Toxic, Metabolic, and Nutritional Diseases

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This section addresses the neurologic complications of substrate deficiencies, toxins, and illicit drugs. These conditions are especially important to recognize and screen for, since accurate diagnosis and treatment can potentially lead to recovery.

Substrate Deficiency

Deficiencies of glucose, the B vitamins, vitamin E, copper, thyroid hormone, and calcium can all cause neurologic symptoms. These are detailed below.

Hypoglycemia

Hypoglycemia can cause detrimental neurologic effects since the brain depends on glucose and oxygen for energy production. The most common clinical manifestations are seizures, coma, and focal deficits. Pathologically, injuries appear similar to those seen with hypoxic injury. Rapid glucose administration can lead to full recovery, although clinical improvement may lag behind glucose level normalization.

Vitamin B₁ (Thiamine) Deficiency

Wernicke-Korsakoff syndrome is caused by vitamin B₁ (thiamine) deficiency. It is most commonly seen in the setting of alcoholism, although it can also occur in other disorders.
of malnutrition. Wernicke encephalopathy is an acute condition recognized by the classic triad of encephalopathy, oculomotor dysfunction, and gait ataxia. Pathologically, petechial hemorrhages are found in the mammillary bodies and diencephalic structures adjacent to the third ventricle. Untreated cases can lead to mortality, although treatment with thiamine can reverse neurologic symptoms within hours to days. Thiamine should be administered before glucose to avoid precipitating an attack of Wernicke encephalopathy in malnourished individuals.

Korsakoff syndrome is due to chronic thiamine deficiency and is characterized by memory impairment (retrograde and anterograde amnesia) and confabulation. It is associated with lesions of the medial dorsal thalamic nuclei. Unlike Wernicke encephalopathy, Korsakoff syndrome is not easily treated.

**Vitamin B₆ (Pyridoxine) Deficiency**

Pyridoxine deficiency is most commonly seen in the setting of isoniazid treatment for tuberculosis. Isoniazid competes with vitamin B₆ as a cofactor for neurotransmitter synthesis. As a result, patients can present with symptoms of neuropathy, including gait disturbance and paresthesia. Administering supplemental vitamin B₆ with isoniazid can prevent neuropathy.

Rarely, pyridoxine deficiency is due to an inborn error of metabolism, causing intractable seizures in infancy. Therapeutic trials of pyridoxine and pyridoxyl-5’-phosphate are indicated for infants with refractory seizures.
**Vitamin B₁₂ Deficiency**

The most significant neurologic complication of vitamin B₁₂ deficiency is degeneration of the dorsal and lateral spinal cord columns, otherwise known as subacute combined degeneration. Patients may present with ataxia, weakness, and paresthesia. Early treatment with supplemental vitamin B₁₂ can reverse symptoms, but untreated cases can progress to spasticity and paraplegia.

Nitrous oxide (NO) toxicity also produces symptoms of vitamin B₁₂ deficiency, as NO converts Vitamin B₁₂ to its inactive form. Inhalation of NO from a whipped cream charger (Whip-It) is one cause of NO toxicity.

**Vitamin E Deficiency**

Vitamin E deficiency can occur in the setting of fat malabsorption, including but not limited to pancreatic insufficiency and Crohn disease, or in rare genetic cases such as ataxia with vitamin E deficiency and familial hypobetalipoproteinemia. Both genetic conditions are autosomal recessive in inheritance. Symptoms mimic spinocerebellar syndromes, and patients typically present with ataxia, hyporeflexia, and loss of proprioceptive and vibratory sensation. Many patients have associated retinitis pigmentosa. Vitamin E supplementation is indicated for symptomatic patients.

**Copper Deficiency**

Copper deficiency can also lead to myeloneuropathy, similar to the subacute combined degeneration seen with vitamin B₁₂ deficiency. Examination can reveal upper motor neuron signs from spinal cord involvement, as well as lower motor neuron signs from
peripheral neuropathy. The most common causes of copper deficiency are malabsorption and zinc deficiency. Menkes disease is a rare X-linked disorder of copper deficiency. In general, treatment involves oral copper supplementation.

