Myelopathy describes any neurologic deficit related to the spinal cord. It is most commonly caused by its compression by neoplasms, degenerative disc disease, trauma, or infection. Less common causes of myelopathy include spinal cord tumors, infection, inflammatory, neurodegenerative, vascular, toxic, and metabolic disorders. Conditions affecting the spinal cord must be recognized as early as possible to prevent progression that may lead to permanent disability. Biopsy is rarely performed, thus the diagnosis and management rely on patient’s history, physical examination, laboratory results, and imaging findings. Here we review the clinical presentations, pathophysiological mechanisms, and magnetic resonance imaging findings of myelopathies related to metabolic or toxic etiologies.
Table 1 Toxic and Metabolic Myelopathies

<table>
<thead>
<tr>
<th>Myelopathies associated with nutrient deficiency</th>
<th>Key Findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalamin or B12 vitamin deficiency</td>
<td>Subacute combined degeneration, peripheral neuropathy and neuropsychiatric disturbances. Megaloblastic anemia may be present.</td>
</tr>
<tr>
<td>Nitrous oxide toxicity (associated with B12 inactivation)</td>
<td>Previous exposure to N2O (anesthesia paresthetica).</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>Similar to B12 vitamin deficiency.</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td>Subacute combined degeneration and history of gastric surgery.</td>
</tr>
<tr>
<td>Vitamin E deficiency</td>
<td>Progressive spinocerebellar syndrome with lesions in the posterior columns on MRI.</td>
</tr>
<tr>
<td>AIDS-associated myelopathy (mechanism not completely understood)</td>
<td>Patients who are HIV positive presenting with lesions in the posterior columns predominantly in the upper thoracic cord on MRI.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxic myelopathies associated with drugs and chemical agents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin myelopathy</td>
<td>Progressive involvement with selective involvement of the ventral pons and lateral and posterior columns of the spinal cord.</td>
</tr>
<tr>
<td>Hepatic myelopathy</td>
<td>Evidence of manganese deposition in the basal ganglia (high signal on T1-WI) is common.</td>
</tr>
<tr>
<td>Organophosphate poisoning</td>
<td>Delayed myelopathy and neuropathy presenting with spinal cord atrophy that persists long after the cholinergic effects of organophosphate had subsided.</td>
</tr>
<tr>
<td>Chemotherapy and radiation therapy-related myelopathies</td>
<td>History of chemotherapy and radiation therapy. The affected spinal cord segment is in the same area as the radiation-induced bone marrow changes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxic myelopathies with geographical predilection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal sea stroke</td>
<td>Spinal cord infarct in patients swimming in the sea of specific locations in the globe.</td>
</tr>
<tr>
<td>Lathyrisism (seen in India, Bangladesh, and Ethiopia) and Konzo (Africa)</td>
<td>Specific dietary habits.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other noninfectious and noninflammatory myelopathies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis myelopathy</td>
<td>Rare complication of diabetic ketoacidosis.</td>
</tr>
<tr>
<td>Spinal cord decompression illness</td>
<td>Patients diagnosed with decompression sickness presenting with patchy areas of increased T2 signal intensity in the spinal cord with no segmental distribution.</td>
</tr>
<tr>
<td>Surfer’s myelopathy</td>
<td>Longitudinally extensive T2 hyperintense central cord lesion in the midthoracic region in novice surfers.</td>
</tr>
</tbody>
</table>

*All listed entities cause a very similar pattern of clinical and imaging involvement of the posterior and lateral columns.

intestinal infections and ileal abnormalities (Helicobacter pylori, Diphyllobothrium latum, human immunodeficiency virus, intestinal tuberculosis or lymphoma, celiac disease, Whipple’s disease, inflammatory bowel disease, radiation enteritis, graft-versus-host disease, pancreatic disease, Zollinger-Ellison syndrome, and tropical sprue, bacterial overgrowth) lead to malabsorption. Other conditions include elderly (related to atrophic gastritis-related hypochlorhydria induced food-Vitamin B12 malabsorption), hereditary enzymatic defects and mutations in genes encoding endocytic receptors involved in ileal absorption and cellular Cbl uptake (Mutations in CUBN and AMN [selective Cbl malabsorption and proteinuria: Imerlund-Gräsbeck syndrome], mutations in gastric intrinsic factor [GIF] or TCN2 [transcobalamin] leading to absence of the protein or presence of abnormal protein, disorders of intracellular processing and utilization of vitamin B12, disorders involving the synthesis of cobalamin cofactors [cblA to cblG], and medications [Antacids, H2 blockers, metformin, sunitinib]).

Coenzyme vitamin B12 (cobalamin), which together with folate, is essential for the formation of methionine from homocysteine tetrahydrofolate. It is absorbed in the ileal microvilli after binding to the intrinsic factor. Tetrahydrofolate is necessary for normal DNA synthesis and methionine is converted to S-adenosylmethionine that is necessary for methylation of myelin sheath phospholipids. B12 deficiency results in decreased activity of cobalamin-dependent methylcobalamin esterase enzyme with resultant elevation of methylmalonic acid and reduced myelin basic protein methylation with fragile myelin that is susceptible to demyelination and vacuolization.

Clinical Presentations

Vitamin B12 deficiency may lead to serious neurologic complications including neuropathy, myelopathy, neuropsychiatric disturbances, and optic neuropathy. These may be accompanied by hematologic manifestations of cobalamin deficiency such as anemia, macrocytosis, neutrophil hypersegmentation, or megaloblastic marrow changes. Subacute...
Myelopathy (subacute combined degeneration)

- Numbness, weakness, and paresthesia of the extremities that primarily affect the lower extremities, often symmetric, and progresses in a distal-to-proximal manner. Later this myelopathy progresses to unsteady gait, poor coordination, sensory deficits, and bowel or bladder dysfunctions.
- Physical examination: signs of dorsal column involvement include loss of position and vibration sense or ataxia. Lateral column involvement includes spasticity, hyperreflexia, and positive Babinski sign. Involvement of the spinothalamic tracts with sensory level may also be present.

