WOUND BOTULISM ACQUIRED IN THE AMAZONIAN RAIN FOREST OF ECUADOR

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Abstract. Wound botulism results from colonization of a contaminated wound by Clostridium botulinum and the anaerobic in situ production of a potent neurotoxin. Between 1943, when wound botulism was first recognized, and 1990, 47 laboratory-confirmed cases, mostly trauma-associated, were reported in the United States. Since 1990, wound botulism associated with injection drug use emerged as the leading cause of wound botulism in the United States; 210 of 217 cases reported to the Centers for Disease Control and Prevention between 1990 and 2002 were associated with drug injection. Despite the worldwide distribution of Clostridium botulinum, wound botulism has been reported only twice outside the United States, Europe, and Australia. However, wound botulism may go undiagnosed and untreated in many countries. We report two cases, both with type A toxin, from the Ecuadorian rain forest. Prompt clinical recognition, supportive care, and administration of trivalent equine botulinum antitoxin were life-saving.

INTRODUCTION

Botulism is a neuroparalytic illness caused by the most potent neurotoxins known, which are elaborated by Clostridium botulinum. Clinically, the disease is characterized by cranial nerve palsies and symmetric, descending, flaccid paralysis of the motor and autonomic nerves. All botulinum neurotoxins act by blocking the release of the neurotransmitter acetylcholine at the neuromuscular junction. Food-born botulism results from ingestion of neurotoxin (type A, B, E, and, rarely, F). Infant botulism results from intestinal colonization by C. botulinum and toxin production, whereas wound botulism results from wound colonization by C. botulinum and toxin production. The resulting paralysis may last weeks to months. The foundations of treatment are meticulous intensive care, with ventilatory support when required, and early administration of botulinum antitoxin to neutralize circulating toxin before binding and uptake by neurons. Debridement of infected wounds to eliminate the anaerobic milieu that supports the growth of C. botulinum is required in wound botulism.

The syndrome of wound botulism was first recognized in 1943. Through 1990, only 47 laboratory-confirmed cases of wound botulism were reported in the United States. Most occurred in young men and were related to trauma. The wounds usually were deep and contained avascular areas, and often were associated with compound fractures or crush injuries. Since 1990, the number of wound botulism cases reported in the United States has increased dramatically; almost all have been associated with injection of black tar heroin in residents of California. A few cases have been reported in association with parasinal sinus infections from cocaine sniffing. Case reports of drug-associated wound botulism from Europe followed. Despite the worldwide distribution of C. botulinum spores in soil and the practice of drug injection in other regions of the world, reports of wound botulism from outside of North America, Europe, and Australia are exceedingly rare. We report two cases of trauma-associated wound botulism that occurred within 10 months in the Ecuadorian jungle. In both cases, appropriate clinical care and provision of antitoxin, facilitated by e-mail communication, were life-saving.

Case 1. In January 2001, a 28-year-old ecologist was impaled on a stick. He pulled a piece of wood out of his right lower neck. A few days later, he came to a local clinic complaining of pain and creamy drainage from the wound. He was treated with ampicillin and analgesics. Twelve days after the injury, he developed fever, malaise, difficulty swallowing, and progressive shortness of breath. His family brought him to the hospital for evaluation.

On examination, he was alert, afebrile, and in moderate distress with rapid shallow respirations. He required support to maintain his head erect. He had bilateral ptosis, impaired extraocular movements, and small pupils (2 mm) with poor reaction to light. His mouth was dry and his speech muted and slurred. He swallowed with difficulty. A 2-cm puncture wound was noted on the right supraclavicular neck; palpation produced pain, crepitus, and discharge of serosanguinous fluid. Traction applied to the skin suggested a subcutaneous foreign body, which was confirmed by computed tomography (Figure 1a). The patient could not stand, and lower extremity strength was moderately limited (3 of 5). Sensory examination and reflexes were normal; there was no meningismus. A gram stain of the drainage from the neck showed gram-positive cocci in chains and gram-negative diplococci and rods. The white blood cell count, hemoglobin level, and biochemical profile were normal. An arterial blood gas showed a pH of 7.48, Pco₂ of 33.6 mm of Hg, Po₂ of 50.7 mm of Hg, and HCO₃⁻ concentration of 24.8 mmol/L; the O₂ saturation was 88.9% on room air.

The patient was intubated and admitted to an intermediate care ward where he received intravenous penicillin and ciprofloxacin. The next day, a fragment of wood was removed surgically from the soft tissue of the neck (Figure 1b). Cultures obtained in surgery grew Escherichia coli, Proteus mirabilis, group G streptococci, and Enterococcus faecalis. On day six of his illness, the patient could not be weaned from the ventilator and his physician called the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia for clinical consultation. Subsequent efforts were coordinated by e-
mail. Botulinum antitoxin was dispatched by airplane, and on day 7 the patient received 7,500 IU of type A antitoxin, 5,500 IU of type B antitoxin, and 8,500 IU of type E antitoxin intravenously after skin testing for sensitivity to horse serum. The patient remained afebrile and was extubated after 11 days of mechanical ventilation, but he had an episode of aspiration pneumonia before his final discharge one month after onset of illness.

