Neurotoxicology

By: Dr. Loukzadeh

GENERAL PRINCIPLES

- A dose-toxicity relationship exists in the majority of neurotoxic exposures.
- Exposure to toxins typically leads to a nonfocal or symmetric neurologic syndrome.
- The nervous system has a limited capability to regenerate, but some recovery is possible after removal of the insulting agent.
  - By contrast, worsening neurologic deficits more than a few months after cessation of exposure to a toxin generally argues against a direct causative role of the toxin.

- There is usually a strong temporal relationship between exposure and the onset of symptoms.
  - Immediate symptoms after acute exposure are often a consequence of the physiologic effects of the chemical. These symptoms subside quickly with elimination of the chemical from the body.
  - Delayed or persistent neurologic deficits that occur after toxic exposures generally are a result of pathologic changes in the nervous system. Recovery is still possible, but it tends to be slow and incomplete.

DIAGNOSIS OF A NEUROTOXIC DISORDER

- (1) a sufficiently intense or prolonged exposure to the toxin
- (2) an appropriate neurologic syndrome based on knowledge about the putative toxin
- (3) evolution of symptoms and signs over a compatible temporal course
- (4) exclusion of other neurologic disorders that may account for a similar syndrome

Peripheral Nervous System

- peripheral nerve is by far the most vulnerable to exogenous toxins

- Because toxins reach the nerves systemically and affect all nerves simultaneously, the resulting syndrome is typically a symmetric peripheral neuropathy.

  - This is also called a **polyneuropathy**

POLYNEUROPATHY

Distal

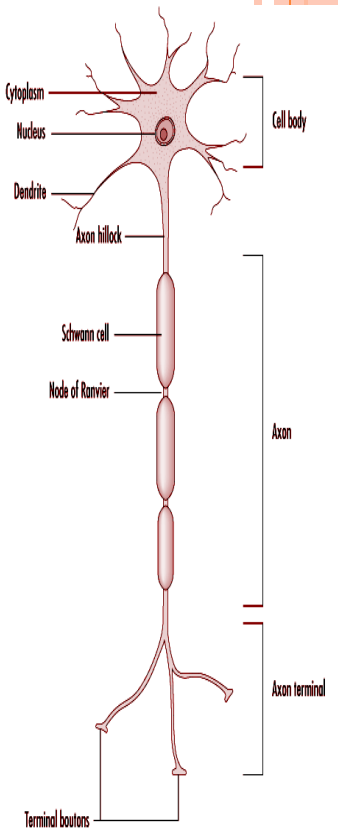
- The hallmark : distal distribution of the clinical symptoms and signs.
- The most common syndrome is subacute onset of tingling or numbness experienced in a symmetric stocking-and-glove distribution.
- Neuropathic pain is sometimes present and is described as:
  - burning, deep aching
  - Lancinating
  - hyperpathia or allodynia
- Involvement of the motor nerve fibers manifests as muscle atrophy and weakness
  - Appear first in the distal-most muscles (ie, the intrinsic foot and hand muscles)
  - More severe cases may involve muscles of the lower legs and forearms: bilateral foot drop or wrist drop

Polyneuropathy

- Physical examination should include:
  - muscle strength
  - Sensation
  - tendon reflexes of all four extremities
  - Are the sensory and motor deficits relatively symmetric?
  - Are the feet more affected than the hands?
    - Because the longest axons are the most vulnerable, neurologic deficits frequently are more severe in the feet than in the hands.
- Most polyneuropathies are accompanied by:
  - diminished or absent stretch reflexes of the Achilles tendons
  - demonstrable sensory impairment in the toes
- Testing of these functions therefore should be included in any screening examination of PNS

LABORATORY EVALUATION

- NCS and EMG are the primary tools in the laboratory evaluation of neuromuscular disorders.
- NCVand EMG occasionally supplemented by nerve biopsy, are important in the pathophysiologic characterization of peripheral neuropathies.
- A fundamental categorization subdivides neuropathies into:
  - those with primary degeneration of nerve axons (axonal neuropathy)
  - those with significant myelin breakdown (demyelinative neuropathy)



NEUROLOGIC DISORDERS CAUSED BY SPECIFIC TOXINS

Arsenic

- Arsenic compounds are used as:
  - wood preservatives
  - as gallium arsenide in the semiconductor industry
  - as defoliant and desiccant in agriculture.
  - Contamination of well water may result from leaching of arsenic by-products in smelting or heavy agricultural use of arsenicals.
- Acute intoxication
  - nausea, vomiting, abdominal pain, and diarrhea
  - Dermatologic lesions, such as hyperkeratosis, skin pigmentation, skin exfoliation, and Mees lines, occur in many patients 1–6 weeks after onset of disease.

