Transverse Myelitis

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KEYWORDS

- Transverse myelitis
- Longitudinally-extensive transverse myelitis
- Multiple sclerosis
- Lupus myelopathy
- Sjogren’s myelopathy
- Idiopathic transverse myelitis

INTRODUCTION

Acute noncompressive myelopathies have been recognized since the nineteenth century.\textsuperscript{1} The terms myelitis and myelopathy are often used interchangeably, but have different connotations. Both suggest a lesion affecting the spinal cord. Whereas myelopathy is a broad, generic term (much like neuropathy or encephalopathy) that

KEY POINTS

- Transverse myelitis (TM) constitutes a pathobiologically heterogeneous syndrome that has significant neurologic implications and requires urgent attention.
- Magnetic resonance imaging (MRI) evaluation of the entire spinal cord axis is mandatory in all myelopathic patients.
- The length of the spinal cord lesion on MRI is an important discriminator with etiologic and prognostic significance; longitudinally extensive transverse myelitis (LETM) refers to lesions that extend over 3 or more vertebral segments.
- Early and timely identification and immunotherapy are critical to minimize, or even prevent, future disability.
- The long-term management should focus on neurorehabilitation and a multidisciplinary approach aimed at managing the various complications of spinal cord damage.
does not imply any particular etiology, myelitis refers to an inflammatory disease process.

Transverse myelitis (TM) includes a pathobiologically heterogeneous syndrome characterized by acute or subacute spinal cord dysfunction resulting in paresis, a sensory level, and autonomic (bladder, bowel, and sexual) impairment below the level of the lesion.\(^2,3\) Etiologies for TM can be broadly classified as parainfectious, paraneoplastic, drug/toxin-induced, systemic autoimmune disorders (SAIDs), and acquired demyelinating diseases like multiple sclerosis (MS) or neuromyelitis optica (NMO).\(^3-6\) Patients with isolated TM present a diagnostic dilemma, as it is common in both MS and NMO, but may also be the initial manifestation of SAIDs. Also, there are noninflammatory etiologies (eg, vascular, metabolic) that may mimic the clinical and radiologic appearance of TM. Further complicating the diagnostic process is the frequent coexistence of systemic autoantibodies in NMO and, sometimes, MS. The implications of an incorrect diagnosis can be severe, as treatment may not only be ineffective, but may exacerbate the underlying disease process. The cause of TM remains unknown despite an extensive workup in about 15% to 30%\(^4\) of patients and is therefore referred to as “idiopathic” according to set criteria.\(^7\) Box 1 explains important terms related to TM.

The annual incidence of TM ranges from 1.34 to 4.60 cases per million,\(^8-10\) but increases to 24.6 cases per million if acquired demyelinating diseases like MS are included.\(^11\) TM can occur at any age, although a bimodal peak in incidence occurs in the second and fourth decades of life.\(^8-10,12\) Half of patients have an antecedent infection.\(^10\)

**Case report**

A 30-year-old white woman presents with 3 days of progressive paraparesis, constipation, and urinary incontinence. In addition, she reports a feeling of circumferential tightness around her abdomen (as though she was wearing a corset). Examination revealed spasticity, hyperreflexia with up-going plantar reflexes, and muscle strength of 3 in her lower extremities. Anal tone was decreased. An T8 sensory level was detected. Spine MRI revealed a T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal with associated contrast enhancement and cord swelling from T2 to 7 vertebral segments. What are the next steps in managing this patient?

**CLINICAL PRESENTATION**

It is important to consider the age and gender of the patient when evaluating myelopathic patients. Older patients (older than 50 years) are more likely to suffer spinal cord infarction. Female patients are at higher risk of having TM. Demographic features are otherwise not particularly useful in distinguishing the etiologic causes of myelopathy.\(^13\)

The temporal profile of the myelopathic features must be elucidated. TM typically has an acute to subacute onset, with neurologic deficits reaching a nadir within a few weeks. An apoplectic onset with deficits reaching the nadir in less than 4 hours indicates a vascular event. An insidious, progressive course in which the deficits continue to worsen beyond 4 weeks is uncharacteristic of TM. Clinically, TM may present as one of several syndromes of the spinal cord. Acute complete TM (ACTM) manifests as paresis/plegia, sensory dysfunction (characterized by numbness, paresthesias, or other manifestations in conjunction with a sensory level), and autonomic impairment below the level of the lesion. Acute partial TM (APTM) results in asymmetric manifestations or deficits specific to particular anatomic tracts; manifestations include the
hemi-cord (Brown-Sequard), central cord, or posterior column syndrome, as well as selective tract impairment. Table 1 describes these syndromes. Distinguishing ACTM and APTM has etiologic and prognostic significance, as discussed later.

