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. Overdose, intentional or inadvertent, of hypoglycemic agents is most commonly implicated; insulin-secreting tumors, Addison disease, multiple organ failure, or sepsis may involve hypoglycemia. The most common clinical manifestations are autonomic, with excessive sweating, nausea, and palpitations, whereas neurologic symptoms progress from confusion and lethargy to seizure and coma.
Focal deficits occasionally occur. Pathologically, injuries appear similar to those seen with hypoxic injury. Rapid administration of oral or IV glucose in unconscious patients, usually proceeded by thiamine to avoid precipitating acute Wernicke syndrome, can lead to full recovery, although clinical improvement may lag behind normalization of glucose levels.

**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 as limited body stores may be depleted after only 4 to 6 weeks of poor nutrition or within 2 to 3 weeks of severe dietary deprivation. 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. As in management of hypoglycemia, 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. The condition emerges in many who survive Wernicke encephalopathy but rarely presents in isolation or concurrently with the initial encephalopathy state. It is associated with lesions
of the medial dorsal thalamic nuclei. Unlike Wernicke encephalopathy, Korsakoff syndrome is not easily treated.

Peripheral nervous system manifestations of thiamine deficiency include dry beriberi, a length-dependent sensorimotor axonal neuropathy that may have autonomic features. Wet beriberi, a state of high cardiac output heart failure, may convert to the dry form after diuresis.

**Vitamin B₆ (Pyridoxine) Deficiency**

As with other vitamin deficiencies, pyridoxine deficiency occurs most often in association with malnourishment, malnutrition, and alcoholism but also is seen as the result of medication use, including several pertinent to the neurologist. Valproate, carbamazepine, and phenytoin increase catabolism and may lead to pyridoxine deficiency. It is also frequently reported in patients on isoniazid treatment for tuberculosis, as this drug competes with vitamin B₆ as a cofactor for neurotransmitter synthesis. Regardless of the cause, patients 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.

Although adults generally tolerate low levels of pyridoxine, requiring severe deficiency to produce symptoms, excess levels due to unintentional overdose or
supplementation can also lead to neurologic symptoms. Most patients present with a sensory ganglionopathy, with some demonstrating superimposed myelopathic features.

Vitamin B<sub>12</sub> Deficiency

The most significant neurologic complication of vitamin B<sub>12</sub> deficiency is degeneration of the dorsal and lateral spinal cord columns, otherwise known as subacute combined degeneration. In addition to the typical myelopathic features, a peripheral neuropathy or optic neuropathy may be present. Deficiency also produces hematologic features, typically a megaloblastic anemia. Patients may present with ataxia, weakness, and paresthesia. Measurement of serum B<sub>12</sub> levels may be insufficient; the identification of abnormal levels of serum methylmalonic acid and homocysteine aids in the identification of patients with functional B<sub>12</sub> deficiency. The American Academy of Neurology recommends all three studies in the evaluation of patients with symmetric polyneuropathy. Early treatment with supplemental vitamin B<sub>12</sub> can reverse symptoms, but untreated cases can progress to spasticity and paraplegia.

Nitrous oxide (NO) toxicity also produces symptoms of vitamin B<sub>12</sub> deficiency, as NO converts vitamin B<sub>12</sub> 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 develop over years 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 peripheral neuropathy; patients present with ataxia, hyporeflexia, and loss of proprioceptive and vibratory sensation. Many patients have associated retinitis pigmentosa, and some have an associated vacuolar inflammatory myopathy. 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 B_{12} deficiency. As with vitamin E deficiency, copper deficiency must be prolonged for clinical manifestations to develop, usually years after the inciting event, which is usually gastric bypass surgery. Examination can reveal upper motor neuron signs from spinal cord involvement, as well as lower motor neuron signs from peripheral neuropathy. In children, a rare form of copper deficiency from birth is caused by Menkes disease, a rare X-linked disorder. The most common causes of copper deficiency in adults are malabsorption and excessive zinc intake. The latter results in upregulation of metallothionein, which preferentially binds copper and sequesters it in enterocytes. Such zinc exposure usually occurs with use of supplements but occasionally arises from consumption of denture cream or other medication or treatment regimens with high zinc content. Diagnosis often requires analysis of a combination of serum copper, ceruloplasmin, and zinc coupled with 24-hour urine studies of copper and zinc. In general, treatment involves removing sources of excessive zinc, if present, along with parenteral or 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, often in the context of another systemic illness. Patients present with hypothermia and altered mental status, progressing to loss of consciousness, organ dysfunction, and death if untreated. Seizures can occur, particularly in the setting of hyponatremia. Diagnosis can be difficult; not all patients have the expected elevations in thyroid-stimulating hormone, making testing of free thyroid hormones a necessity. 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. Myopathy and periodic paralysis are less commonly reported. Seizures and encephalopathy can occur in the setting of acute thyrotoxicosis. In the acute setting, strategies to inhibit thyroid hormone synthesis (eg, propylthiouracil) or release (eg, sodium iodine) are coupled with the use of beta-blockers to reduce the peripheral effects of existing thyroid hormone. Beta-blockers are also effective in reducing anxiety and tremor.

