I

mproved understanding of the differential diagnosis and improved investigative techniques, particularly neuroimaging and serologic testing, have facilitated the diagnosis of patients with acute and subacute myelopathy and reduced the proportion of patients who are labeled as having “idiopathic transverse myelitis.” Additionally, these advances have identified subgroups of patients in whom progression of deficit or future relapses are anticipated, allowing intervention and prophylaxis as appropriate. However, early management remains empiric and consists of high-dose corticosteroids for most patients. In the event of an inadequate response to corticosteroids or a subsequent atypical course, further investigations to detect diagnoses other than “transverse myelitis” should be considered and additional treatments, such as plasmapheresis, may be appropriate. Individualized diagnosis and treatment is more feasible now than in the past.

IS IT AN ACUTE MYELOPATHY?

Localizing an acute neurologic process to the spinal cord is often, but not always, straightforward (table 1). The ascending sensory symptoms of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) may confuse the diagnosis, as this complaint is also highly associated with acute myelopathy. Unequivocal upper motor neuron signs exclude AIDP, but are often not apparent in the early stages of a spinal cord insult. Although not invariably present, an unequivocal sensory level on the torso, sensory loss indicating involvement of spinal tracts (e.g., spinothalamic modality impairment contralateral to motor findings), or urinary retention localize to the spinal cord. Myopathy or neuromuscular junction disorders may be mistaken for myelopathy, particularly if the lower limbs are predominantly affected, but the absence of any sensory abnormality should suggest the correct localization. Bilateral mesial frontal lobe lesions (e.g., bilateral anterior cerebral artery distribution infarcts) could mimic a myelopathy, although abulia or other signs of frontal lobe dysfunction typically coexist. Autoimmune or paraneoplastic muscle stiffness syndromes, such as stiff-person syndrome associated with glutamic acid decarboxylase or amphiphysin autoantibodies, may be confused with spasticity and erroneously lead one to suspect myelopathy.

Occasionally patients with chronic myelopathy may present a history that mistakenly suggests an acute process. For example, patients with primary progressive multiple sclerosis (MS) may experience acute, transient worsening (pseudoeexcacerbation) in the setting of an underlying infection or heat exposure. In such cases, careful history will uncover symptoms that have been insidiously progressive over a longer interval than first
suspected. Patients with myelopathy who have no clear lesion on spinal MRI or multiple chronic-appearing lesions should be questioned to uncover subtle previous symptoms of chronic myelopathy and examined to detect cognitive or bulbar impairment localizing elsewhere in the nervous system.

**Table 1**

<table>
<thead>
<tr>
<th>Signs strongly indicating myelopathy</th>
<th>Signs consistent with but not diagnostic of myelopathy</th>
<th>Signs suggesting alternative diagnosis</th>
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<tbody>
<tr>
<td>Sensory level on torso</td>
<td>Sensory level on torso</td>
<td>Sensory level on torso</td>
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<tr>
<td>Spinal tract crossed findings (e.g., unilateral pyramidal signs with contralateral spinothalamic findings)</td>
<td>Spinal tract-specific sensory findings (e.g., selective spinothalamic findings with preserved dorsal column findings; suspended band of spinothalamic sensory loss)</td>
<td>Spinal tract-specific sensory findings (e.g., selective spinothalamic findings with preserved dorsal column findings; suspended band of spinothalamic sensory loss)</td>
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<tr>
<td>Urinary retention</td>
<td>Urinary retention</td>
<td>Urinary retention</td>
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**Occasionally patients with chronic myelopathy may present a history that mistakenly suggests an acute process**

Other diagnoses that may be made confidently in most instances include cord compression, vascular disorders, toxic/metabolic syndromes, neoplasm, paraneoplastic syndromes, and sarcoidosis. Although compression is often obvious as the cause of myelopathy on MRI, spinal stenosis may cause impressive and occasionally longitudinally extensive T2 signal abnormalities (≥3 vertebral segments) on spinal MRI that may lead one to suspect an inflammatory myelopathy. Circumscribed gadolinium enhancement at the point of maximal stenosis and a history of progressive symptoms over many weeks to months are consistent findings in such cases (figure 1, A and B).

