Metabolic and Toxic Myelopathies

By Natalie Elizabeth Parks, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **This article describes the clinical presentation, relevant diagnostic investigations, and treatment of metabolic and toxic myelopathies.**

RECENT FINDINGS: **Metabolic myelopathies, including those due to deficiency of vitamin B_{12}, folate, copper, or vitamin E, are preventable and typically respond to supplementation. In metabolic myelopathy, early recognition and treatment are important to reduce morbidity, particularly due to subacute combined degeneration of the spinal cord. Toxic myelopathies, including those due to medical interventions (eg, methotrexate, radiation), dietary toxins (eg, lathyrism, konzo), and drugs of abuse (eg, heroin), typically result in permanent neurologic deficits. Toxic myelopathy due to hepatic dysfunction may be reversible if patients receive early intervention, whereas nitrous oxide myelopathy responds to vitamin B_{12} replacement and cessation of exposure. In toxic myelopathy, it is best to avoid the provoking factor when possible or attempt to mitigate risk by identifying risk factors for developing myelopathy.**

SUMMARY: **Metabolic and toxic myelopathies are important causes of morbidity that require a high index of suspicion for diagnosis.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE: Dr Parks discusses the unlabeled/investigational use of bevacizumab for the treatment of radiation myelopathy.

INTRODUCTION

It is important for clinicians to recognize metabolic and toxic myelopathies, as almost all are preventable or treatable. Accurate diagnosis relies on a complete neurologic history and neurologic examination accompanied by relevant diagnostic investigations, including MRI of the spinal cord. Metabolic myelopathies typically have an insidious onset and a chronic progressive course, whereas toxic myelopathies have a more variable time course. Accurate diagnosis relies on symptom recognition in the appropriate context, such as living in an endemic area, dietary habits, recreational drug use, and medical comorbidities.

METABOLIC MYELOPATHIES

Metabolic myelopathies, including those due to deficiency of vitamin B_{12}, folate, copper, or vitamin E, are preventable and typically respond to supplementation (TABLE 6-1).

Vitamin B_{12} Deficiency

The prevalence of vitamin B_{12} (cobalamin) deficiency varies by geographic location, with higher prevalence in socioeconomically disadvantaged regions.[1] In

high-income countries, an association is seen between vitamin B_{12} deficiency and advanced age, with 6% of individuals 70 years of age or older in the United States and 10% of individuals 75 years of age or older in the United Kingdom having vitamin B_{12} deficiency. Among those with vitamin B_{12} deficiency and neurologic symptoms, approximately 50% experience myelopathy symptoms either alone or in combination with peripheral neuropathy (myeloneuropathy).[2]

The term *subacute combined degeneration of the spinal cord* is used to describe the myelopathy accompanying vitamin B_{12} deficiency to emphasize the posterior (dorsal) and lateral column damage encountered clinically and pathologically (FIGURE 6-1).[3,4] Initially, swelling of the myelin sheath is seen, followed by myelin breakdown with infiltration of macrophages. Over time, gliosis with axonal degeneration ensues.

Symptoms resulting from myelopathy due to vitamin B_{12} deficiency typically begin with the insidious onset of paresthesia and gait difficulty because of dorsal column dysfunction.[2,5] Individuals often describe difficulty maintaining balance

TABLE 6-1 **Metabolic Myelopathies**

Nutrient deficiency	Etiologies	Symptoms/signs	MRI	Diagnostic tests	Treatment
Vitamin B_{12}	Vegetarian diet, pernicious anemia, stomach/small bowel surgery, Crohn disease, gastritis, medications (H2 blockers, proton pump inhibitors, metformin, colchicine), tapeworm, nitrous oxide	Subacute combined degeneration of spinal cord beginning with paresthesia and sensory ataxia (positive Romberg sign, pseudoathetosis) followed by pyramidal symptoms and signs; frequent mixture of central and peripheral sensory and motor signs due to coexisting peripheral axonal neuropathy; may be associated with optic neuropathy and cognitive impairment	T2 hyperintensity in posterior columns with inverted V sign; may extend over several levels in cervical or thoracic cord; rarely gadolinium enhancement	Serum cobalamin: low Plasma methylmalonic acid: high Plasma homocysteine: high Complete blood cell count: macrocytic anemia, hypersegmented neutrophils Intrinsic factor antibodies: high specificity, low sensitivity for pernicious anemia among those with vitamin B_{12} deficiency	Cyanocobalamin 1000 mcg IM or subcutaneous daily for 5 days followed by 1000 mcg IM or subcutaneous monthly indefinitely; 1000 mcg orally daily is a possible alternative chronic regimen

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when visual input is removed (eg, in darkness or when eyes are closed). Neurologic examination reveals diminished vibration/proprioception that may be accompanied by a wide-based unsteady gait from sensory ataxia and a positive Romberg test. In addition, patients may have lower limb greater than upper limb weakness that is often associated with upper motor neuron signs, including spasticity, hyperreflexia, and upgoing plantar responses. Peripheral neuropathy frequently occurs with myelopathy due to vitamin B_{12} deficiency, causing a mixed picture of peripheral and central patterns of sensory and motor signs. In addition, optic neuropathy and cognitive dysfunction are recognized accompaniments. Patients may have an associated megaloblastic anemia, although neurologic symptoms may occur before the development of hematologic abnormalities.

Vitamin B_{12} is present in many animal proteins, such as meat, eggs, and milk, but is not found in plants. Today, many foods are fortified with vitamin B_{12}. Vitamin B_{12} undergoes several steps in the digestive process to enable successful

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Nutrient deficiency	Etiologies	Symptoms/signs	MRI	Diagnostic tests	Treatment
Folic acid	Alcoholism, small bowel surgery, celiac disease, inflammatory bowel disease, medications (methotrexate, pyrimethamine, trimethoprim, sulfasalazine)	Same as vitamin B_{12} deficiency	Same as vitamin B_{12} deficiency; no reports of gadolinium enhancement	Serum folate: low Red blood cell folate: low Plasma homocysteine: high Complete blood cell count: macrocytic anemia, hypersegmented neutrophils	Folic acid 3 mg orally daily until hematologic parameters normalize and then folic acid 1 mg orally daily
Copper	Bariatric surgery, partial gastrectomy, zinc excess (supplements, denture cream), celiac disease, Menkes disease	Same as vitamin B_{12} deficiency	Same as vitamin B_{12} deficiency; no reports of gadolinium enhancement	Serum copper: low Serum ceruloplasmin: low Complete blood cell count: anemia, leukopenia Assess serum zinc and celiac serology	Copper 2-4 mg orally daily with repeat serum copper to adjust dose; avoid zinc
Vitamin E	Cystic fibrosis, cholestatic liver disease, small bowel surgery, abetalipoproteinemia, ataxia with vitamin E deficiency	Sensory ataxia with absent reflexes and upgoing plantar responses, with or without pigmentary retinopathy	No characteristic spinal cord findings; MRI brain may demonstrate mild cerebellar atrophy	Plasma α-tocopherol: low Consider genetic testing (cystic fibrosis, abetalipoproteinemia, ataxia with vitamin E deficiency)	Vitamin E 300-1000 mg orally daily

IM = intramuscular; MRI = magnetic resonance imaging.

