



“I’m Seeing Double”

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A 43-year-old woman presented after a week of upper respiratory tract infection symptoms. She had been evaluated the week prior and treated with cephalexin. Since her initial evaluation she had complained of continued dry mouth, sore throat, diplopia, and episodes of slurred speech. On evaluation in a California emergency department, the patient complained of diplopia and trouble swallowing. She was noted to be “sleepy”, with drooping eyelids, but she was able to answer all questions appropriately and did not appear intoxicated. On careful questioning, the patient admitted to being an injection drug abuser. Past medical history was non-contributory. She used no medications and denied any surgical history. She had no history of drug allergies and family history was negative.

Physical exam demonstrated a woman sitting on a gurney with her eyes partially closed. She answered all questions without any sign of confusion. Airway was open, but the patient had to repeatedly clear her throat. Pulse was 105, BP 125/90 lying and 93/70 standing, and respiratory rate was 18. Temperature was 37.1 and oxygen saturation was 98% on room air. The patient’s pupils were equal at 7mm and reacted to light. Bilateral ptosis was noted. Her soft palate was symmetrical. A mild facial asymmetry. Upper extremity strength was noted to be 4+/5, while lower extremities were 5/5. Deep tendon reflexes were symmetrically decreased.

Key Clinical Questions

When should botulism be considered highly in the differential of weakness?

When is the optimal timing of imaging, procedures, and therapy in patient with suspected botulism infection?

What empiric therapy should be initiated in patients with suspected wound botulism?

Key Learning Points

- The initial signs of botulism can mimic other disease processes; a history of intravenous drug abuse and a physical exam consistent with descending paralysis should alert the emergency physician to this diagnosis.
- Early testing with electromyelography (EMG), lumbar puncture and airway management can aid in the rapid diagnosis and treatment of botulism.
- Whenever botulism is highly suspected, treatment with antitoxin should not be delayed for confirmatory testing, along with penicillin therapy.

Wound Botulism

Background, Risk Factors and Epidemiology

Wound botulism was first described in 1951 by Merson and McDowell who reported a child with symptoms compatible with botulism after having an open fracture of her leg. Wound botulism attributable to drug injection was first reported in 1982 in New York City. Since then, three-fourths of wound botulism cases have come from California. From 1951 to 1998, 127 cases were identified, with 93 in the last 5 of these years. All but one of the last 102 cases of wound botulism have been reported among black-tar heroin injection users (“skin poppers”).(1) During this same period, California’s heroin abusers have shifted from traditional forms of heroin toward black tar. Whether the drug change or a change in manufacturing process is the culprit is not known.

The demographics of affected populations mirror that of California intravenous drug abusers. Unlike botulinum toxin, the spores of *C. botulinum* are not inactivated by heating. These spores are inoculated into the subcutaneous tissue of the skin by “skin popping” and germinate to produce clinical symptoms.

Anatomy and Pathophysiology

Wound botulism is caused by a gram positive, anaerobic, spore-forming bacteria, *C. botulinum*, which is naturally found in soil. Germination of its spores produces the botulinum toxin which produces clinical effects. Environments with low acidity (pH>4.6) and low oxygen foster *C. botulinum* growth. Both home canning with inadequate, pressure sterilization and wounds provide such environments. The toxin that is produced is the most deadly natural toxin; a dose of one nanogram (10^{-9} grams) is lethal. It is 15,000 to 100,000 more potent than sarin gas.(2)

Seven types of botulinum neurotoxin (types A to G) have been described, but type A, B, and E are most important; all three are caused by *C. botulinum*. After the toxin is absorbed in the blood, the toxin binds irreversibly to the presynaptic nerve endings and prevents the transmission of acetylcholine through the neuromuscular junction. This effectively denervates muscles by preventing acetylcholine transmission.(3) Clinical symptomatology relates to the number of neuromuscular junctions involved. The effects can range from weakness to complete, flaccid paralysis with atrophy.

ED Presentation

Patients presenting with the four D’s (diplopia, dysphagia, dry mouth, and dysarthria) and a history of injection drug abuse should immediately arouse suspicion for wound botulism. In such a case a thorough examination for cellulitis or an abscess is warranted; the wound can easily be small and missed. Classically, patients with botulism present with a flaccid, symmetrical, descending paralysis with ophthalmoplegia, ptosis and bulbar muscle weakness. Symptoms may progress rapidly; consider mechanical ventilation early. The earliest neurologic symptoms are dysphagia, dysarthria, dysphonia and peripheral muscle weakness. In addition to motor dysfunction, autonomic dysregulation is common: vomiting, dry mouth, diarrhea and orthostatic hypotension are common.

Wound botulism presents in a similar fashion to food botulism except for a paucity of gastrointestinal symptoms. Symptom onset usually occur 18 to 36 hours post exposure. Since the toxin only works on peripheral nerves, the patients are usually awake and alert. Clinical symptoms resolve over 2-3 months. Electron microscopy suggests that clinical resolution correlates with new presynaptic end plates.

