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Descending Paralysis
Ascending the Path to Diagnosis

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Acute diffuse weakness that progresses to paralysis can have several causes. What important clues to diagnosis can be found in the history and physical exam?

Case

A 59-year-old man with a history of hypertension and schizoaffective disorder presents to the emergency department complaining of difficulty speaking for 6 hours. Initial vital signs are as follows: blood pressure, 130/74 mm Hg; heart rate, 100 beats/min; respiratory rate, 20 breaths/min; temperature, 98.7°F. Although the patient has no other neurologic complaints or deficits, his voice is low and muffled; there is no aphasia. Brain CT is performed to assess for cerebrovascular accident; findings are normal. The patient is admitted for further evaluation. Two hours after arrival, the patient complains of difficulty swallowing, which rapidly progresses to an inability to manage secretions, for which he is intubated. Two hours post-intubation, the patient cannot move his eyes and has sluggishly reactive pupils.

What is the differential diagnosis for this patient's clinical presentation?

Acute diffuse weakness beginning in the bulbar region and progressing to paralysis can have several causes, and often the history and physical exam lead to the diagnosis. Important historical features include recent febrile illness, the pattern of progression, affected body regions, and any other neurologic deficits. Table 1 lists the differential diagnosis of acute paralysis that a clinician may encounter in the emergency department.

Guillain-Barré syndrome (GBS) is an autoimmune disorder in which the immune response to an infectious agent is misdirected against structurally similar peripheral nerve antigens. This in turn causes an ascending flaccid paralysis. In the Miller Fisher variant of GBS, the initial symptoms include complete ophthalmoplegia, limb ataxia, and areflexia. Approximately 70% of patients report a febrile illness in the days to weeks preceding the onset of symptoms.[1] The weakness may be mild or may progress to total motor paralysis over several days. Approximately 30% of patients develop significant weakness of respiratory muscles and require ventilator support.[1] Reflexes are markedly reduced and frequently absent, even relatively early in the clinical course, when there may be only mild weakness. Patients can experience muscle pain, especially in the thighs and back. Lumbar puncture is the diagnostic test most commonly used; findings associated with GBS include elevated protein with only minimal or no pleocytosis (cytoalbuminologic dissociation). However, this finding is often absent early in the disease process, and a normal cerebrospinal fluid (CSF) does not exclude GBS. Even when present, the elevation of CSF protein is too nonspecific to be considered diagnostic.

Myasthenia gravis, a disease caused by antibodies directed against postsynaptic nicotinic acetylcholine receptors in the neuromuscular junction, presents with weakness, especially in the proximal limbs and neck muscles. It should therefore be considered in any patient with new onset of bulbar palsies without sensory

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Table 1. Differential Diagnosis of Paralysis

Disease	Key Signs/Symptoms	Diagnostic Test	Treatment
Guillain-Barré syndrome	Ascending paralysis	Lumbar puncture	IVIG
Miller Fisher syndrome (variant of Guillain-Barré syndrome)	Ophthalmoplegia, limb ataxia, areflexia	Lumbar puncture looking for cytoalbuminologic dissociation, serology for anti-GQ1b antibody	IVIG
Myasthenia gravis	Fluctuating bulbar and extra-ocular muscle weakness, worsens with repeated use, improves with rest	Edrophonium test, serology for AChR antibody, NIF test	Pyridostigmine, IVIG
Lambert-Eaton myasthenic syndrome	Limb or truncal weakness worsened by continued use, no response to anticholinesterase drugs	Oncology workup	No emergency treatment available
Botulism	Bulbar palsy, descending paralysis	Mouse bioassay, PCR	Antitoxin
Viral encephalitis	Altered mental status, seizure, fever	Lumbar puncture	Antivirals, supportive care
Intracranial hemorrhage	Severe headache, trauma, blood thinners, other nonmotor neurologic deficits	CT	Operative, reverse anticoagulants/anti-platelet medication
Organophosphate pesticides poisoning	Cholinergic toxidrome	Cholinesterase activity	Atropine/2-PAM
Hypokalemia/ Hypermagnesemia		Electrolyte panel	Repletion
Diphtheria	Cranial nerve involvement (fever, dysphagia, respiratory symptoms, rash if bacterial infection)	Throat and blood cultures	Antitoxin, antibiotics
Porphyria	Abdominal pain, photosensitivity	Porphyrin tests	Hemin, phlebotomy, chloroquine, beta-carotene