Acutely, limb tone and muscle stretch reflexes may be diminished and even absent (“spinal shock syndrome”) leading to possible diagnostic confusion with Guillain-Barre syndrome (GBS). Clinically, spinal shock may persist for days to weeks, with a mean duration of 4 to 6 weeks following an insult.14 Over time, spasticity, hyper-reflexia, and extensor plantar responses (ie, classic features of the upper motor neuron [UMN] syndrome) become evident.

Sensory symptoms (both positive and negative) are common in TM. Some patients report a circumferential band of dysesthesia, attributable to the dermatomes just rostral to the sensory level, around their trunk. In some cases, this may be associated with a constricting sensation (colloquially referred to as the “MS hug”) that ranges from mild discomfort to a severe spasmodic or burning pain. In the authors’ experience, this symptom may be so distressing that it may be more appropriately called the “anaconda squeeze”! TM-related pain may be a central, deep aching pain or radicular in nature.3 Exacerbation of spinal pain with recumbency may indicate a neoplastic lesion involving the spinal cord.15 Phantom limb phenomenon has been observed.16 Lhermitte phenomenon (paresthesia traveling down the limbs and trunk with neck flexion) suggests an intrinsic cervical spinal cord lesion, typically affecting the dorsal columns. A reverse Lhermitte phenomenon (paresthesia with neck extension) usually indicates a compressive extra-axial cervical lesion.17 Inverse Lhermitte phenomenon (paresthesia traveling upward) is another reported variation.18

Autonomic dysfunction is almost always present in the form of perturbations of bladder, sexual, gastrointestinal, cardiovascular, and thermoregulatory functions. Priapism is a rare acute manifestation.19,20 These features are discussed later.

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**Box 1**

**Nosology of transverse myelitis**

- **Myelopathy:** a broad, generic term referring to a lesion affecting the spinal cord
- **Myelitis:** refers to an inflammatory disease of the spinal cord
- **Transverse myelitis (TM):** classically describes a pathobiologically heterogeneous syndrome characterized by acute or subacute spinal cord dysfunction resulting in paresis, a sensory level, and autonomic impairment below the level of the lesion
- **Acute Complete TM (ACTM):** TM causing paresis of the lower and/or upper extremities, sensory dysfunction (characterized by a sensory level), and autonomic impairment below the level of the lesion. On magnetic resonance imaging (MRI), there is typically a single lesion spanning 1 or 2 vertebral segments; on axial sections, there is either full-thickness involvement, or the central portion of the spinal cord is maximally affected.
- **Acute Partial TM (APTM):** TM causing asymmetric neurologic impairment (localizable to the spinal cord) or deficits attributable to a specific anatomic tract. On MRI, it spans 1 or 2 vertebral segments; there is involvement of a small portion of the spinal cord on axial sections.
- **Longitudinally-Extensive TM (LETM):** a spinal cord lesion that extends over 3 or more vertebral segments on MRI. On axial sections, it typically involves the center of the cord over more than two-thirds of the spinal cord area.
- **Secondary TM:** TM related to a systemic inflammatory autoimmune disorder (eg, lupus, Sjögren syndrome, sarcoidosis). It is typically an ACTM.
- **Idiopathic TM:** TM without any clear etiology despite a thorough investigation. It should meet the criteria listed in Table 8.
Certain clinical signs can aid in localizing the level of the lesion and are described in Table 2.

The list of differential diagnoses of TM is long; hence, a meticulous history and detailed physical examination are indispensable. A systematic and careful history may help exclude other mimics of TM (these are discussed in Box 2). An antecedent infection or prior vaccination may implicate acute disseminated encephalomyelitis (ADEM) or parainfectious TM. Travel abroad may indicate more exotic infectious causes of TM, such as schistosomiasis. Risk factors for or concomitant existence of malignancy may implicate a paraneoplastic etiology.