Lab Studies

As for other critically ill patients, multiple laboratory tests will be obtained. Intravenous access, CBC, serum blood chemistries, coagulation studies, and blood cultures should be obtained. With the exception of electrolyte imbalance, these will unlikely aid in the diagnosis or treatment. Serum, stool and wound cultures samples should all be tested for *C. botulinum*. Differentiating between food-borne and wound botulism can be difficult, but the paucity of gastrointestinal symptoms with the latter is usually helpful. The most reliable and proven test is the mouse inoculation test. This test can be performed in most state laboratories and the CDC. In this test, the toxin type is determined by the response of mice injected with type-specific neutralizing antitoxin and the unknown sample. Symptoms of botulism and death, but survival with antitoxin indicate the type of botulism.(4) PCR, ELISA and PCR testing are under investigatory status at this point.

A normal CSF protein level helps to exclude Guillain-Barré syndrome, but botulism can cause occasionally produce a slight elevation in CSF protein and early Guillain-Barré syndrome can have normal protein levels.(5, 6)

Imaging Studies

A CT or MRI is required to exclude cerebrovascular infarction. Otherwise, radiography is of little help.

Procedures

A lumbar puncture is warranted to obtain CSF to exclude meningitis, Guillain-Barré syndrome, and poliomyelitis. A computed tomography should be performed first to exclude a mass lesion given the focal neurologic findings of early botulism.

Electromyography (EMG) testing should be performed to help differentiate botulism from other myopathies. The EMG should demonstrate nonspecific decreased amplitude of action potential for botulism. Rapid, repetitive testing at 50 Hz should demonstrate potentiation from this supramaximal stimulation with jitter and blocking, or single-fiber EMG should demonstrate jitter and blocking.(7, 8) While this test may be helpful to exclude Guillain-Barré syndrome, these response will not differentiate between Lambert-Eaton syndrome and botulism. Increased strength with sustained contraction differentiates Lambert-Eaton from botulism.

An edrophonium chloride test (Tensilon®) test can help differentiate between botulism and myasthenia gravis. Myasthenia would be supported by an improvement in neurologic symptoms after edrophonium administration, but botulism occasionally can have a transient response.

Emergency Department Care

Early consideration and evaluation for wound botulism is essential for accurate diagnosis. A thorough skin exam on all injection-drug abusers is essential, but the nidus of infection can be quite small and frequently overlooked. It is not uncommon for wound botulism patients to have been previously misdiagnosed as having a viral illness.

Treatment for wound botulism patients is largely supportive. Early provision of fluid resuscitation is important as many wound botulism patients will already have autonomic instability, manifested by orthostatic hypotension, on initial exam. If the patient has a negative inspiratory flow that is weaker than -25 cm H₂O or any trouble clearing secretions, early, controlled intubation with subsequent mechanical ventilation is advised.

All clinically suspected cases of botulism should be immediately reported to local or state public health agencies to both aid in arranging confirmatory laboratory diagnosis and obtaining trivalent (types A, B, and E) antitoxin. If unable to reach local or state officials, the CDC may be reached directly at (404) 639-2206 (Monday to Friday, 8am to 4:30pm, Eastern Standard Time) or (404) 639-2888 at other times. In California, health care providers should contact the California Department of Health Services (CDHS) at (510) 540-2308.

Mortality and length of stay are both reduced with early administration of antitoxin.(9, 10) Dosage is 2 vials (10,000 IU IV), and theoretically provides a 100-fold higher dose of antitoxin than is required. The circulating antitoxin has a half-life of 5 to 8 days and hypersensitivity reactions occur in 9% of patients.(11) Pregnancy does not contraindicate administration.

Wound sites must be débrided and irrigated early, preferably after administration of antitoxin. The use of penicillin (10-20 million units per day) is considered the antibiotic of choice, but its efficacy is debatable.(12) Aminoglycosides are contraindicated as they may potentiate neuromuscular blockade. The current antitoxin is of equine origin. A human botulism immune globulin (BIG-IV) is available from the CDHS at (510) 231-7600 for infantile botulism and may be an option for patients with a contraindication to the equine derivative.

Consultations and Admission

Patients with botulism need constant airway monitoring; intensive care unit admission is prudent. Mechanical ventilatory support is common, but a small subset of patients may be observed. Surgical consultation is advisable to evaluate large wounds for operative débridement. Overall mortality is 10% with early treatment with antitoxin: 15% mortality if treatment within 24 hours, 15% over 24 hours and 48% without antitoxin.(13) Ventilatory support is frequently needed form two to eight weeks.(14)

References

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9. Tacket CO, Shandera WX, Mann JM, Hargrett NT, Blake PA. Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med* 1984;76:794-8.
10. Sandrock CE and Murin S. Clinical Predictors of Respiratory Failure and Long-term Outcome in Black Tar Heroin-Associated Wound Botulism. *CHEST* (2001); 120:562-66.
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13. Tacket CO, Shandera WX, Mann JM, Hargrett NT, Blake PA. Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med.* 1984;76:794-98.
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Patient Outcome

Diagnosis: Wound botulism secondary to subcutaneous drug use (“skin popping”) of Black Tar heroin.