IVIG = intravenous immunoglobulin; GBS = Guillain-Barré syndrome; AChR = acetylcholine receptor; NIF = negative inspiratory force; PCR = polymerase chain reaction; 2-PAM = pralidoxime.

findings. This is especially true when isolated bilateral ptosis is the presenting complaint. Administration of the acetylcholinesterase inhibitor edrophonium followed by assessment for improved muscle strength may aid the diagnosis, but it is not a sensitive or specific test.

Routine laboratory studies have little utility in the evaluation of acute paralysis, but the serum potassium level may help diagnose hypokalemic periodic paraly-

Table 2. Selected Toxins That Can Cause Paralysis[3]

Curare and related drugs (eg, vecuronium)
Snakes (rare in US but common elsewhere)
Mojave rattlesnake venom
Coral snake venom
Saxitoxin (*Protogonyaulax catenella*, *Protogonyaulax tamarensis*—paralytic shellfish poisons)
Tetrodotoxin (puffer fish)
Tarichotoxin (newt)
Batrachotoxin (Columbian poison dart frog)
Maculotoxin (blue-ringed octopus)
Conotoxins (cone snails)
Gelsemine (Carolina yellow jessamine plant)
Buckthorn fruit

Adapted from Horowitz.[3]

sis. However, periodic paralysis and tick paralysis, two other uncommon causes of symmetric myopathies, predominantly affect the proximal large muscles rather than the cranial nerves.

Although certain marine species, frogs, and snakes produce paralytic toxins, these are not common in most areas of the United States and the diagnosis will likely be based on history of exposure (Table 2). Most other central neurologic lesions, such as strokes, tumors, and trauma, present with unilateral findings and some degree of an altered level of consciousness.

Case Continued

A second noncontrast head CT shows unremarkable findings, and lumbar puncture results are normal. Routine laboratory testing does not reveal any abnormalities. The medical team contacts family to get more history, and they report that the patient often improperly stores his food and gets food poisoning frequently. The department of health is contacted about the possibility of botulism.

What is botulism?

Botulinum neurotoxin (BoNT) is considered the most potent toxin known, and there is continued concern that it could be used as a bioterrorism agent. The toxin interferes with release of acetylcholine from presynaptic motor and autonomic nerve terminals, which prevents signaling at the neuromuscular junction and autonomic terminals. The result is flaccid paralysis and autonomic dysfunction. The toxin does not interfere with other signaling pathways, so sensation and cognition remain intact.

Botulinum toxin is produced by *Clostridium botulinum*. Clostridia are gram-positive, spore-forming bacteria found in the soil, seawater, and air. As a result of this ubiquity, outbreaks have been reported all over the world.[2] Although there are seven serotypes of BoNT—types A through G—serotypes A, B, and E cause the vast majority of disease in humans. Type F can affect humans, but testing for the various species of *Clostridium* that produce this toxin is difficult; therefore, its extent may be underreported.[3] In the United States, type A toxin is typically found in the soil west of the Mississippi River, whereas type B is found to the east.[2] Type E has been found predominately in the Pacific Northwest, Alaska, and areas near the Great Lakes.[2]

Clostridium spores are dormant and highly resistant to environmental damage. They can withstand boiling at 212°F (100°C) for hours but can be destroyed by 30 minutes of moist heat at 248°F (120°C).[2] Risk factors for the germination of spores in food are pH greater than 4.5, sodium chloride content less than 3.5%, and a low nitrite concentration. Acid-based preservatives, such as citric acid, are often added to canned vegetables for this reason. Similarly, the addition of nitrites to cured meat is intended to prevent germination of spores. Food contaminated with toxin types A and B may look or smell putrefied because of the action of proteolytic enzymes.[2] However, food contaminated with type E toxin may look and taste normal because the organisms that produce toxin type E are saccharolytic and not proteolytic.[2]