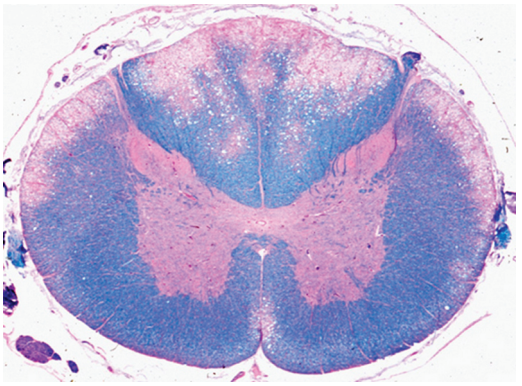

FIGURE 6-1
Subacute combined degeneration with demyelination of the posterior and lateral columns of the spinal cord.
Figure courtesy of Agamanolis DP, Neuropathology-web.org.[3]

absorption (FIGURE 6-2).[6] Vitamin B_{12} is cleaved from animal protein by gastric acid secreted by gastric parietal cells and becomes bound to intrinsic factor secreted by gastric parietal cells while both are passing through the duodenum. Vitamin B_{12} bound to intrinsic factor is absorbed in the ileum. Only 1% of vitamin B_{12} is absorbed as free vitamin B_{12}, independent of intrinsic factor. Absorbed vitamin B_{12} becomes bound to transcobalamin II, which delivers vitamin B_{12} to body tissues.

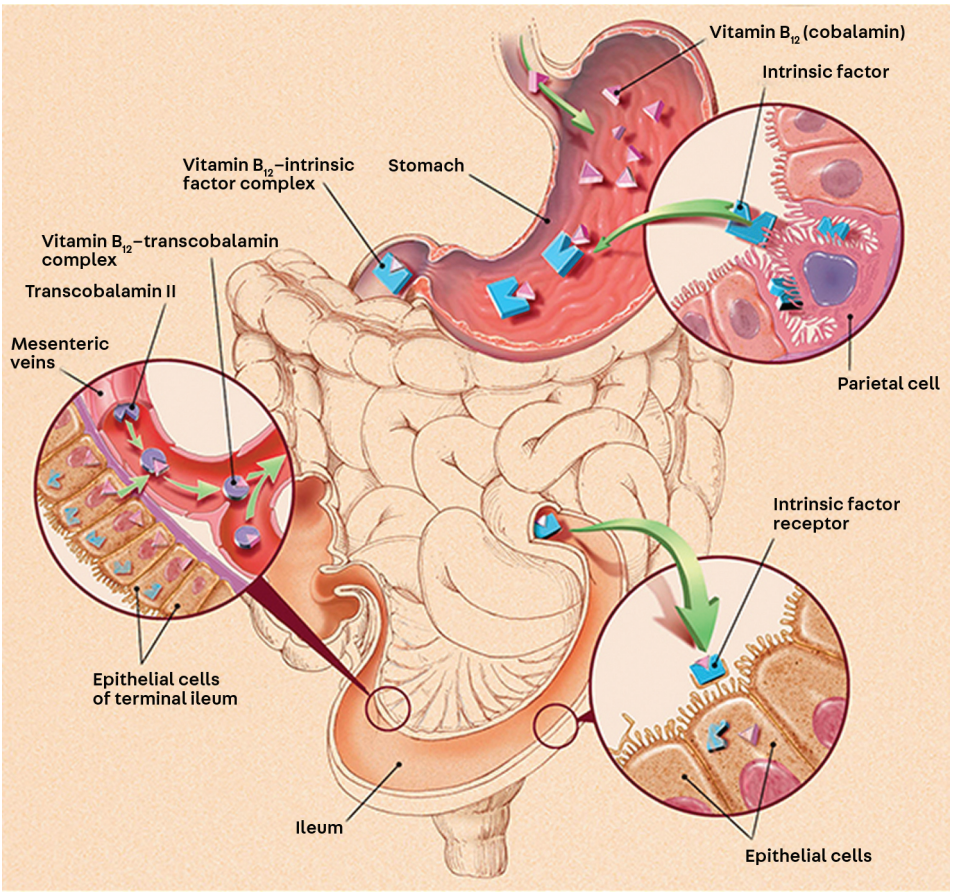

FIGURE 6-2
Vitamin B_{12} absorption. Vitamin B_{12} binds to intrinsic factor secreted by gastric parietal cells while in the duodenum. Vitamin B_{12} bound to intrinsic factor is absorbed in the ileum. Absorbed vitamin B_{12} binds to transcobalamin II for systemic transport.
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Vitamin B_{12} is an essential cofactor in the conversion of homocysteine to methionine, methylmalonic acid to succinyl-coenzyme A, and methyltetrahydrofolate to tetrahydrofolate (FIGURE 6-3).[7] These reactions are necessary for DNA synthesis, myelin synthesis, and the Krebs cycle, all of which contribute to nervous system function.

Vitamin B_{12} deficiency may arise from reduced intake, inadequate absorption, or abnormal metabolism.[8] A diet low in vitamin B_{12} may result from eating exclusively plant-based food (ie, a vegan diet). A disruption in the absorption process may also result in vitamin B_{12} deficiency. This disruption may be because of surgery on the stomach or small bowel (eg, gastric bypass weight loss surgery). Pernicious anemia is an autoimmune disease that affects parietal cells, which secrete gastric acid and intrinsic factor needed for vitamin B_{12} absorption. Gastritis caused by *Helicobacter pylori* also reduces parietal cell secretions. Crohn disease may preferentially affect the terminal ileum, reducing absorption. Medications such as histamine-2 receptor antagonists and proton pump inhibitors result in more alkaline gastric juices, reducing vitamin B_{12} breakdown by gastric acid. Additional medications linked to vitamin B_{12} deficiency include metformin, colchicine, and cholestyramine. Parasitic infection by the tapeworm *Diphyllobothrium latum* may interfere with absorption of vitamin B_{12} in the terminal ileum. Nitrous oxide may also affect vitamin B_{12} function, as discussed below.

