TOXINS AND DISORDERS OF NEUROMUSCULAR TRANSMISSION

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Toxin-induced Acute Weakness

Toxin-induced weakness is rare. However, it is important to consider toxins in the differential diagnosis of both spastic and flaccid weakness, especially when the history suggests an exposure, because removal of exposure source (e.g. tick paralysis) and administration of antidotes or antitoxin can be vital in management.

Clinical presentation may provide the key to diagnosis. Cholinergic symptoms with or without seizures should prompt consideration of organophosphate, carbamate or nicotine toxicity. Descending paralysis is the hallmark of botulism, while ascending paralysis is characteristic of the demyelinating polyneuropathy of diphtheria. Botulism, diphtheria, tick paralysis and anthracenone toxicity are associated with flaccid paralysis. Tetanospasmin, strychnine, and latrotoxin (black widow spider) cause severe muscle spasms. Botulism, scorpion venom, and *Elapidae* snake venom are associated with cranial nerve palsies.

The following text will review the pathophysiology, clinical features, and treatment of selected toxins that cause acute weakness secondary to effects at the neuromuscular junction.

Case #1

A husband and wife present to the Emergency Department (ED) with weakness, dizziness, and double vision. Two days prior, they had received "local injections" at a nearby clinic. The next day, they began to experience dizziness and weakness, which worsened over the following 24 hours, leading to their presentation in the ED. On examination, they have normal mental status. Pupils are 6 mm and nonreactive. They have ophthalmoparesis, dysarthria, dysphagia, and diffuse weakness with normal sensory exam. Investigation of the nearby clinic and the "local injections" received two days prior to presentation reveals administration of botulinum toxin of research grade that is 20,000 times as concentrated as medical grade botulinum toxin.

The source of botulinum toxin is the bacteria *Clostridium botulinum* (toxin types A, B, and E). The bacteria *Clostridium butyricum* (toxin type E), *Clostridium argentinense* (toxin type G) and *Clostridium baratii* (toxin type F) are less common sources of botulinum toxin.[1] Exposure can occur by:
   ❖ Ingestion of food contaminated by *Clostridium* species
   ❖ Wound exposure to *Clostridium* species
   ❖ *In vivo* intestinal colonization
   ❖ Bioterrorism
   ❖ Injection of pharmaceutical or research grade botulinum neurotoxin

Botulinum toxin is the most potent toxin known. The lethal dose for humans, by oral exposure, is 1 mcg/kg.[2] Approximately 70% of outbreaks involve only one person, 20% involve two people, and 10% involve more than two people. Toxin type E has the shortest incubation period at 0-2 days, with a range of 0-7 days for all toxin types (A, B, E). Toxin type A is associated with more severe illness.[3]

The mechanism of action of botulinum toxin is inhibition of presynaptic vesicular fusion resulting in prevention of acetylcholine (ACh) release at the neuromuscular junction. Each of the toxin types cleaves a specific protein of the vesicular fusion system. Types A, C, and E cleave synaptosomal associated protein (SNAP)-25. Types B, D, F, and G cleave vesicle-associated membrane protein (VAMP)/ synaptobrevin.

Clinical presentation is characterized by cranial nerve palsies followed by descending, flaccid paralysis. However, gastrointestinal symptoms may predominate initially (especially in toxin type E botulism), resulting in delay of diagnosis. Diagnosis is made by stool studies (bacterial culture or toxin level), serum toxin level, and/or electromyography with nerve conduction studies (EMG/NCS). Toxin levels were positive in approximately 40% of serum and stool specimen obtained within 3 days of exposure and approximately 20% of specimen obtained after 3 days. Stool specimen were positive in 37% of specimen obtained after 3 days.[3] Food specimen may also be tested by anaerobic culture and mouse bioassay. Edrophonium testing has been used to differentiate botulism from myasthenia gravis.

CDC definition for foodborne botulism in a patient with bulbar weakness and symmetrical paralysis [4]:
- ❖ Botulinum toxin detected in serum, stool, or food specimen **OR**
- ❖ Positive stool cultures for *C .botulinum* **AND**
- ❖ Clinically compatible case with an epidemiologic link to another confirmed case

Neurophysiological findings of botulism include [5]:
- ❖ Reduced resting compound motor action potential (CMAP) amplitude
- ❖ ≥40% facilitation of CMAP amplitude after activation
- ❖ Persistence of facilitation for ≥2 minutes after activation
- ❖ Absence of post-activation exhaustion

The diagnosis of botulism should result in immediate notification of the local health department. Supportive care should be provided, and gastrointestinal decontamination with activated charcoal should be considered.[6] In cases of wound botulism, wound debridement is essential.