Peripheral neuropathy and optic neuropathy may be seen.

Neurologic manifestations (may be the earliest and often the only manifestation of B12 deficiency)

Hematologic manifestations

- Megaloblastic anemia or megaloblastic marrow changes
- Pancytopenia (leukopenia and thrombocytopenia)

Pathophysiology

Methylcobalamin, the active form of intracellular vitamin B12, is required by the methionine synthetase enzyme to convert homocysteine into methionine and methyltetrahydrofolate into tetrahydrofolate. N2O inactivates vitamin B12 by irreversible oxidation of the cobalt center of methylcobalamin from the monovalent to bivalent and trivalent forms. The methionine synthesis pathway is thereby inhibited. In normal subjects, blocking of methionine synthesis by N2O does not cause symptoms. However, subclinical vitamin B12-deficient individuals are prone to neurologic degeneration because N2O causes exhaustion of the residual stocks of vitamin B12.

Clinical Presentations

Myloneuropathy results from chronic exposure or after a single exposure in individuals with B12 deficiency. Signs and symptoms appear rapidly with N2O toxicity and may be seen despite a normal serum B12 level. Less commonly, symptoms may be delayed up to 2 months after acute exposure. Neurologic manifestations may include a myelopathy (subacute combined degeneration) presents as a myelopathy (clinical manifestations are summarized in Table 2).
combined degeneration), neuropathy, myeloneuropathy, and mental status changes.\textsuperscript{1,12}

Pathology Findings
Neuropathologically, the findings are similar to Vitamin B\textsubscript{12} related subacute spinal degeneration which are characterized by reversible swelling of myelin sheaths in the posterior and lateral columns. Later, myelin sheath and axonal degeneration are seen leading to irreversible Wallerian-type degeneration of the long tracts.\textsuperscript{12}

Imaging Findings
MRI typically shows high T2 signal intensity in the posterior columns (sometimes in the lateral and anterior columns) of the cervical or thoracic spinal cord with often several vertebral bodies in length (Fig. 3). Modest expansion of the spinal cord may be seen. Contrast enhancement is rare and generally mild when it present.\textsuperscript{9,12,13}

Diagnosis
The diagnosis of myeloneuropathy because of N\textsubscript{2}O is a clinical one and should be considered in patients who develop neurologic symptoms following surgical and dental procedures (“anesthesia paresthetica”) or in recreational users.\textsuperscript{1,12}

Treatment or Prognosis
Prevention includes prophylactic administration of vitamin B\textsubscript{12} weeks before surgery in individuals with a borderline vitamin serum level who receives N\textsubscript{2}O anesthesia.\textsuperscript{1} Treatment involves high doses of vitamin B\textsubscript{12}. Administration of methionine may also be required. Exogenous methionine provides a direct substrate for methionine synthetase whereas the body slowly replaces the inactive vitamin B\textsubscript{12} and starts depletion of...
endogenous methionine. Improvement of symptoms and MRI changes are seen after replacement therapy is started.\textsuperscript{12}

**Folate Deficiency**

**Definition**

Folate deficiency rarely exists in a pure state and is often associated with conditions that affect other nutrients. The most common manifestation of folate deficiency is a myelopathy or myeloneuropathy resembling subacute combined degeneration seen with B\textsubscript{12} deficiency.\textsuperscript{1}

**Pathophysiology**

Folate is a water-soluble B vitamin present in fresh green vegetables, citrus fruits, legumes, and liver. As with B\textsubscript{12}, folate acts as an important cofactor in DNA synthesis and methylation pathways. Its deficiency results from reduced intake of folate-rich products, impaired absorption, or increased folate metabolism. It is associated with alcoholism, small bowel disorders, and drugs such as methotrexate and trimethoprim. Folate absorption may be decreased with reduced gastric secretions in patients after gastric surgery, atrophic gastritis, acid-suppressive therapy, and acid neutralization by treatment of pancreatic insufficiency.\textsuperscript{1,14}

**Clinical Presentations**

Folate deficiency causes similar manifestations to those of vitamin B\textsubscript{12} deficiency because of its importance in production of methionine and tetrahydrofolate. For unclear reasons, neurologic and hematologic manifestations due to folate deficiency are rare, mild, and confounding. Neurologic manifestations of folate deficiency include a myelopathy, peripheral neuropathy, optic neuropathy, and cognitive or behavioral manifestations.\textsuperscript{1,14}

**Pathology Findings**

Pathologically, folate deficiency myelopathy is identical to vitamin B\textsubscript{12} deficiency myelopathy and characterized by reversible swelling of myelin sheaths in the posterior and lateral columns.\textsuperscript{1,5,10,14}

**Imaging Findings**

Subacute combined degeneration due to folate deficiency resembles other forms of subacute combined degeneration (Fig. 4).\textsuperscript{1,4,9,14}

**Diagnosis**

Attribution of neurologic manifestations to pure folate deficiency requires exclusion of other causes. Serum folate levels between 2.5 and 5 \( \mu \)g/L may be indicative of a mildly compromised folate status. Erythrocyte folate is more reliable than plasma folate because its levels are less affected by short-term fluctuations in intake. Plasma homocysteine levels are typically elevated in patients with clinically significant folate deficiency.\textsuperscript{1,14}

**Treatment or Prognosis**

Daily doses, as high as 20 mg, may be necessary in patients with malabsorption. Reduced folates are required only when folate metabolism is impaired by drugs such as methotrexate or inborn errors of metabolism. Plasma homocysteine is best for monitoring response to therapy as it decreases within a few days of instituting folate therapy but does not respond to inappropriate vitamin B\textsubscript{12} therapy.\textsuperscript{1,14}

**Copper Deficiency**

**Definition**

Acquired copper deficiency may cause myelopathy or myeloneuropathy that resembles subacute combined degeneration.\textsuperscript{1,15}

