Adult Intestinal Botulism: A Rare Presentation in an Immunocompromised Patient With Short Bowel Syndrome

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Abstract

The cholinergic heat-labile neurotoxin produced by *Clostridium* species is primarily responsible for the clinical manifestations of botulism. The classic phenotypic presentation of botulism consists of subacute descending flaccid paralysis with intact sensory function. Traditionally, it is classified into 3 main forms (foodborne, wound-related, and infantile) on the basis of primary site of toxin entry into the human nervous system. Toxemia is the common pathophysiology in all forms of botulism. Adult intestinal toxemia botulism is an extremely rare form of the disease with pathogenesis similar to that of infant-type botulism. Symptomatic adults usually have an anatomic abnormality in the gastrointestinal tract leading to changes in normal gut flora. The current case is an addition to the growing literature on this unusual clinical variant of botulism.

REPORT OF CASE

A 66-year-old woman presented to the emergency department with a 1-day history of worsening low back pain, difficulty raising her arms and walking up stairs, and a “thick tongue” with progressive dysphagia and dysarthria. She also reported a 3-day history of bloating, abdominal pain, and constipation (her daily normal was 2-3 bowel movements per day). She had no fever, vomiting, diarrhea, insect or tick bites, or presence of new skin lesions. She was hemodynamically stable on admission. She was alert and oriented, with normal heart, lung, and abdominal physical examination findings. Her neurologic examination revealed proximal lower and upper extremity motor weakness, normal pupillary size and reaction to light, no ptosis, normal deep tendon reflexes, and normal rectal tone. She was admitted to the medical ward under supervision of the neurology team. The patient’s medical history included autoimmune hemolytic anemia, short bowel syndrome following complications of a cholecystectomy leading to ileal resection, lumbago, hypertension, and...
hypothyroidism. She had been chronically immunosuppressed with oral corticosteroids (10-15 mg/d) for her autoimmune anemia. Her personal and family histories were unremarkable.

She experienced worsening tachypnea and dysarthria and had bilateral ptosis, lateral gaze palsy with no convergence of the right eye, and sluggish pupillary reaction to light within 12 hours of admission. Physical examination findings were notable for decreased strength in the neck, shoulder, and hip girdle muscles, with normal sensory function. The initial differential diagnosis considered by the neurology team included spinal cord lesions, myasthenia gravis, and atypical variants of Guillain-Barré syndrome. With myasthenia crisis high on the differential list, empiric intravenous immunoglobulins, high-dose corticosteroids, and oral pyridostigmine were initiated.

On day 2 of hospitalization, worsening respiratory muscle weakness developed, as evidenced by declining negative inspiratory forces and vital capacity. She required tracheal intubation and mechanical ventilatory support for hypercapnic respiratory failure and was transferred to the intensive care unit for further care. Neurologic assessment revealed features of worsening descending symmetrical flaccid paralysis, complete ophthalmoplegia, profound ptosis, dilated pupils, absent gag reflex, dysphagia, dysarthria, inability to lift her head, and an intact sensory nervous system. Botulism was strongly suspected as well as the neurologic conditions that can affect the cranial nerves, brain stem, and spinal cord.

Electromyography revealed myopathic features without marked effects of repetitive stimulation. Nerve conduction studies showed low-amplitude motor action potentials with normal conduction velocity and normal sensory action potential. Lumbar puncture was not performed. Her C-reactive protein level, white blood cell count, and erythrocyte sedimentation rate were normal, as were thyroid, liver, and renal function and results of a myasthenia serology panel. Magnetic resonance imaging of the brain and spine revealed no abnormalities.

With strong suspicion for botulism, further therapy with corticosteroids, pyridoxine, and intravenous immunoglobulin was discontinued. The Centers for Disease Control and Prevention (CDC) was contacted for guidance and assistance in obtaining botulinum antitoxin therapy. With the help of the CDC team, botulism antitoxin was administered to the patient within 8 hours of diagnostic suspicion on day 2 of her hospital stay. Stool cultures for Clostridium botulinum were not performed; confirmatory toxin testing including serum and stool studies performed at a reference laboratory were reported to be positive for botulinum toxin A. Results of an investigation for exposure to contaminated food conducted by the Florida Department of Health and Epidemiology were negative. Polyethylene glycol solution was administered to facilitate excretion of the toxin and spore-forming bacteria from the intestine. A 2-week regimen of oral metronidazole and intravenous penicillin G was initiated to facilitate the eradication of the C botulinum from the gastrointestinal tract. Surgical tracheostomy was performed for ventilatory support on hospital day 7 because of persistent respiratory failure. The patient had symptomatic improvement as evidenced by improved facial movements, increased ability to nod her head and write letters with her hand, and increased shoulder and hip movements. She was discharged to a rehabilitation facility after 16 days of hospitalization. However, she was readmitted 40 days after her initial admission with paralytic ileus. Although recurrence of botulism ileus was suspected, the patient improved with conservative management and was discharged after 5 days. Unfortunately, she ultimately experienced recurrent deep venous thrombosis, a complication of her prolonged illness, and died in the rehabilitation facility.

