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CASE REPORT

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.

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Botulism, a rare infectious clinical entity caused by several *Clostridium* species, is predominantly manifested as a paralytic neurologic disease in humans.[1] Because of the dangerous toxins they produce and the potential for mass public involvement, botulism is a nationally notifiable disease.[2] Traditionally, botulism has been classified into 3 main forms— infantile, foodborne, and wound-related—based on the primary route of toxin entry to the human body.[3] There is also an extremely rare variant called infant-like botulism or adult intestinal toxemia botulism,which mainly affects children older than than 12 months and adults.[4] The clinical presentations are similar in all varieties of botulism. The affected patient presents with descending, symmetric, flaccid paralysis involving the motor and autonomic nervous system. The sensory nervous system is not affected in botulism.[3,4] We report a case of suspected adult intestinal colonization (intestinal toxemia) botulism and discuss the clinical features to increase awareness among physicians about this rare disease.

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

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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 immunoglobin 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.[3,4] Human disease from the toxin produced by *Clostridium butyricum* and *Clostridium baratii* has also been reported in case series.[4-8] According to the CDC's Botulism Surveillance Summary 2016,[9] 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.

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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.[9]

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.[10] 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.[11] 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* (*botulinum*, *butyricum*, and *baratii*) have been incriminated as the causes of clinical botulism resulting from intestinal toxemia.[4] 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.[4] 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.[9] 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.[4] 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.[3]

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.[24] 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.[24] 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.[4] 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.[3] 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

TABLE. Summary of Reported Cases of Intestinal Botulism[a]

Reference, year	Country, year of diagnosis[b]	Age/ sex	Underlying GI pathology	Prior antibiotic use	Time to diagnosis	Organism and type of toxin incriminated	Antitoxin therapy received	Outcome
Bradley et al,[11] 1980	US	47/M	Unknown	None	Unknown	*Clostridium botulinum* type B	Unknown	Survived
McCroskey & Hatheway,[12] 1988	US, 1980	33/F	Ileojejunal bypass	Unknown	2 d	*C 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	*C botulinum* type B	Unknown	Survived
Green et al,[5] 1983	US, 1981	54/M	None	None	Unknown	*C botulinum* type F	Unknown	Survived
Gupta et al,[6] 2005	US, 1986	23/M	Unknown	Unknown	Unknown	type F	Yes	Survived
	US, 1992	55/M	None	None	1 d	*C baratii* type F	Yes	Survived
	US, 1993	59/F	None	None	Unknown	*C baratii* 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	*C baratii* type F	Yes	Survived
	US, 1997	33/M	None	Yes	<1 d	*C baratii* type F	Yes	Survived
	US, 2000	65/F	Esophageal dilation	No	2 d	*C baratii* type F	Yes	Survived
	US, 2000	76/F	Diverticulitis	No	1 d	type F	Yes	Survived
	US, 2001	45/F	Gastric stapling	Yes	<7 d	type F	Yes	Recovery
	US, 2002	52/F	Colonoscopy	Yes	<7 d	*C baratii* type F	Yes	Recovery
Chia et al,[13] 1986	US	37/F	Antrectomy, vagotomy, and Billroth type I	None	Unknown	*C botulinum* type A	Yes	Died
Freedman et al,[14] 1986	US	45/F	Intestinal obstruction and resection	Unknown	5 d	*C botulinum* type B	No	Survived
McCroskey et al,[15] 1991	US, 1987	54/M	Truncal vagotomy and pyloroplasty	None	2 d	*C baratii* type F	Yes	Survived
Shen et al,[16] 1994	US	3/F	None	Yes	Unknown	*C botulinum* type A	Yes	Died
Fenicia et al,[17] 1999	Italy, 1994	9/M	Meckel diverticulum	Yes	5 d	*C butyricum* type E	No	Survived
	Italy, 1995	19/F	Meckel diverticulum	Yes	2 d	*C butyricum* type E	Yes	Survived
	Italy, 1997	56/M	None, but heart surgery and antibiotic use 1 mo before	Yes	30 d	*C botulinum* type A	Unknown	Survived
Griffin et al,[18] 1997	US	67/M	IBD + colonic resection	Unknown	3 d	*C botulinum* type A	Yes	Survived
Arnon,[4] 1995	US	48/F	Colostomy for bowel cancer	Unknown	Unknown	*C botulinum* type B	Unknown	Unknown
	US	51/F	Ileojejunal bypass	Yes	Unknown	*C botulinum* type B	Unknown	Unknown
Harvey et al,[7] 2002	US, 2001	43/F	None	Yes	<7 d	*C barati* type F	Yes	Survived
Kobayashi et al,[19] 2003	Japan	12/F	None	No	5 d	*C botulinum* type A	Yes	Survived
Sheppard et al,[8] 2012	Canada	45/M	Unknown	No	6 d	*C botulinum* type B	Yes	Recovery

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TABLE. Continued

Reference, year	Country, year of diagnosis[b]	Age/ sex	Underlying GI pathology	Prior antibiotic use	Time to diagnosis	Organism and type of toxin incriminated	Antitoxin therapy received	Outcome
	Canada	50/F	IBD, bowel surgery	No	3 d	*C botulinum* type A	Yes	Recovery
	Canada	63/F	IBD, bowel surgery	No	1 d	*C botulinum* type A	Yes	Recovery
Hannett et al,[20] 2014	US	79/M	Endoscopy 3 d prior	No	3 d	*C baratii* type F	Yes	Died
	US	68/F	None	Yes	3 d	*C baratii* type F	Yes	Recovery
Schaack et al,[21] 2017	US	33/F	Gastric bypass	Unknown	10 d	*C botulinum* type F	Yes	Survived
Freund et al,[22] 2017	US	43/F	None	No	21 d	*C botulinum* type A	Yes	Survived
Parameswaran et al,[23] 2017	US	27/F	Graft-vs-host disease	Yes	59 d	*C botulinum* type A	Yes	Died

[a]F = female; GI = gastrointestinal tract; IBD = inflammatory bowel disease; M = male; US = United States.
[b]Year of diagnosis provided when available.

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.[25] 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

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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