**Pathophysiology**

Copper permits electron transfer in key enzymatic pathways. It is a component of metalloenzymes, including cytochrome-c oxidase, that have a critical role in the structure and function of the nervous system. Reduction in cytochrome-c oxidase activity may be the basis for neurologic dysfunction in copper deficiency.\textsuperscript{16} Because of copper’s ubiquitous distribution and low daily requirement, acquired dietary copper deficiency is rare. The coexistence of multiple causes of copper deficiency...
increases the chances of development of a clinically deficiency state. The most common cause of acquired copper deficiency is a history of gastric surgery. Typically, neurologic manifestations are delayed by years following gastric surgery. Excessive zinc ingestion is also a recognized cause of copper deficiency. Additionally, copper deficiency has been reported in enteropathies associated with malabsorption such as cystic fibrosis, sprue, bacterial overgrowth, and inflammatory bowel disease.1

**Clinical Presentations**

Neurologic manifestations are similar to those seen with B12 deficiency with which they may coexist. The most common manifestation is that of a myelopathy presenting with a spastic gait and prominent sensory ataxia because of dorsal column dysfunction. Central nervous system (CNS) demyelination, peripheral neuropathy, and optic neuritis also occur.1,16

**Pathology Findings**

Copper deficiency–associated myelopathy has been well described in animal models. The typical distribution of spinal cord lesions is that of greater involvement of the cervical cord with less severe changes in the thoracic and lumbar segments. Wallerian degeneration and demyelination with microcavitation of the white matter of the spinal cord, particularly affecting the dorsal columns and brainstem, are typical.16

**Imaging Findings**

The most common abnormality on the spine MRI is increased T2-WI signal in the dorsal columns, mostly in the cervical cord; contrast enhancement is not seen (Fig. 5). Additionally, signal changes involving the lateral columns and extension of the pyramidal tract signal changes into the brainstem have been reported. These findings are similar to those seen in patients with vitamin B12 deficiency.1,15-18

**Diagnosis**

Laboratory indicators of copper deficiency include a decrease in serum copper or ceruloplasmin and in 24-hour urinary copper excretion. Changes in serum copper usually parallel ceruloplasmin concentration. Serum zinc and 24-hour urinary zinc excretion levels should be obtained and an elevation in these should prompt an aggressive search for an exogenous source of zinc.1,16

**Treatment or Prognosis**

Oral copper supplement is the method of supplementation. Response of hematological parameters (including bone marrow findings) is prompt and often complete. Recovery of neurologic signs and symptoms is variable. In patients in whom excess zinc ingestion is the cause, stopping zinc supplements may suffice and no additional copper supplements may be required.1,15,18

**Vitamin E Deficiency**

**Definition**

Vitamin E deficiency manifests as a progressive spinocerebellar syndrome.

**Pathophysiology**

Vitamin E is as a fat-soluble antioxidant preventing peroxidation of membrane fatty acids. Most vitamin E in the human body is localized in adipose tissues. More than 2 years are required for adipose tissues to reach steady-state levels in response to changes in dietary intake. In adults, vitamin E deficiency is most often associated with fat malabsorption syndromes (celiac disease, cystic fibrosis, and cholestasis) and other intestinal disorders. In children, vitamin E deficiency may be seen because of genetic in alphacopherol transfer protein, abetalipoproteinemia, or defects in chylomicron synthesis and secretion.1

---

**Figure 4** Folate deficiency. Axial (A) and sagittal (B) T2-WI in a patient with folate deficiency show high-signal intensity involving the dorsal columns (arrows).
Clinical Presentations
Neurologic manifestations of vitamin E deficiency include a progressive spinocerebellar syndrome, similar to those of Friedreich ataxia, and a peripheral neuropathy with gait difficulty, hyporeflexia or areflexia, pyramidal signs, impaired position and vibration perception, and dysarthria. Pigmented retinopathy, myopathy, movement disorders, and gaze palsies have also been reported.\(^1,19\)

Pathology Findings
Lesions in the dorsal root ganglia, posterior medullary tracts, cerebellar cortex, spinocerebellar tracts, anterior horn cells, and peripheral nerves have been reported.\(^20\)

Imaging Findings
MRI may show high-signal lesions on T2-WI in the posterior columns. Cerebellar atrophy may be present.\(^21,22\)

Diagnosis
Serum vitamin E levels are dependent on concentrations of serum lipids. Hyperlipidemia or hypolipidemia can increase or decrease serum vitamin E without reflecting similar alterations in tissue levels. Effective serum vitamin E levels are calculated by dividing the serum vitamin E by the sum of serum cholesterol and triglycerides. In patients with neurologic manifestations serum vitamin E levels are frequently undetectable.\(^1\)

Treatment or Prognosis
Replacement of vitamin E is treatment of choice. Improvement of neurologic symptoms or signs in severe cases may not occur.\(^1\)

AIDS-Associated Myelopathy
Definition
AIDS-associated myelopathy, also called vacuolar myelopathy, is a spinal cord disease in human immunodeficiency virus (HIV) positive patients. Clinical manifestations, imaging findings, and histopathology resemble that of subacute combined degeneration because of vitamin B\(_{12}\) deficiency. It may occur at any stage during the course of HIV infection but is more common with advanced immunosuppression. Reliable data on the incidence and prevalence of myelopathy in HIV patients are not available.\(^1,23\)

Pathophysiology
The cause of vacuolar myelopathy is unknown. Increased prevalence of B\(_{12}\) deficiency occurs in HIV patients with neurologic symptoms but its significance is unclear. Impairment in methylation pathways related or not to viral infection of the spinal cord have been proposed.\(^1,23,24\)

Clinical Presentations
Manifestations of vacuolar myelopathy are varied and often include painless spastic paraparesis that is slowly progressive with a sensory ataxia. There may be an associated sphincter and erectile dysfunctions. Overlapping peripheral neuropathy may confound the diagnosis. Hyperreflexia at the knees with reduced ankle reflexes are common.\(^23\)

Pathology Findings
Vacuolar myelopathy is characterized by intralamellar vacuolation in the spinal white matter throughout the lateral and posterior columns of the thoracic and cervical segments.\(^23,25\)

Imaging Findings
MRI features of vacuolar myelopathy include high T2 intensity lesions in the posterior columns predominantly in the upper thoracic cord. Frequenty, the spinal cord may be normal or show atrophy and nonspecific patchy T2-WI abnormalities.\(^23,25\)

Diagnosis
Diagnosis is made by exclusion by ruling out vitamin B\(_{12}\) deficiency, human T-lymphotrophic virus-1, and neurosyphilis. Cerebrospinal fluid (CSF) may be normal or show mild pleocytosis with mild protein elevation. Similar findings may be seen in asymptomatic HIV patients.