**DISCUSSION**

The neurotoxin produced by C botulinum, a gram-positive anaerobic spore-forming rod, is responsible for paralytic disease manifestations in humans. Human disease from the toxin produced by Clostridium butyricum and Clostridium baratii has also been reported in case series. According to the CDC’s Botulism Surveillance Summary 2016, there were 205 confirmed and 10 probable cases of human botulism that year. Distribution of the major types of botulism such as infantile, food, and wound are 73%, 14%, and 12%, respectively.
Only 1% of cases were reported to be of other etiology. Among the probable cases, 80% are suspected to be foodborne, and the remaining 20% are attributed to wound botulism.

Intestinal colonization and growth of *C. botulinum* as a possible mechanism of intoxication was suspected as far back as in 1921, but it was never recognized until 1976 when the pathogenesis of infant botulism was documented. Most cases of infant botulism were confined to children aged less than 12 months. However, since early 1980, there have been sporadic cases of noninfant intestinal colonization, and its consequent clinical manifestations were reported from different continents of the world. Since the first case description in 1986, a total of 33 cases of intestinal toxemia botulism have been described in the literature. Three species of *Clostridium* (*butyricum*, *botulinum*, and *baratii*) have been incriminated as the causes of clinical botulism resulting from intestinal toxemia. A detailed summary of published cases is presented in the Table.

The 7 antigenic variants of botulinum neurotoxin, designated by the letters A through G, are some of the most lethal toxins known to mankind. Human botulism is predominantly caused by toxin types A, B, and E. Type A is the major toxin incriminated in 56% of reported cases, followed by toxin type B and type E in 41% and 3% of cases, respectively, in the latest CDC report. Neurotoxin produced by *C. butyricum* and *C. baratii* are referred to as “botulinum-like” and can be neutralized by either botulinum type E or type F antitoxin. Toxin specificity to motor neuronal synapses and inhibition of acetylcholine release leading to blockage of synaptic transmission are responsible for the lethality of the toxin.

Spores from *C. botulinum* are ubiquitous in our environment and can be isolated from soil, dust, food, and water sources. Biodiversity of the normal adult intestinal gut milieu normally does not allow germination, vegetation, and toxin production of the ingested *C. botulinum* spores. Infants are susceptible to *C. botulinum* colonization because of an immature gut mucosal barrier and a weak local immune response. All patients with adult intestinal toxemia have an underlying structural abnormality, an alteration of normal intestinal flora, or both. Structural abnormalities include either an anatomic defect or altered anatomy of the gastrointestinal tract by surgery or inflammatory bowel disease. The alterations of intestinal microflora are related to the prevalence of broad-spectrum antibiotic usage. The development of adult intestinal botulism is believed to be caused by ingestion and germination of spores resulting in intestinal colonization of bacteria, in situ production of the botulism neurotoxins within the gastrointestinal tract, and subsequent systemic absorption. This process differs from classic foodborne botulism in that the causative toxin is acquired from intra-intestinal production rather than from food contaminated with preformed toxin. We believe that short bowel syndrome related to her prior surgical complication and immunosuppression due to long-term corticosteroid use are the 2 predisposing factors for presumptive *C. botulinum* intestinal colonization (intestinal toxemia) in our patient.