Women of reproductive age are at higher risk of acquired demyelinating diseases and SAIDs with the exception of Behcet disease (BD) and ankylosing spondylitis (AS). A history of relapsing-remitting attacks of neurologic deficits, eg, acute optic neuritis (AON) or internuclear ophthalmoparesis (INO), would suggest MS. Uhthoff phenomenon (discussed later) may be present in demyelinating diseases. A thorough neurologic examination may reveal evidence of prior neurologic impairments suggestive of MS exacerbations disseminated in time and space. NMO usually causes attacks of severe AON (sometimes bilateral) and brainstem lesions resulting in intractable nausea, vomiting, or hiccups.21–24 Although the manifestations of NMO may be similar to MS, attacks are typically more devastating.25 In cases of NMO mistakenly diagnosed as MS, treatment with interferon beta-1a would dramatically increase attacks.26

Autoimmune disorders, in particular systemic lupus erythematosus (SLE), BD, AS, Sjögren’s syndrome (SS), and antiphospholipid syndrome (APS), are known causes of TM. In some, TM may be the initial clinical manifestation of such a disorder. Fatigue

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**Table 1**

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<thead>
<tr>
<th>Syndrome</th>
<th>Tracts Involved</th>
<th>Clinical Manifestations</th>
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<tbody>
<tr>
<td>Complete transverse myelitis</td>
<td>All</td>
<td>Paresis, sensory loss, and autonomic impairment below the level of the lesion</td>
</tr>
<tr>
<td>Hemicord (Brown-Sequard)</td>
<td>Ipsilateral corticospinal; Ipsilateral dorsal columns; contralateral spinothalamic</td>
<td>Ipsilateral paresis and impaired dorsal column sensation; contralateral pain and temperature loss</td>
</tr>
<tr>
<td>Dorsal column</td>
<td>Bilateral dorsal columns</td>
<td>Bilateral loss of vibratory and proprioceptive sensation; Lhermitte phenomenon</td>
</tr>
<tr>
<td>Subacute Combined Degeneration</td>
<td>Bilateral dorsal columns and corticospinal tracts</td>
<td>Bilateral dorsal column dysfunction; paresis and upper motor neuron signs below the level of the lesion</td>
</tr>
<tr>
<td>Central cord</td>
<td>Crossing spinothalamic fibers, and corticospinal tracts</td>
<td>Dissociated sensory loss (diminished pain and temperature with normal dorsal column function) in a shawl-like pattern. Saddle-sparing sensory loss. Upper motor neuron weakness below the level of the lesion.</td>
</tr>
<tr>
<td>Conus medullaris</td>
<td>Sacral autonomic fibers</td>
<td>Early and prominent sphincter and sexual impairment; saddle pattern sensory loss; mild weakness</td>
</tr>
<tr>
<td>Tract-specific dysfunction</td>
<td></td>
<td>Depending on involved tract</td>
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Table 2
Clinical signs with useful localizing value in myelopathic patients

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Description</th>
<th>References</th>
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<tr>
<td>Beevor sign</td>
<td>Describes the upward migration of the umbilicus during the act of sitting up from supine position owing to weakness of the lower half of the rectus abdominis (because the upper rectus segments pull in a direction opposite of the lower segments, the movement of the abdomen is upward). In some cases, downward migration of the umbilicus may be observed. This sign indicates a lesion at the level of the T10–12 spinal cord and/or roots.</td>
<td>22</td>
</tr>
<tr>
<td>Superficial abdominal reflexes</td>
<td>A lesion above T6 segmental cord level will abolish all superficial abdominal reflexes. A lesion at or below T10 spares the upper and middle abdominal reflexes. All the reflexes are present with a lesion below T12.</td>
<td>23</td>
</tr>
<tr>
<td>Cremasteric reflex</td>
<td>Lost in lesions at or above L2 segmental cord level.</td>
<td>23</td>
</tr>
<tr>
<td>Bulbocavernous reflex</td>
<td>Mediated by S2–4 nerve roots; hence, is abolished in lesions above S2 segmental cord level.</td>
<td>24</td>
</tr>
<tr>
<td>Anal wink reflex</td>
<td>Mediated by S2–4 nerve roots; hence, is abolished in lesions above S2 segmental cord level.</td>
<td>24</td>
</tr>
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</table>