The diagnosis of vitamin B_{12} deficiency is challenging because no gold standard test has been established[9]; thus, it is important to interpret laboratory

KEY POINTS

- **Vitamin B_{12} deficiency is common among older adults.**
- **Subacute combined degeneration of the spinal cord presents with posterior column dysfunction (reduced vibration/proprioception) along with variable severity of lateral column dysfunction (upper motor neuron signs).**

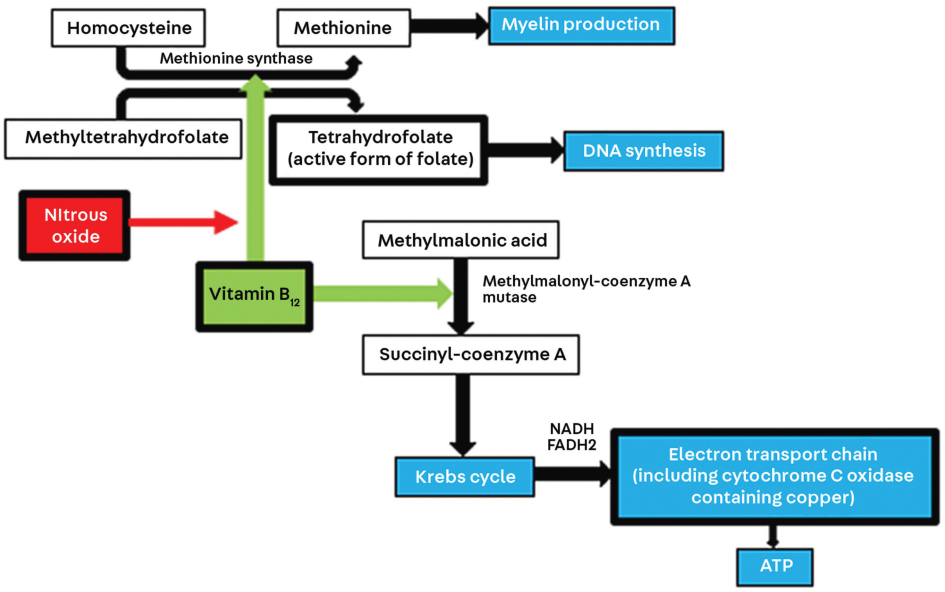

FIGURE 6-3

Vitamin B_{12} biochemistry. Vitamin B_{12} is an essential cofactor in the conversion of homocysteine to methionine, methylmalonic acid to succinyl-coenzyme A, and methyltetrahydrofolate to tetrahydrofolate. These reactions are necessary for myelin production, DNA synthesis, and the Krebs cycle, all of which contribute to nervous system function. Nitrous oxide causes inactivation of vitamin B_{12}, interfering with the ability of methionine synthase to convert homocysteine to methionine or methyltetrahydrofolate to tetrahydrofolate.

ATP = adenosine triphosphate; FADH2 = flavin adenine dinucleotide; NADH = nicotinamide adenine dinucleotide.

results in the context of clinical symptoms. Serum cobalamin is the standard initial diagnostic test.[9] In vitamin B_{12} deficiency, serum cobalamin may be low, but it may also be in the borderline or normal range[10,11]; plasma methylmalonic acid and homocysteine are particularly useful in this situation to help confirm cellular vitamin B_{12} deficiency. Methylmalonic acid or homocysteine may be elevated in vitamin B_{12} deficiency as vitamin B_{12} acts as a cofactor in the reaction needed to metabolize these compounds. Elevation of methylmalonic acid is more specific than elevation of homocysteine, which is also seen in other vitamin deficiencies, including folate (vitamin B_9) and pyridoxine (vitamin B_6).[9] Elevated methylmalonic acid may also occur if a patient has renal insufficiency or methylmalonic acidemia.[12] Elevated homocysteine may occur in renal insufficiency or homocystinuria.

MRI of the spinal cord in patients with vitamin B_{12} deficiency may demonstrate T2 hyperintensity in the posterior or lateral columns (FIGURE 6-4[13]). Imaging changes typically occur contiguously over several segments in the cervical or upper thoracic spinal cord. The appearance may resemble an inverted V (or inverted rabbit ears) in the posterior columns on axial images (FIGURE 6-4).[5,13] The T2 signal change is only rarely accompanied by contrast enhancement. Imaging findings often improve with adequate treatment.[5,14]

A number of additional investigations may be considered. Nerve conduction studies and EMG may be performed to investigate for evidence of a peripheral neuropathy, with a length-dependent axonal pattern typically encountered. Visual evoked potentials may demonstrate evidence of optic neuropathy. A complete blood cell count and peripheral blood smear may demonstrate macrocytic anemia with hypersegmented neutrophils. Anti–intrinsic factor antibody has high specificity but low sensitivity for identifying pernicious

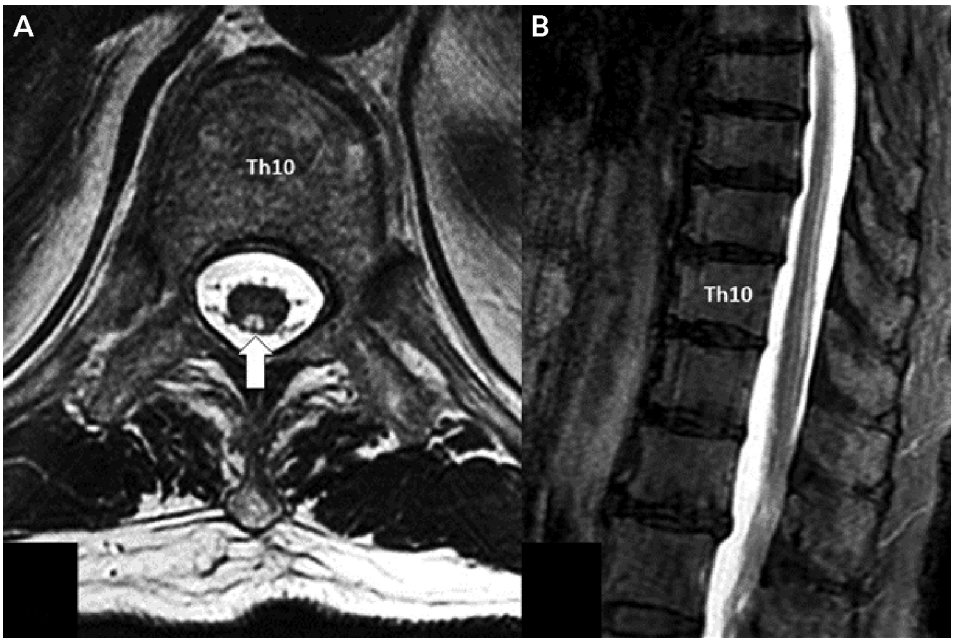

FIGURE 6-4

Subacute combined degeneration due to vitamin B_{12} deficiency. Axial (*A*) and sagittal (*B*) T2-weighted images of the spinal cord show hyperintensity in the posterior columns affecting the thoracic spinal cord on sagittal image (*B*), with an inverted V appearance on axial image (*A, arrow*).

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anemia among those with vitamin B_{12} deficiency,[9] whereas anti–parietal cell antibody and elevated gastrin are not specific for pernicious anemia. The Schilling test for pernicious anemia is no longer used in clinical practice.[12]

The treatment for vitamin B_{12} deficiency is vitamin B_{12} replacement, although no standard protocol has been established.[12] Injected vitamin B_{12} is commonly cyanocobalamin in North America and hydroxocobalamin in Europe. British guidelines recommend that for cases of vitamin B_{12} deficiency with neurologic involvement, IM hydroxocobalamin 1000 mcg be given every 2 days with reassessment after 3 weeks, followed by a maintenance dose of IM hydroxocobalamin 1000 mcg every 2 months.[9] Another reasonable approach for vitamin B_{12} deficiency causing myelopathy is IM or subcutaneous cyanocobalamin 1000 mcg/d for 5 days followed by a maintenance dose of IM or subcutaneous cyanocobalamin 1000 mcg once per month.[15] Replacement is recommended indefinitely for subacute combined degeneration of the spinal cord.[11] Low-quality evidence suggests that oral and IM vitamin B_{12} result in similar serum vitamin B_{12} levels.[16] As a result, it may be reasonable to continue maintenance therapy with 1000 mcg vitamin B_{12} given orally every day after initial parenteral replacement as an alternative.

