WCN, Dubai 2019

Intoxications & the Nervous System

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Disclosures

- No Conflict of interest related to this topic

Learning Objectives

- Course objectives are to familiarize participants with the mechanisms underlying neurotoxicity and to expose shortly the main neurotoxic disorders a clinician can encounter.
- For practical purposes, Toxic substances are divided into terrestrial, marine, industrial & environmental toxins, and nerve agents and their effect on the nervous system is shortly described.

Key Message

- Neurotoxicology is the scientific study of chemical agents that cause adverse **structural** or **functional** effects on the nervous system
- Neurotoxic agents can affect directly the central and/or peripheral neurons, or provoke an axonopathy, a myelinopathy or interfere with synaptic components.
- The source of toxins is also variable: plants, animals, drugs & drugs of abuse, agriculture & industrial agents, and metabolic abnormalities
- Cases of botulism, neurotoxic mushrooms & fishes, exposure to industrial & environmental toxics, & nerve war agents will illustrate the topic
- Toxic hypotheses for some neurodegenerative disorders will also be exposed

Neurotoxicology & Neurotoxins

- **Neurotoxicology** is defined as the science that deals with the adverse effects of **naturally occurring** and **synthetic chemical agents** on the **structure** or **function** of the **nervous system**.
- Neurotoxins can act on:
  - **Ion Channels (Ex: snakes, marine toxins)**
  - **Neuron cells (Ex: MPTP)**
  - **Axons (Ex: Hexane, Acrylamide)**
  - **Myelin (Ex: Lead)**
  - **Neurotransmission (Ex: Organophosphate pesticides)**

Outline

I. Terrestrial Biotoxins:
   A. From Bacteria: Diphteria, Botulism, Tetanus,
   B. From Plants: Lathyrism, Datura, Mushroms
   C. From animals: Snakes, Scorpions

II. Marine Biotoxins: Ciguatera, pufferfish, jellyfish

III. Industrial & environmental toxins: Heavy metals, Solvents, Pesticides, Gazes.

IV. Nerve agents (Chemical Weapons)

V. Toxic Hypotheses for Neurodegenerative Diseases

I.Terrestrial biotoxins

A. Toxins produced by Bacteria

- *Corynebacterium diphtheriae* produces an exotoxin which inhibits protein synthesis resulting in **cell death**.
- *Clostridium botulinum* produces a toxin **blocks the release of acetylcholine** at the neuromuscular junction**.**
- *Clostridium tetani* produces a toxin that blocks the release of glycine and GABA from inhibitory neurons, including **Renshaw cells**.

I.Terrestrial biotoxins

A1. Diphteria

- One of the most common severe complications of diphtheria is an **acute demyelinating polyneuropathy.**
- Neurologic manifestations of diphtheria are biphasic. It is characterized by an **early bulbar disturbance** (weeks 3 to 5) and a **late motor weakness in the trunk and extremities** (weeks 5 to 8).
- It is important to give **antibiotic therapy** in combination with **antitoxin** within 48 hours of diagnosis to decrease the chances of developing diphtheritic polyneuropathy but the only measure for effective control against diphtheria is **universal immunization**.

I. Terrestrial biotoxins
A2. Botulism

- The characteristic **descending paralysis** starts in the extraocular and bulbar muscles, with associated autonomic features.
- A variety of **immunoassays** are available to detect the toxin in stool or food but are not standardized.
- **Antibiotics** play no role in food-borne botulism. With wound botulism, debridement is recommended. Antibiotics (penicillin) should be administered, but only after antitoxin has been given as lysis of the bacteria can increase the amount of toxin released.
- Generally no significant risk occurs in getting therapeutic botulinum injections for whatever reason. The 50% lethal dose is 3000 units, and the usual therapeutic dose of botulinum toxin does not exceed 400 units.

I. Terrestrial biotoxins

A3. Tetanus

- In World War I, tetanus killed more victims of war wounds than the wounds themselves did.
- Early manifestations of generalized tetanus include a **localized stiffness** near the site of the wound followed by **trismus** and with a distinct straightening of the upper lip causing the famous *risus sardonicus*.
- This is soon followed by **rigidity of the axial muscles** (opisthotonos) and abdomen. **Paroxysmal reflex spasms** can occur in severe cases.
- Elimination of the source of toxin, toxin neutralization, control of muscle rigidity and spasms, and ventilatory support are the main strategies in treatment.