Box 2
Red flags arguing against TM in myelopathic patients

1. Apoplectic onset (reaching the nadir less than 4 hours from onset).
2. Insidious progressive course.
3. Older age of onset.
4. Preceding trauma, pain, and/or vertebral tenderness would suggest traumatic myelopathy.
5. Vascular instrumentation (in particular, aortic and cardiac surgery) or maneuvers that increase intra-abdominal pressure (eg, weight-lifting or straining) before the acute/subacute appearance of myelopathic features may implicate spinal cord infarction.
6. Prior bariatric surgical procedures, malabsorption syndromes, dietary restrictions, malnutrition, use of zinc supplements, excessive use of zinc-containing denture cream, alcoholism, and/or drug/toxin exposure may implicate a metabolic or toxic etiology.
7. Prior radiation therapy.
8. Immunocompromised state (HIV/AIDS or immunosuppressive therapy).
10. Paralysis with dissociated sensory loss (loss of pinprick and temperature but preserved dorsal column function) indicates an anterior spinal artery infarction.
11. The exacerbation of spinal pain with recumbency suggests malignancy.
12. Foix-Alajouanine syndrome (congestive venous myelopathy) is characterized by exacerbation of myelopathic features with exercise and relief with rest.
and constitutional complaints are common in patients with autoimmune disorders. A thorough integumentary examination may offer valuable clinical signs. Systemic (eg, renal, cardiac) and nonmyelopathic neurologic manifestations (eg, mononeuritis multiplex, myositis, cerebellar ataxia) may occur in some SAIDs. The presence of peripheral nervous system deficits rules out MS and NMO, unless there are concomitant disorders in the same patient (eg, diabetic peripheral neuropathy). Table 3 describes some salient manifestations of selected systemic autoimmune disorders.

**EVALUATION AND DIAGNOSIS**

Magnetic resonance imaging (MRI) of the complete spinal axis is mandatory in any patient with myelopathic features to exclude structural lesions, particularly those amenable to emergent neurosurgical intervention. The spinal cord cephalad to the suspected level of the lesion should always be imaged owing to possibly misleading signs, eg, paraparesis attributable to cervical lesions. The most sensitive MRI sequence for detecting spinal cord lesions (especially MS plaques) are short-tau inversion recovery (STIR) fast spin-echo and T2-weighted fast spin-echo sequences.

The location and length of the cord lesion on MRI may also provide clues about the underlying disease. Based on clinical and radiologic data, TM can first be dichotomized into longitudinally limited and longitudinally extensive TM (LETM). Longitudinally limited TM can be further classified as ACTM or APTM. ACTM and APTM span 1 or 2 vertebral segments. ACTM causes a complete spinal cord syndrome; on axial sections, there is either full-thickness involvement, or the central portion of the spinal cord is maximally affected. APTM results in asymmetric spinal cord involvement or neurologic deficits attributable to a specific anatomic tract; on axial sections, there is involvement of a portion of the spinal cord. Patients with APTM are at increased risk of recurrence and transition to MS. Conversely, ACTM carries a lower risk of transition to clinically definite multiple sclerosis (CDMS) and is usually related to other

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<th>Disorder</th>
<th>Clinical Sign/Symptom</th>
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<tr>
<td>Sjögren syndrome</td>
<td>Xerophthalmia, xerostomia, parotid gland enlargement, Raynaud phenomenon, dysphagia, and dry cough (owing to xerotracea). A positive Schirmer test detects deficient tear production.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Joint pains, morning stiffness, myalgias, and integumentary manifestations (alopecia, unguium mutilans, perniotic lesions, leuconychia, splinter hemorrhages, nail-fold hyperkeratosis, ragged cuticles, malar rash, Raynaud phenomenon, photosensitivity, and/or discoid lupus).</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>History of deep vein thromboses, pulmonary embolism, multiple miscarriages, and/or young-onset stroke.</td>
</tr>
<tr>
<td>Behcet disease</td>
<td>Classic triad of recurrent aphthous ulcers, genital ulcers, and uveitis. Other manifestations: ophthalmic (hypopyon and retinal vasculitis) and cutaneous (pseudofolliculitis, erythema nodosumlike lesions, or acneiform lesions). Positive pathergy test.</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Back pain, enthesitis, and limited spinal flexion.</td>
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causes (eg, SAIDs). LETM refers to lesions that extend over 3 or more vertebral segments; on axial sections, it typically involves more than two-thirds of the spinal cord thickness (maximally affecting the central portion). Box 3 summarizes the differential diagnoses of LETM. The unique radiologic features of different etiologies are explored later.