Symptomatic and imaging improvement of subacute combined degeneration of the spinal cord are often seen after supplementation, particularly if patients receive early diagnosis and treatment.[14]

NITROUS OXIDE. Nitrous oxide (laughing gas) is an anesthetic gas used in surgical and dental procedures. In addition, it is used in aerosol cans that dispense whipped cream; inhaling nitrous oxide from these aerosol devices is called "doing whippets." Nitrous oxide has been exploited as a recreational drug as it causes euphoria.

Nitrous oxide causes irreversible inactivation of vitamin B_{12}, resulting in an identical clinical presentation to that of vitamin B_{12} deficiency. Nitrous oxide results in oxidation of the cobalt center of methylcobalamin from monovalent to bivalent and trivalent forms.[7] This inactivated form of vitamin B_{12} cannot be used by methionine synthase to convert homocysteine to methionine or methyltetrahydrofolate to tetrahydrofolate (FIGURE 6-3), which results in interference with DNA and myelin synthesis.

The subacute combined degeneration of the spinal cord associated with nitrous oxide toxicity is clinically and radiographically identical to vitamin B_{12} deficiency.[17,18] Subacute combined degeneration of the spinal cord may result from relatively brief exposure to nitrous oxide during routine surgical procedures in as little as 30 minutes (CASE 6-1).[19] Subacute combined degeneration of the spinal cord may also be caused by habitual recreational exposure to nitrous oxide from whippets.[20]

The diagnosis of nitrous oxide myelopathy requires a high index of suspicion as no single diagnostic test has been established. Among those with nitrous oxide toxicity, serum cobalamin level is low in approximately 70%, whereas plasma methylmalonic acid or plasma homocysteine, or both, are elevated in more than 90%.[17] Nitrous oxide toxicity is treated with vitamin B_{12} supplementation and cessation of nitrous oxide use.[20]

Folate Deficiency

Folate deficiency is encountered much less frequently since national fortification programs resulted in an increase in dietary folate.[21] Folate fortification was

KEY POINTS

- Vitamin B_{12} deficiency may be present despite serum cobalamin within the normal range, although plasma methylmalonic acid or plasma homocysteine, or both, may be elevated.
- The treatment for subacute combined degeneration of the spinal cord due to vitamin B_{12} deficiency is IM or subcutaneous cyanocobalamin 1000 mcg/d for 5 days followed by 1000 mcg once per month.
- Vitamin B_{12} replacement should be given indefinitely following subacute combined degeneration of the spinal cord due to vitamin B_{12} deficiency.
- Nitrous oxide causes inactivation of vitamin B_{12}, which may result in subacute combined degeneration of the spinal cord.
- Folate deficiency is uncommon since the introduction of national fortification programs aimed at improving folate levels among reproductive-age women to reduce neural tube defects in their offspring.

introduced in many countries, including the United States and Canada, because of a strong association between folate deficiency among reproductive-age women and neural tube defects in their offspring. In adults, the neurologic complications of folate (vitamin B_9) deficiency include myelopathy, peripheral neuropathy, optic neuropathy, and cognitive dysfunction.[22,23] Neurologic manifestations of folate deficiency (including myelopathy) are rare, and the myelopathy takes the form of a subacute combined degeneration of the spinal cord.[22,24,25]

CASE 6-1

A 78-year-old woman underwent extraction of a painful broken tooth. During the procedure, she received nitrous oxide anesthetic gas. Approximately 2 days after the procedure, she began to note difficulty walking in low lighting, with the need to hold on to the wall. Over the next several weeks, she began to experience tingling in her feet and then her hands. Her past medical history included hypertension and atrophic gastritis due to *Helicobacter pylori* infection. She had lost 9 kg (20 lb) over the previous 2 years because of reduced dietary intake since her husband died and, more recently, because of dental pain.

Approximately 2 months after the dental procedure, neurologic examination was remarkable for absent vibration distal to the tibial tuberosity, diminished proprioception at the great toes, reduced ankle jerks, bilateral extensor plantar responses, and positive Romberg sign.

MRI of her spinal cord demonstrated T2 hyperintensity in the posterior columns extending from C2 to C6, with an inverted V configuration. MRI of her brain demonstrated nonspecific T2 hyperintensities, most in keeping with chronic small vessel ischemia. Nerve conduction studies demonstrated a length-dependent axonal neuropathy affecting the lower extremities to a greater extent than the upper extremities. A complete blood cell count demonstrated macrocytic anemia, and her serum cobalamin was 103 ng/L (lower limit of normal 150 ng/L) and plasma methylmalonic acid was 0.7 nmol/mL (upper limit of normal 0.4 nmol/mL).

She was diagnosed with vitamin B_{12} deficiency unmasked following exposure to nitrous oxide during a dental procedure and was treated with IM cyanocobalamin 1000 mcg/d for 5 days followed by maintenance therapy of IM cyanocobalamin 1000 mcg once per month. Over the next 2 months, she experienced improvement in paresthesia and improved stability while walking. She was advised to continue with IM cyanocobalamin 1000 mcg once per month indefinitely.

COMMENT

The patient in this case had multiple risk factors for vitamin B_{12} deficiency, including age older than 70 years, a diet low in animal protein, and atrophic gastritis secondary to *H. pylori*. The neurologic examination features were consistent with involvement of the dorsal and lateral columns (subacute combined degeneration of the spinal cord). Parenteral (subcutaneous or IM) cyanocobalamin is recommended to treat vitamin B_{12} deficiency with neurologic manifestations.

Folate is naturally found in dark green vegetables, legumes, and liver. In many countries, foods such as white flour are fortified with folate. Folate is absorbed primarily in the jejunum.[23] The active form of folate is tetrahydrofolate; folate may be converted to dihydrofolate then tetrahydrofolate by dihydrofolate reductase. In addition, 5-methyltetrahydrofolate, formed in the enterocyte, is demethylated to tetrahydrofolate by methionine synthase. The methionine synthase reaction also uses cobalamin to convert homocysteine to methionine. Tetrahydrofolate is required in nucleic acid synthesis for DNA (FIGURE 6-3).[7]

Folate deficiency may result from inadequate intake, inadequate absorption, or abnormal metabolism.[23] Low dietary intake may result from cooking food (as folate is destroyed by heat) or alcohol use disorder. Impaired absorption in the jejunum may be secondary to surgery, celiac disease, or inflammatory bowel disease. Sulfasalazine impairs folate absorption by acting as a noncompetitive inhibitor of the reduced folate carrier. A number of medications are dihydrofolate reductase inhibitors, including methotrexate, pyrimethamine, and trimethoprim, leading to impaired folate metabolism. The requirement for folate is increased during pregnancy and in states with increased cell turnover, including malignancy, hemolytic anemia, and psoriasis.

