

Pearls: Myelopathy

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ABSTRACT

Both general neurologists and neurologists with a broad spectrum of subspecialty interests are often asked to evaluate patients with disorders of the spinal cord. Over the past decade, there have been significant advances in our understanding of a wide spectrum of immune-mediated, infectious, metabolic, hereditary, paraneoplastic, and compressive myelopathies. Advances have been made in the classification and management of spinal vascular malformations. Aortic reconstruction surgery has led to an increased incidence of spinal cord stroke. It is important to recognize a dural arteriovenous fistula as a cause of progressive myelopathy. In the past, noninfectious inflammatory myelopathies have frequently been categorized as idiopathic transverse myelitis. Advances in neuroimaging and discovery of a serum antibody marker, neuromyelitis optica-immunoglobulin G (NMO-IgG), have allowed more specific diagnoses, such as multiple sclerosis and neuromyelitis optica. Abnormalities suggestive of demyelinating disease on brain magnetic resonance imaging (MRI) are known to be highly predictive of conversion to multiple sclerosis in a patient who presents with a transverse myelitis (“clinically isolated syndrome”). Acquired copper deficiency can cause a clinical picture that mimics the subacute combined degeneration seen with vitamin B₁₂ deficiency. A history of bariatric surgery is commonly noted in patients with copper deficiency myelopathy. Genetics has advanced our understanding of the complex field of hereditary myelopathies. Three hereditary myelopathy phenotypes are recognized: predominantly cerebellar (e.g., Friedreich’s ataxia), predominantly motor (e.g., hereditary spastic paraparesis), and a leukodystrophy phenotype (e.g., adrenomyeloneuropathy). Evaluation of myelopathies when no abnormalities are seen on spinal cord imaging is a commonly encountered diagnostic challenge. This article presents some “clinical pearls” in the evaluation and management of spinal cord diseases in context of these recent developments.

KEYWORDS: Myelopathies, vascular, inflammatory, metabolic, hereditary, compressive

- Vascular disease involving the spinal cord differs from cerebrovascular disease in several ways: involvement of the spinal cord blood vessels by atherosclerosis or thrombosis is relatively uncommon; spinal cord transient ischemic attacks rarely precede spinal cord infarction; pain (radicular or visceral) is often an accompanying feature; it may take several hours to

reach maximal deficit in spinal cord ischemia; urinary retention may be seen in the acute phase; and physical activity may be a precipitant of acute spinal cord infarction (this link is particularly strong in the context of mechanical spinal disease).¹

- Spinal cord infarction is much less frequent than cerebral infarction. Aortic aneurysm reconstruction surgery, particularly when complicated by intraopera-

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Neurologic Pearls; Guest Editor, Stephen G. Reich, M.D.

Semin Neurol 2010;30:38–43. Copyright © 2010 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.
DOI: <http://dx.doi.org/10.1055/s-0029-1244993>.
ISSN 0271-8235.

tive hypotension, is a common cause for spinal cord infarction. Often the cause of spinal cord infarction is undetermined. The localization of spinal cord infarction is often far beyond the site of vascular occlusion.²

- A spinal dural arteriovenous fistula causes slowly progressive myelopathy, often with stepwise worsening.³ Recurrent weakness may be related to upright posture. Hemorrhage or thrombosis may result in acute worsening. The mechanism for slowly progressive myelopathy is venous congestion. The venous congestion often leads to nonspecific symptoms, which in turn delay diagnosis. By the time patients with spinal dural arteriovenous fistulas have neurologic deficits, magnetic resonance imaging (MRI) is almost always abnormal. Longitudinally extensive, poorly delineated, central intramedullary hyperintensity on T2-weighted images is seen (Fig. 1). Dilated perimedullary vessels may be seen as flow voids on T2-weighted sequences (Fig. 1). If small, perimedullary vessels may be seen only with contrast. Their spontaneous thrombosis may prevent visualization. Flow voids related to perimedullary vessels have to be differentiated from cerebrospinal fluid (CSF) pulsation artifact. Longitudinally extensive intramedul-



Figure 1 Sagittal T2-weighted thoracic cord magnetic resonance imaging (MRI) shows longitudinal, poorly delineated, central intramedullary hyperintensity (arrow) due to venous congestion secondary to dural arteriovenous fistula. Also noted are dilated and tortuous perimedullary vessels seen as flow voids on the dorsal aspect of the cord (dotted arrow).

lary signal change is also seen in neuromyelitis optica, intramedullary tumors, and spinal cord infarction.