Botulinum heptavalent antitoxin is obtained from the CDC, along with dosing instructions, and should be given in severe cases. Acute allergic reactions may occur during administration of the equine-derived antitoxin. Pretreatment with antihistamines with or without epinephrine may be considered, and immediate availability of these medications during the initial infusion is wise.[7]

Use of molecules derived from 3,4-diaminopyridine for the treatment of botulism is under investigation.[8, 9] Human-derived botulinum immune globulin should be given in cases of infant intestinal botulism.[10]

Case #2

Five people from a picnic present with nausea, vomiting, abdominal pain, blurred vision, dysarthria, salivation and paresthesia of the tongue and lips. They are diagnosed with food poisoning. Two days later, two more patients present with similar symptoms after a picnic and are diagnosed with gastroenteritis. Two days after that, a family of six presents with nausea, vomiting, abdominal pain and blurred vision. One 45 year-old woman complains of chest pain, diaphoresis, and twitching muscles. By the following day, 264 cases of similar symptoms are reported across 3 states. All symptoms occur within 2 hours of eating. An astute clinician notes miosis in one of these patients and calls the health department. After surveillance and testing of food sources, residues of a carbamate insecticide are found in a supply of watermelon. The watermelon is traced to a specific distributor and further exposures are drastically limited.[11]

Organophosphate and carbamate cholingergic toxicity may occur by exposure to insecticides (e.g. suicidal or unintentional ingestion, as well as dermal exposure in areas recently treated) or via bioterrorism (e.g. VX, sarin gas). The mechanism of toxicity is inhibition of acetylcholinesterase (AChE) via bonding to a serine residue at the ACh site, resulting in accumulation of acetylcholine at the neuromuscular junction and subsequent desensitization of ACh receptors to ACh. The structure of carbamate insecticides is very similar to the AChE inhibitors used therapeutically for myasthenia gravis, including pyridostigmine.

Clinical presentation is characterized by systemic cholinergic toxicity:
- ❖ Agitated delirium/Coma
- ❖ Seizures
- ❖ Miosis
- ❖ SLUDGE symptoms*
- ❖ Bronchospasm/Bronchorrhea
- ❖ Bradycardia
- ❖ Muscle fasciculations
- ❖ Paralysis

*SLUDGE symptoms include Salivation, Lacrimation, Urination, Defecation, increased Gastrointestinal motility, and Emesis.

Most patients develop symptoms within 8 hours of exposure and nearly all have symptoms by 24 hours.[12] Organophosphates have higher central nervous system penetration than the carbamates, so organophosphate toxicity is more likely to result in encephalopathy and seizures. Organophosphate molecules can bind irreversibly to acetylcholinesterase after 12-24 hours, also known as aging. Carbamates do not age, so duration of symptoms is usually less than 24 hours in carbamate toxicity.

Diagnosis is made by the characteristic constellation of symptoms and may be supported by additional testing including plasma and/or red blood cell (RBC) cholinesterase levels, EMG/NCS, and atropine challenge testing. The toxicologic differential diagnosis of cholinergic syndrome includes pharmaceutical cholinesterase inhibitors (e.g. pyridostigmine), cholinomimetics (e.g. pilocarpine, muscarine-containing mushrooms) and nicotine alkaloids.

RBC cholinesterase levels are more reflective of synaptic inhibition and are more specific for exposure, but are also more difficult to measure. Plasma cholinesterase (butyrylcholinesterase) levels decline before RBC cholinesterase levels and are easier to assay. Therefore, a plasma cholinesterase level is a better choice in acute poisoning.[13] EMG/NCS in organophosphate toxicity would demonstrate spontaneous repetitive potentials or fasciculation following single stimulation.

Atropine challenge testing can be diagnostically useful in cases suggestive of cholinergic syndrome in which no exposure history exists. A test dose of 1-5 mg of the antimuscarinic agent, atropine, given intravenously produces symptoms of antimuscarinic toxicity in the absence of organophosphate or carbamate compounds. In the presence of one of these compounds, muscarinic cholinergic signs and symptoms persist.[12] This test is most useful in severe toxicity, as mild-to-moderate cases may respond to the test dose of atropine.