The diagnosis of folate deficiency should include serum folate level, which reflects recent intake, as an initial test.[9] Red blood cell folate, which reflects intake over the past 3 months, may be performed if serum folate is normal. Plasma homocysteine may also be tested, as folate is needed for the conversion of homocysteine to methionine by methionine synthase. Elevated homocysteine may be consistent with folate deficiency, although elevated homocysteine may be seen in other conditions, including vitamin B_{12} deficiency. Abnormalities on MRI, electrophysiology, and complete blood cell count are identical to those seen in vitamin B_{12} deficiency discussed above.[25]

The treatment for folate deficiency is folate replacement, although no standard treatment protocol has been established. British guidelines recommend folic acid 5 mg/d for at least 4 months in the presence of megaloblastic anemia.[9] Another reasonable approach for folate deficiency is folic acid 1 mg 3 times a day until hematologic abnormalities normalize, followed by folic acid 1 mg/d.[26] Folic acid replacement is typically oral, although parenteral administration may be considered in patients who are acutely ill.

Subacute combined degeneration of the spinal cord due to folate deficiency often shows symptomatic improvement with folic acid replacement, particularly with early diagnosis and treatment of the deficiency.[22,24]

Copper Deficiency

Copper deficiency is an underrecognized cause of myelopathy that mimics vitamin B_{12} deficiency. The prevalence of copper deficiency is as high as 10% in individuals having undergone bariatric surgery with a Roux-en-Y gastric bypass.[27] The best characterized neurologic complication is myelopathy with or without neuropathy (CASE 6-2).

Copper deficiency myelopathy is almost identical to the subacute combined degeneration of the spinal cord encountered with vitamin B_{12} deficiency, often resulting in sensory ataxia and spasticity.[28,29] An associated length-dependent axonal peripheral neuropathy is frequently seen. Additional neurologic manifestations that may be associated with copper deficiency are isolated peripheral neuropathy, optic neuropathy, and cognitive dysfunction.

KEY POINTS

- Serum folate level reflects recent folate intake, whereas red blood cell folate level reflects intake over approximately the past 3 months.
- Copper deficiency is an underrecognized cause of subacute combined degeneration of the spinal cord.

Copper is absorbed in the stomach and proximal duodenum[28,29] and is transported into enterocytes by copper transporter protein-1 before transport from enterocytes into the portal circulation by ATP7A. A number of enzymes use copper as a cofactor, including cytochrome c oxidase in the mitochondrial electron transport chain. Copper is transported out of the liver to systemic tissues bound to ceruloplasmin.

Copper deficiency may be caused by inadequate intake or decreased absorption. Copper is found in high amounts in shellfish, organ meat, nuts, and beans. The most common cause of copper deficiency myelopathy is decreased absorption following gastrointestinal surgery (eg, Roux-en-Y gastric bypass), accounting for approximately 50% of cases, but celiac disease and excessive zinc consumption as a supplement or in denture cream are other common etiologies.[28,29] Zinc upregulates metallothionein, a chelator in enterocytes that has a higher affinity for copper than for zinc. Copper bound to the chelator remains in the enterocytes until enterocytes are shed and excreted in feces. Menkes disease is a genetic form of copper deficiency due to reduced copper absorption from a mutation in *ATP7A*.

CASE 6-2

A 56-year-old man presented with a 3-year history of gradually increasing difficulty with balance while walking and numbness that began in his feet and gradually ascended to the knees. Over the previous year, he had started to note paresthesia in his fingers. His past medical history was remarkable for a Roux-en-Y gastric bypass at age 49 for medically complicated obesity.

Neurologic examination was remarkable for absent vibration distal to the tibial tuberosity, diminished proprioception at the great toes, brisk reflexes, wide-based gait, and positive Romberg sign. MRI of the spinal cord demonstrated T2 hyperintensity in the posterior columns extending from C3 to C6, with an inverted V configuration. MRI of his brain was normal. Nerve conduction studies were normal. A complete blood cell count was also normal, as were serum cobalamin, serum folate, and plasma methylmalonic acid levels. Serum copper was 8.7 µmol/L (lower limit of normal 11.2 µmol/L), and serum ceruloplasmin was 54 mg/L (lower limit of normal 232 mg/L); serum zinc was normal.

He was diagnosed with copper deficiency myelopathy resulting from decreased copper absorption following bariatric surgery and was treated with oral copper 2 mg/d for 3 months, with improvement in balance and paresthesia. At 3 months, a repeat serum copper level was normal. He was advised to continue with oral copper 2 mg/d indefinitely.

COMMENT

Copper deficiency myelopathy mimics the subacute combined degeneration of the spinal cord encountered with vitamin B_{12} deficiency both clinically and radiologically. Gastric bypass surgery is a recognized risk factor for both vitamin B_{12} deficiency–associated and copper deficiency–associated myelopathies. Low serum copper can confirm the diagnosis, and oral supplementation can lead to improvement in neurologic function.

Measurement of serum copper is the diagnostic test of choice for copper deficiency; low copper levels may be accompanied by low ceruloplasmin.[29] Evaluating serum zinc level may help identify the cause of copper deficiency, and assessing for celiac disease is also useful.

MRI of the spinal cord demonstrates features in keeping with subacute combined degeneration of the spinal cord.[28,29] Approximately 50% of cases of copper deficiency myelopathy demonstrate T2 hyperintensity in the posterior region of the cervical or thoracic spinal cord, or both, without contrast enhancement.

Nerve conduction studies and EMG may demonstrate evidence of a length-dependent axonal polyneuropathy.[28] A complete blood cell count often reveals anemia or leukopenia, or both.

The treatment for copper deficiency is copper replacement, although no standard treatment protocol has been established.[28] Typically, copper deficiency myelopathy is treated with the equivalent of elemental copper 2 mg/d to 4 mg/d, although higher doses are sometimes required.[29] Copper is usually administered orally but may be given intravenously. It may be necessary to administer copper indefinitely depending on the underlying cause of copper deficiency. In the case of copper deficiency due to zinc supplementation, it is important to avoid zinc consumption. Stabilization or partial improvement of symptoms due to copper deficiency myelopathy often occurs following copper replacement.[29]

KEY POINTS

- Copper deficiency may be caused by bariatric surgery, celiac disease, or excessive zinc intake as a supplement or in denture cream.
- Serum copper and serum ceruloplasmin levels are typically low in copper deficiency.
- Vitamin E deficiency that results in spinocerebellar ataxia is an increased risk among those with impaired fat absorption from disorders such as cystic fibrosis and rare genetic conditions, including ataxia with vitamin E deficiency and abetalipoproteinemia.