- Transverse myelitis is a focal inflammatory disorder of the spinal cord. The diagnostic criteria for acute transverse myelitis suggest that progression to nadir is between 4 hours and 21 days following onset of symptoms.^{4,5} Ischemic myelopathy may mimic transverse myelitis because spinal cord ischemia may progress over hours before maximal deficit. In patients with transverse myelitis, the presence of white matter lesions on brain MRI is the strongest predictor of future development of multiple sclerosis (MS). Idiopathic transverse myelitis is a diagnosis of exclusion.
- Myelitis may herald evolving meningoencephalitis. The presence of fever and mental status changes may be clues to an infectious cause for the myelitis. A coexisting encephalopathy may obscure myelopathic manifestations. Other clues pointing to infection as the cause of myelitis include recent or active infection, presence of a rash or lymphadenopathy, immunocompromised state, and significant inflammatory changes in CSF.⁶ An infectious cause should be considered in all patients with acute myelitis. Infectious myelitis may be associated with viral (HIV, human T cell lymphotropic virus, herpesviruses like varicella zoster virus, picornaviruses like polio virus, flaviviruses like West Nile virus), bacterial, spirochetal, or mycobacterial infections; it may rarely be due to parasitic or fungal agents. Acute myelitis in a patient with AIDS suggests co-infection with another agent.
- Many different serum autoantibodies may be seen in patients with neuromyelitis optica (NMO) and indicate a predisposition toward autoimmune disease.⁷ Connective tissue disorders may cause myelopathy, but should be diagnosed using standard rheumatologic criteria rather than the presence of autoantibodies alone.
- Neuromyelitis optica is not a variant of MS. It is a distinct inflammatory demyelinating disease.⁸ The female-to-male ratio is 9:1 for NMO compared with 2:1 for MS. The age of onset is a decade later for NMO (late 30s) compared with MS (late 20s). Neuromyelitis optica is more commonly seen in non-whites than in persons of white ancestry. Attacks of myelitis in NMO usually cause more severe deficits compared with MS. Paroxysmal tonic dystonic spasms are more common in NMO than in MS. In NMO, extension of cervical lesions into the brainstem may cause hiccups and respiratory failure. The spinal cord lesion in NMO is central and extends over three or more vertebral segments (Fig. 2A). This lesion may break up into shorter noncontiguous segments weeks later, and as such the timing of cord imaging in relation to the myelitis attack is an important con-



Figure 2 (A) Sagittal and axial (inset) T2-weighted magnetic resonance imaging (MRI) from a patient with neuromyelitis optica (NMO) shows central, longitudinally extensive cervicothoracic lesion that occupies more than three vertebral segments (arrow). Such a lesion can be seen in idiopathic transverse myelitis but is also suggestive of NMO spectrum disorder with future risk of relapse. (B) Sagittal T2-weighted MRI shows two separate short-segment lesions (arrows) characteristic of multiple sclerosis (MS). The axial cut (inset) shows the asymmetric nature and peripheral location of the lower cervical lesion. (Fig. 2B adapted with permission from Wingerchuk DM. Spinal cord, root, and plexus disorders. *Continuum Lifelong Learning Neurol* 2008;14(3):36–57. Copyright © 2008, American Academy of Neurology. All rights reserved.)

sideration. In MS, the cord lesion is shorter, asymmetric, and more peripheral in location (Fig. 2B).

