

# NEUROTOXICOLOGY AND NEUROLOGIC EMERGENCIES

**Michel Toledano, MD**  
Mayo Clinic  
Rochester, MN

The central nervous system (CNS) and peripheral nervous system (PNS) are vulnerable to insult from a broad range of industrial and environmental toxins. Early identification of the exposure and the toxin can be instrumental in the diagnosis and management of toxin-induced neurological emergencies. Illustrative cases will be presented in an interactive manner in the accompanying course.

## Toxin-associated acute encephalopathy and seizures

Toxin-induced encephalopathy often results from a combination of cortical and white matter injury. The acuity and severity of the presenting symptoms depend both on the toxin itself as well as the dose and duration of exposure.

**Carbon monoxide:** Carbon monoxide (CO) is a tasteless, odorless, non-irritating, and toxic gas. It is formed from the incomplete combustion of carbon-containing fuels. Sources of carbon monoxide intoxication include motor vehicle exhaust, smoke inhalation, and combustion appliances (furnaces, water heaters, wood stoves). Carbon monoxide binds to hemoglobin to form carboxyhemoglobin. It competes with oxygen for binding with hemoglobin thus decreasing the oxygen carrying capacity of the blood and resulting in tissue hypoxia. CO also causes demyelination via lipid peroxidation.

Carbon monoxide intoxication is the commonest fatal accidental poisoning in the United States. Headache, dizziness, blurred vision, nausea, vomiting, and irritability are signs of early exposure. Additional manifestations include confusion, memory loss, drowsiness, disorientation, seizures, coma, and death. The classic cherry-red discoloration of the skin and cyanosis are rarely seen. Sequelae of severe hypoxia associated with acute toxicity include a broad range of extrapyramidal features, aphasia, spasticity, apraxia, dementia, cortical blindness, and seizures. An estimated 30% of patients experience a delayed onset encephalopathy after apparent full recovery.

Blood level testing of carboxyhemoglobin is sensitive but can be elevated in smokers. Carbon monoxide poisoning is associated with brain magnetic resonance imaging (MRI) lesions involving the globus pallidus and cerebral deep white matter. Lesions in the hippocampi, substantia nigra, cerebral cortex, and cerebellum can also be present. Prompt administration of hyperbaric-oxygen treatments following acute carbon monoxide poisoning may decrease the risk of short and long term cognitive sequelae.

**Methyl alcohol:** Methyl alcohol (methanol) is used as an industrial solvent and as adulterant to denature ethanol to prevent its abuse when used as an industrial solvent. Methanol neurotoxicity results from the end products of its metabolism: formaldehyde and formate. Most cases result from accidental ingestion or occupational exposure. Neurologic symptoms appear after 12-24 hours of intoxication and include an encephalopathy with visual symptoms (including blindness), and seizures. Other sign and symptoms include headache, nausea, and vomiting, abdominal pain, tachypnea, and anion gap metabolic acidosis.

The characteristic MRI finding is infarction or hemorrhage of the putamen. Treatment includes removal of methanol by lavage or hemodialysis, inhibition of its conversion to formaldehyde by fomepizole or ethanol, and correction of the accompanying metabolic acidosis with sodium bicarbonate.

**Organophosphates and Carbamates:** Organophosphate and carbamate cholinergic toxicity may occur by accidental or intentional exposure to insecticides or via bioterrorism (e.g., Tokyo Sarin gas attack in 1992). Most organophosphates and carbamates are lipid-soluble agents and are well absorbed from the skin, oral mucous membranes, conjunctiva, gastrointestinal, and respiratory routes. Inhibition of acetylcholinesterase is the likely mechanism of toxicity in the acute stage. Clinical presentation is characterized by systemic cholinergic toxicity (agitated delirium, miosis, bronchorrhea, increased secretions and gastrointestinal motility, bradycardia, and muscle fasciculations). Most patients develop symptoms within 8 hours of exposure and most will develop symptoms by 24 hours. Organophosphates are more likely to result in encephalopathy and seizures as they

have higher CNS penetration. Morbidity and mortality result from (a) muscarinic effects on cardiopulmonary system resulting in bradycardia and bronchorrhea, (b) nicotinic effects on skeletal muscle leading to respiratory paralysis, and (c) seizure and coma.

Diagnosis is made based by recognition of the characteristic toxidrome and can be supported by laboratory testing (plasma butyrylcholinesterase or RBC cholinesterase levels), and by response to an atropine challenge. The pungent-garlic-like odor associated with sulphurated organophosphate agents can be a valuable clue. Atropine can be used to counteract the muscarinic effects of organophosphates and carbamates. Pralidoxime is a reactivator of inhibited acetylcholinesterase and is effective at treating both nicotinic and muscarinic symptoms. It should **NOT** be administered without concurrent atropine as it can cause transient inhibition of acetylcholinesterase. Seizures are treated with benzodiazepines. Atropine has added benefit when used with benzodiazepines.

