Toxic and Metabolic Disorders of the Nervous System
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Reading: Robbins & Cotran, 9th edition, pp 410-13; 417-19; 849-850; 1304-5
Robbins Basic Pathology, 9th edition, pp 274-277; 280-282; 835-6

The term “toxin” includes heavy metals, organic compounds, poisons, products of combustion, endogenous products of metabolism, drugs (of addiction or therapy) and anesthetics. Many of them produce multisystem disorders as well as damage to the nervous system. The general principles of these disorders are well described in Chapter 9 of the textbook.

Metals

**Lead** - Once widely used in paint and gasoline; still found in older painted surfaces, battery casings, ammunition and radiators.

Lead binds sulfhydryl groups, affects porphyrin metabolism and heme synthesis, leading to anemia. It also causes both acute and chronic neurologic syndromes. Acute lead intoxication produces marked brain edema, seizures, coma and death due to herniation. More chronic exposure leads to headache, malaise, anorexia, abdominal pain and peripheral neuropathy (segmental demyelination; motor > sensory, hands>feet). In children, chronic lead intoxication leads to neurobehavioral disorders and mental retardation.

**Mercury** – “quicksilver and slow death” - mercury poisoning became recognized in the 17th century after the introduction of mercuric nitrate as an agent in curing felt which was used to make hats. The symptoms of mercury poisoning in the hatting industry included florid personality change and tremors (“hatter’s shakes”). This left the enduring expression “mad as a hatter.” More recently, mercury poisoning on a larger scale happened after the dumping of methylmercury-containing compounds into Minamata Bay, Japan. Prominent symptoms were tremors, ataxia, and visual loss, and corresponding pathologic changes included destruction of granule cells in the cerebellar cortex, and of neurons in the calcarine (visual) cortex. Concerns about mercury have led to warnings about fish consumption, especially by pregnant women. Thimerosal, an ethylmercury-containing preservative, was once widely used in vaccines, and is still used in most flu vaccines. It has been blamed for so-called “vaccine-induced disease,” but the FDA, the American Academy of Pediatrics and the World Health Organization all believe it is safe. MMR, varicella, polio, pneumococcal, and Hib vaccines never contained thimerosal. This appears to be an outrageous example of scientific fraud that is having a pronounced negative effect on health care. The specific example of the attempt to link autism to vaccinations will be discussed at length in the lecture presentation.

**Arsenic** – formerly used as a treatment for syphilis and as a component of gas warfare; currently used in pesticides and herbicides. Intoxication may cause encephalopathy (headache, drowsiness, confusion, delirium, seizures) and/or peripheral neuropathy (sensory> motor; painful, burning sensations, most prominent in lower extremities. Pathology in the brain characteristically involves widespread petechial hemorrhages, predominantly in the white matter. The peripheral nerves demonstrate distal axonal degeneration, followed by secondary loss of myelin sheaths.

**Manganese** – interferes with acetylcholinesterase and adenosine deaminase, and stimulates
monoamine oxidase. Miners or other manganese workers who are exposed may develop extrapyramidal syndromes resembling Parkinsonism. Some of these respond to treatment with L-dopa.

**Phosphorus and organophosphorus compounds** – found in rat poisons, match heads and insecticides. Potent inhibitors of acetylcholinesterase, they acutely produce headache, vomiting, sweating, abdominal cramps, miosis and bronchospasm. Most of these can be reversed by atropine. Delayed neurotoxic effects, appearing 2-5 weeks after exposure, include a symmetric peripheral neuropathy characterized by a “dying back” pattern in which the distal ends of long motor fibers are affected first. A similar pattern is produced by acrylamide, carbon disulfide, disulfiram (Antabuse).

**Carbon Monoxide Intoxication**
A form of hypoxia due to altered oxygen-carrying capacity of hemoglobin, CO intoxication has a somewhat more selective localization of injury, which includes:
- The globus pallidus, often with bilateral necrosis, a highly characteristic finding
- Layers 3 & 5 of the cerebral cortex
- Sommer’s sector of the hippocampus
- Purkinje cells

**Vitamin Deficiency**

Vitamin B1 (Thiamine) deficiency produces a progressive disorder including the components of the Wernicke-Korsakoff Syndrome. This is most often encountered in the context of alcoholism, discussed below.

Vitamin B12 deficiency can have severe, potentially irreversible effects on the CNS, particularly the spinal cord. There is swelling and vacuolation of myelin layers, beginning at the midthoracic level, followed by axonal degeneration in both the ascending sensory tracts and the descending corticospinal tracts, producing bilateral numbness, tingling, ataxia and spastic weakness in the lower extremities. This characteristic combination is called **Subacute Combined Degeneration**.

**Alcohol-related disorders**

Acute effects of alcohol intoxication include a continuum from mild inebriation to coma, and are produced by a dose-dependent depressant effect of alcohol on neurons.

Withdrawal syndromes, which occur while the blood alcohol level is falling during a period of abstinence after a period of sustained inebriation, are marked by tremulousness (“the shakes”), disordered perception termed “hallucinosis,” seizures (“rum fits”) and delirium tremens, a situation of profound confusion, vivid hallucinations, delusions and increased autonomic activity.