A total of 112 laboratory-confirmed cases of botulism were reported to the CDC in 2010.[4] Foodborne botulism accounted for nine cases (8%); infant botulism, 85 cases (76%); wound botulism, 17 cases (15%); and botulism of unknown or other etiology, one case.[4] Infant botulism usually is due to the ingestion of spores that are able to grow and produce toxin in the immature gut. For this reason, the course is more indolent, as

it takes time for the toxin to be produced. Wound botulism is seen predominately in injection drug users, especially those who inject subcutaneously ("skin-pop"). A fourth classification, or undefined botulism, is recognized; this type has also been designated adult-type infant botulism.[3] This delayed-onset neurologic syndrome occurs mainly in adults with abnormal gastrointestinal pathology that affects natural gut immunity, such as peptic ulcer disease, diseases requiring Billroth surgery, and Crohn disease.

Of the nine cases of foodborne botulism in 2010, toxin type A accounted for three cases; toxin type B, three cases; and toxin type E, two cases; the toxin type was unknown for one case.[4] In infant botulism cases, toxin type A accounted for 30 cases (35%) and toxin B for 54 (64%). One case was caused by toxin type F (produced by *Clostridium barattii*).[4] The 17 cases of wound botulism were from California (16 cases) and Arkansas (one case). Toxin type A accounted for 15 of the cases and toxin type B for one; the toxin type was unknown for one case.[4] All but one of the cases of wound botulism were in injection drug users.

Inadvertent (injection-related) botulism is a fifth category associated with therapeutic misadventures from injection of pharmaceutical botulinum toxin.[3] Both botulinum type A toxin and type B toxin are available for use in cosmetic procedures and to treat a variety of spastic myopathies. An infamous outbreak has been reported involving a physician who inappropriately used laboratory-grade botulinum toxin for cosmetic purposes and poisoned four people, including himself.[5] Possible use of inhalational botulism for bioterrorist purposes is a major concern, but to date there have been only three cases of inhalational botulism, and these were in lab workers who were working with the toxin.[3]

In the past 50 years, home-processed food has accounted for 65% of foodborne outbreaks and commer-

Table 3. The Dozen D's: Symptoms of Botulism in Order of Manifestation[3]

- Dry mouth
- Diplopia (double vision)
- Dilated pupils
- Droopy eyes (ptosis)
- Droopy face
- Diminished gag reflex
- Dysphagia (difficulty swallowing)
- Dysarthria (difficulty articulating speech)
- Dysphonia (difficulty phonating/whispered speech)
- Difficulty lifting head
- Descending paralysis
- Diaphragmatic paralysis

Adapted from Horowitz.[3]

cially processed food for 7%.[2] In the remaining cases, the origin remains unknown. Common errors are improper refrigeration and sterilization of low-acid and low-salt foods.

How is the diagnosis of botulism made?

The first case of a botulism outbreak or an isolated case is often a diagnostic dilemma. True outbreaks in which more than one person is affected often are diagnosed once a link between the source and disease is established. Diagnosis of the first case of a foodborne outbreak is often delayed, as the initial phase of the disease typically involves gastrointestinal symptoms such as nausea and abdominal pain, which could be mistaken for other forms of food poisoning. These symptoms usually begin from 1 to 5 days after exposure. Wound botulism and injection-related exposures do not cause gastrointestinal symptoms. Neurologic symptoms can develop as early as 12 to 24 hours after exposure and classically involve cranial nerves first. Even when these features manifest, misdiagnosis occurs easily, given the relative frequency of the other likely etiologies. A descending flaccid paralysis develops. Bulbar palsies present first as paralysis of the motor functions of the cranial nerves.[3] Eventually, the larger muscles of the arms and legs are affected, proximally to distally. Ultimately, if botulism is unrecognized and untreated, the intercostal muscles and the diaphragm are compromised and respiratory failure occurs. Once paralysis progresses to respiratory failure, the patient will need ventilatory support until the motor end-plate recovers, which could take several months. Table 3 lists botulism symptoms, often referred to as the "dozen D's," in order of occurrence[3]; the presence of any three of these symptoms should prompt suspicion for botulism. Botulism does not affect mentation or sensation, so any alterations in mental status or sensorium should suggest other etiologies. Fever is also not associated with botulism, as the underlying issue is not a *Clostridium* infection, but rather an accumulation of neurotoxin. In wound botulism, it is not common to see signs of cellulitis or fever for similar reasons.

