Clinical Reasoning: A 44-year-old woman with rapidly progressive weakness and ophthalmoplegia

SECTION 1
A 44-year-old woman with rapidly progressive weakness and ophthalmoplegia presented to the emergency department. Two days prior to presentation, she had symptoms of nausea and vomiting, headache, fever, and diarrhea. On examination, she was noted to have bilateral ptosis and mydriatic, reactive pupils. Eye movements were limited in all cardinal directions. She was areflexic except for trace reflexes in the patellar tendon bilaterally; toes were mute. Sensation was grossly intact.

Questions for consideration:
1. Where would you localize this patient’s rapidly progressive, generalized weakness?
2. What is the differential diagnosis for a patient with rapidly progressive weakness and ophthalmoplegia?
Rapidly progressive weakness can localize to many areas. In this patient, ophthalmoplegia and facial weakness with intact mental status helps narrow the localization to brainstem, nerves, or neuromuscular junction.

The differential diagnosis for rapidly progressive weakness with ophthalmoplegia is relatively limited (table). The striking features on examination were rapid decompensation along with nearly absent reflexes and prominent bulbar symptoms. The initial concern was for acute inflammatory demyelinating polyneuropathy (AIDP), possibly due to HIV given her history of IV drug use. The differential diagnosis for rapidly progressive weakness with ophthalmoplegia is relatively limited (table). The striking features on examination were rapid decompensation along with nearly absent reflexes and prominent bulbar symptoms. The initial concern was for acute inflammatory demyelinating polyneuropathy (AIDP), possibly due to HIV given her history of IV drug use. Another consideration was a myasthenia gravis (MG) crisis. In a patient consuming questionable food products or with a history of heroin abuse, botulism toxicity was a consideration. The patient’s complaints of abdominal pain, vomiting, and diarrhea preceding presentation made acute intermittent porphyria a possibility.

**Question for consideration:**

1. What diagnostic evaluation should be performed in this patient?
SECTION 3
EMG with nerve conduction studies (NCS) of radial, median, ulnar, and sural nerves showed normal sensory nerve action potential (SNAP) amplitudes and conduction velocities. Motor responses had normal amplitudes, latencies, conduction velocities, and F-waves. Motor unit action potentials (MUAP) were absent in proximal muscles, but present in the distal muscles, though they tended to be small and short in duration. There were widespread sharp waves and fibrillations.

Initial laboratory testing including serum creatine kinase, heme-8, C-reactive protein, and chemistry panel was unremarkable. A lumbar puncture revealed the following: 1 leukocyte per mm³, 1 erythrocyte per mm³, glucose 99 mg/dL (serum 168 mg/dL), protein 26 mg/dL. Venereal disease research laboratory, cryptococcal antigen, fungal culture, viral PCRs (herpes simplex virus, varicella-zoster virus, West Nile virus, cytomegalovirus, Epstein-Barr virus, and enterovirus), immunoglobulin G index, and oligoclonal bands were all negative. An MRI of the brain and cervical spine was unremarkable. A thorough skin evaluation was only notable for track marks on bilateral forearms.

Questions for consideration:
1. What treatment should be pursued?
2. Is further diagnostic testing indicated?

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SECTION 4
The patient was empirically administered IV immunoglobulin (IVIg 0.4 g/kg/day for 5 days) on presentation over concern for AIDP, achieving minimal improvement in symptoms. An expanded panel of laboratory studies and delayed results from initial investigations (including GQ1b-Ab, AChR-Ab, MusK, urine porphobilinogen, HIV antibodies, viral hepatitis serologies, Lyme antibiotics, heavy metals, thyroid function tests, aldolase, and plasma catecholamines) were notable only for a moderately elevated erythrocyte sedimentation rate at 66 mm/hour. Since a lumbar puncture is only 50% sensitive for cytoalbuminologic dissociation in the first week of symptoms but increases to 75% by the third week, a repeat lumbar puncture was performed, also showing a normal profile.

Based on the negative clinical workup, lack of cytoalbuminologic dissociation, and minimal response to IVIg, the clinical picture was concerning for acute botulism. Samples of the patient’s pre-IVIg-administration serum and stool were sent to the health department for testing and she was administered the quadrivalent botulinum immunoglobulin on day 6 of hospitalization.

To confirm our diagnosis of botulism, follow-up EMG/NCS was performed, revealing decreased compound motor action potential (CMAP) amplitudes as compared to previous results. Distal latencies, conduction velocities, and F-wave latencies remained normal. Repetitive stimulation was performed at 3 Hz with no decrement of 10% or more (figure, A). Rapid repetitive stimulation was performed at 50 Hz, with no increment (figure, B). EMG of multiple muscles showed positive sharp waves, fibrillation potentials, and few units with poor activation.