Treatment or Prognosis
There is no effective therapy for HIV-associated myelopathy. The role of antiretroviral therapy is not established, however following antiretroviral therapy MRI may show significant reduction of the T2 hyperintensity of the posterior columns.\(^23,25\)
**Toxic Myelopathies Associated With Drugs and Chemical Agents**

**Heroin Myelopathy**

**Definition**
Myelopathy induced by heroin is progressive with selective involvement of the ventral pons and lateral and posterior columns of the spinal cord and may be associated with inhalation (“chasing the dragon”) or intravenous use.\(^1,2,6,27\)

**Pathophysiology**
Proposed mechanisms include direct toxicity, vasculitis, or hypersensitivity reaction. Isolated toxicity seems less probable as systemic toxins typically involve the nervous system more diffusely along with other organs. Generalized vasculitis would be unlikely to first affect the spinal cord.\(^27\) Thus, hypersensitivity is the predominant explanation as the myelopathy may occur after a period of abstinence followed by a single use.\(^1,2,6,29\) Hypotension may possibly result in border-zone infarctions in the cord.\(^1\) However, hypotension is unlikely to be severe enough to damage the spinal cord and spare the more ischemia-sensitive neurons of the brain. Furthermore, although the level of injury varies among reported cases, no pattern fitting the vascular “watershed zones” of the spinal cord has been documented.\(^27\)

**Clinical Presentations**
Clinical picture consists of an initial flaccid paraparesis or paraplegia of sudden onset with sensory loss in the legs and lower thoracic dermatomes and urinary sphincter disturbances. Occasionally the sensory and motor levels extend to the cervical region,\(^31\) resembling symptoms of transverse myelitis.

**Pathology Findings**
Extensive necrosis of the cervical and thoracic cord has been described in some patients.\(^31\)

**Imaging Findings**
MRI is frequently normal. Hyperintense lesions on T2-WI and fluid attenuation inversion recovery (FLAIR) images affecting the posterior and lateral columns, pontomedullary region, and ventral pons may be seen. Findings consistent with acute transverse myelitis have also been reported. Contrast enhancement is variable and usually patchy.\(^27\)

**Diagnosis**
Most reports describe normal CSF findings although pleocytosis and increased total protein may occur.\(^28-30,32\)

**Treatment or Prognosis**
Treatment with either intravenous corticosteroids or immunopheresis may limit immune response preventing disability but their efficacy requires further validation.\(^27\) Prognosis is often poor, with residual spastic paraparesis and sensory deficits, and in some patients death.\(^30\) Full recovery has been reported occasionally.\(^31\)

**Hepatic Myelopathy**

**Definition**
Hepatic myelopathy or portosystemic myelopathy is a rare neurologic complication of chronic liver disease with portal hypertension usually associated with portosystemic shunting either surgically created or spontaneous. It is characterized by an insidious onset of pure motor spastic paraparesis without sensory or sphincter involvement.\(^33\)

**Pathophysiology**
Pathophysiology is poorly understood and it is broadly accepted that nitrogenous products such as ammonia, fatty acids, indoles, and mercaptans bypassing the liver through a portocaval shunt play an important role.\(^34\) These metabolites cause myelin damage resulting in demyelination in the brain and spinal cord. Selective predisposition of the motor system has been demonstrated by involvement of the lateral corticospinal tracts in autopsy studies. Other causative factors include nutrient deficiencies and deranged liver metabolism.\(^33\) Additionally, the myelopathy may also be related to elevated manganese levels with MRI evidence of manganese deposition in the basal ganglia without extrapyramidal manifestations or clinical evidence of decompensated cirrhosis.\(^1,2,6,35\)

**Clinical Presentations**
The typical clinical presentation is a progressive pure motor spastic paraparesis with minimal or no sensory deficits and no bowel or bladder involvement. Most patients report prior episodes of hepatic encephalopathy and often the development of myelopathy follow the creation of surgical shunts. However, preceding portosystemic encephalopathy is not invariably present.\(^7\) Early and accurate diagnosis is important because patients with early stages of the disease can recover following liver transplantation.\(^33,36\)

**Pathology Findings**
Neuropathologic studies show demyelination in the lateral corticospinal tracts with varying degrees of axonal loss.\(^33,37\)

**Imaging Findings**
MRI usually shows symmetric high T2 signal intensity in the lateral corticospinal tracts and less commonly in the ventral pyramidal tracts, posterior columns, and spinocerebellar tracts.\(^36\) Increased pallidal T1 signal in presence of elevated serum manganese may also be present.

**Diagnosis**
Hepatic myelopathy is diagnosis of exclusion. Motor evoked potential studies may be suitable for the early diagnosis even in patients in the preclinical stages of the disease.\(^35,38\)

**Treatment or Prognosis**
Hepatic myelopathy is a rare and debilitating disorder with no effective treatment. However, its early identification and exclusion of other treatable causes is important. Some patients improve following liver transplantation\(^26\) but the therapeutic potential of liver transplantation for preventing progression and allowing recovery needs to be further validated.\(^39\)
Organophosphate Poisoning

Definition
The most common complication of organophosphate poisoning is an acute intoxication with a cholinergic crisis because of the inhibition of acetylcholinesterase. Some patients subsequently develop organophosphate-induced delayed myelopathy and neuropathy, also known as organophosphate-induced delayed neurotoxicity (OPIDN).