Infant botulism presents differently. Approximately 95% of cases occur before the age of 6 months, and it is rare for infant botulism to occur after age 1 year.[3] Symptoms begin with bulbar weakness, such as poor suck and inability to hold the head upright. Caregivers frequently report constipation in the child. This nonspecific presentation often causes misdiagnosis early in the disease course. As infant botulism progresses, a more generalized muscle weakness occurs, creating the common findings of a hypotonic, floppy baby; a weak, hoarse cry; and ptosis. Most cases do not progress to respiratory failure, but all babies in which the diagnosis of botulism is suspected need to have ICU-level monitoring for respiratory failure and secondary infections.

Ultimately, clinical suspicion based on history and physical exam should be enough to prompt the physician to discuss the case with their state department of health and ultimately the CDC. CSF analysis to test for GBS and its variants can take days, if not weeks, so a prudent option is to seek the antidote while these tests are running.

Testing with administration of edrophonium, an acetylcholinesterase inhibitor, can distinguish myasthenia gravis from botulism. However, the test is subjective and equivocal results can occur. In myasthenia gravis, the edrophonium should cause a transient but dramatic improvement in muscle strength. Edrophonium should have no effect in botulism as there is no acetylcholine being released to metabolize. However,

early in the course of the disease, there still may be some acetylcholine release, so the test may be read as a false positive.

Electromyography can also help distinguish botulism from other etiologies of muscle weakness, but an experienced practitioner is required to administer the test and interpret the results. It is rare to be able to have this test performed quickly in an emergency setting.

Serum, stool, and suspected contaminated foods can be sent to the local health department or the CDC for a mouse bioassay and polymerase chain reaction testing for the toxin.

What is the role for antitoxin?

As of March 2010, the CDC only stores a heptavalent botulism antitoxin for noninfant botulism.[6,7] This antitoxin is an equine-derived Fab antibody fragment directed against botulism types A through G. The risk of hypersensitivity reactions is substantially lower with the heptavalent antitoxin than with the previous whole antibody bivalent antitoxin.

Infant botulism is treated with a pentavalent (types A through E) human-derived immune globulin that is often referred to as BabyBIG (botulism immune globulin). This antitoxin is harvested by plasmapheresis from human donors who have received multiple immunizations with pentavalent botulinum toxoid.[2] Because this antitoxin is human derived, it is associated with lower risk of hypersensitivity reactions than the equine-derived adult product. It is indicated in the treatment of patients younger than 1 year with infant botulism caused by toxin type A or type B.

Ideally, the antidote should be administered early enough to prevent respiratory failure and intubation. The antitoxin cannot reverse paralysis that has already occurred. In one study, mortality was 10% in patients who received the equine derived antitoxin within 24-hours of onset of symptoms, 15% when it

was administered later than 24 hours, and 46% when not given at all.[8] Death is often due to complications from being ventilator-dependent and secondary infections. Additionally, infants treated with botulism immune globulin have significantly shorter hospital and ICU stays, as well as a shorter duration of mechanical ventilation and parenteral feeding.[2]

How is botulinum antitoxin obtained?

Once the diagnosis of botulism is entertained, the local health department or poison center should be contacted to facilitate discussion with the CDC. The CDC stores antitoxin at nine regional facilities and makes the final decision to release the antitoxin on a case-by-case basis.[6] The California Department of Health manages use of BabyBIG.

Case Resolution

The patient received the heptavalent botulinum antitoxin 36 hours after presenting to the emergency department. He eventually was sent with a tracheostomy and feeding tube to a subacute care facility. The patient could move his fingers and toes at the time of discharge to this facility. **EM**

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