The classic triad of botulism consists of the acute or subacute presentation of a symmetric, descending flaccid paralysis involving the bulbar muscles, a clear sensorium, and the absence of fever. Clinical presentation without cranial nerve involvement is extremely rare. Similar to infantile botulism, the adult intestinal variety can present with constipation, lethargy, and poor feeding. Our patient had all of these features before hospital admission. Although not performed in most clinical microbiology laboratories, definitive diagnosis of intestinal toxemia botulism is performed by demonstration of neurotoxigenic species, with or without concomitant presence of toxin, in the stool of the patient with clinical features compatible with botulism. Detection of botulinum toxin in the serum of an adult patient is also diagnostic. Electromyography, cerebrospinal fluid and serum toxin assays, and imaging are helpful to exclude other etiologies in the differential diagnosis such as Guillain-Barré syndrome, myasthenia gravis, organophosphate poisoning, tick bite, and other metabolic abnormalities. However, in a patient with a classic history and characteristic physical findings, prompt testing for botulinum toxin should be arranged through the CDC or the state health department laboratory. In our case, testing for *C. botulinum* or...
| Reference, year         | Country, year of diagnosis | Age/sex | Underlying GI pathology | Prior antibiotic use | Time to diagnosis | Organism and type of toxin incriminated | Antitoxin therapy received | Outcome |
|------------------------|---------------------------|---------|--------------------------|----------------------|------------------|----------------------------------------|---------------------------|---------|
| Bradley et al., 1980   | US, 1980                  | 47/M    | Unknown                  | None                 | Unknown          | Clostridium botulinum type B           | Unknown                   | Survived |
| McCroskey & Hatheway, 1988 | US, 1980            | 33/F    | Ileojeunal bypass       | Unknown              | 2 d              | Clostridium botulinum type A           | Unknown                   | Died     |
|                        | US, 1988                 | 70/M    | Unknown                  | None                 | Unknown          | Clostridium baratii type F             | Unknown                   | Survived |
|                        | Iceland, 1988            | 27/M    | None                     | None                 | 25 d             | Clostridium botulinum type B           | Unknown                   | Survived |
| Green et al., 1983     | US, 1981                 | 54/M    | None                     | None                 | Unknown          | Clostridium botulinum type F           | Yes                       | Survived |
| Gupta et al., 2005     | US, 1986                 | 23/M    | Unknown                  | Unknown              | 1 d              | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 1992                 | 55/M    | None                     | None                 | 1 d              | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 1993                 | 59/F    | None                     | None                 | Unknown          | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 1995                 | 61/M    | None                     | None                 | <1 d             | Clostridium butyricum type E           | Yes                       | Survived |
|                        | US, 1995                 | 54/F    | None                     | Yes                  | <1 d             | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 1997                 | 33/M    | None                     | Yes                  | <1 d             | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 2000                 | 65/F    | Esophageal dilation      | No                   | 2 d              | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 2000                 | 76/F    | Diverticulitis           | No                   | 1 d              | Clostridium botulinum type F           | Yes                       | Survived |
|                        | US, 2001                 | 45/F    | Gastric stapling         | Yes                  | <7 d             | Clostridium botulinum type F           | Yes                       | Recovery |
|                        | US, 2002                 | 52/F    | Colonoscopy              | Yes                  | <7 d             | Clostridium botulinum type F           | Yes                       | Recovery |
| Chia et al., 1986      | US                       | 37/F    | Antrectomy, vagotomy, and Billroth type I | Unknown             | Unknown          | Clostridium botulinum type A           | Yes                       | Died     |
| Freedman et al., 1986  | US                       | 45/F    | Intestinal obstruction and resection | Unknown             | 5 d              | Clostridium botulinum type B           | No                        | Survived |
| McCroskey et al., 1991 | US, 1987                 | 54/M    | Truncal vagotomy and pyloroplasty | None                | 2 d              | Clostridium botulinum type F           | Yes                       | Survived |
| Shen et al., 1994      | US                       | 3/F     | None                     | Yes                  | Unknown          | Clostridium botulinum type A           | Yes                       | Died     |
| Fenicia et al., 1999   | Italy, 1994              | 9/M     | Meckel diverticum        | Yes                  | 5 d              | Clostridium butyricum type E           | No                        | Survived |
|                        | Italy, 1995              | 19/F    | Meckel diverticum        | Yes                  | 2 d              | Clostridium butyricum type E           | Yes                       | Survived |
|                        | Italy, 1997              | 56/M    | None, but heart surgery and antibiotic use 1 mo before | Yes                | 30 d             | Clostridium botulinum type A           | Unknown                   | Survived |
| Griffin et al., 1997   | US                       | 67/M    | IBD + colonic resection | Unknown             | 3 d              | Clostridium botulinum type A           | Yes                       | Survived |
| Amon, 1995             | US                       | 48/F    | Colostomy for bowel cancer | Unknown             | Unknown          | Clostridium botulinum type B           | Unknown                   | Unknown |
|                        | US                       | 51/F    | Ileojeunal bypass       | Yes                  | Unknown          | Clostridium botulinum type B           | Unknown                   | Unknown |
| Harvey et al., 2002    | US, 2001                 | 43/F    | None                     | Yes                  | <7 d             | Clostridium botulinum type F           | Yes                       | Survived |
| Kobayashi et al., 2003 | Japan                    | 12/F    | None                     | No                   | 5 d              | Clostridium botulinum type A           | Yes                       | Survived |
| Sheppard et al., 2012  | Canada                   | 45/M    | Unknown                  | No                   | 6 d              | Clostridium botulinum type B           | Yes                       | Recovery |