**Wernicke's Encephalopathy and Wernicke-Korsakoff syndrome**

Due to thiamine deficiency
Usually seen in malnourished chronic alcoholics
Confusion, ocular palsies, and ataxia are the major symptoms
Grossly there are multiple small hemorrhages in mammillary bodies, periventricular and periaqueductal gray matter and thalamus
Capillaries are increased in number and "leaky"
Central Pontine Myelinolysis
Usually seen in alcoholics or poorly nourished patients, particularly following a binge.
Patients may present with confusion/delirium, then rapidly evolving limb weakness progressing to quadriplegia, with a mixture of other pontine signs, including conjugate gaze problems, dysarthria, dysphagia, "locked-in syndrome," etc. The major lesion is located in the central part of the pons (of course), and the basic process is demyelination ("myelinolysis"), with sparing of axons and neurons. Many macrophages are seen in demyelinated areas.
Pathogenesis is thought to involve rapid correction of hyponatremia producing edema in formerly dehydrated areas with acute pontine swelling; the "grid" arrangement of fiber tracts in the basis pontis may make them particularly susceptible to compression. Hypoxemia may also contribute to the development of lesions.

Diseases of uncertain etiology seen in alcoholics:

Alcoholic cerebellar degeneration
- Loss of neurons in the anterior vermis
- More frequent in men
- Patients have truncal ataxia and wide-based gait

Marchiafava-Bignami disease
- Degeneration of corpus callosum and other commissural systems
- Much more frequent in men
- Symptoms non-specific, include mental and motor slowness, confusion, primitive reflexes; often improve during hospitalization

Fetal Alcohol Syndrome (FAS)

FAS is the most severe form of a spectrum of abnormalities (Fetal Alcohol Spectrum Disorders –FASD) caused by drinking during pregnancy. Components may include:
- Small size for gestational age or small stature
- Facial abnormalities such as short palpebral fissures, flattened philtrum
- Poor coordination
- Hyperactive behavior
- Learning disabilities
- Developmental disabilities (e.g., speech and language delays)
- Mental retardation or low IQ
- Problems with daily living
- Poor reasoning and judgment skills
- Sleep and sucking disturbances in infancy
There is no "safe" level of alcohol intake during pregnancy. Alcohol-related disorders may occur in the children of women who drink as little as one drink a day while pregnant, but are more commonly associated with drinking large amounts at once than with smaller amounts more frequently.
Estimates of incidence range from 0.33/1,000 to 2/1,000 live births, but it is assumed that FASDs are under-reported.

Metabolic disorders due to endogenous products of metabolism

Hepatic Encephalopathy
Associated with liver failure due to cirrhosis and other kinds of severe hepatic disease
Caused by neurotoxins, especially ammonia which is detoxified by the liver
Clinical symptoms include impaired mental status and asterixis
Brain is grossly normal
Reactive astrocytes called “Alzheimer type 2” cells are seen in cerebral cortex and basal ganglia. They have enlarged, misshapen nuclei with clear centers and marginated chromatin, and they lack the typical prominent pink cytoplasm associated with ordinary “reactive” astrocytes. This is reversible; they may disappear if hepatic function and encephalopathy improve.

**Kernicterus** (“nuclear jaundice”) is due to entry of bilirubin into the brain. The normal blood-brain barrier excludes bilirubin, but the barrier is immature in neonates, especially in premature infants, so any condition which causes jaundice in the newborn period may be associated with accumulation of bilirubin in the brain. Areas which are particularly vulnerable include nuclear groups, such as basal ganglia, thalamus and brain stem nuclei.

**Wilson's Disease** (“hepatolenticular degeneration”)
This is an autosomal recessive disorder linked to the ATP7B gene on chromosome 13, which encodes a transmembrane copper-transporting ATPase. Deficiency impairs the incorporation of copper into ceruloplasmin and inhibits ceruloplasmin secretion into the blood. Non-ceruloplasmin-bound copper enters the circulation and deposits in other tissues. The most profound changes are due to copper deposits in the liver (cirrhosis), putamen and globus pallidus (“hepatolenticular degeneration”).

Brain lesions are grossly cavitary and brown, with severe loss of neurons and reactive gliosis. Alzheimer type 2 astrocytes are prominent throughout the brain. Characteristic copper deposits in the cornea are called Kayser-Fleischer rings.

**Renal failure**
Severe chronic uremia will produce encephalopathic symptoms similar to those in hepatic failure. Again, Alzheimer type 2 astrocytes will be present. These astrocytes may also be found in patients who have encephalopathy due to hypercalcemia.

**Objectives for Toxic and Metabolic Disorders of the Nervous System**

Describe the effects on the nervous system of environmentally-encountered toxins such as lead, mercury, arsenic and manganese.

Describe the neuropathological effects seen in chronic alcoholism, including Wernicke's encephalopathy, central pontine myelinolysis, alcoholic cerebellar degeneration and Marchiafava-Bignami disease.

Describe the pathologic features and pathogenesis of:
- Carbon Monoxide intoxication
- Vitamin B12 deficiency
- Kernicterus
- Wilson’s Disease
- Hepatic Encephalopathy