Morbidity and mortality from organophosphate and carbamate insecticide toxicity occurs secondary to (1) nicotinic effects on skeletal muscle resulting in respiratory paralysis, (2) muscarinic effects on the cardiopulmonary systems resulting in bradycardia and bronchorrhea, or (3) seizure and coma resulting in hypoxia.[13]

Treatment of cholinergic syndrome starts with supportive care and decontamination via clothing removal and bathing of the skin in cases of dermal exposure. Gastrointestinal decontamination with single dose activated charcoal should be considered in cases of insecticide ingestion.[13] Treatment of cholinergic symptoms secondary to organophosphate toxicity is atropine for muscarinic symptoms (e.g. bronchorrhea, bronchospasm, vomiting, diarrhea) and pralidoxime for nicotinic symptoms (i.e. weakness). Because carbamates do not age, consider avoiding pralidoxime if the agent is known to be a carbamate as the carbamylated AChE reactivates rapidly; therefore, the pralidoxime may worsen AChE inhibition temporarily. When pralidoxime is given for organophosphate toxicity, it should be administered before aging occurs. Seizures are best treated with benzodiazepines.

Case #3

An 8 year-old girl presents to the ED with ascending weakness. She had been previously healthy and takes no medications. Symptoms began four days prior to presentation with paresthesia of the hands and feet, and her family noted that she seemed irritable. She noted weakness in her ankles on the day prior to presentation with progression over the next 24 hours to include the legs and hands. She also noted slurred speech and difficulty swallowing. Travel history includes a recent trip to Colorado one week prior to presentation; all others in her family are asymptomatic. On examination, she is somnolent and irritable. Pupils are reactive with intact extraocular movements. Mild bifacial weakness is present. Strength is 4/5 in proximal upper extremities; otherwise strength is 3/5. MSRs are absent. Laboratory studies reveal normal complete blood count and comprehensive metabolic panel. CSF analysis: RBC 0, WBC 1, Protein 70 mg/dL, Glucose 40 mg/dL. The diagnosis of Acute Inflammatory Demyelinating Polyneuropathy is made. EEG and Brain MRI are planned in evaluation of her somnolence. The EEG technician discovers the diagnosis when a tick is found on her scalp during electrode placement.

Tick paralysis occurs by exposure to the Ixodid family of ticks. In North America, *Dermacentor andersoni* and *Dermacentor variabilis* are the ticks most commonly associated with tick paralysis. In one large case series, 21% of cases were adults (>16 years of age). Of adults, 83% were men. Of children, 67% were girls.[14]

Ixovotoxin is excreted from the salivary glands of the tick and prevents ACh release at the neuromuscular junction. Several days are required for the toxin to accumulate and provoke symptom onset.[15] Irritability, ataxia, paresthesia, and diarrhea may precede the onset of an ascending, areflexic, flaccid paralysis. Weakness of respiratory muscles may necessitate mechanical ventilation. Cranial nerve involvement can result in facial weakness, ophthalmoparesis, and fixed, dilated pupils.

Diagnosis is made by physical examination revealing the tick, and is commonly made by nursing staff or EEG technicians. Differential diagnosis includes acute inflammatory demyelinating polyneuropathy (AIDP), botulism, and myelopathy. Composition of cerebrospinal fluid is normal, thus helping to differentiate tick paralysis from AIDP.[16]

Treatment begins with tick removal and supportive care. Care must be taken to remove the entire tick. This is done by using tweezers to grasp the body of the tick as close to the skin as possible and pulling with steady pressure. Maximal clinical weakness may not occur until after the tick is removed. Antitoxin has been used rarely for severe cases, as this canine-derived antitoxin is very antigenic and is associated with high rates of acute allergic reaction and serum sickness.[17]

Case #4

*A 47 year-old man presents to a local ED for a snake bite. He reports that he was using a stick to "help it molt" and the snake climbed the stick and bit him on the left index finger. Shortly thereafter, he began to experience weakness of his arms and legs. On examination, he is diffusely weak with dysarthria and hyporeflexia. Detailed questioning of the patient reveals that the snake in question was an Eastern Green Mamba (*Dendroaspis augusticeps*) in his private collection of fourteen exotic snakes. A call is made to the local zoo for possible acquisition of antivenom.*

The Eastern green mamba is a member of the Elapid family of snakes and its venom contains two toxins, dendrotoxin and fasciculin. Dendrotoxin inhibits neuronal potassium channels, facilitating ACh release. Fasciculin inhibits acetylcholinesterase. The combination of these toxins results in release of large amounts of ACh into the neuromuscular junction, with accumulation of the neurotransmitter due to inhibition of acetylchoinesterase. Clinical presentation is characterized by local swelling at the bite site and nausea, followed by cranial nerve palsies and paralysis.