Pathophysiology
Organophosphates are common components of pesticides available in many homes. A major chemical that causes symptoms is triorthocresyl phosphate. Signs and symptoms of acute organophosphate toxicity are because of acetylcholinesterase inhibition and resulting muscarinic and nicotinic dysfunctions. In the neuromuscular junction, acetylcholine is released when a nerve impulse reaches terminal axonal end and it diffuses across the synaptic cleft and binds to cholinergic nicotinic receptors on the muscle fibers, causing them to contract. The enzyme, cholinesterase splits acetylcholine into acetic acid and choline, stopping its action. End products of the metabolism of acetylcholine are taken up by nerve fibers and resynthesized into acetylcholine. In organophosphate poisoning, cholinesterases are phosphorylated by the phosphate end of organophosphates resulting in excessive accumulation of acetyl chloride with resultant effects on muscarinic, nicotinic receptors in the CNS. After resolution of a cholinergic crisis, an intermediate syndrome can develop in some patients. It is likely a neuromuscular junction defect syndrome. OPIDN is a late complication of some organophosphorus compounds and is possibly because of phosphorylation and subsequent aging of neurotoxic esterases in the nervous system.

Clinical Presentations
After organophosphate poisoning, 3 well-defined clinical phases may be seen as follows: an initial acute cholinergic crisis, an intermediate syndrome, and OPIDN. Pinpoint pupils, excessive salivation, generalized weakness, and respiratory collapse characterize the acute cholinergic crisis. The intermediate syndrome is characterized by weakness of neck flexors, proximal limbs, and respiratory muscles. OPIDN occurs 1-3 weeks after acute exposure and following an uncertain duration after chronic exposure. OPIDN may occur in absence of the cholinergic or intermediate phase. Symptoms include distal paresthesias, progressive leg weakness and wasting, and cramping muscle pain. There may be evidence of upper limb involvement and pyramidal tract dysfunction. Sensory loss when present is mild.

Pathology Findings
Studies in chicks with organophosphate-induced delayed neuropathy show severe damage in the ventral and lateral tracts of the thoracic spinal cord. The same neuropathologic changes may be associated with prominent and diffuse spinal cord atrophy especially in the thoracic region.

Imaging Findings
MRI at the late phase of exposure may reveal evidence of spinal cord atrophy that persists long after the cholinergic effects had subsided.

Diagnosis
There is usually a delay in onset of clinical symptoms after exposure to organophosphates. Measurement of cholinesterase activity in red blood cells helps confirm the diagnosis because red blood cells cholinesterase activity is less rapidly depressed than serum cholinesterase activity. In the late phase somatosensory evoked potentials are often abnormal.

Treatment or Prognosis
Acute symptoms are best treated with pralidoxime and atropine. Pralidoxime is a reactivator of inhibited acetylcholinesterase and is its specific antidote.

Chemotherapy-Related Myelopathies

Definition
Acute myelopathy is a rare but devastating complication of chemotherapy treatment. It has been reported following administration of different chemotherapeutic agents including methotrexate, cytarabine, cisplatin, cladarabine, doxorubicin, vincristine, and cytoxine arabinoside.

Pathophysiology
Intrathecal methotrexate and cytarabine are the most frequently implicated agents. Acute or chronic leukoencephalopathy is the most common type of methotrexate-induced neurotoxicity and subacute myelopathy is rare. The pathogenesis of methotrexate-induced myelopathy is not clear but it is probably multifactorial; Following 2 major mechanisms have been proposed: indirect inhibition of methionine synthesis and direct toxicity. Methotrexate inhibits the enzyme dihydrofolate reductase and prevents folic acid from converting to tetrahydrofolate acid causing folate deficiency. This deficiency indirectly inhibits the synthesis of methionine, as folate is an important cofactor in DNA synthesis and methylation pathways. As methionine is necessary for formation and maintenance of myelin sheaths, its deficiency may lead to vacular degeneration of white matter. This mechanism is similar to that of subacute combined degeneration of the spinal cord because of vitamin B12 deficiency. A constitutional predisposition or abnormal sensitivity to methotrexate such as genetic polymorphisms or mutations related to methionine metabolism may also play a role in the pathogenesis as the reported frequency of severe methotrexate myelopathy is disproportionately low considering the large number of patients receiving the drug intrathecally. Another proposed mechanism is direct injury of endothelial cells in venules and capillaries of the spinal cord with blood-brain barrier disruption, increased vascular permeability, and insinuation of plasma proteins into the vascular walls which lead to their degeneration and necrosis and vascular degeneration of white matter. Vascular injury also allows the drug to diffuse into the CNS causing direct toxic effects. Direct toxic effect of intrathecal
administration of methotrexate on the pia mater and white matter is probably caused by pia-glial barrier disruption and myelin sheaths and oligodendrocytes injuries.46

Known risk factors for development of methotrexate myelopathy include the following: cumulative intrathecal doses and continuous exposure to the drug more than a prolonged period of time, systemic administration, concurrent radiotherapy, and CNS involvement by the primary disease.47

Clinical Presentations
There is a variable clinical course in regard to time and rate of onset after therapy, severity of disease, and degree of recovery.48 Overall, 2 clinical patterns of paraparesis have been described.49 A transient, flaccid, and areflexic paraparesis with pain and anesthesia may occur soon after intrathecal injection. Rarely, the paralysis may ascend with respiratory compromise and death. A less common form is a progressive spastic-ataxic paraparesis with sphincter dysfunction seen after weeks of a series of intrathecal treatments.1 The latency to onset of symptoms is variable and can be long.