Vitamin E Deficiency

Vitamin E deficiency is rare in the general population of developed countries such as the United States.[30] Specific populations, including those with cystic fibrosis, are at increased risk of vitamin E deficiency with a clinical phenotype similar to Friedreich ataxia, including ataxia, reduced proprioception, absent reflexes, and upgoing plantar responses.[31] Pathology demonstrates degeneration of the posterior columns with accumulation of lipofuscin in the dorsal root ganglia.[32]

Vitamin E is a fat-soluble vitamin absorbed in the small intestine primarily as α-tocopherol. Vitamin E is absorbed bound to bile salt, which is part of a micelle composed of fatty acids. Fatty acids are formed from the breakdown of lipids by pancreatic lipase. In the enterocyte, vitamin E is incorporated into a chylomicron for transportation to the liver. Vitamin E is then transported from the liver in very-low-density lipoprotein (VLDL) particles that become low-density lipoprotein (LDL) particles that are absorbed by body tissues.

Vitamin E deficiency may be caused by inadequate intake, decreased absorption, or impaired metabolism.[30] Vitamin E is found in high amounts in green vegetables and nuts. Decreased absorption occurs in cholestatic liver disease, cystic fibrosis, and extensive resection of the small intestine. In cholestatic liver disease, the production of bile salts that are needed for vitamin E absorption is impaired. In cystic fibrosis, fat absorption is decreased because of thickened pancreatic secretions interfering with pancreatic lipase function. Genetic conditions, including ataxia with vitamin E deficiency (AVED) and abetalipoproteinemia, interfere with vitamin E metabolism. AVED is the result of a mutation in α-tocopherol transfer protein, which is needed to incorporate vitamin E into VLDL for transport out of the liver.[33] Abetalipoproteinemia is the result of a mutation in microsomal triglyceride transfer protein, resulting in impaired formation of chylomicra, VLDL, and LDL.

The diagnosis of vitamin E deficiency should include obtaining the patient's plasma α-tocopherol level. Plasma vitamin E in the low range is supportive of vitamin E deficiency. A lipid profile demonstrating absent or very low LDL is supportive of abetalipoproteinemia. Genetic testing for inherited conditions associated with vitamin E should be considered, including AVED, abetalipoproteinemia, and cystic fibrosis.

CT or MRI of the brain may demonstrate mild cerebellar atrophy.[31,33] No imaging findings are characteristic of myelopathy secondary to vitamin E deficiency, with MRI of the spinal cord reported as normal.[31]

Eye examination may reveal pigmentary retinopathy in genetic disorders such as abetalipoproteinemia and AVED. Nerve conduction studies and EMG may demonstrate mild axonal sensorimotor neuropathy.[31]

The treatment for vitamin E deficiency is vitamin E replacement. Vitamin E replacement is typically provided by oral supplementation, although parenteral forms are available. Vitamin E supplementation in some studies of AVED ranged from 300 mg/d to 2400 mg/d, with some individuals experiencing symptom stabilization, whereas others experienced ongoing neurologic deterioration.[31,33] In cystic fibrosis, vitamin E 100 mg/d is sufficient to prevent vitamin E deficiency in most individuals.[34]

TOXIC MYELOPATHIES

Toxic myelopathies often result in permanent neurologic deficits. If avoidance of the provoking factor is not possible, identifying risk factors for developing myelopathy may be helpful in creating a risk-mitigation strategy (TABLE 6-2).

Dietary Toxicity

Neurolathyrism is a toxic myelopathy that occurs in populations in which diet consists largely of grass peas (*Lathyrus sativus*), red chickling vetch (*Lathyrus cicera*), or purple Spanish vetchling (*Lathyrus clymenum*).[35] Cases of neurolathyrism have been reported in Europe, Asia, and Africa. *Lathyrus* species are hearty plants that grow in conditions unfavorable to other crops, leading to preferential consumption in socioeconomically disadvantaged populations, particularly during famine. Risk factors for neurolathyrism include malnutrition, male sex, and physical exertion.[36] These plants contain the neurotoxin β-*N*-oxalyl-L-α,β-diaminopropionic acid (ODAP). ODAP is a glutamate receptor agonist, leading to glutamate toxicity in the central nervous system, particularly in the longest axons in the corticospinal tract.[36] Pathology demonstrates degeneration of the lateral and ventral corticospinal tracts. Neurolathyrism results in spastic paraparesis that develops over a variable period of time ranging from acute (hours) to subacute (10 to 15 days) to chronic (months), with acute onset being the most common.[36,37] Typically, patients have upper motor neuron findings with preserved sensation and sphincter function. The severity of neurolathyrism is graded based on the patient's ability to ambulate. Spasticity is often out of proportion to weakness, and the upper extremities are rarely affected. Diagnosis is based on history of exposure, clinical features, and exclusion of alternative causes. MRIs of the brain and spinal cord of a limited number of affected individuals were unremarkable.[38] Treatment of neurolathyrism includes discontinuing *Lathyrus* consumption. After the discontinuation of *Lathyrus* consumption, symptoms typically stabilize, although neurologic deficits are often permanent.

Konzo is a toxic myelopathy that occurs in populations in which diet consists largely of bitter cassava (*Manihot esculenta* Crantz), which contains cyanogens that result in cyanide toxicity.[39] Cassava is a hearty plant that grows in sub-Saharan Africa in conditions that are unfavorable for other crops. Risk factors for konzo include malnutrition and female sex. Detoxification through the wetting method (in which cassava flour is mixed with water then spread in a thin layer to dry) reduces cyanogens by allowing the escape of hydrogen cyanide gas.[40] Konzo results in spastic paraparesis with acute or subacute (<1 week) onset, often following physical exertion.[39] Typically, upper motor neuron findings are seen, with preserved sensation and sphincter function. The most prominent symptom is often a spastic gait. The severity of konzo is graded based on the patient's ability to ambulate. The upper extremities are rarely affected. Sometimes, a bilateral optic neuropathy is seen. Diagnosis is based on history of exposure, clinical features, and exclusion of alternative causes. Exposure to cyanogens may be estimated by measuring urine or plasma thiocyanate, a cyanide metabolite.[39] MRIs of the brain and spinal cord of a limited number of affected individuals were unremarkable.[41] Treatment includes limiting further consumption of cyanogens by using the wetting method for cassava preparation or discontinuing consumption of bitter cassava.[40] Following avoidance of cyanogens, symptoms stabilize, although neurologic deficits are typically permanent.[39]

Medication Toxicity

Methotrexate is a chemotherapy drug that acts as a folate antagonist by inhibiting dihydrofolate reductase. Methotrexate administered intrathecally has been associated with myelopathy presenting as subacute combined degeneration of the spinal cord (CASE 6-3).[42,43] Methotrexate toxicity is an increased risk among individuals with C667T polymorphism in the gene for methylenetetrahydrofolate reductase (*MTHFR*), which may also contribute to an increased risk of methotrexate myelopathy.[44] Additional risk factors include higher total intrathecal methotrexate exposure, systemic methotrexate, radiation therapy, and hematologic malignancy affecting the brain or spinal cord.[42] Neurologic examination demonstrates features in keeping with subacute combined degeneration of the spinal cord.[43] Diagnosis is based on exposure to intrathecal methotrexate and may be supported by low serum folate and elevated plasma homocysteine. MRI of the spinal cord demonstrates T2 signal abnormalities in the dorsal and lateral columns consistent with subacute combined degeneration of the spinal cord. Treatment of methotrexate myelopathy includes folate supplementation and discontinuation of methotrexate.[25] Methotrexate myelopathy often results in permanent neurologic deficits with poor prognosis.[25,42,43]