Continued on next page
botulinum toxin in stool was not performed on samples collected on admission. Because of the hazardous nature of botulinum toxin, and in accordance with regulatory guidance from the U. S. Centers for Medicare and Medicaid Services, clinical microbiology laboratories are specifically instructed to not perform culture isolation, identification studies, or toxin analysis for *C. botulinum*. Routine stool culture for specific detection of *C. botulinum* is also not recommended because of biosafety considerations.

Improved critical care practice has resulted in reduction in case fatality rates, even though the number of botulism outbreaks has remained steady over the years. Supportive care is the mainstay of therapy in suspected or confirmed botulism cases. Neutralization of the antitoxin and eradication of the *Clostridium* species are also advised. The CDC guidelines advocate administration of botulism antitoxin for adult patients as soon as a clinical diagnosis is made, without waiting for laboratory confirmation. Heptavalent botulinum antitoxin (HBAT), containing antitoxin against the neurotoxin subtypes A through G, is available through the CDC. Antibiotic therapy in botulism remains controversial. Treatment with penicillin and metronidazole are recommended in wound-related botulism cases. Because of concern about disease aggravation by bacteriolysis and release of toxin, antibiotics are not recommended in infantile botulism. However, the adult intestinal toxemia variant is characterized by its protracted course and also risk of relapse even after treatment with antitoxin because of the ongoing intraluminal production of toxin. Restoration of the normal gut microbial flora by elimination of the toxin-producing bacteria is necessary for disease control. In the absence of guidelines for any additional treatment such as antibiotics in cases of intestinal colonization, we decided to use metronidazole and penicillin G to eradicate the bacteria colonizing the intestinal tract. Recurrence of botulism was reported 10 days after administration of botulism antitoxin in a patient with intestinal colonization. The authors proposed that once HBAT cleared (the half-life of HBAT is 12-24 hours) from the patient’s system, the continued absorption of toxin

| Reference, year | Age/sex | Underlying GI pathology | Prior antibiotic use | Time to diagnosis | Organism and type of toxin incriminated | Antibiotic therapy received | Outcome |
|-----------------|---------|-------------------------|---------------------|-----------------|----------------------------------------|---------------------------|---------|
| Hannett et al,20 | US 68/F | None                    | No                  | 3 d             | *C. baratii* type F                     | Yes                       | Recovery |
| US 68/F | None | No | 3 d | *C. baratii* type F | Yes | Recovery |
| Schaack et al,21 | US 33/F | Gastric bypass | Unknown | 10 d | *C. botulinum* type A | Yes | Survived |
| Freund et al,22 | US 43/F | None | No | 21 d | *C. botulinum* type A | Yes | Died |
| Parameswaran et al,23 | US 27/F | Graft-vs-host disease | No | 59 d | *C. botulinum* type A | Yes | Died |

References:

1. F = female; GI = gastrointestinal; IBD = inflammatory bowel disease; M = male; US = United States.

2. The year of diagnosis provided when available.
from the colonized intestines was possibly responsible for the recurrence. In our case, the patient returned to the hospital with constipation, which could be explained by the recurrence of botulism. RETrospectively, we believe that our patient had rebound botulism neurotoxicity and could have benefited from an additional dose of antitoxin. Guidance in the literature is scarce regarding when to proceed with a second antitoxin dose.

CONCLUSION
Adult intestinal toxemia botulism is rare and underrecognized. Astute clinical acumen and prompt antitoxin therapy may be lifesaving in this rare disease.