Samples of serum, stool, and the piece of wood removed from the patient’s neck were frozen and sent to CDC. Type A botulinum toxin was detected in the anaerobic culture of the wood fragment but not in serum or fecal specimens.

Case 2. In August 2001, a 19-year-old construction worker in the eastern rain forest of Ecuador was well until he stepped on a nail. Three days later, he came to a local hospital with cellulitis of the foot and received tetanus toxoid and oral antimicrobial medication. The next day he returned to the hospital with fever and chills; he was admitted and was treated with oxacillin, gentamicin, and metronidazole. He then developed generalized malaise, non-specific abdominal pain, nausea, blurred vision, dysphagia, and progressive respiratory insufficiency nine days after his injury. After a respiratory arrest, he was intubated and transferred to a regional referral hospital where he required mechanical ventilation. On examination, he was alert and afebrile, with complete paralysis of extraocular, facial, and neck muscles. His distal arm strength was diminished (4 of 5), and he had a fluctuant wound on the dorsal side of his left foot (Figure 2). He received penicillin, ceftriaxone, oxacillin, and metronidazole and underwent surgical debridement of the wound. Botulism was suspected, and the patient was transferred to a tertiary care hospital in the capital city to the care of the physician who diagnosed case 1. Samples of serum, stool, and pus from the wound were frozen and sent to CDC. Antitoxin (anti-A, B, and E) was urgently dispatched from CDC and administered on the third day after respiratory arrest. Botulinum toxin type A was detected in the pus, but not in serum or fecal specimens. The patient required mechanical ventilation for 50 days and was in hospital for 2 months, but recovered fully.

MATERIALS AND METHODS

We searched Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Biosis databases to identify reports of wound botulism published between 1951 and 2003 from outside the United States, Europe, and Australia.

RESULTS

We identified one case of wound botulism from China (a 25-year-old woman with a scalp laceration sustained in a construction site explosion 12 days before onset) published in English and one case from Argentina published in Spanish (a 34-year-old man with a traumatic amputation of the left foot and extensive soft tissue damage secondary to injury with a farm rake).

DISCUSSION

We report two cases of trauma-associated, laboratory-confirmed wound botulism that were treated by the same physician within one year in Ecuador. To our knowledge, only two wound botulism cases had been previously reported outside the United States, western Europe, and Australia. Our findings suggest that wound botulism may be vastly underreported in the developing world. Although toxin was not detected in the serum of either patient, toxigenic C. botulinum was cultured from a foreign body in case 1 and from pus in case 2 and the clinical syndromes were classic. Toxin may not have been detected in serum because of diminished production by a lower bacterial load of C. botulinum in the wounds at the time serum was collected.

Wound botulism was first recognized in 1943; CDC initiated national surveillance in the United States two decades later. Merson and Dowell summarized the first 3 decades in 1973. Of nine reported cases, six were laboratory-confirmed (all type A). The median age was 15 years. Seven were males; three had been injured in an open field, and four by a metal object. In all cases, the wound was on an extremity, and in four the wound was purulent. Symptoms followed an incubation period of 4–14 days. Four (44%) of the nine died; all
three diagnosed pre-mortem received antitoxin. MacDonald and others reviewed the next 16 laboratory-confirmed cases of wound botulism in the United States (1976–1984).\textsuperscript{20} Type A toxin caused 11 cases and type B caused 5 cases. The median incubation period was 10 days. The first two cases of botulism associated with intravenous drug use were reported in this group. In 1993, Weber and others reviewed all 47 cases of laboratory-confirmed wound botulism reported to CDC between 1951 and 1990.\textsuperscript{3} Cases were still mostly young (median age = 27 years) males. A geographic pattern emerged; type A toxin caused disease in 30 (86%) patients from states west of the Mississippi River, whereas type B did in 8 of 10 of patients from eastern states. The mean incubation time was 8 days (range = 4–18 days). Thirty-six patients had wounds on the extremities; seven reported intravenous drug use. Among patients requiring mechanical ventilation, the mean duration was 54 days.