A brain MRI with and without gadolinium administration should also be obtained on all patients to look for evidence of concomitant or prior lesions that may provide clues about the etiology. The presence of MS-like brain lesions in patients with partial TM portends an 80% risk of transition to clinically definite MS at 3 to 5 years.13

Serum vitamin B12 level, thyroid function tests, syphilis, and HIV serologies should be obtained to evaluate for potentially treatable causes of myelopathy. Vitamin E, serum copper, and ceruloplasmin levels are checked in those at risk of deficiency (see later in this article for further details). Serum aquaporin-4–specific autoantibodies (NMO-immunoglobulin [Ig]G) should be checked on all patients with TM because of its high specificity for NMO or NMO spectrum disorders (NMOSD).31,32 NMO-IgG seropositivity is rarely found in patients with APTM30 but its presence would have profound implications on treatment. In suspected parainfectious TM, serologic evidence of recent infection (eg, *Mycoplasma* antibody titers) should be sought. Serum paraneoplastic profiles should be performed in suspected cases of paraneoplastic TM; additionally, in such cases, appropriate investigations should be undertaken to search for the occult malignancy, the identification of which can have profound ramifications for the patient; even a cure if a malignancy can be confirmed and eradicated before pathologic dissemination.

Cerebrospinal fluid (CSF) analysis is essential in the evaluation of TM. CSF cell count, differential, protein, glucose, oligoclonal bands (OCBs) and IgG index should be checked on all patients with TM. Isoelectric focusing is the superior method for the detection of OCBs, providing a much higher yield and specificity. OCBs are useful in predicting conversion to MS, as OCBs are present in 85% to 90% of patients

### Box 3

**Differential diagnosis of LETM**

1. Neuromyelitis optica (NMO) or NMO-spectrum disorders
2. Acute disseminated encephalomyelitis (ADEM)
3. Systemic autoimmune disorders: systemic lupus erythematosus (SLE), Sjögren syndrome (SS), neurosarcoïdosis, neuro-Bechter disease
5. Paraneoplastic TM (in particular, anti-collapsin response-mediator protein [CRMP]-5 antibodies)
6. Mimics of TM
   a. Neoplasms: primary intramedullary spinal cord tumors, metastatic intramedullary tumors, lymphoma
   b. Radiation myelitis
   c. Metabolic myelopathies: B12 deficiency, copper deficiency, nitrous oxide toxicity
   d. Vascular myelopathies: anterior spinal artery infarction, spinal dural arteriovenous fistula
with MS, in 20% to 30% of patients with NMO or SAIDs, and rarely in other causes of TM.\textsuperscript{13} Bear in mind that their mere presence clearly does not militate against being reflective of a myriad of inflammatory, infectious, and neoplastic or paraneoplastic processes.

A neuro-ophthalmological evaluation is warranted to look for ophthalmic manifestations that may provide valuable diagnostic clues, especially when radiologic and laboratory investigations are unremarkable. For example, different subtypes of uveitis are associated with unique etiologic underpinnings.\textsuperscript{34} Demyelinating diseases affecting the brainstem and/or cerebellum commonly cause ocular motor manifestations.\textsuperscript{35} Electrophysiologic tests may be very useful in assessing patients with TM. Nerve conduction studies and electromyography (EMG) may reveal and help characterize any peripheral nervous pathology, the exclusion of which would lend compelling support for a spinal cord process. This latter principle is especially salient in that acute TM can present as a spinal shock variant, one that may mimic a polyneuropathic process like GBS. In early TM, F-waves may be absent,\textsuperscript{36} an observation that can serve to misguide even the most experienced neurologic consultant (especially when the MRI is unremarkable) to localize the disease process to the peripheral nervous system. EMG-evidence of anterior horn cell dysfunction may portend a poor prognosis for recovery.\textsuperscript{37} Somatosensory evoked potentials may offer evidence of a myelopathy in the presence of a normal spinal cord MRI. In addition,