Because of the prevalence of Crotalids in the US and the relative lack of a significant Elapid population, the most commonly used antivenom in the US is Crotalid antivenom. However, this antivenom is ineffective for Elapid species, and there are countless Elapids in private collections across the country. Elapid antivenom is more difficult to obtain and usually requires coordination with a poison center (1-800-222-1222) or local zoo. The Association of Zoological Parks and Aquariums (301-562-0777) keeps an Antivenom Index that can be useful for determination of appropriate therapy and can direct acquisition of the antivenom.

Treatment for an Elapid snake bite is pressure immobilization of the wound with supportive care. Monovalent antivenom, if available, should be administered if the species is known. If the species is unknown or a monovalent antivenom is not available, a polyvalent antivenom should be used. As the local reaction to the bite may be minimal and symptoms may be delayed in onset, empiric administration of antivenom should be considered if envenomation of an identified Elapid snake is strongly suspected and the specific antivenom is available. Pretreatment with antihistamines with or without epinephrine may be considered, and immediate availability of these medications during the initial infusion is wise. Local wound care should be provided. Tetanus prophylaxis should be considered. Routine use of antibiotics is not recommended.

The above patient was given 5 vials of equine-derived South African polyvalent antivenom obtained from the Indianapolis Zoo. He experienced resolution of his neurologic symptoms and did not have an acute allergic reaction to the antivenom, but did present 2 days later with symptoms of serum sickness.

Case #5

A 35 year-old man presents to an Arizona ED with nausea and muscle spasms. His blood pressure is 160/95 and he has diffuse rigidity on examination. He reports that he noted a sharp pain in his leg after getting dressed, about an hour prior to symptom onset. During his ED stay, his muscle spasms worsen resulting in significant pain and difficulty breathing. He is given benzodiazepines for the spasms and is intubated with mechanical ventilation for respiratory support.

Latrodectus mactans (black widow spider) is found in warm regions of the United States. It is the only species of the widow spiders that has the characteristic red hourglass markings, and this is more predominant in the female of the species. The females are also larger and more venomous. Black widow spiders are nocturnal and reclusive. Thus, envenomation occurs when their webs are disturbed or when inadvertent contact is made in clothing or shoes.

There are six active components of black widow spider venom.[18] Of these, α-latrotoxin is toxic to humans. Latrotoxin stimulates neurotransmitter release by intracellular activation of exocytosis. Thus, fusion of vesicles containing norepinephrine, dopamine, acetylcholine and others occurs, resulting in vesicle depletion.

The bite itself causes a sharp local pain, followed by the development of a bite mark. The bite may be followed by proximal migration of the pain with subsequent development of "latrodectism" over the next 30-60 minutes. Latrodectism is characterized by diffuse muscle spasms and rigidity, associated with hypertension, tachycardia, nausea, and diaphoresis.

Muscle spasms typically start at the site of envenomation and spread proximally. The larger muscle groups are involved earlier in the disease course. Classic findings include facial muscle spasm and severe spasm of the abdominal wall that may be misdiagnosed as surgical abdomen. No specific laboratory testing is available for confirmation of the diagnosis.

Supportive care with airway management and symptomatic benzodiazepines are the mainstays of therapy. Use of equine-derived black widow spider antivenom is controversial due to high rates of anaphylaxis and serum sickness and is therefore reserved for severe cases. Indications for use include severe muscle spasms, hypertensive crisis, and/or respiratory distress that do not respond to supportive therapies.[19] Pretreatment with antihistamines with or without epinephrine may be considered, and immediate availability of these medications during the initial infusion is wise. Local wound care should be provided. Tetanus prophylaxis should be considered. Routine use of antibiotics is not recommended.

*I give the American Academy of Neurology permission to use this written work for their education program. I retain the right to use this material for publication in textbook chapters and review articles written at the request of my colleagues. In addition to the references below, this syllabus has been adapted from the following chapter with references: Tormoehlen LM. "Neurotoxicology Emergencies." *Emergency Neurology.* Roos KL, ed. Springer, 2012.

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