The patient’s symptoms were highly suggestive for wound botulism and this condition was considered early. A CT was order which did not support the diagnosis of stroke. While waiting for neurology consultation, the patient’s condition deteriorated and the patient was intubated for airway protection. Botulism anti-toxin was requested from the CDHS and given prior to any confirmatory testing.

A lumbar puncture was obtained which showed a normal protein and glucose level, without any RBC’s or WBC’s. Gram stain was negative. Routine serum chemistries and routine blood cultures were negative.

After intubation, a careful skin examination revealed a small abscess on the patient’s buttock. Surgical consultation was obtained and a small abscess was identified. Mouse assay testing of this wound later confirmed the diagnosis of botulism.

The patient was admitted to the intensive care unit and penicillin was given. After a month of ventilatory support, the patient was able to be weaned from ventilatory support. After three months of rehabilitation therapy, the patient was discharged in a usual state of health.

Annotated Bibliography

- 1. Werner SB, Passaro D, McGee J, Schechter, Vudia DJ. Wound Botulism in California, 1951-1998: Recent Epidemic in Heroin Injectors. *Clinical Infectious Disease* 2000;31:1018-24.**

All cases (127) of wound botulism reported to the California Department of Health Services were reviewed from 1951-1998. Characteristics of wound botulism among injection drug users were compared to non-users to determine important epidemiological factors. The economic burden of this condition was also assessed for patients in 1995. Clinical and laboratory features are discussed and conditions that mimic botulism are reviewed.

- 2. Centers for Disease Control and Prevention: Botulism in the United States, 1899-1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers, Atlanta, GA. Centers for Disease Control and Prevention, 1998.**

<http://www.cdc.gov/ncidod/dbmd/diseaseinfo/botulism.pdf> Accessed 8/20/03.

The CDC handbook provides a through review of botulinum toxin and offers an in-depth coverage of laboratory testing. The handbook offers health care providers with instructions on how to both collect samples and how to test for botulinum toxin. Epidemiology and methods of control are provided.

- 3. Arnon SA, Schechter R, Inglesby TV, Henderson DA, Barlett JG, et al. Botulism Toxin as a Biological Weapon. *JAMA* (2001);285(8): 1059-70.**

Working group consensus document from US experts on botulism. Provides a succinct review of the mechanism of botulism toxin, factors relating to the virulence of *C. botulinum*, and a table of common mimics for botulism. Considerations for deployment of botulism as a weapon are analyzed and epidemiology is reviewed.

- 4. Maselli RA, Ellis W, Mandler RN, Sheikh F, Senton G, et al. Cluster of Wound Botulism in California: Clinical, Electrophysiologic, and Pathologic Study. *Muscle and Nerve*. (1997); 20(10): 1284-95.**

Comprehensive review of the electrophysiology of botulism and electromyography. Cluster of California wound botulism cases are presented and their results of their EMG results are presented. In-vitro microelectrode studies are also presented which demonstrate functional denervation of the motor end plate.

- 5. Sandrock CE and Murin S. Clinical Predictors of Respiratory Failure and Long-term Outcome in Black Tar Heroin-Associated Wound Botulism. *CHEST* (2001); 120:562-66.**

Consecutive series of 20 patients with wound botulism were retrospective analyzed. Median duration of mechanical ventilation were recorded and compared to time of antitoxin and antibiotic administration. Antitoxin administration within 12 hours shortened stays from 54 days to 11 days. Antibiotic administration within 12 hours also shortened hospital stay from 54 to 35 days.

Questions

- 1. Which of the following is a finding in botulism?**
 - a. Diplopia
 - b. Dysarthria
 - c. Dry mouth
 - d. Dysphagia
 - e. All of the above

- 2. Which of the following are frequently mistaken for botulism?**
 - a. Guillain-Barré syndrome
 - b. Myasthenia gravis
 - c. Lambert-Eaton Syndrome
 - d. Stroke
 - e. All of the above

- 3. Which state has the highest incidence of wound botulism?**
 - a. Texas
 - b. Arizona
 - c. California
 - d. Hawaii
 - e. None of the above

- 4. Which of the following is the antibiotic of choice for wound botulism?**
 - a. cephalexin
 - b. erythromycin
 - c. vancomycin
 - d. penicillin
 - e. None of the above

- 5. Which population is at highest risk for wound botulism?**
 - a. Subcutaneous, injection drug abusers of black tar heroin
 - b. Coal miners
 - c. Mechanics
 - d. Welders with exposure to acetylene
 - e. None of the above

Answers

1. Answer e.

Botulism causes all of these “D”’: dysphagia, dysarthria, diplopia, and dry mouth

2. Answer e

All of these can mimic botulism.

3. Answer c.

Over 75% of all cases are found in California.

4. Answer d.

While its efficacy is debated, penicillin is considered the drug of choice for botulism.

5. Answer e.

All but one of the recent (>10 years) of wound botulism has occurred in injection drug abusers of heroin.