Pathology Findings
Reports on the neuropathologic findings of methotrexate-induced myelopathy are rare and findings vary from vacuolar degeneration of the lateral and posterior columns in association with severe loss of axons and myelin sheaths to complete transverse necrosis of the spinal cord or a combination of both.46 The gray matter is relatively spared.46

Imaging Findings
MRI findings are nonspecific and the initial imaging examination is often normal. Symmetric increased T2 signal in dorsal and lateral columns of the cord without abnormal contrast enhancement similar to that of subacute combine degeneration has been described (Fig. 6). Cord swelling and contrast enhancement have also been reported. Long-term outcome is generally that of cord atrophy with normal T2 signal intensity demonstrated as early as 6 months after clinical onset of disease.48,50

Diagnosis
Chemotherapy-induced myelopathy is a diagnosis of exclusion. The main differential diagnosis includes malignancy, viruses, radiation, and paraneoplastic myelopathy.38

Treatment or Prognosis
Chemotherapy-induced myelopathy carries a poor prognosis. Preservative-containing chemotherapeutic agents or diluents should not be used intrathecally4 and multiple and frequent intrathecal treatment should be avoided.1 Mettucious neurologic monitoring of methotrexate concentration in CSF is important to prevent the occurrence of this complication.46 Immediate discontinuation of intrathecal methotrexate treatment and supplementation of derivatives of folic acid and methionine or homocysteine metabolic pathway, such as S-adenosylmethionine and cyanocobalamin, are the best treatment options.51 However, further research is required to establish an effective and definite treatment.52

Radiation-Induced Myelopathies
Definition
Radiation myelopathy is defined as injury caused by ionizing radiation.52 There are 2 main reasons for spinal cord exposure to radiation—an intentional delivery to treat primary or secondary lesions or its inevitable inclusion in a radiation field which intends to treat an adjacent neoplasm. In either case, factors such as total radiation dose, radiation dose per fraction, time between applications, spinal cord level and associated chemotherapy affect the incidence and severity of myelopathy.52 Radiation myelopathy is divided into the following 4 categories: acute transient radiation myelopathy, acute paraplegia or quadriplegia, lower motor neuron findings, and chronic progressive radiation myelopathy also known as delayed radiation myelopathy (DRM). DRM is rare but is the most feared complication and typically occurs after a certain latent period that ranges from months to few years following irradiation.26,52

Pathophysiology
The pathogenesis of DRM is likely to be multifactorial with no single target cell and no single pathway solely responsible. Damage to vascular endothelial cells,53 direct injury of oligodendroglia and myelin sheaths,54 and disturbance of the intra-spinal venous drainage because of lesions in the vein walls55 have been considered most important.40 It is known that the spinal cord has an enhanced radiosensitivity relative to other organs and that there is no uniformly accepted “spinal cord tolerance” and that no precise threshold dose is considered safe.56 A total dose of 45 Gy with fractions of 1.8-2 Gy is generally accepted as dose limit using conventional radiotherapy,1 although 40 Gy poses however a small risk of myelopathy. Doses of 45 Gy and 52 Gy to the cervical cord result myelopathy rates of 0.1% and 1% respectively with a lower incidence in the thoracic cord.48,56 Reports of myelopathy after stereotactic radiosurgery to spinal lesions are rare.50 Concomitant chemotherapy is a recognized risk factor for development of radiation myelopathy. In the past years, targeted antibody and antireceptor therapies have emerged, but the extent to which these agents contributed to the development of radiation myelopathy remains unknown.57 Previous exposure to radiation, particularly less than 2 years, may also carry an increased risk as spinal cord damage is most likely to become overt during this period.50 The volume and length of spinal cord as well as the spinal cord segment irradiated may also influence the incidence of radiation myelopathy.50

Other factors in the patients’ medical history and physical status make the spinal cord sensitive to radiation injury. Hypertension, diabetes, autoimmune disease, congenital and acquired spinal cord abnormalities, pre-existing CNS injury, elevated hemoglobin, hypotension, alcohol abuse, and infectious disease also enhance the cord’s sensitivity to radiation damage.60

Clinical Presentations
Overall, 4 clinical syndromes of radiation myelopathy have been described are as follows: (1) an acute transient radiation
myelopathy (most common) characterized by Lhermitte’s sign with no other abnormalities on neurologic examination, (2) an acutely developing paraplegia or quadriplegia presumably secondary to ischemia and hemorrhage of the spinal cord caused by radiation-induced blood vessel damage, (3) a lower motor neuron disease in the upper or lower extremities, presumably caused by selective anterior horn-cell damage, and (4) DRM.52,56,61 Although the second and the third syndromes are exceedingly rare, the last one is the one most concerning.

Acute transient radiation myelopathy is a self-limiting early delayed reaction usually treated with corticosteroids. It occurs after a latent period of 2-4 months and is characterized by brief electric-like sensations in the spine and extremities triggered by neck flexion or extension (Lhermitte’s sign). Clinical improvement is generally seen within 2-9 months followed by complete recovery. There is no correlation between acute transient radiation myelopathy and DRM. Conversely DRM is a devastating condition, which may be permanent. It generally occurs after a latent period of time of 9-18 months but has been reported up to 3-4 years after completion of radiation treatment. Various combinations of motor and sensory deficits occur and depend on the anatomic level of cord injury. Development of bowel and bladder dysfunctions may occur. DRM may be fatal if it involves the upper cervical level.

Pathology Findings
Myelinated fibers and blood vessels are the most affected structures. In chronic progressive radiation myelopathy white matter necrosis and demyelination with vascular lesions including stenosis, thrombosis, hemorrhage, fibrinoid vascular necrosis, and venous wall thickening and hyalinization are seen.62 There is also gray matter involvement, including

Figure 6 Methotrexate myelopathy. Midsagittal (A) and axial (B-D) STIR images in a patient who underwent intrathecal methotrexate therapy for acute lymphoblastic leukemia. Images show high-signal intensity in dorsal and lateral columns (arrows) mimicking subacute combined degeneration. STIR, short-tau inversion recovery. ( Courtesy: Lazaro Amaral, Sao Paulo, Brazil.)