Agent	Treatments
<i>Ginkgo biloba</i> , False more mushroom ( <i>Gyrometra esculenta</i> , Isoniazid)	Pyridoxine
Methylxanthines (theophylline, caffeine)	Barbiturates > Benzodiazepine. Hemodialysis.
Baclofen withdrawal	Benzodiazepine

### Toxin-associated acute paralysis

**Botulinum neurotoxin (BoNT):** BoNT is the most potent toxin known. Oral intake of 1 mcg/kg is lethal in humans. *Clostridium botulinum*, a gram negative, anaerobic, rod-shaped bacteria, which produces BoNT types A, B, and E which are the most common cause of human botulism. Ingestion of food contaminated by *Clostridium* species is the most common source of exposure in adults but other known or potential sources include, wound exposure to *Clostridium* species, *in vivo* intestinal colonization, injection of pharmaceutical BoNT, and bioterrorism.

The mechanism of action is inhibition of presynaptic vesicular fusion which prevents acetylcholine release at the neuromuscular junction. Clinically, it presents with cranial nerve palsies followed by descending, flaccid paralysis. Gastrointestinal symptoms may precede weakness which can be a clue.

Diagnosis is made based on serum toxin level, stool studies (toxin level and/isolation of *clostridium* spores), as well as electromyography with nerve conduction studies.

BoNT heptavalent antitoxin is available and should be given in moderate to severe case. Antitoxin is most effective when administered early. Close monitoring of respiratory function and intensive care admission in those with evidence of respiratory compromise are important component of management.

Toxin	Bacterial source	Clinical presentation	Treatment
Tetanospasmin	<i>Clostridium tetani</i>	Tetany (opisthotonos, trismus, risus sardonicus), increased sympathetic activity	Diphtheria antitoxin Antibiotics
Diphtheria toxin	<i>Corynebacterium diphtheriae</i>	Tonsillar pseudomembrane followed within weeks by ASCENDING flaccid paralysis	Tetanus immunoglobulin

**Tick paralysis:** Ixovotoxin is excreted from the salivary glands of the Ixodid family of ticks. Ixovotoxin prevents acetylcholine release at the neuromuscular junction resulting in "tick paralysis." In North America, *Dermacentor andersoni* and *Dermacentor variabilis* are the ticks most commonly associated with this disorder. In Australia tick paralysis is associated with the scrub tick, *Ixodes holocyclus*.

It takes several days for the toxin to accumulate and provoke symptoms and a history of exposure may not be readily apparent. Fatigue, myalgia, paresthesia, ataxia, and irritability/restlessness can precede the onset of ascending flaccid paralysis. Fever is absent. Paralysis may be localized to one arm or leg, and isolated facial

paralysis can occur in patients who have ticks attached to their external ear canal. Although patients complain of sensory disturbances, sensation is intact with patients with tick paralysis. Composition of CSF is normal helping to distinguish it from acute inflammatory demyelinating polyneuropathy.

Patients with paralysis due to *Dermacentor* ticks will substantially improve within a few hours after the removal of the tick. However, weakness and paralysis may worsen for 24 to 48 hours after *Ixodes holocyclus* ticks are removed.

**Shellfish and Pufferfish:** Tetrodotoxin (TTX) is produced by marine bacteria of the Vibrionaceae family and selectively block the action potentials of voltage gated sodium channels. TTX has been isolated from animals of four different phyla, including puffer fish, the California newt, and the blue-ringed octopus. The toxin is concentrated in the liver, viscera, and gonads. Onset of symptoms usually occurs within 30 minutes of ingestion. Oral paresthesias are the first symptom, followed by gastrointestinal symptoms, paresthesias of the extremities and hypersalivation. Flaccid paralysis including bulbar weakness invariably ensues within hours along with refractory hypotension. Complete cardiovascular collapse precedes death. Treatment is supportive

Toxin	Species/Exposure	Symptoms/Signs	Management
Saxitoxins	Alexandrium species of dinoflagellate -- Ingestion of shellfish particularly during red tides	Facial paresthesias, cranial nerve dysfunction, vertigo followed by flaccid paralysis	Supportive
Ciguatoxin	<i>Gambierdiscus toxicus</i> --Ingestion of fish (barracuda, grouper, sea bass, parrot fish, mahi-mahi)	Gastroenteritis, headache, perioral paresthesias, ataxia, weakness, myalgias	Volume repletion Mannitol IV 1 gm/kg as a 20% solution within 10 hours of symptom onset

**Intermediate syndrome:** Exposure to organophosphates can result in a triphasic illness. Inhibition of cholinesterases is the likely mechanism of toxicity in the acute stage. The initial cholinergic phase is followed in approximately 20% of subjects by the intermediate syndrome. The final phase is that of organophosphate induced delayed neuropathy (OPIND). OPIND is a distal axonopathy that affects peripheral nerves and long tracts of the spinal cord. Most modern organophosphate pesticides don't cause OPIND, however.

Intermediate syndrome usually occurs 24 to 96 hours following resolution of the initial cholinergic phase. Patients usually present with weakness of neck flexion and proximal muscle weakness leading to respiratory failure. Early recognition of the syndrome and prompt initiation of supportive care can prevent death. Spontaneous recovery occurs in 5 to 18 days.

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