**Hypothyroidism**

Neurologic manifestations of hypothyroidism can involve the central or peripheral nervous systems. CNS manifestations, including Hashimoto encephalopathy and myxedema coma, can be quite severe. Hashimoto encephalopathy presents with progressive altered mental status, confusion, focal deficits, and seizures. Many patients with Hashimoto encephalopathy are euthyroid at the time of presentation, but of the remainder, most have hypothyroidism and a few have hyperthyroidism. Diagnosis cannot be made without the presence of antithyroid antibodies (thyroid peroxidase or thyroglobulin) since the pathophysiology is thought to be immune regulated and not a direct effect of thyroid hormone. Steroid therapy is effective in over 90% of patients, and the outcome is generally good if treatment is initiated early.

Myxedema coma occurs in cases of severe hypothyroidism, leading to altered level of consciousness, organ dysfunction, and death, if untreated. Seizures can occur in the setting of hyponatremia. Myxedema coma is a medical emergency that requires aggressive treatment, including IV thyroid hormone, supportive care, and glucocorticoids for the possibility of coexisting adrenal insufficiency.

Peripheral manifestations of hypothyroidism are less severe and include carpal tunnel syndrome, peripheral neuropathy, and myopathy. Carpal tunnel syndrome is thought to be due to mucopolysaccharide complex aggregation within the median nerve.
Nerve conduction studies often reveal a mixed axonal and demyelinating process. Symptoms improve with thyroid hormone replacement.

Common neurologic symptoms of hyperthyroidism include delirium, tremor (high-frequency, low-amplitude), and sensory polyneuropathy. Seizures and encephalopathy can occur in the setting of acute thyrotoxicosis. Beta-blockers are effective in reducing anxiety and tremor.

**Hypocalcemia**

Neurologic manifestations of hypocalcemia are classified into acute and chronic processes. Acute hypocalcemia is associated with tetany (muscle spasms due to neuromuscular irritability) and seizures. On examination, the Trousseau and Chvostek signs can be present. The Trousseau sign consists of contraction of hand muscles after a blood pressure cuff is inflated over the forearm for 3 minutes. The Chvostek sign consists of facial muscle contraction caused by tapping over the facial nerve where it exits the skull.

Chronic manifestations of hypocalcemia are most commonly associated with hypoparathyroidism. Basal ganglia calcifications can lead to parkinsonism and behavioral changes. There are rare case reports of extrapyramidal symptoms improving with vitamin D and calcium treatment.

*Hypercalcemia* can lead to declining mental status and even coma in the acute and severe setting. Hypercalcemia may be seen in the setting of malignancy and primary hyperparathyroidism. Neuropsychiatric symptoms, including depression, anxiety, and cognitive dysfunction, are seen with hyperparathyroidism.
Endogenous Toxins

Various metabolic disorders involving the liver produce endogenous toxins that may cause neurologic symptoms; these disorders include Wilson disease, hepatic encephalopathy, kernicterus, and Reye syndrome.

Wilson Disease

Wilson Disease, also known as hepatolenticular degeneration, is an autosomal recessive disorder characterized by abnormal copper transport and decreased biliary copper excretion, leading to toxic accumulation of copper in the liver, brain, and eye. Neurologic manifestations include parkinsonism and neuropsychiatric symptoms due to involvement of the caudate and putamen. Kayser-Fleischer rings, copper deposits in the eye, are commonly seen. Diagnosis is made by finding decreased levels of serum ceruloplasmin, Kayser-Fleischer rings, and increased 24-hour urine copper excretion. Liver biopsies should be obtained in uncertain cases. Treatment with chelation therapy, such as penicillamine, reduces copper levels and can gradually improve neurologic symptoms. Untreated cases progress to liver failure and fatality. Liver transplantation is curative and should be considered for patients who do not respond to chelation therapy.