Tumor necrosis factor-α (TNF-α) inhibitors and immune checkpoint inhibitors are associated with transverse myelitis.[45-47] TNF-α inhibitors (eg, adalimumab, etanercept, infliximab) bind to the cytokine TNF to inhibit binding to TNF receptors for the treatment of rheumatologic conditions (eg, rheumatoid arthritis) and inflammatory bowel disease (eg, Crohn disease). TNF-α inhibitors are associated with demyelinating disease, including rare cases of isolated myelitis.[45] Immune checkpoint inhibitors upregulate the activity of T cells by blocking targets such as anti–programmed cell death 1 (PD1) (eg, nivolumab) and anti–cytotoxic T-lymphocyte associated protein 4 (CTLA4)

KEY POINTS

- **Grass peas (*Lathyrus sativus*) contain a neurotoxin that may result in neurolathyrism manifesting with acute-onset spastic paraparesis.**
- **Bitter cassava contains cyanogens that may cause konzo, manifesting with spastic paraparesis, due to cyanide toxicity.**
- **Subacute combined degeneration of the spinal cord may occur with intrathecal methotrexate, which is a folate antagonist.**
- **Tumor necrosis factor-α inhibitors and immune checkpoint inhibitors are associated with transverse myelitis.**

TABLE 6-2 Toxic Myelopathies

Toxin	Etiology	Symptoms/signs	MRI	Diagnostic tests	Treatment
Nitrous oxide	Inactivation of vitamin B_{12} by nitrous oxide used as anesthetic gas or whippets (recreational use of aerosol used in dispensing whipped cream)	Subacute combined degeneration of spinal cord beginning with sensory ataxia (positive Romberg sign, pseudoathetosis) followed by pyramidal symptoms and signs, with or without peripheral axonal neuropathy	T2 hyperintensity in posterior columns with inverted V sign; may extend over several levels in cervical or thoracic cord	Low serum cobalamin, high plasma methylmalonic acid, high plasma homocysteine	IM or subcutaneous cyanocobalamin 1000 mcg/d for 5 days followed by IM or subcutaneous 1000 mcg monthly indefinitely; 1000 mcg/d orally is a possible alternative chronic regimen; avoid nitrous oxide
Neurolathyrism caused by neurotoxin β-*N*-oxalyl-L-α,β-diaminopropionic acid	Diet largely consisting of grass pea (*Lathyrus sativus*), red chickling vetch (*Lathyrus cicera*) or purple Spanish vetchling (*Lathyrus clymenum*)	Spastic paraparesis typically developing over hours	MRI spinal cord, no specific findings	Diagnosis relies on history of exposure along with exclusion of other causes	Improved nutrition; avoid consumption of *Lathyrus* plants
Konzo caused by cyanogens	Diet largely consisting of bitter cassava (*Manihot esculenta* Crantz)	Spastic paraparesis typically developing over <1 week, with or without optic neuropathy	MRI spinal cord, no specific findings	Diagnosis relies on history of exposure along with exclusion of other causes; estimate cyanogen exposure by measuring urine or plasma thiocyanate	Improved nutrition, wetting method for cassava preparation or avoid consumption of bitter cassava
Methotrexate (intrathecal)	Chemotherapy drug acting as folate antagonist	Subacute combined degeneration of the spinal cord, with or without peripheral neuropathy	T2 hyperintensity in posterior columns with inverted V sign; may extend over several levels in cervical or thoracic cord	Exposure to intrathecal methotrexate; low serum folate, high plasma homocysteine	Methotrexate cessation, folic acid supplementation
Tumor necrosis factor-α (TNF-α) inhibitors (eg, adalimumab, etanercept, infliximab)	Bind cytokine TNF to inhibit binding to TNF receptors, promoting neuroinflammation	Transverse myelitis	Variable, short-segment eccentric T2 hyperintensity or longitudinally extensive transverse myelitis, with or without gadolinium enhancement	Exposure to TNF-α inhibitor, with or without CSF oligoclonal banding	TNF-α inhibitor cessation, IV methylprednisolone 1000 mg/d for 5 days, with or without plasma exchange

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Toxin	Etiology	Symptoms/signs	MRI	Diagnostic tests	Treatment
Immune checkpoint inhibitors (eg, ipilimumab, nivolumab)	Upregulate T cells by blocking anti-programmed cell death 1 (PD1)/programmed death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4)	Transverse myelitis	Variable, short-segment eccentric T2 hyperintensity or longitudinally extensive transverse myelitis, with or without gadolinium enhancement	Exposure to immune checkpoint inhibitor, with or without CSF oligoclonal banding	Immune checkpoint inhibitor cessation, IV methylprednisolone 1000 mg/d for 5 days, with or without plasma exchange
Heroin	IV heroin administered after a period of abstinence	Acute onset of complete spinal cord syndrome, with flaccid paralysis, sensory level, and sphincter dysfunction	T2 hyperintensity involving the complete cross section of the spinal cord, typically over several levels with predilection for thoracic cord	Exposure to IV heroin after period of abstinence	Avoid heroin, consider opiate reversal agent (eg, naloxone), IV methylprednisolone 1000 mg/d for 5 days
Radiation	Fractionated or stereotactic radiation for malignancy	Delayed onset of myelopathy 6-24 months following radiation	T2 hyperintensity within prior radiation field, gadolinium enhancement	Prior exposure to radiation with exclusion of other causes	Dexamethasone, consideration of bevacizumab, avoid further radiation
Hepatic myelopathy due to accumulation of toxins, likely nitrogen products	Chronic liver disease with portosystemic shunting	Spastic paraparesis	MRI spinal cord no specific findings; MRI brain T1 hyperintensity in globus pallidus	Features in keeping with chronic liver disease	Liver transplant, shunt-limiting surgery
Decompression myelopathy likely due to nitrogen bubbles	Diving for prolonged duration with rapid ascent	Flaccid paralysis, sensory alteration, sphincter dysfunction within 1 hour of diving	MRI spinal cord; often no specific findings although T2 hyperintensity may be seen in posterior and lateral columns	Recent diving	Hyperbaric oxygen

CSF = cerebrospinal fluid; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging.

(eg, ipilimumab) for the treatment of cancer (eg, melanoma, lung cancer). Combination therapy with nivolumab and ipilimumab results in greater than 10% risk of experiencing immune-related adverse events, including rare cases of transverse myelitis.[46,47] Treatment includes stopping the immunomodulatory drug (TNF-α inhibitor or immune checkpoint inhibitor) along with administration of high-dose IV steroids, typically IV methylprednisolone 1000 mg/d for 5 days. If no improvement is seen with steroids, plasma exchange should be considered.