**Hypocalcemia**

Neurologic manifestations of hypocalcemia are classified into acute and chronic processes. Acute hypocalcemia is associated with acral and perioral paresthesia, tetany (ie, muscle spasms due to neuromuscular irritability), particularly carpopedal spasm, encephalopathy, 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, either idiopathic or iatrogenic, although symptoms can also develop in cases of severe, prolonged vitamin D deficiency. 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, granulomatous disease, various medications (eg, lithium) and primary hyperparathyroidism. Neuropsychiatric symptoms are common, primarily depression, anxiety, and cognitive dysfunction with progression to coma only in severe cases.

**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 due to mutations in ATP7B (chromosome 13q14) and 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 (including a characteristic wing-beating tremor), dystonia, and neuropsychiatric symptoms due to involvement of the caudate and putamen. Bulbar dysfunction with dysarthria and facial grimacing referred to as “risus sardonicus” may be present. Kayser-Fleischer rings, copper deposits in the eye, are best appreciated with the slit lamp exam. Diagnosis is made by finding decreased levels of serum ceruloplasmin, Kayser-Fleischer rings, and increased 24-hour urine copper excretion. Imaging may reveal T2-weighted hyperintensity in the basal ganglia and ventrolateral thalamus or, less commonly, the
giant panda sign, characterized by high-intensity T2 signal in the tegmentum surrounding spared red nuclei and pars reticulate. Liver biopsies should be obtained in uncertain cases. Treatment with chelation therapy, such as penicillamine, reduces copper levels and can gradually improve neurologic symptoms, although additional symptomatic therapy may be required for tremor or dystonia. Untreated cases progress to liver failure and death. 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, whereas 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, and the correlation between ammonia levels and symptom severity is poor. Classic EEG findings of frontal slowing and triphasic waves are not specific to this disease process and can be seen in a variety of metabolic encephalopathies. Lactulose, rifaximin, and neomycin reduce serum ammonia levels and improve symptoms of hepatic encephalopathy. Definitive treatment requires addressing the underlying liver disease, usually with transplantation as the definitive course of action.
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 chest pain, shortness of breath, headache, nausea, vomiting, dizziness, and altered mental status 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. Survivors may experience residual memory, cognitive, and mood disorders, along with persistent motor and vestibular deficits, all of which may persist for years. Similar symptoms may develop with low level chronic exposure.

Diagnosis may be challenging, especially in an unconscious patient with limited history, particularly as conventional pulse oximetry measurements cannot distinguish between carboxyhemoglobin and oxyhemoglobin. Pulse CO oximetry is available but should be compared to laboratory measurements. A variety of imaging findings are reported, often with a similar predilection for the globus pallidus, but these nonspecific changes in white matter generally are not helpful for diagnosis. A high index of suspicion is required, and in known or suspected exposures, laboratory confirmation of the diagnosis should not delay initiation of treatment 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>
</table>
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.


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This article provides an overview of the diagnosis, clinical manifestations, natural history, and treatment of minimal hepatic encephalopathy. The authors provide a recommended algorithm for diagnosis and treatment of cirrhotic patients with minimal hepatic encephalopathy.


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.