I.Terrestrial biotoxins
B. From Plants: B1. Lathyrism

- In parts of Europe and India, spastic paraplegia has developed as a consequence of the consumption of a variety ofchickpea named ***Lathyrus***.
- The toxin is a **powerful agonist of AMPA glutamate receptors** and is linked to **mitochondrial dysfunction**, leading to upper and lower motor neuron cell death. If seeds are immersed in water for 24 hours before cooking, the toxin leaches away.
- Neurolathyrism is characterized by a **purely motor spastic paresis** very similar to HTLV-1 tropical spastic paraparesis.
- The onset of the symptoms and complaints occurs over the course of several weeks.

I. Terrestrial biotoxins

B2. Datura & other plants containing atropinic substances

- The Belladonna alkaloids (hyoscine, hyoscyamine, atropine, and scopolamine) are present in the **belladonna berries** that have been used for centuries for headache, menstrual symptoms, peptic ulcer disease, motion sickness, etc.
- Belladona alkaloids are also present in the ***Datura*** **species**, including angel's trumpet. The plants are sometimes used for recreational purposes, producing vivid hallucinations.
- Accidental overdose may elicit subsequent symptoms as dilated pupils, tachycardia, dyspnea, flushing, dry throat, hyperthermia, and urinary retention. Cardiovascular collapse can occur.

I.Terrestrial biotoxins

B3. Toxic mushroms

- Toxic mushrooms include *Amanita phalloides* & the gyromitrin, muscarine, and psilocybin species.
- Mortality with ***Amanita*** varies from 30% to 90%, which in part is due to hepatic encephalopathy.
- The two toxins that have been isolated from *A. phalloides*, phalloidin and α-amatoxin, contribute to separate phases of the clinical presentation after ingestion.
- Phalloidin leads mainly to GI toxicity 6-12h after ingestion.
- α-Amatoxin becomes toxic when it reaches the hepatocytes (after 36-48h) where it inhibits protein synthesis and ultimately provokes hepatocyte death.
- The final stage can evolve quite rapidly with coagulopathy, hepatic encephalopathy, and acute hepatic failure.

I.Terrestrial biotoxins

B3. Muscarinic mushroms & Psilocybin species

- **Muscarinic mushrooms** from the genera *Inocybe* and *Clitocybe* are commonly found in yards and public parks. Signs and symptoms related to the ingestion of these mushrooms typically appear after 0.5 to 2 hours and may last 6 to 24 hours.
- Usual presentation is sweating, salivation, urination, defecation, gastric cramps, miosis, emesis, bronchospasm, and bradycardia.
- ***Psilocybe cubensis*** (“magic mushrooms”) contain the hallucinogens psilocybin and psilocin. These mushrooms are not deadly and are not known to provoke internal organ damage.
- The hallucinogenic effect begins within 20 minutes of ingestion and lasts about 6 hours. Side effects include muscle weakness, drowsiness, and nausea.

I. Terrestrial biotoxins
C1. Snakes

- About **15%** of the approximately 3000 species of snakes found throughout the world are known to be **dangerous** to humans.
- All snake bites are associated with terror, and autonomic reactions that must be differentiated from systemic reactions to toxins.
- **Pit viper venom** is a complex mixture of proteins, mostly enzymes designed to digest fat, protein, nucleic acids, and connective tissues.
- Hemolysis of red cells and pooling of blood products and fluid in the microcirculation can lead to **hypovolemic shock** and **lactic acidosis**, sometimes resulting in **renal failure** with their neurological consequences.
- Incision and suctioning at the bite site within minutes can remove venom. Antivenin should be administered ASAP

I. Terrestrial biotoxins
C2. Scorpions

- In some of the Central American countries, for every person killed by a poisonous snake, 10 are killed by a scorpion.
- Scorpion venom contains neurotoxins, cardiotoxins, nephrotoxins, hemolytic toxins, cytokine releasers, and other active substances such as hyaluronidases, histamine & serotonin.
- Typically, after initial **regional pain** and swelling at the sting site,, there is a temporary surplus of **cholinergic activity**, resulting in salivation, lacrimation, urinary incontinence, defecation, gastroenteritis, and emesis.
- **CNS involvement** occurs frequently and includes confusion, agitation, ataxia, myoclonic and dystonic movements, involuntary muscle spasms, diffuse fasciculations. Other reported CNS signs and symptoms include venom-induced cerebral artery occlusions, and seizures.
- Antivenin is the treatment of choice after supportive care is established

II. Marine Biotoxins

- Thermostable nonprotein lipid-soluble toxins are formed by **marine microorganisms**, producing clinical syndromes following ingestion of seafood containing the microorganisms or their preformed toxins.
- They act principally at the **sodium channels** of **peripheral nerves and muscle membranes**.
- **Contact toxins** (jellyfish, sea anemone & venomous fish) and **envenomation toxins** (sea snakes and cone snails) are peptide neurotoxins. These neuropeptides are secreted directly by the offending marine creatures, which then bite or sting to envenomate humans or kill their preys.

