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Toxic and Metabolic Myelopathies

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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.
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Introduction

Myelopathy is a term used to describe neurologic deficits related to the spinal cord. It is usually compressive in nature, typically associated with neoplasm, degenerative disease, trauma, or infection, which may be managed surgically to relieve the cord compression in hopes of restoring normal function. Less common noncompressive myelopathies include inflammatory etiologies such as autoimmune, demyelinating, paraneoplastic, or infectious diseases and noninflammatory myelopathies, such as metabolic, toxic, or vascular disorders, which may not be amenable to surgical intervention and require different approaches to diagnosis and treatment.

Toxic and metabolic myelopathies may be further subdivided into (1) metabolic myelopathies associated with an identified nutrient deficiency including cobalamin or B_{12} vitamin, folate, copper, or vitamin E deficiencies; (2) toxic myelopathies associated with drugs and chemical agents such as heroin abuse, organophosphate poisoning, chemotherapeutic agents, and radiation therapy; (3) metabolic myelopathies with geographical predilection such as lathyrism and Konzo seen in India, Bangladesh, and Ethiopia and, (4) other rare noninfectious and noninflammatory myelopathies including ketoacidosis myelopathy, spinal cord decompression illness, and surfer's myelopathy (Table 1). Toxic and metabolic myelopathies share clinical, electrophysiological, neuropathologic, and imaging features. Variable degrees of peripheral nerve and optic nerve involvement are present and usually known as a myeloneuropathy and preferential involvement of the dorsal columns and corticospinal tracts is seen. Our purpose is to review the uncommon toxic and metabolic myelopathies giving special emphasis to their clinical presentation, pathophysiological mechanisms and magnetic resonance imaging (MRI) findings.

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Myelopathies Associated With Nutrient Deficiencies

Cobalamin or B_{12} Vitamin Deficiencies

Definition

Vitamin B_{12} deficiency causes myelopathy, neuropathy, and neuropsychiatric disturbances. In the spinal cord, it manifests as a subacute combined degeneration, characterized by degeneration of the lateral and posterior columns. It is considered the most common metabolic myelopathy.[1-3]

Pathophysiology

Vitamin B_{12} deficiency is due to inadequate intake and malabsorption. Inadequate intake is seen in strict vegetarians and is considered rare in the Western World. Pernicious anemia (the most common cause in the West), gastrectomy,

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Table 1 Toxic and Metabolic Myelopathies

	Key Findings*
Myelopathies associated with nutrient deficiency	
Cobalamin or B_{12} vitamin deficiency	Subacute combined degeneration, peripheral neuropathy and neuropsychiatric disturbances. Megaloblastic anemia may be present.
Nitrous oxide toxicity (associated with B_{12} inactivation)	Previous exposure to N_2O ("anesthesia paresthetica").
Folate deficiency	Similar to B_{12} vitamin deficiency.
Copper deficiency	Subacute combined degeneration and history of gastric surgery.
Vitamin E deficiency	Progressive spinocerebellar syndrome with lesions in the posterior columns on MRI.
AIDS-associated myelopathy (mechanism not completely understood)	Patients who are HIV positive presenting with lesions in the posterior columns predominantly in the upper thoracic cord on MRI.
Toxic myelopathies associated with drugs and chemical agents	
Heroin myelopathy	Progressive involvement with selective involvement of the ventral pons and lateral and posterior columns of the spinal cord.
Hepatic myelopathy	Pure motor spastic paraparesis with involvement of the lateral corticospinal tracts. Evidence of manganese deposition in the basal ganglia (high signal on T1-WI) is common.
Organophosphate poisoning	Delayed myelopathy and neuropathy presenting with spinal cord atrophy that persists long after the cholinergic effects of organophosphate had subsided.
Chemotherapy and radiation therapy-related myelopathies	History of chemotherapy and radiation therapy. The affected spinal cord segment is in the same area as the radiation-induced bone marrow changes.
Toxic myelopathies with geographical predilection	
Spinal sea stroke	Spinal cord infarct in patients swimming in the sea of specific locations in the globe.
Subacute myelo-optico neuropathy (clioquinol toxicity)	Subacute myelo-optic neuropathy after clioquinol treatment.
Lathyrism (seen in India, Bangladesh, and Ethiopia) and Konzo (Africa)	Specific dietary habits.
Other noninfectious and noninflammatory myelopathies	
Ketoacidosis myelopathy	Rare complication of diabetic ketoacidosis.
Spinal cord decompression illness	Patients diagnosed with decompression sickness presenting with patchy areas of increased T2 signal intensity in the spinal cord with no segmental distribution.
Surfer's myelopathy	Longitudinally extensive T2 hyperintense central cord lesion in the midthoracic region in novice surfers.

*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[1,4]. Other conditions include elderly (related to atrophic gastritis-related hypochlorhydria induced food-Vitamin B_{12} 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: Imerslund-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 B_{12}, disorders involving the synthesis of cobalamin cofactors (cblA to cblG), and medications (Antacids, H2 blockers, metformin, sunitinib).[1]

Coenzyme vitamin B_{12} (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. B_{12} 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.[1,4]

Clinical Presentations

Vitamin B_{12} 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