Hepatic Encephalopathy

Hepatic encephalopathy is seen in up to 80% of patients with cirrhosis; about half of these patients present with overt symptoms. The severity of encephalopathy ranges from mild confusion and behavior changes to coma. Asterixis can be seen at any stage of the
disease, while bradycardia, hyperreflexia, and myoclonus are indicative of more severe disease. Diagnosis is made by history and physical examination, after excluding other causes of encephalopathy such as cerebrovascular disease. Serum ammonia is typically elevated, but normal levels do not exclude the diagnosis. Lactulose reduces serum ammonia levels and improves symptoms of hepatic encephalopathy.

**Kernicterus**

Highly elevated indirect serum bilirubin levels can cause a classic triad of sensorineural hearing loss, impaired upward gaze, and opisthotonus, consistent with the diagnosis of kernicterus. Gross pathologic examination of the brain reveals yellow discoloration in the basal ganglia, superior and inferior colliculi, vestibular nuclei, inferior olive, and dentate nucleus. Kernicterus was essentially eradicated in developed countries because of administration of Rh(D) immunoglobulin to Rh-negative mothers and newborn bilirubin screening, which promotes early and effective treatment of hyperbilirubinemia.

**Reye Syndrome**

Reye syndrome is a serious disorder of hepatic dysfunction (fatty degeneration of the liver) and encephalopathy associated with use of aspirin, typically in children with influenza or varicella infections. Symptoms rapidly progress to seizures and coma due to increased intracranial pressure. Some inborn errors of metabolism, such as fatty acid oxidation disorders, are considered risk factors for Reye syndrome. Fortunately, due to advisories against the use of aspirin in febrile children in the 1980s, the incidence of Reye
syndrome significantly decreased and is now quite rare. As with any medication, the risks and benefits should be weighed before starting aspirin in children.

**Exogenous Toxins**

Poisoning by carbon monoxide, certain heavy metals such as mercury and lead, cyanide, and alcohol may all result in severe neurologic dysfunction. These are described below.

**Carbon Monoxide**

Carbon monoxide (CO) poisoning most frequently occurs during the winter months since gas heaters and other fuels at home put families at risk for exposure. CO is odorless and colorless, making it more difficult to identify. CO binds to heme with high affinity, preventing oxygen binding and causing the oxyhemoglobin dissociation curve to shift to the left.

Mild symptoms include headache, nausea, and dizziness, while severe symptoms can lead to seizures, encephalopathy, and coma. Cerebral edema can develop after a few hours, and gross pathologic examination reveals a cherry red brain. After 24 hours, petechial hemorrhages develop in the globus pallidus and white matter, eventually leading to pallidal necrosis.

Treatment should be initiated with high flow oxygen, which decreases the half-life of carboxyhemoglobin (CO-Hb) from 300 minutes to 90 minutes. Hyperbaric oxygen is even more effective and is recommended for treating unconscious patients, those with evidence of end organ ischemic damage, or those with high CO-Hb levels.
Mercury

Neuropsychiatric symptoms may result from chronic exposure to low levels of elemental mercury vapor. Symptoms are nonspecific, including anxiety, irritability, depression, and memory loss, associated with a severe intention tremor. Organic mercury toxicity can lead to neuropathy with symptoms including paresthesia, deafness, and ataxia. Chelation therapy is used for treatment of elemental mercury poisoning but is ineffective for organic mercury toxicity.

There is no evidence that thimerosal, a mercury-containing preservative used in vaccinations, causes any adverse neurodevelopmental or neurocognitive outcomes, including autism.

Lead

Lead was used in household paint until the 1970s, when it was removed because of the high prevalence of lead toxicity in children. Currently, all children are screened for lead poisoning in order to efficiently identify and treat this condition. The most common clinical manifestations of lead poisoning are neurobehavioral, including attention deficit hyperactivity disorder, learning disabilities, and pervasive developmental delay. Rarely, lead poisoning leads to hearing loss and peripheral neuropathy, particularly involving the extensor muscles of the wrist and causing wrist drop. Encephalopathy is only seen at levels greater than 100 mcg/dL (elevated levels are defined as >5 mcg/dL). Chelation therapy is recommended for severe cases.