Downloaded from ClinicalKey.com at Centro Hospitalar Lisboa Central September 16, 2016. For personal use only. No other uses without permission. Copyright ©2016. Elsevier Inc. All rights reserved.
astrocytosis and hyalinosis of the vessel walls, but neurons are usually spared.60

**Imaging Findings**
In acute transient radiation myelopathy MRI is usually normal. In DRM, MRI shows cord swelling initially and a long intramedullary lesion with increased T2 signal and contrast enhancement (Fig. 7). The MRI findings correlate with neurologic symptoms. In the chronic stage MRI demonstrates cord atrophy. Radiation-induced bone marrow changes indicate the extension of the irradiated field and may help in reaching the correct diagnosis.

Positron emission tomography-computed tomography studies might have a role in differentiating radiation myelopathy from primary spinal cord lesions and spinal metastases. However, very few positron emission tomography-computed tomography studies have been conducted in the spinal cord and their results need validation.52

**Diagnosis**
Diagnostic criteria for DRM include—(1) the affected spinal cord segment must be in the irradiated zone, (2) symptomatology must correspond to the radiated spinal cord segment, (3) and the latency period should be more than 6 months. The differential diagnosis represents a challenging problem. Metastatic tumor is the most common cause of cord lesions in oncologic patients presenting with myelopathy.52 Primary intramedullary neoplastic lesions and other neurologic pathologies presenting with myelopathy must also be ruled out including paraneoplastic syndrome, zoster myelopathy, and myelopathy secondary to chemotherapy.52 Nerve conduction studies show slowing or complete block in spinal conduction. CSF examination is usually normal but mild elevation of protein levels and lymphocytosis may be seen.52,63,64

**Treatment or Prognosis**
No treatment has conclusively been shown to be of value in DRM. Several therapies such as corticosteroids, anticoagulation, pentoxifylline, vitamin E, and hyperbaric oxygen have been tried with limited benefits. Some patients derive a short-term benefit from steroids which may be related to decreasing edema and inflammation.52

**Toxic Myelopathies Associated With Geographical Predilection**

**Spinal Sea Stroke**

**Definition**
Spinal sea stroke is characterized by spinal and brainstem infarctions that occur in patients swimming in the North Carolina and Virginia coasts probably caused by contact with toxic marine animals.
Pathophysiology
Brainstem and spinal cord strokes in young adults are extremely rare. Jellyfish toxins have been proposed as a cause but the mechanism of neural tissue damage is unknown. It is also unclear why in all of the reported cases the abnormalities involved only the spinal cord and brainstem but spared the brain. Some jellyfish toxins affect the calcium channels of neurons, a process that could lead to cytotoxic edema, failure of cellular energetics, and eventually to irreversible damage such as seen in ischemia. Some authors have postulated that damage to the spinal cord is not direct but due to systemic hypotension with subsequent infarctions.

Clinical Presentations
Patients typically present with an acute severe dysfunction of sensory and motor systems. Neurologic signs and symptoms depend on the level of spinal cord involvement and include severe back pain, loss of sphincter control, paraplegia or paraparesis, or quadriplegic or tetraplegia in patients with higher cord lesions.

Pathology Findings
None of the published cases of spinal sea stroke report pathology findings.

Imaging Findings
The hallmark of spinal cord infarction is high T2 signal intensity in the cord (Fig. 8) especially involving the anterior two-third of the cord that correspond to the territory supplied by the anterior spinal artery. Diffusion weighted imaging shows restricted diffusion of the lesion.

Diagnosis
The diagnosis is generally made clinically. MRI should be obtained in all patients with suspected spinal cord infarction to confirm the diagnosis and to exclude other possible treatable causes of myelopathy.

Treatment or Prognosis
Spinal cord infarctions have a poor prognosis with little chance of recovery and significant sequelae.

Subacute Myelo-Optico Neuropathy (Clioquinol Toxicity)
Clioquinol (iodochlorhydroxyquin) is an antifungal-antiprotozoal drug used to treat intestinal parasitic diseases. Clioquinol’s use has been restricted or discontinued in some countries because of events in Japan (from 1955-1970) where more than 10,000 people developed a subacute myelo-optic neuropathy (SMON). SMON is characterized by subacute onset of lower limb paresthesias and spastic paraparesis with optic atrophy. Examination findings include hyperreflexia and extensor plantar responses. The pathophysiology mechanism is unknown but clioquinol is a copper or zinc chelator and this has led to the speculation that clioquinol-induced neurotoxicity may be a consequence of copper deficiency.

Lathyism (India, Bangladesh, and Ethiopia) and Konzo (Africa)
Lathyism is a self-limiting neurotoxic disorder endemic in Bangladesh, India, and Ethiopia, caused by beta-N-oxalyl-aminol alanine, an excitotoxic amino acid present in Lathyrus sativus. Ingestion of this neurotoxin results in increased intracellular levels of reactive oxygen species and subsequent impairment of the mitochondrial oxidative phosphorylation chain. It presents as a subacute or insidious onset spastic paraparesis. Degeneration is most prominent in motor cortex and pyramidal tracts that are responsible for lower extremity function.

Konzo is a tropical myelopathy seen in Africa resulting from weeks of high dietary cyanide exposure due to consumption of insufficiently processed cassava (Manihot esculenta Crantz) that contains cyanide. It is characterized by the abrupt onset of spastic non-progressive paraparesis. Years of cassava consumption have also been implicated in a syndrome of slowly progressive ataxia, peripheral neuropathy, and optic atrophy seen in parts of Africa. The diagnosis is based on a history of exposure and measurement of serum thiocyanate levels.

Lathyism and Konzo are irreversible and non-progressive conditions. MRI studies are negative. Somatosensory evoked potentials may show abnormalities which indicate poor conduction through the spinal cord. There are no specific treatments for these entities.

Other Noninfectious and Noninflammatory Myelopathies
Ketoacidosis Myelopathy
Definition
Myelopathy is a rare complication of diabetic ketoacidosis characterized by spinal cord edema and infarction usually associated with cerebral findings.