Clioquinol is a metal chelator that was developed as an antimicrobial. Clioquinol has been associated with the syndrome of subacute myelo-optico-neuropathy that occurred in Japan before 1970, when the medication was removed from the market.[48] Individuals with subacute myelo-optico-neuropathy experienced primarily lower extremity sensory symptoms, gait instability, and visual impairment. Neurologic examination demonstrates primarily lower extremity reduced tactile sensation/vibration, lower extremity weakness with spasticity, and visual impairment. Around the time of clioquinol exposure, green deposits may be seen in the mouth ("green hairy tongue") due to an iron chelate.[49] The mechanism of clioquinol toxicity is speculated to be because of

CASE 6-3

A 23-year-old man was diagnosed with acute lymphoblastic leukemia. He was treated with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) induction chemotherapy. In addition, he received intrathecal methotrexate and cytarabine for prevention of central nervous system involvement. After three rounds of intrathecal methotrexate, he began to report numbness and weakness in his legs.

Neurologic examination demonstrated reduced pin sensation below T10, reduced proprioception at the great toes, absent vibration distal to the iliac crests, hyporeflexia, and upgoing plantar responses. MRI of his spinal cord demonstrated T2 hyperintensity in the posterior columns extending from T8 to the conus medullaris without contrast enhancement. MRI of his brain was normal. CSF analysis demonstrated no evidence of malignant cells, a white blood cell count of 2 cells/mm^3 (normal 0 cells/mm^3 to 5 cells/mm^3), and elevated protein. Serum cobalamin and plasma methylmalonic acid were normal. Serum folate was 4.3 nmol/L (lower limit of normal 7.0 nmol/L).

He was diagnosed with methotrexate myelopathy secondary to intrathecal methotrexate, which acts as a folate antagonist. Intrathecal chemotherapy was discontinued, and he was treated with oral folic acid 3 mg/d. Despite folic acid replacement, he continued to experience increasing leg weakness over several weeks, requiring the use of a wheelchair.

COMMENT

Intrathecal methotrexate can result in a toxic myelopathy indistinguishable from that of vitamin B_{12} deficiency clinically and radiologically. Deficits are often severe, and discontinuing methotrexate and folate supplementation is the mainstay of treatment.

reduced copper availability.[49] Diagnosis was based on clinical assessment and prior exposure to clioquinol with exclusion of other etiologies. Treatment included discontinuing clioquinol. Subacute myelo-optico-neuropathy resulted in long-term neurologic deficits, although greater symptomatic improvement of myelopathic deficits than of visual impairment has been seen over time.[48]

Heroin Toxicity

Heroin is an opiate used as a recreational drug. Administration of IV heroin after a period of abstinence has been associated with the acute onset (within hours) of myelopathy.[50] The mechanism for heroin myelopathy is unclear, although theories include immune-mediated and vascular causes.[50,51] Patients with heroin myelopathy have a complete spinal cord syndrome with flaccid paralysis, sensory level, and sphincter dysfunction. MRI of the spinal cord typically demonstrates T2 hyperintensity affecting the complete cross section of the spinal cord over several levels, with a predilection for the thoracic region. Diagnosis is based on clinical assessment and prior exposure to heroin with exclusion of other causes. Treatment is discontinuation of heroin, consideration of administering an opiate reversal agent, and steroids, including IV methylprednisolone 1000 mg/d for 5 days.[50,51] Neurologic deficits are typically severe and largely permanent.

Iatrogenic Toxicity

Radiation myelopathy is a delayed complication of radiation therapy used in the treatment of malignancy. The risk of permanent spinal cord injury is believed to be less than 1%, provided the cumulative dose of fractionated radiation to which the spinal cord is exposed does not exceed 45 Gy to 50 Gy administered in 1.8 Gy to 2 Gy daily fractions.[52] Stereotactic body radiation therapy has emerged as a treatment for spinal and paraspinal tumors given very focused administration of high-dose radiation. Lhermitte syndrome after radiation therapy refers to transient spinal cord symptoms that may occur 2 to 4 months following radiation, with paresthesia in the back and extremities with neck flexion that resolves over months without permanent myelopathy. Radiation myelopathy typically develops approximately 6 to 24 months following exposure.[52,53] Clinical symptoms range in severity, and patients may present with hemicord symptoms consistent with Brown-Séquard syndrome. MRI of the spinal cord demonstrates focal T2 hyperintensity associated with contrast enhancement.[52] In radiation myelopathy, reactive gliosis, demyelination, and necrosis of white matter are seen, along with vascular injury.[52,53] Treatment typically includes a course of a steroid such as dexamethasone. The role of hyperbaric oxygen is controversial. Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, may be beneficial in the treatment of radiation myelopathy.[53] Prognosis is variable, although median survival following diagnosis of radiation myelopathy is 8 months.[52]

Hepatic myelopathy occurs in chronic liver disease with portosystemic shunting, typically because of a transjugular intrahepatic portosystemic shunt (TIPS) used to reduce portal hypertension.[54] The mechanism of hepatic myelopathy is not fully known, but nitrogen products bypassing the liver may have a toxic effect on the spinal cord. Progressive spastic paraparesis is seen, without significant sensory symptoms or sphincter dysfunction. Rarely, patients may have a spastic quadriparesis. MRI of the spinal cord typically is normal, whereas MRI of the brain may demonstrate T1 hyperintensity in the globus pallidus from manganese deposition that accumulates with liver failure. Treatment includes liver

KEY POINTS

- Subacute myelo-optico-neuropathy was caused by clioquinol, a metal chelator that may cause copper deficiency.
- Reintroduction of heroin following a period of abstinence may cause acute-onset complete myelopathy.
- Radiation myelopathy is a delayed effect of radiation occurring 6 to 24 months after radiation exposure.
- Hepatic myelopathy occurs in chronic liver disease with portosystemic shunting.

KEY POINT

● **Decompression myelopathy occurs within 1 hour of diving and is treated with hyperbaric oxygen therapy, typically with good recovery.**

transplantation or shunt-limiting surgery, which may be particularly effective if performed within 6 months of onset of myelopathy symptoms.

Decompression Sickness

Decompression sickness occurs because of nitrogen gas coming out of solution from body tissues as a diver ascends; the decompression myelopathy typically occurs within 1 hour of diving. The mechanism is not fully known but may be because of venous occlusion or nitrogen bubbles in tissue.[55] Decompression myelopathy is included here as a toxic myelopathy given that it is triggered by a toxic exposure despite a potential vascular etiology. Risk factors include prolonged dives with rapid ascent and patent foramen ovale with right-to-left shunting. Onset is acute (within hours), with symptoms including weakness (typically flaccid), sensory alteration, and sphincter dysfunction. MRI of the spinal cord may demonstrate T2 hyperintensity primarily in the dorsolateral region, although up to 70% of individuals have normal imaging. Treatment is hyperbaric oxygen therapy, which is continued until no further improvement is seen for two consecutive treatments. Prognosis is typically good, with expected improvement in neurologic deficits.

CONCLUSION

Metabolic myelopathies are important to recognize as they are preventable and typically respond to supplementation, particularly if treatment is initiated soon after symptom onset. Toxic myelopathies often lead to more fixed neurologic impairment but are important to recognize for future risk mitigation.

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