal cell, thus reducing the HBAT efficacy. Treatment involves a multidisciplinary team involving laboratory technicians, pharmacists, neurologists, intensivists, and internists. The patients received HBAT at varying times during their hospital course. The time to antitoxin administration and patients' clinical courses differed greatly. The patient in Case 1 received HBAT within 36 hours of admission and had the least severe disease progression as well as the quickest recovery. The patient in Case 2 received HBAT within 96 hours of admission and required intubation during his 14-day hospital stay. The patient in Case 3 received HBAT within 120 hours of admission and had the most severe disease progression and the longest length of hospital stay requiring prolonged intubation and tracheostomy. Although the severity of the presenting symptoms differed among the patients due to several factors, particularly the time elapsed since the last drug injection, the initial presentation of bulbar weakness was consistent.

The differential diagnosis of wound botulism often includes other conditions such as the Miller Fisher variant of Guillain-Barré syndrome, myasthenia gravis, and brainstem strokes.[13] However, a history of injection drug use and signs of infection around injection sites further increase the suspicion of wound botulism and the need for prompt treatment with HBAT. As seen in the reported cases, the timely administration of HBAT may significantly lessen the duration and severity of wound botulism. With the rise of cases in California and the western United States, it is crucial to report cases to local health departments in attempts to monitor for similar cases and potential outbreaks. Knowledge about the prevalence of wound botulism and its known areas of distribution will allow for better management of future cases from public health authorities, shelter personnel, and physicians.[14]

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Ethics Approval

Ethical approval to report this case was obtained from IRB Kern Medical with IRB #21010.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because of the patient's altered mental status. The patient's age and other personal identifiers were anonymized for this case report.

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