Vascular myelopathies include those due to infarction resulting from arterial embolism or hypoperfusion, hemorrhage, or vascular malformations associated with venous hypertension. Dural arterio-
Figure 1  MRI of representative cases of acute and subacute myelopathies

(A, B) Sagittal T2 and gadolinium-enhanced T1 MRI showing longitudinally extensive cord signal change (A) and focal signet ring gadolinium enhancement (B) due to severe spinal stenosis. (C) Sagittal T2 and axial gadolinium-enhanced T1 (inset) MRI demonstrating longitudinally extensive, tract-specific lateral column enhancement due to paraneoplastic disorder in a patient with renal cell carcinoma. (D) Sagittal gadolinium-enhanced T1 and axial T2 (inset) MRI demonstrating focal enhancement and T2 signal change in the periphery of the cord in a patient with partial transverse myelitis due to multiple sclerosis. (E) Sagittal T2 and axial gadolinium-enhanced T1 (inset) MRI showing longitudinally extensive transverse myelitis extending rostrally into the medulla and central cord enhancement due to neuromyelitis optica–associated myelitis. (F) Sagittal and axial T2 (inset) MRI showing anterior cord signal change due to anterior spinal artery infarct. (G) Sagittal and axial T2 (inset) MRI, longitudinally extensive signal change extending to the conus and flow voids (eccentric to the left side of the cord) characteristic of dural arteriovenous fistula. (H) Sagittal and axial gadolinium-enhanced T1 (inset) MRI demonstrating nodular and subpial enhancement due to sarcoidosis.
venous fistula (DAVF)–associated myelopathies may be distinguished by the distinctive history of stepwise progression or transient worsening precipitated by walking or prolonged standing. This myelopathy can be successfully treated by obliteration of the fistula and should not be missed. Toxic myelopathy due to nitrous oxide abuse is a consideration in younger patients and medical professionals; patients with underlying vitamin B12 deficiency are particularly vulnerable. Vitamin and trace metal deficiencies usually cause chronic myelopathies, but as these etiologies are readily treatable, vitamin B12 and copper levels should be tested in unexplained steroid nonresponsive myelopathy. Spinal cord tumors may present subacutely or with apoplectic onset in the case of hemorrhage into tumor and are usually readily identifiable on MRI, although rarely they may be mistaken radiologically for myelitis. Screening for serum paraneoplastic autoantibodies including collapsin response mediator protein-5 (CRMP-5) antibody should be considered in patients with known cancer, constitutional symptoms, smoking history, or suggestive neuroradiology with isolated, tract-specific involvement. Sarcoidosis may present as isolated myelopathy. Definitive diagnosis requires biopsy evidence of noncaseating granulomatous inflammation, either from the nervous system or other involved organs. A high serum angiotensin-converting enzyme level is suggestive but nonspecific. A diagnosis of isolated CNS sarcoidosis should be suspected when subacute myelopathy is accompanied by patchy, asymmetric, slowly evolving, and persistently enhancing gadolinium cord lesions. A satisfactory therapeutic response to empiric, long-term (months to years) corticosteroid treatment provides a reasonable basis for a tentative but usually correct diagnosis.