Question for consideration:
1. Are the EMG/NCS findings consistent with a diagnosis of botulism?
SECTION 5
The repeat EMG/NCS study showed abnormal spontaneous activity, decreased motor activation, and myopathic motor unit potentials (decreased size and duration of motor units). The sensory nerves remained normal; however, the motor nerves had developed decreased CMAP amplitudes without evidence of demyelination (normal distal latencies, conduction velocities, and F-waves). This pattern suggested a myopathic or neuromuscular junction disorder. The clinical history, normal creatine kinase, bulbar-predominant pattern of weakness, and EMG/NCS were most consistent with a diagnosis of botulism. The classic findings on electrodiagnostic studies in botulism are decreased amplitude in MUAPs with facilitation at 20–50 Hz using repetitive stimulation. Of note, facilitation with repetitive stimulation is only seen in 50%–60% of patients, and it is typically less dramatic than in Lambert-Eaton myasthenic syndrome.

Question for consideration.
1. What evaluations can be used to confirm a diagnosis of botulism?
SECTION 6
The diagnosis of botulism is made using a mouse inoculation assay. Serum or stool samples from affected individuals are injected into mice along with toxin type-specific antitoxin. Symptoms develop in mice without the antitoxin against the specific toxin type the affected individual carries. The assay is dependent on the presence of active botulinum toxin and most sensitive within 24 hours of presentation, but can still be positive up to 7 days after presentation. Overall sensitivity is low (33%–46%). Stool can also be cultured for the organism, which increases sensitivity to ~70%. In our patient, the mouse inoculation assay was negative; however, mass spectrometry on the serum sample was positive for botulinum toxin, type A.

Our patient survived 2 ventilator-associated pneumonias and a urinary tract infection before being weaned off the ventilator and percutaneous tube feeds. Four months after her admission, she was able to ambulate independently and care for herself. She continues to make gains in strength and endurance.

DISCUSSION Clostridium botulinum is a Gram-positive, anaerobic, spore-forming bacillus. Currently, there are 7 toxin types (A–G), though human botulism is primarily caused by A, B, and E. The most common form is infant botulism (71%), then foodborne (24%), and wound (3%). Symptoms typically begin 18–36 hours after exposure for foodborne botulism and 4–14 days after exposure for wound botulism. In foodborne botulism, preformed toxin is consumed—causing early symptoms of nausea, vomiting, and diarrhea—while in wound botulism, the organism grows within a wound and produces toxin. An increased frequency of wound botulism was seen several years ago attributed to the popularity of skin popping (subcutaneous injection of heroin) with an impure form of heroin known as black tar heroin. Our patient had prominent track marks and subcutaneous granulomas on both of her forearms from IV drug use and intermittent skin popping, which was likely the source of her exposure.

The most common clinical presentation of botulism is early cranial nerve abnormalities, gastrointestinal symptoms, and autonomic symptoms (dry mouth, blurred vision, bradycardia) without the characteristic volatile dysautonomia of AIDP, followed by a descending paralysis. Ophthalmoparesis with dilated pupils that are fixed and poorly reactive is present in about half of patients with botulism. Early differentiation of botulism from other neurologic emergencies such as AIDP or MG can be challenging, and the emphasis should be stabilization in a critical care setting while undertaking an expedited diagnostic evaluation focusing on early therapeutic intervention. The initial investigations should include a thorough physical examination, electrodiagnostic studies, a CT followed by MRI (time permitting) to rule out brainstem pathologies, a lumbar puncture to investigate CNS infections vs AIDP, and standard serologic studies focused on precipitants of acute infectious etiologies such as HIV, diphtheria, and polio. Botulinum toxin is extremely potent and irreversibly cleaves SNAP-SNARE-complex proteins, important facilitators of vesicle fusion at the synaptic membrane, thereby preventing synaptic vesicle release. Antitoxin binds free toxin and prevents it from inactivating further synapses. Due to the potency of botulinum toxin, antitoxin should be empirically administered immediately if the clinical suspicion is high though clinical trial data are scarce. Currently, mortality is relatively low at 3%–5%, but there is often a long invalid period with average intubation lasting 2–8 weeks. Patients often recover completely if they survive the initial high-risk ventilated period. However, it is a slow recovery process and some patients still have exercise limitations and subjective shortness of breath years after diagnosis.

AUTHOR CONTRIBUTIONS
Dr. Karisa Schreck analyzed and interpreted the data, conceptualized the case, and wrote the manuscript. Dr. Logan Schneider analyzed and interpreted the data and wrote the manuscript. Dr. Romerygyko G. Geocadin analyzed the case and revised the manuscript for intellectual content.

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