In the 1990s, the epidemiology of wound botulism changed dramatically.\textsuperscript{6,7} Cases associated with trauma nearly disappeared and were replaced by an epidemic of wound botulism associated with injection drug use, specifically “skin popping” with black tar heroin. Three-fourths of the cases in the United States were reported from California.\textsuperscript{7,21–24} Since injection of heroin has been practiced in the western United States for decades, presumably some change in heroin production or processing that permitted contamination with \textit{C. botulinum} spores had been introduced. Hispanics have been involved disproportionately and women increasingly so.\textsuperscript{5,7} Cases outside the United States have been reported most frequently from the United Kingdom and occasionally elsewhere in Europe and in Australia.\textsuperscript{11–17,25}

And what of the less-developed world? Given the wide distribution of spores of \textit{C. botulinum} in soil and marine environments, the frequency of traumatic injury in impoverished areas, and the presumed occurrence of injection drug use as well, cases of wound botulism would be expected to occur globally. However, an extensive literature search disclosed only one case of wound botulism in China and another in Argentina.\textsuperscript{18,19} Under-recognition, under-reporting, or both are plausible explanations.

Familiarity with the distinctive clinical syndrome of cranial nerve palsies followed by descending paralysis in a patient with a wound or a history of injection drug use will facilitate diagnosis and treatment. The differential diagnosis includes Guillain-Barré syndrome, organophosphate poisoning and other intoxications, myasthenia gravis, cerebrovascular accident of the brainstem, tumor, encephalitis, Eaton-Lambert syndrome,\textsuperscript{7} and other, rarer entities. Careful history and neurologic examination will help narrow the diagnosis. Normal protein levels in the spinal fluid help distinguish botulism from atypical Guillain-Barré syndrome cases. The wound may or may not appear infected. Except when associated with co-infected purulent wounds, fever is absent. Unilateral sensory changes can result from trauma, but botulinum toxin does not cause sensory changes. Gastrointestinal symptoms do not occur in wound botulism, in contrast to food-borne botulism.\textsuperscript{25} The median incubation period is longer (7 days, range = 4–14 days) in wound botulism\textsuperscript{3} than in food-borne botulism (median 1 day, range 6 hours to 8 days)\textsuperscript{26} because \textit{C. botulinum} must multiply within the wound to elaborate sufficient toxin to cause symptoms. In injection drug users, however, the incubation period is difficult to determine because chronic injection wounds may be present, or the duration of a small subcutaneous wound may be unknown. Standard blood work and radiologic studies are not useful in diagnosing botulism. Brain imaging may help rule out rare stroke syndromes that produce non-lateralizing symptoms. The edrophonium (Tensilon) test helps diagnose myasthenia gravis. In experienced hands, electromyography can be an exceedingly helpful adjunct to diagnosis. In affected muscles, findings consistent with neuromuscular junction blockade, normal axonal conduction, and potentiation with rapid repetitive stimulation are indicative of botulism. Rapid, repetitive stimulation (> 20 Hz) by electromyography provokes facilitation and is specific to botulism and the Eaton-Lambert syndrome.\textsuperscript{21,27–30}

Treatment with botulinum antitoxin should be based on clinical impression and undertaken immediately because the standard laboratory test, the mouse bioassay, may require several days and is not available in many countries. Although laboratory confirmation is highly desirable, the inherent delay precludes waiting for results before making the decision to treat with antitoxin. Laboratory confirmation of wound botulism requires detecting botulinum toxin in the patient’s serum, culture of the infected wound, or both. Assays for botulinum toxins have been described.\textsuperscript{31} A mouse bioassay with toxin neutralization is done at CDC.\textsuperscript{32} Debrided tissue should be cultured anaerobically.

Treatment of wound botulism is similar to that of food-borne botulism. Respiratory failure may require prolonged ventilatory support, as was required in our patients. Botulinum antitoxin should be administered as soon as possible, immediately after collection of blood and wound samples for toxin analysis. Prompt administration halts progression of paralysis, but does not reverse it.\textsuperscript{33} A recent series\textsuperscript{34} noted that prompt delivery of antitoxin may be important; rapid recovery occurred in two patients who received antitoxin within four days of onset of symptoms, whereas a poor outcome was seen in four who received antitoxin after eight days of symptoms and one who did not receive it at all. A retrospective analysis of 20 patients with injection drug–associated wound botulism suggested that antitoxin administration within 12 hours may drastically diminish the duration of ventilatory support required (median = 11 days versus 54 days for those who did not receive antitoxin within 12 hours).\textsuperscript{35} Early tracheostomy may also improve outcome. Thorough debridement, drainage, and irrigation of the wound are required; adjunctive antimicrobial therapy with penicillin, or other agents depending on culture results, is indicated only if the wound is superinfected.

Since no licensed vaccine against botulism exists and \textit{C. botulinum} spores are ubiquitous, prevention of mortality from wound botulism requires meticulous intensive care, prompt diagnosis, and early administration of antitoxin. Wound botulism should be considered in patients with a wound or history of injection drug use and cranial nerve palsies followed by descending paralysis. Rapid acquisition of appropriate specimens for diagnosis and provision of antitoxin is imperative.

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