II. Marine Biotoxins
A. Ciguatera

- Food poisoning common in the Pacific area producing gastrointestinal and sensorimotor symptoms beginning within 24 hours of ingestion of tropical reef fish or their predators is termed *ciguatera*.
- Ciguateric toxins are thermostable and unaffected by cooking or freezing. Affected fish look, smell, and taste normal. Toxin concentrations are concentrated in the visceral organs, roe, and brains of affected fish.
- At least 4 neurotoxins (CTX, MTX, scaritoxin, and palytoxin) have been identified. Each toxin is produced by marine micro-organisms and then passed up the food chain from herbivorous to carnivorous fish to man.
- Clinical symptoms include early GI symptoms with nausea, emesis, and diarrhea followed over the next 10 to 18 hours by headache, myalgias & sensory-motor neuropathy.

II. Marine Biotoxins
B. Puffer Fish, Tetrodotoxin

- TTX is a potent toxin produced by several marine bacteria. TTX blocks the action potentials of voltage-gated sodium channels along the membranes of skeletal and cardiac muscles, as well as along axons of sensory nerves and some motor nerves.
- Several marine creatures have TTX-resistant channels, which allow the creatures to tolerate TTX, including the puffer fish (Lagocephalus scleratus) that is considered a delicacy in Japan (Fugu).

III. Marine Biotoxins
C. Jellyfish & Anemones

- Marine coelenterates are simple creatures with radial appendages that surround an internal gastrovascular cavity. Sea anemones represent the polyp form, fixed to a substrate such as the ocean floor. Jellyfish represent the free-floating medusa form.
- Coelenterates deliver toxin by injection of venom. The result is a localized dermatitis with pruritus and urticaria, often with severe and immediate pain.
- Anaphylaxis may occur. Hemolytic and cytolytic properties of the venom may result in localized hemorrhagic necrosis.
- Stings covering more than one limb or 50% of the body surface may produce hyperthermia, abdominal colic, and waves of severe myalgic pains.
- Certain species are particularly toxic and may provoke seizures, severe myalgias, spastic or flaccid paralysis, mononeuritis multiplex, coma, and death.

III. Industrial & environmental toxins

- The central and peripheral nervous systems are vulnerable to insult from a broad range of industrial and environmental toxins.
- In most neurotoxic exposures, a temporal relationship exists between the exposure and symptom onset. Neurologic manifestations appear after cumulative exposure reaches a threshold level.
- The neurologic manifestations can be **acute** in onset or **delayed**. At times deterioration may continue for weeks despite removal from the toxic source. The neurologic manifestation associated with acute high-level exposure is often different from that seen with prolonged low-level exposure.

Neurologic Manifestations of industrial toxics

Syndrome	Clinical Presentation	Example
Acute Encephalopathy	Varying combination of headache, fatigue, irritability, disorientation, amnesia, ataxia, slurred speech, psychosis, anxiety, depression, convulsions, stupor, and coma	Acute exposure to toxins such as organic solvents
Chronic Encephalopathy	Varying combination of cognitive and psychiatric disturbances or nonspecific symptoms, including headache, fatigue, memory disturbance, insomnia, irritability, and changes in mood or personality	Chronic moderate-dose to high-dose exposure to toxins such as solvents
Parkinsonism	Tremor, rigidity, bradykinesia, postural instability	Manganese
Myeloneuropathy	Gait ataxia, hyperreflexia, Babinski sign, paresthesias, sensory loss, weakness	Nitrous oxide
Polyneuropathy	Paresthesias, numbness, weakness, decreased or absent reflexes, autonomic dysfunction	metals (arsenic, lead, mercury), organophosphates, N-hexane, Acrylamide, Platinum-based drugs, trichloroethylene

List of some Toxins & their common effects (heavy metals)