Arsenic

ارسنیک---گیلن باره

- After a single massive dose:
  - an acute polyneuropathy develops within 1–3 weeks.
  - mimics Guillain-Barré syndrome and respiratory failure may occur rarely
  - Symmetric paresthesias and pain may occur in isolation or may be accompanied by distal weakness. With progression of neuropathy, sensory and motor deficits spread proximally
  - Shoulder and pelvic girdle weakness, as well as gait ataxia, are common in severe cases.
- Chronic exposure :
  - insidious sensori-motor polyneuropathy.

Arsenic

- EMG and nerve-conduction studies :nonspecific axonal neuropathy.
- Arsenic in blood and urine

- Arsenic in hair and nails for months after exposure.
  - Pubic hair is preferable to scalp hair for its lesser susceptibility to contamination.

Hexacarbons (n-Hexane & Methyl n-Butyl Ketone)

- Human disease is a result of a toxic intermediary metabolite g-diketone 2,5-hexanedione

- Toxic exposure results from:
  - Inhalation especially in poorly ventilated spaces
  - Excessive skin contact

Hexacarbons (n-Hexane & Methyl n-Butyl Ketone)

يوفوريا

- hexacarbons can induce an acute encephalopathy characterized by:
  - euphoria, hallucination, and confusion (recreational drug)
- The most well-known syndrome is a distal symmetric sensori-motor polyneuropathy.
  - the so-called glue-sniffer's neuropathy
- Early symptoms are paresthesia and sensory loss
- Weakness follows and involves distal muscles initially
- Proximal musculatures are affected in more severe cases
- Patients complain of easy tripping because of ankle weakness
- Optic neuropathy and facial numbness may be present
- Autonomic symptoms are uncommon and are present only in very severe cases

Hexacarbons (n-Hexane & Methyl n-Butyl Ketone)

- On examination
  - sensory loss
  - Weakness
  - Achilles stretch reflexes are lost early in the disease.
- Recovery begins after a few months of abstinence and may be incomplete
- In some instances, spasticity and hyper-reflexia appear paradoxically during the recovery stage

Hexacarbons (n-Hexane & Methyl n-Butyl Ketone)

- n-Hexane neuropathy has a distinctive neuropathology
  - Multiple foci of neurofilament accumulations form inside the nerve axons
  - Demyelination is common, but it is probably secondary to the axonal pathology
  - Because of this demyelination :slowing of motor NCV
  - CSF protein content is typically normal, in contrast to most other demyelinating neuropathies, which are associated with elevated CSF protein.

Lead

- Lead is present in:
  - paint
  - Batteries
  - Pipes
  - Solder
  - ammunition
  - cables
- Nonindustrial sources include:
  - Pottery
  - bullet fragments
  - traditional folk remedies

- Chronic low-level exposure to lead:
  - impaired intellectual development in children
  - decreased global IQ,
  - behavioral disturbances, such as poor self-confidence, impulsive behavior, and shortened attention span
- adults with past industrial exposure may have a faster rate of cognitive decline.
- High bone lead has also been associated with increased risk of Parkinson disease and amyotrophic lateral sclerosis.

- Peripheral neuropathy is a well-recognized complication of chronic lead poisoning in adults.
  1. The best-known clinical syndrome is a predominantly motor neuropathy with little sensory symptoms
     - The classic description emphasizes bilateral wrist drop and foot drop
  2. also may manifest as a generalized proximal and distal weakness and loss of the tendon reflexes.
  3. Some patients have preserved reflexes, and their syndrome thus mimics a motor neuron disease such as ALS
  4. some patients may present with distal limb paresthesias and no weakness
     - This is especially likely in patients with long-term low-level lead exposure.