Pathophysiology
There are no existing explanations for the spinal cord edema associated with diabetic ketoacidosis probably due its rarity. Current explanations are limited to diabetic children with cerebral edema but the pathophysiological mechanisms for cerebral edema and infarctions are not clear. Systemic hypotension and hypoxia, rapid changes in serum osmolality, disseminated intravascular coagulation, and thrombosis secondary to dehydration; hemocoagulation and hyperviscosity have all been proposed as possible causes.
Clinical Presentations
Clinical presentation depends on the affected spinal cord level.

Pathology Findings
No neuropathologic findings have been described in reported cases.

Imaging Findings
Cord edema is seen as high T2 signal in the spinal cord usually associated with cord expansion (Fig. 9). Spinal cord infarction is seen as areas of bright T2 signal that show restricted diffusion. Patchy enhancement after gadolinium administration has been reported. Atrophy may be seen in late stages.

Diagnosis
Ketoacidosis myelopathy is a diagnostic of exclusion.

Treatment or Prognosis
There is no effective treatment. The prognosis is poor and varies according with the severity of the disease. Cardiac failure and pulmonary edema are rare but possible complications in critically ill patients with diabetic ketoacidosis.75

Spinal Cord Decompression Illness
Definition
Decompression sickness is a clinical syndrome caused by alterations in environmental pressure resulting in liberation of
inert gas bubbles in tissues or blood. Sport divers generally use compressed air as their breathing mixture and the inert gas that is liberated during decompression is nitrogen. There are following 2 types of decompression illness: type I is characterized by joint pain, skin marbling, small patchy hemorrhage, and lymphatic obstruction and type II is characterized by CNS involvement. CNS involvement may be further subdivided in cerebral and spinal cord subtypes. Spinal cord involvement accounts for 77% of CNS diving injuries. The population at risk includes, in addition to sport divers, naval and commercial divers, aviators, astronauts, and compressed air workers.

Pathophysiology
The pathophysiological mechanism of spinal cord decompression is not totally understood. Hypotheses include embolization of arterial bubbles via a right-to-left shunt, development of bubbles within the spinal cord, or embolization of the epidural vertebral venous system causing congestion and venous cord infarctions. The last hypothesis is the best documented one as the alteration of spinal cord venous draining resulting from the obstruction of the epidural venous system has been shown experimentally. Secondary immune-inflammatory processes may contribute to worsening of symptoms.Nitrogen bubbles lodge in spinal veins at the thoracic level; there the spine mobility is restricted by the rib cage.

Clinical Presentations
The great majority of spinal cord decompression sickness results in subjective sensory abnormalities distributed according to the dermatomes. A less frequent but more characteristic presentation corresponds to numbness in the limbs with a progressive ascending level of both sensory and motor deficits often accompanied by disturbances of bladder function.

Pathology findings
Spinal cord lesions are scattered throughout the white matter with no segmental distribution. The dorsolateral white matter is more vulnerable because of its high fat content in which nitrogen is readily stored.

Imaging Findings
MRI is reliable in the early detection of spinal cord lesions that occur in decompression accidents leading to prompt hyperbaric treatment and in the follow-up during and after hyperbaric recompression. MRI may demonstrate patchy areas of increased T2 signal intensity in the white matter tracts (Fig. 10).

Diagnosis
The diagnosis relies on clinical history, physical examination, and MRI findings.

**Figure 9** Ketoacidosis myelopathy. Sagittal (A) and axial (B-D) T2-WI of thoracic spine show high T2-WI signal intensity involving the central aspect of the cord (arrows). Sagittal T1-WI (E) and postcontrast fat sat T1-WI (F) show areas of contrast enhancement.
Thrombotic infarction of the artery of Adamkiewicz that occurs as the result of hyperextension of the spinal cord whereas individuals are lying prone on a surfboard.\textsuperscript{81,82}

**Imaging Findings**

Surfer’s myelopathy is usually associated with a longitudinally extensive T2 hyperintense central cord lesion on the midthoracic region with variable cranial and caudal extension. Patchy increased T1 signal presumably related to petechial hemorrhage have been described.\textsuperscript{67} Enhancement of the ventral roots of the cauda equina have also reported.\textsuperscript{51,82,84,85}

**Diagnosis**

The characteristic clinical history associated with the longitudinally extensive T2 hyperintense spinal cord lesion on MRI suggests the diagnosis.

**Treatment or Prognosis**

No treatment is available. Recovery is variable ranging from complete recovery of function to persistent paraplegia.

**Conclusion**

Toxic and metabolic myelopathies and myeloneuropathies are relatively rare clinical conditions that share clinical, neuropathologic, and imaging features. Acquaintance with these entities may lead to accurate diagnosis with successful identification of the underlying cause and appropriate treatment which may revert or prevent progression of symptoms associated with these incapacitating disorders.

---

**Surfer’s Myelopathy**

**Definition**

Surfer’s myelopathy is a rare non-traumatic injury that occurs in novice surfers who lay prone on a surfboard with the lumbar spine hyperextended for prolonged periods of time. It is probably underdiagnosed and underreported as it is a rare condition only recently recognized.\textsuperscript{81}

**Pathophysiology**

The pathophysiology of surfer’s myelopathy is unknown. Arterial insufficiency from hyperextension of the lumbar spine, venous hypertension associated with obstruction of the inferior vena cava by the liver whereas lying in a prone position, fibrocartilaginous embolism caused by retrograde embolism of the nucleus pulposus into the radicular spinal cord arteries, or avulsion of perforating arteries have all been proposed.\textsuperscript{81,82}

**Clinical Presentations**

Surfer’s myelopathy is usually preceded by back discomfort followed by acute myelopathy with variable motor-sensory involvement and urinary incontinence.

**Pathology Findings**

No definite histopathologic confirmation has been published, but surfer’s myelopathy probably is the result of a vascular phenomenon involving dynamic compression, vasospasm, or thrombotic infarction of the artery of Adamkiewicz that occurs as the result of hyperextension of the spinal cord whereas individuals are lying prone on a surfboard.\textsuperscript{81,82}

**References**