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Abbreviations and Acronyms: CDC = Centers for Disease Control and Prevention; HBAT = heptavalent botulinum antitoxin

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REFERENCES
1. Shapiro RL, Hatheway C, Swardlow DL. Botulism in the United States: a clinical and epidemiologic review. Ann Intern Med. 1998;129(3):221–228.
2. Aron SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. JAMA. 2001;285(8):1059-1070.
3. Brook I. Botulism: the challenge of diagnosis and treatment. Rev Neurol Dis. 2006;3:182-189.
4. Aron SS. Botulism as an intestinal toxemia. In: Buser MP, Smith PO, Greenberg HB, Guentert RL, Ravdin JI, eds. Infections of the Gastro-Intestinal Tract. New York, NY: Raven Press; 1995:257-271.
5. Green J, Spear H, Brinsson RR. Human botulism (type F)—a rare type. Am J Med. 1983;75(5):893-895.
6. Gupta A, Sumner CJ, Castor M, Maslanka S, Sobel J. Adult botulism type F in the United States. 1981-2002. Neurology. 2005;65(11):1694-1700.
7. Harvey SM, Surgeon J, Dassay DE. Botulism due to Clostridium botanti type F toxin. J Clin Microbiol. 2002;40(6):2260-2262.
8. Sheppard YD, Middleton D, Whitfield Y, et al. Intestinal toxemia botulism in 3 adults, Ontario, Canada. 2006-2008. Emerg Infect Dis. 2012;18(1):1-6.
9. Centers for Disease Control and Prevention. National Botulism Surveillance Summary 2016. Atlanta, GA: US Dept of Health and Human Services; 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/botulism/pdf/Botulism-2016-SUMMARY-508.pdf. Accessed May 30, 2018.
10. Midura TF, Aron SS. Infant botulism: identification of Clostridium botulinum and its toxins in faeces. Lancet. 1976;2(7992):934-936.
11. Bradley WG, Shahnai BT, Hyslop HY Jr. Case Records of the Massachusetts General Hospital: Case 48-1980—rapidly progressive neurologic disorder following gastrointestinal symptoms. N Engl J Med. 1980;303(23):1347-1355.
12. McCroskey LM, Hatheway CL. Laboratory findings in four cases of adult botulism suggest colonization of the intestinal tract. J Clin Microbiol. 1988;26(5):1052-1054.
13. Chia J, Clark JB, Ryan CA, Pollack M. Botulism in an adult associated with food-borne intestinal infection with Clostridium botulinum. N Engl J Med. 1986;315(5):239-241.
14. Freedman M, Armstrong RM, Killian JM, Boland D. Botulism in a patient with jejunoileal bypass. Ann Neurol. 1986;20(5):641-643.
15. McCroskey LM, Hatheway CL, Woodruff BA, Greenberg JA, Jurgenson P. Type F botulism due to neurotoxigenic Clostridium botanti from an unknown source in an adult. J Clin Microbiol. 1991;29(1):2618-2620.
16. Shen WP, Felsing N, Lang D, Goodman G, Cairo MS. Development of infant botulism in a 3-year-old female with neuromuscular disease following autologous bone marrow transplantation: potential use of human botulinum immune globulin. Bone Marrow Transplant. 1994;13(3):345-347.
17. Fenicia L, Franciosa G, Pourshaban M, Aureli P. Intestinal toxemia botulism in two young people, caused by Clostridium butyricum type E. Clin Infect Dis. 1999;29(6):1381-1387.
18. Griffin PM, Hatheway CL, Rosenbaum RB, Sokolov R. Endogenous antibody production to botulinum toxin in an adult with intestinal colonization botulism and underlying Crohn’s disease. J Infect Dis. 1997;175(3):633-637.
19. Kobayashi H, Fujisawa K, Saito Y, et al. A botulism case of a 12-year-old girl caused by intestinal colonization of Clostridium botantii type Ab. Jpn J Infect Dis. 2003;56(2):73-74.
20. Hannett GE, Schaffzin JK, Davis SW, et al. Two cases of adult botulism caused by botulinum neurotoxin-producing Clostridium botanti. Anz Microbiol. 2014;30C:178-180.
21. Schaack L, Weisland J, Steck A. Intestinal botulism: the lurking threat of bariatric surgery [abstract]. J Med Toxicol. 2017;13(1):25. Abstract 64.
22. Freund B, Hayes L, Rivera-Lara L, et al. Adult intestinal colonization botulism mimicking brain death. Muscle Nerve. 2017;56(4):E27-E281.
23. Parameswaran L, Rao A, Chastain K, et al. A case of adult intestinal toxemia botulism during prolonged hospitalization in an allogeneic hematopoietic cell transplant recipient. Clin Infect Dis. 2018;66(suppl 1):S99-S102.
24. Moberg LJ, Sugiyama H. The rat as an animal model for infant botulism. Clin Infect Dis. 1980;29(2):819-821.
25. Fagan RP, Neil KP, Sasich R, et al. Initial recovery and rebound of type F intestinal colonization botulism after administration of investigational heptavalent botulinum antitoxin. Clin Infect Dis. 2011;53(9):e125-e128.