- Subacute combined degeneration is the term that has traditionally been used to describe the myeloneuropathy seen with vitamin B₁₂ (cobalamin) deficiency. On examination, these patients have evidence of involvement of the dorsal column, corticospinal tract, and peripheral nerves. Acquired copper deficiency can cause identical clinical and MRI pictures (Fig. 3).⁹ It is unclear if folate deficiency in isolation can cause myeloneuropathy. Although vitamin E deficiency has been reported to cause a similar clinical picture, there is more often evidence of involvement of cerebellar pathways. Direct HIV infection may not be responsible for myelopathy seen in patients with AIDS; HIV myelopathy has been associated with derangement in the vitamin B₁₂-dependent pathways. Nitrous oxide produces irreversible oxidation of the cobalt core of cobalamin and renders methylcobalamin inactive. Nitrous oxide toxicity can also result in subacute combined degeneration.¹⁰
- Although it is a widely used screening test, serum cobalamin measurement has technical and interpretive problems, and lacks sensitivity and specificity for the diagnosis of cobalamin deficiency. Serum cobalamin can be normal in some patients with cobalamin deficiency. Elevated serum methylmalonic acid and total homocysteine levels are useful in diagnosing patients with cobalamin deficiency. Methylmalonic acid level is at least as sensitive for the diagnosis of cobalamin deficiency as homocysteine levels but has superior specificity. Metabolic evidence of cobalamin deficiency may not be accompanied by clinical manifestations. This subclinical cobalamin deficiency is particularly common in the elderly, and its clinical significance is poorly understood.¹¹ The presence of low cobalamin levels does not necessarily imply metabolically significant cobalamin deficiency. A low cobalamin level in association with neurologic manifestations does not imply cause and effect.
- Nitrous oxide (“laughing gas”) is an inhalational anesthetic that has been abused by medical personnel and others because of its euphoriant properties.



Figure 3 Sagittal and axial (inset) T2-weighted magnetic resonance imaging (MRI) in a patient with copper deficiency myelopathy shows hyperintensity involving the cervical dorsal column (arrow).

Subacute combined degeneration due to nitrous oxide toxicity may result from chronic exposure or after a single exposure in individuals with unsuspected cobalamin deficiency.^{10,12} Myeloneuropathy due to nitrous oxide should be considered in the patient who develops neurologic symptoms following surgical or dental procedures (“anesthesia parasthetica”).¹⁰ Symptom onset may be delayed by weeks.

- The most common manifestation of acquired copper deficiency is myelopathy or myeloneuropathy that resembles the subacute combined degeneration seen with cobalamin deficiency.¹³ Copper and cobalamin deficiencies can coexist. Hematological manifestations of acquired copper deficiency include anemia and neutropenia. Typical bone marrow findings include a left shift in granulocytic and erythroid maturation, with cytoplasmic vacuolization in erythroid and myeloid precursors, and the presence of ringed sideroblasts. Some patients may be misdiagnosed as having a myelodysplastic syndrome. Hematological manifestations are not always present with neurologic manifestations. Often the cause of copper deficiency is unknown. Of the known causes of acquired copper deficiency, the most common is prior history of gastric surgery. Excess zinc ingestion can cause copper deficiency. Zinc is an over-the-counter supplement that is commonly used for a variety of reasons, such as

prevention of the common cold. Excess use of zinc-containing denture creams can cause copper deficiency.¹⁴ Zinc causes upregulation of metallothionein production in enterocytes. Metallothionein is an intracellular ligand, and copper has a higher affinity for metallothionein than zinc. Copper displaces zinc from metallothionein, binds preferentially to metallothionein, remains in enterocytes, and is lost in stools as the intestinal cells are sloughed off.

- Neurologic manifestations of vitamin E deficiency include a progressive spinocerebellar syndrome with corticospinal tract dysfunction and peripheral neuropathy.⁹ Additional features include dorsal column dysfunction, pigmentary retinopathy, myopathy, and gaze palsies. The phenotype is similar to that of Friedreich’s ataxia. Serum vitamin E levels depend on the concentrations of serum lipids. Hyperlipidemia or hypolipidemia can independently increase or decrease, respectively, serum vitamin E level without reflecting similar alterations in tissue levels of the vitamin. In patients with neurologic manifestations due to vitamin E deficiency, the serum vitamin E levels are frequently undetectable. Vitamin E deficiency may coexist with copper deficiency.¹⁵
- When approaching a possible hereditary myelopathy, an attempt should be made to see if it fits into a cerebellar phenotype (e.g., Friedreich’s ataxia) or a predominantly motor phenotype with dorsal column dysfunction (e.g., hereditary spastic paraplegia) or a white matter or leukodystrophy phenotype (when there may be involvement of the peripheral nerves, vision, hearing, cerebellum, or cognition).¹⁶ Except for some hereditary spastic paraplegias, myelopathy is rarely the only manifestation of hereditary myelopathies. Myelopathy can be the presenting or predominant manifestation during a stage of the disease process. Most hereditary myelopathies have some involvement outside the spinal cord.
- Hereditary spastic paraplegia may begin at any age, from early childhood through the eighth decade. The primary neurologic disturbance is bilateral, symmetric, lower extremity spastic weakness with mild lower limb dorsal column dysfunction.¹⁷ Urinary urgency is a common symptom. Upper limb hyperreflexia may be present, but patients generally do not report symptoms referable to the upper limbs. Complicated hereditary spastic paraplegia refers to spastic paraparesis accompanied by other features (mental retardation, dementia, dysarthria, extrapyramidal features, ataxia, peripheral neuropathy, ichthyosis, deafness, cataracts, optic atrophy, retinopathy, muscle atrophy, seizures). A family history may not be present (due to, for example, incomplete ascertainment, reduced penetrance, de novo mutations, premature death of transmitting parent, underdiagnosis). In sporadic cases of myelopathy,