Metals	Source of Toxicity	Acute intox	Chronic Intox
Arsenic	Mining, Drinking well water (Bangladesh), traditional & herbal medicines	A gastrointestinal illness as presenting symptom. This may be followed by an encephalopathy, renal failure, pulmonary edema, cardiovascular instability, bone marrow suppression, hemolysis, skin rash, and rhabdomyolysis.	PN, alopecia, and Mees lines (transverse white lines across nails)
Manganese	Miners, battery industry, Liver disease, total parenteral nutrition	nonspecific symptoms including headache, asthenia, somnolence, insomnia & anorexia	Behavioral changes & Parkinsonism
Lead	House painting, old plumbing systems of drinking water, battery industry	Encephalopathy	NP, irritability, behavioral changes
Mercury	Dental amalgams, sphygmomanometers and thermometers. Seafood. Manufacture of fluorescent light bulbs, electric meters, and batteries.	gingivitis, tremor, and a neuropsychiatric illness, which has been called erethism (Mad Hatters Disease)	Tremors, ataxia, slurred speech, visual field constriction, decreased hearing, paresthesias & Behavioral changes. Severe toxicity may be associated with blindness, delirium, coma, and death.

List of some some Toxins & their common effects (Solvents & other chemicals)

	Source of Toxicity	Acute intox	Chronic Intox
N-hexane	Industrial solvents & household glues (glue sniffers)	Acute exposure causes CNS narcosis.	progressive, symmetric, ascending, sensorimotor, distal axonopathy.
Acrylamide	waste and water treatment flocculator, grouting agent, and in the textile, cosmetic, and papermaking industries.	Encephalopathy & gait ataxia	progressive, distally prominent, symmetric, dying-back, large- fiber, axonal, sensorimotor neuropathy
Organophosphates	They have been used as insecticides and nerve gases. Less toxic forms have been used in flame retar- dants, fuel additives, hydraulic fluids, and lubricants.	Severe cholinergic Syndrome by inhibition of cholinesterase	Polyneuropathy

IV. Nerve agents

- The 5 nerve agents, **tabun** (GA), **sarin** (GB), **soman** (GD), **cyclohexylsarin** (GF), and **VX**, have chemical structures similar to the common organophosphate pesticide Malathion, acting by **blocking of acetylcholinesterase**.
- They are generally colorless to amber-colored. Agents sarin and VX are odorless; tabun has a slightly fruity odor and soman has a slight camphor odor.
- Nerve agents produce various signs and symptoms depending on the agent, its concentration, and length of exposure.
- Liquid agents easily penetrate skin and clothing. Symptoms may begin anywhere from 30 minutes to 18 hours after skin exposure. Vapor inhalation produces poisonous symptoms within seconds to several minutes.

Nerve agents (2)

- Poisoning by a nerve agent leads to constriction of pupils, profuse salivation, convulsions, and involuntary urination and defecation.
- Death by asphyxiation or cardiac arrest may follow due to paralysis of respiratory muscles.
- The five basic principles of acute nerve agent casualty treatment are: (1) decontamination; (2) supportive care, particularly respiratory; (3) anticholinergic therapy; (4) Pralidoxime therapy; and (5) anticonvulsant therapy

V. Toxic Hypotheses for Neurodegenerative Disorders

A. Alzheimer's Disease

- Several epidemiologic studies have examined the possible link between **aluminum** and AD, with conflicting results. Exposure through antiperspirants, drinking water & other sources did not establish clear link.
- No association was observed for occupational exposure to **lead, mercury, iron** or other metals.
- Also no clear association was established between **pesticides**, **fumigants** and **defoliants** and AD

V. Toxic Hypotheses for Neurodegenerative Disorders

B. Parkinson's Disease

- Substantial numbers of epidemiologic studies have found positive associations between PD and exposure to **pesticides**, herbicides, and insecticides.
- Residence in **rural locations** & use of **well water (**possibly containing pesticides or other environmental contaminants) was found to be associated with PD in a number of studies. Yet no association was found in a few other and decreased risk was reported in others.
- The association between PD and exposure to **metals** & **solvents** has been intensely investigated. But a relationship could not be confirmed.

V. Toxic Hypotheses for Neurodegenerative Disorders
C. Amyotrophic Lateral Sclerosis

- Some studies have suggested an association of ALS with occupation in welding or soldering, exposure to pesticides, lead, Zinc, copper, Mercury, Iron Mn, but these results were not confirmed by other studies.
- Possible associations for which evidence is also inconclusive include military service and smoking

- In conclusion, epidemiologic evidence for an association between environmental agents and neurodegenerative disease is **inconclusive**.

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