**WHAT CLINICAL FEATURES SUGGEST A PARTICULAR DIAGNOSIS?** The time course (figure 2), specific spinal cord syndrome, and symptoms other than those referable to the spinal cord may provide useful clues as to the diagnosis. Apoplectic onset suggests a cord infarct or spinal hemorrhage, both of which may worsen over hours to days. Parainfectious or idiopathic myelitis, myelitis related to inflammatory demyelinating diseases, and some paraneoplastic

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>T2 hyperintense signal &lt; 3 vertebral segments in length</th>
<th>T2 hyperintense signal ≥ 3 vertebral segments in length</th>
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<tbody>
<tr>
<td>OR (nadir 3 weeks from onset)</td>
<td>- Idiopathic/parainfectious TM</td>
<td>- Idiopathic/parainfectious TM</td>
</tr>
<tr>
<td></td>
<td>- MS-associated TM</td>
<td>- NMO spectrum disorder*</td>
</tr>
<tr>
<td></td>
<td>- Spinal cord infarct</td>
<td>- ADEM</td>
</tr>
<tr>
<td></td>
<td>- Cord compression</td>
<td>- DAVF</td>
</tr>
<tr>
<td></td>
<td>- Chronic infection** (HIV, HTLV, syphilis, etc.)</td>
<td>- Sarcoïdosis*</td>
</tr>
<tr>
<td></td>
<td>- Intrinsic cord tumor</td>
<td>- Cord compression</td>
</tr>
<tr>
<td></td>
<td>- Sarcoïdosis*</td>
<td>- Intrinsic cord tumor</td>
</tr>
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<td></td>
<td></td>
<td>- SCD**</td>
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<tr>
<td></td>
<td></td>
<td>- Copper deficiency**</td>
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<td></td>
<td></td>
<td>- MS</td>
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<tr>
<td></td>
<td></td>
<td>- Sarcoïdosis*</td>
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<tr>
<td></td>
<td></td>
<td>- NMO</td>
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<tr>
<td></td>
<td></td>
<td>- Myelitis due to SD*</td>
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</table>

*Relapses upon withdrawal of corticosteroids/immunosuppression. **MRI may be normal. ADEM = acute disseminated encephalomyelitis; DAVF = dural arteriovenous fistula; HTLV = human T-lymphotropic virus; MS = multiple sclerosis; NMO = neuromyelitis optica; SCD = subacute combined degeneration; SD = systemic disease; TM = transverse myelitis.
Electrodiagnostic studies

<table>
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<tr>
<th>Test used to evaluate for:</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>EMG</td>
<td>++</td>
<td>++</td>
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Abbreviations: DAVF = dural arteriovenous fistula; IgG = immunoglobulin G; MS = multiple sclerosis; NMO = neuromyelitis optica; SS = Sjögren syndrome.

* The symbols +, ++, and +++ indicate low, intermediate, and high sensitivity/specificity, respectively.

The clinical syndrome of spinal cord involvement may suggest a particular etiology, although none are specific. Incomplete Brown-Séquard syndrome (loss of pain and temperature sensation contralateral to weakness) may be associated with either compression or an intrinsic cord lesion such as demyelination. An anterior spinal cord syndrome with bilateral corticospinal and spinothalamic involvement sparing dorsal column function is typical of anterior spinal artery distribution infarction, but may also occur in MS. A complete spinal cord syndrome with bilateral involvement of all spinal tracts is rarely caused by an MS relapse or infarct, but may occur in idiopathic or neuromyelitis optica (NMO)–associated transverse myelitis or cord compression. NMO-associated myelitis more commonly presents with clinical and imaging signs of central cord involvement than does MS-associated myelitis, which more commonly affects the periphery of the cord. Highly selective tract involvement (e.g., pure corticospinal tract involvement), especially when confirmed by MRI evidence of highly localized enhancing tractopathy, is characteristic of a paraneoplastic disorder (figure 1C).

Neurologic or constitutional symptoms not referable to the spinal cord focus the differential diagnosis, but may be irrelevant and distract one from the true diagnosis. Optic neuritis or a prior diagnosis of intermediate uveitis may suggest MS. Severe optic neuritis and an episode of unexplained intractable nausea or hiccoughs are characteristic of NMO. Coexisting peripheral neuropathy can occur in sarcoid, Sjögren syndrome, lupus, metabolic disorders (e.g., subacute combined degeneration), and paraneoplastic syndromes.