it is important to rule out nongenetic causes of spasticity.

- Both primary lateral sclerosis and hereditary spastic paraplegia can present with a spastic gait. If progression is associated with speech involvement and impaired swallowing, then primary lateral sclerosis is the likely diagnosis. The concept of “apparently sporadic spastic paraplegia” as a transitional diagnosis is a useful construct.¹⁸ If a pathogenic mutation in a hereditary spastic paraplegia gene is identified, then the diagnosis is changed to hereditary spastic paraplegia; if the disorder progresses to involve speech, swallowing, and upper limbs, then the diagnosis changes to primary lateral sclerosis. Follow-up may reveal an alternative diagnosis like amyotrophic lateral sclerosis.
- It can be clinically impossible to differentiate hereditary spastic paraplegia from X-linked adrenomyeloneuropathy.¹⁹ Half of female carriers of adrenomyeloneuropathy develop spastic paraparesis. Compared with adrenomyeloneuropathy in men, the disease seen in symptomatic female heterozygotes is milder, of later onset, and progresses more slowly. Cerebral or adrenal involvement is rare in females. Twenty percent of carriers have normal plasma concentration of very long chain fatty acids, and genetic analysis may be required for diagnosis.¹⁹
- Friedreich’s ataxia should be considered in all patients with sporadic/recessive ataxic myelopathy, except for those with severe MRI evidence of olivopontocerebellar atrophy. Atypical presentations of Friedreich’s ataxia are being increasingly recognized.²⁰ These include patients with a milder phenotype, later age of onset, and retained reflexes. These patients may not have the non-neurologic stigmata of Friedreich’s ataxia such as skeletal manifestations (pes cavus, scoliosis) or cardiomyopathy.
- Although spinal pain is a common complaint, the presence of worsening pain in the supine position is a potentially worrisome finding, suggesting metastatic or primary involvement of the spine by a neoplasm.²¹
- The incidence of spinal epidural abscess is rising. Most patients with spinal epidural abscess have an underlying disease (diabetes mellitus, intravenous drug abuse, alcoholism, infection), a spinal abnormality or intervention, or a potential local or systemic source of infection. The classic triad of back pain, fever, and neurologic deficit may not be present.²² In the absence of neurologic deficits, the diagnosis may be delayed.
- Chronic myelopathy with a normal spine MRI often falls into the hereditary, metabolic, or degenerative category. Diffuse cord atrophy or other nonspecific findings may be present. Additional issues to consider include²³:

- Are the images of adequate quality (motion artifact, pulsation artifact, low-strength magnet, open MRI, dilated central canal)?
- Were the images taken too early or too late?
- Is there evidence of subtle focal atrophy that may suggest a prior area of demyelination?
- Was contrast administered in conditions where inflammatory myelopathy is suspect?
- Is the lesion too small to be evident on MRI?
- Has a compression been missed (epidural lipomatosis, dynamic compression that may be evident only on flexion-extension studies)?
- Is there prior history of radiation (subacute or insidious onset of deficits in delayed radiation myelopathy)?
- Is it really myelopathy? The differential diagnosis includes: CNS disorders (parasagittal meningioma, anterior cerebral artery thrombosis, normal pressure hydrocephalus, vascular parkinsonism, central pontine myelinolysis), ganglionopathy (Sjögren syndrome, vitamin B₆ toxicity, paraneoplastic disorders), and peripheral nerve disorders (acute or chronic inflammatory demyelinating polyradiculoneuropathy).
- Is there evidence of superficial siderosis?
- Is it nonorganic?

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