Cyanide
Cyanide inhibits oxidative phosphorylation, forcing cells to use anaerobic metabolism for energy. Acutely, patients may develop headache, delirium, vertigo, seizures, and coma. Since the basal ganglia are especially susceptible to injury, survivors may develop parkinsonism. Chronic, low exposure to cyanide is seen with excessive cassava intake, which can lead to tropical ataxic neuropathy. Tropical ataxic neuropathy is characterized by paresthesia, hearing loss, ataxia, and optic neuropathy. Hydroxocobalamin binds to cyanide directly and is the preferred antidotal treatment for cyanide poisoning.

**Ethanol and Other Alcohols**

Ethanol, a water-soluble molecule found in alcoholic beverages, is the most common exogenous toxin diagnosed and treated in the emergency department. The legal blood alcohol concentration limit in most states is 80 mg/dL. Acute intoxication causes incoordination, slurred speech, loss of inhibition, stupor, and memory impairment. Patients with chronic alcohol abuse are at risk for developing Wernicke-Korsakoff syndrome, cerebellar degeneration, neuropathy, and myopathy.

Acute cases of severe anion-gap metabolic acidosis should raise suspicion for methanol or ethylene glycol intoxication. Likewise, a non-anion gap metabolic acidosis with ketones suggests isopropyl alcohol ingestion.

**Illicit Drugs**

Illicit drugs account for many medical and psychiatric hospital admissions. Currently, there is a rising heroin epidemic in the United States. Intoxication with drugs of abuse can result in myriad neurologic symptoms and signs. **Table 1** lists common illicit drugs, along with their pharmacology and typical neurologic effects.
Table 1 Illicit Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacology</th>
<th>Clinical Manifestations of Intoxication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Mu opioid receptor activation</td>
<td>Lethargy, euphoria, depressed vital signs, miotic pupils</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Inhibits presynaptic neurotransmitter release inhibitor</td>
<td>Euphoria, impaired coordination, hyperphagia, conjunctival injection</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Dopamine reuptake inhibitor</td>
<td>Anxiety, hypervigilance, tachycardia, hypertension</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>Catecholamine reuptake inhibitor</td>
<td>Euphoria, increased alertness, sexual arousal</td>
</tr>
<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td>5-HT activator</td>
<td>Hallucinations, delusions, mydriatic pupils, tachycardia</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>N-methyl-D-aspartate (NMDA) antagonist</td>
<td>Aggression, impulsivity, overt psychosis, nystagmus</td>
</tr>
</tbody>
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Annotated Bibliography


This article reports a rare case of idiopathic hypoparathyroidism presenting with extrapyramidal and cerebellar dysfunction, with a review of literature.

This brief report summarizes data from emergency departments throughout the United States regarding illness in patients with carbon monoxide exposure. The data are from 2001 to 2003 emergency department visits, and 2001 to 2002 death certificates.

This article provides an overview of the many neurologic complications of alcoholism.


This review article discusses complications of carbon monoxide exposure and focuses on diagnosis and treatment in the emergency department.

This review discusses peripheral nervous system manifestations related to the deficiency of key nutrients and neurologic complications associated with bariatric surgery.


This article discusses 13 patients with myelopathy associated with copper deficiency. The authors conclude that unrecognized copper deficiency is a common cause of idiopathic myelopathy in adults.


This excellent retrospective study from Denmark evaluates the incidence of autism before and after the discontinuation of thimerosal-containing vaccines. The authors report no correlation between thimerosal-containing vaccines and the incidence of autism.


These guidelines provide an overview of Wilson disease and present evidence-based recommendations for the approach to diagnosis and treatment of patients with Wilson disease.

This evidence-based review of aspirin and Reye syndrome focuses on etiology, pharmacodynamics of salicylates, and epidemiology. The author concludes that the evidence does not support a defined cause-effect relationship between aspirin and Reye syndrome.


This article reports the case of a 17–month–old infant with symptoms of Reye syndrome, who was found to have medium-chain acyl-CoA dehydrogenase deficiency on postmortem examination.


This article summarizes a review of 71 articles discussing the pharmacokinetic and pharmacodynamic aspects of hydroxocobalamin and its efficacy in human cyanide poisoning. The authors conclude that hydroxocobalamin is an effective antidote to cyanide.