Manganese

- used
  - manufacture of steel, alloys
  - Welding
  - alkaline batteries
  - various fungicides
- Poisoning occurs most commonly in:
  - Mining
  - Smelting
  - Milling
  - battery-manufacturing industries
  - potential risk of organic manganese in the form of methylcyclopentadienyl manganese tricarbonyl (MMT), an additive used in gasoline.

- The classic syndrome:
  - Manganism: appearance of an extrapyramidal disorder that resembles idiopathic Parkinson disease.
    - Tremor, rigidity, masked facies, and bradykinesias develop slowly
- manganese-induced parkinsonism is usually symmetrical and includes atypical features such as facial grimacing, early foot dystonia and gait disturbance (so called "cock-walk"), and pronounced psychiatric features.
- Compared with Parkinson disease, the extrapyramidal symptoms of manganism are minimally responsive to dopaminergic therapy.

- Manganese accumulates in the globus pallidus and selectively damages neurons in globus pallidus and the striatum

- Brain MRI
  - manganese accumulation can be visualized as increased signal on T1-weighted images in the globus pallidus, a distinctive finding not seen in Parkinson disease

Mercury

- Mercury is used in:
  - Batteries
  - Fungicides
  - Electronics
  - Mercury in sludges and waterways is methylated by microbes into methyl mercury that is readily absorbed by humans
- Several large endemics resulted from methyl mercury contamination
- Overall, there is no definitive evidence to associate low-level exposure with significant neurologic disease.

- Neuropathy is associated primarily with inorganic mercury
  - A subacute predominantly **motor neuropathy** has been reported after metallic mercury or mercury vapor exposure
  - If acute, the syndrome resembles Guillain-Barré syndrome, whereas a more subacute syndrome may mimic amyotrophic lateral sclerosis
  - Nerve-conduction study and nerve biopsy suggest a primary axonal loss

Nitrous Oxide

- Excessive exposure to nitrous oxide, usually in the setting of substance abuse
- myeloneuropathy indistinguishable from vitamin B12 (cobalamin) deficiency:
  - inactivates vitamin B12 and interferes with B12-dependent conversion of homocysteine to methionine
    - Serum vitamin B12 and the Schilling test often are normal
    - whereas the serum homocysteine level may be elevated
- Repeated exposures are necessary to cause symptoms in normal individuals

BUT

- A brief exposure to NO is sufficient to precipitate symptoms in patients with asymptomatic B12 deficiency

- Patients present with:
  - paresthesias in the hands and feet
  - Gait ataxia
  - sensory loss
  - Romberg sign
  - leg weakness
  - Tendon reflexes may be diminished or lost (peripheral neuropathy) or may be pathologically brisk (spinal cord involvement; ie, myelopathy)

Organic Solvents

- Clinically important exposure to organic solvents occurs primarily as a result of industrial contact or volitional abuse.
- Most organic solvents possess acute narcotizing properties.
- Brief exposure at high concentrations causes a reversible encephalopathy. Coma, respiratory depression, and death occur after extremely high exposures.
- Chronic exposure to moderate or high levels of solvent can cause a dementing syndrome, with personality changes, memory disturbances, and other nonspecific neuropsychiatric symptoms.
- A sensorimotor polyneuropathy also may be present either as the only manifestation or in combination with CNS dysfunction

- Despite general agreement on the effects of moderate to high doses of organic solvents, the effect of chronic low-level exposure is less certain.
- The sequelae of this low-level exposure have been variously termed painters' syndrome, chronic solvent encephalopathy, and psycho-organic solvent syndrome.
- The neurologic symptoms are diverse and nonspecific and include headache, dizziness, asthenia, mood and personality changes, inattentiveness, forgetfulness, and depression.

Zinc

- **Zinc myeloneuropathy** may present similarly to a nitrous oxide myelopathy.
- Zinc is present in various common foods and in some denture creams. Zinc may also be inhaled as an occupational hazard in welding, construction, or the automotive industry.
- Excessive zinc ingestion antagonizes copper absorption, leading to hypocupremia, a condition associated with myelopathy and neuropathy.
- The diagnosis is made by the presence of elevated zinc and depressed copper levels in the serum.