**WHAT INVESTIGATIONS SHOULD BE PERFORMED?** MRI scan of the spinal cord with and without gadolinium contrast is the initial investigation of choice in the evaluation of acute myelopathy. Contraindications are limited to MRI-incompatible ferromagnetic medical devices or foreign bodies and incompatibility with the scanner due to habitus. With careful coordination between cardiologists and radiologists, MRI can be performed in selected patients with cardiac pacemakers who are not entirely pacemaker-dependent. For patients unable to undergo MRI, CT myelography may be considered when cord compression is suspected. CSF evaluation including cell count, glucose, protein, oligoclonal bands, immunoglobulin G (IgG) index, and cytology is appropriate unless imaging, history, and examination already suggest a clear diagnosis. The results of spinal MRI and clinical suspicion should guide the selection of additional investigations (table 2).

For noncompressive myelopathy, the results of MRI can be broadly subdivided into 3 categories:

1. **Short T2 hyperintensity (<3 vertebral segments in length).**

   Focal, discrete lesions that do not occupy the entire cord in axial cross-section are highly suggestive of MS (figure 1D), although remote, sometimes forgotten trauma can occasionally produce such lesions. MRI scan of the brain may help to clarify the cause; detection of 1 or more brain lesions typical of MS (discrete periventricular, juxtacortical, or infratentorial T2 hyperintense foci) correlates with at least an 85%–90% future risk of developing MS. Oligoclonal bands and elevated CSF IgG index help to confirm a suspected MS diagnosis, but CSF analysis may be
2. Longitudinally extensive T2 hyperintensity (≥3 vertebral segments in length).

Longitudinally extensive transverse myelitis occurs in idiopathic transverse myelitis, NMO (figure 1E), acute disseminated encephalomyelitis, cord infarction, and myelitis associated with systemic diseases such as systemic lupus erythematosus. Serum NMO IgG testing is indicated before assigning a diagnosis of idiopathic transverse myelitis.\(^7\) Brain lesions on MRI eventually occur in the majority of patients with NMO, but usually NMO does not lead to the discrete Dawson finger pattern of periventricular lesions characteristic of MS. However, confluent and linear lesions encircling the ventricles may occur in NMO. CSF oligoclonal bands are usually absent in NMO. Certain patterns of signal abnormality on MRI predict a vascular disorder. Anterior and central cord signal change and swelling with sparing of the posterior columns suggest infarct, particularly in patients with a suggestive history (figure 1F). Posterior flow voids on spinal MRI representing dilation of the epidural venous plexus are a fairly specific but less sensitive indicator of DAVF, whereas longitudinally extensive gadolinium enhancement and T2 hyperintensity often extending to the conus are typical but nonspecific findings (figure 1G). Magnetic resonance angiography may help to visualize a DAVF, but spinal angiography is required for definitive diagnosis and treatment.

If symptoms suggestive of recent infection or CSF pleocytosis (≥50 leukocytes/µL) are present, CSF PCR testing for herpesviruses (e.g., herpes simplex, cytomegalovirus, varicella zoster) and serologic testing for HIV, syphilis, and Lyme disease should be considered. Prominent CSF pleocytosis and occasionally neutrophilic pleocytosis may occur in myelitis associated with NMO. Symptoms and signs of systemic inflammatory disease such as polyarthritis should prompt autoimmune serologic testing (i.e., antinuclear antibodies, SS-A, SS-B antibodies). In the absence of clinical indications of these diseases, positive serologic tests may be unimportant, although they may indicate NMO; a quarter of NMO spectrum disorder patients have nonspecific serologic evidence of autoimmunity, usually in the absence of clinical signs of other autoimmune disorders.\(^6\) Indiscriminate use of autoantibody testing in all patients with myelitis is not recommended. MRI findings including nodular and persisting (>2 months) gadolinium enhancement or meningeal and nerve root enhancement suggest sarcoidosis (figure 1H) or, rarely, lymphoma.

3. Normal MRI.

Patients with suspected myelopathy and apparently normal MRI should undergo careful review of the images for subtle findings of cord signal change, atrophy, or extrinsic compression by uncommon causes (e.g., epidural lipomatosis). If examination demonstrates unequivocal evidence of a spinal cord process and the MRI is normal, consider and test for degenerative, infectious, and metabolic causes of myelopathy. EMG and nerve conduction studies occasionally help to identify a primary peripheral process (e.g., AIDP) or myelopathy associated with concomitant peripheral neuropathy as can be seen in sarcoidosis and subacute combined degeneration.

**HOW SHOULD AN ACUTE MYELOPATHY BE TREATED?** Controlled studies of treatment of acute myelitis are lacking. In myelitis due to demyelinating, inflammatory, or undetermined cause, expert consensus favors high-dose IV corticosteroids, typically 1 gram of IV methylprednisolone daily for 5 days. This treatment should not be withheld in the case of suspected recent viral infection; the role of steroid treatment in patients with definitive evidence for direct viral infection of the cord (e.g., myelitis occurring simultaneously with or within days of a zoster eruption) is unclear. Plasmapheresis should be considered in patients who continue to have significant impairment after high-dose corticosteroids. In a sham-controlled trial of plasma exchange in patients with an acute relapse of demyelinating disease unresponsive to corticosteroid treatment, many of whom had acute myelitis, 8 of 19 (42.1%) treated patients experienced moderate to marked improvement vs 1 of 17 (5.9%) who received sham treatment.\(^9\) There are no established treatments for patients with cord infarction.

Long-term treatment to reduce recurrent attacks or progression of deficit is required for patients with NMO, neurosarcoidosis, and systemic inflammatory disorders. Options to be considered for NMO include azathioprine, mycophenolate mofetil, mitoxantrone, and rituximab. Sarcoidosis is usually treated with prolonged high-dose oral corticosteroids (e.g., prednisone 1 mg/kg/day for 6–12 months). Oral steroids and steroid-sparing immunosuppressive agents are also typically prescribed when systemic inflammatory processes involve the nervous system. Immunomodulatory treatment should be considered in patients who are at high risk for developing relapsing-remitting MS by virtue of having additional lesions on MRI of the head.
Ongoing clinical observation is an important part of the care of patients with an unexplained myelopathy. Subsequent appearance of new neurologic or systemic symptoms may reveal a demyelinating or systemic inflammatory disorder. Patients with relentlessly progressive symptoms despite appropriate empirical treatment may require spinal cord biopsy for definitive diagnosis, particularly when follow-up imaging demonstrates worsening.

**DISCUSSION**

Acute and subacute myelopathies require urgent medical evaluation. Imaging, preferably by MRI, should be performed without delay to exclude a compressive lesion. Subsequently, history and physical examination should guide subsequent investigations to reach a definitive diagnosis. As the etiology is often unclear at initial presentation, empirical treatment should be provided while conducting further investigations to determine the etiology of myelopathy. A thorough evaluation often reveals evidence of a treatable disorder or one that may relapse without preventive treatment.

**DISCLOSURE**

Dr. Schmalstieg reports no disclosures. Dr. Weinshenker has served on data safety monitoring boards for Novartis and Biogen Idec; serves on the editorial boards of *Multiple Sclerosis*, the *Canadian Journal of Neurological Sciences*, and the *Turkish Journal of Neurology*; receives research support from the Guthy-Jackson Charitable Foundation; and receives license royalties from RSR Ltd. and may receive royalties from Mayo Medical Ventures for a patent/intellectual property re: Aquaporin-4 associated antibodies for diagnosis of neuromyelitis optica.

**REFERENCES**


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