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<th>Box 4</th>
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<td><strong>Investigations into suspected TM</strong></td>
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<tr>
<td><strong>Must be obtained on all patients:</strong></td>
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<tr>
<td>1. Magnetic resonance image (MRI) of the spine</td>
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<tr>
<td>2. Brain MRI</td>
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<tr>
<td>3. Cerebrospinal fluid (CSF): cells, differential, protein, glucose, Venereal Disease Research Laboratory (VDRL), immunoglobulin (Ig)G index, oligoclonal bands, cytologic analysis</td>
</tr>
<tr>
<td>4. Serum: B12, methylmalonic acid, HIV antibodies, syphilis serologies, thyroid stimulating hormone (TSH), Free T4, 25-hydroxyvitamin D</td>
</tr>
<tr>
<td><strong>Must be obtained on all patients with LETM:</strong></td>
</tr>
<tr>
<td>1. Serum NMO-IgG</td>
</tr>
<tr>
<td>2. Serum erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, antibodies to extractable nuclear antigen, rheumatoid factor, antiphospholipid antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA)</td>
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<tr>
<td>3. Visual-evoked potentials</td>
</tr>
<tr>
<td><strong>May need to be obtained:</strong></td>
</tr>
<tr>
<td>1. Neuro-ophthalmological evaluation</td>
</tr>
<tr>
<td>2. Paraneoplastic panel</td>
</tr>
<tr>
<td>3. Infectious serologies and CSF studies (cultures and viral polymerase chain reaction)</td>
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<tr>
<td>4. Serum copper and ceruloplasmin</td>
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<tr>
<td>5. Serum vitamin E level</td>
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<tr>
<td>6. Computed tomography of the chest</td>
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<td>7. Nerve conduction studies and electromyography</td>
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<tr>
<td>8. Minor salivary gland biopsy</td>
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conventional and multifocal visual-evoked potentials (VEP) may provide evidence of subclinical demyelination along the afferent visual pathways not clearly identified on imaging. Evidence of such disruption may support the diagnosis of MS or NMO but are by no means specific for these disease entities (discussed in greater detail later).

A list of investigations into TM is provided in Box 4.

**CAUSES OF TM**

**Box 5** summarizes the causes of TM.

**Multiple Sclerosis**

MS is a disabling progressive neurologic disorder affecting approximately 400,000 people in the United States. First attacks of MS, called clinically isolated syndrome (CIS), usually consist of AON, brainstem syndromes, or APTM. The probability for APTM to transition to CDMS ranges from 10% to 62%. APTM may be a CIS with a higher risk of conversion to MS.

TM in MS most commonly presents with sensory phenomena. Spine MRI typically reveals an asymmetrically placed lesion (usually occurring in the posterolateral or lateral portion of the spinal cord) less than 2 segments in length (ie, APTM) with a predilection for the cervicothoracic cord.

The most important investigation that helps determine the risk of conversion to CDMS is the brain MRI. If it is normal, only 10% of patients with APTM will develop CDMS at 61 months; this increases to 21% risk of progression at 20 years follow-up according to another study of CIS. White matter lesions predict higher risk of conversion to MS (with rates of up to 88% reported). If the lesions meet at least 3 of the Barkhof criteria, this risk is increased substantially.

Another important factor that helps predict the risk of transition to CDMS is CSF OCBs. In the setting of TM, OCBs have been shown to have a robust predictive value of for predicting conversion to MS. In patients with TM with normal brain MRIs, the presence of OCBs and/or an elevated IgG index portends a higher risk of developing MS. The risk of developing MS is less than 10% with a normal brain MRI and CSF findings.

Longitudinally extensive lesions in the context of TM is actually quite rare in MS and, when present, is significantly shorter than those seen in NMO. When MS is confirmed, spinal lesions tend to favor a cervical localization, and tend to have less cord swelling and gadolinium-enhancement. In general, patients with LETM have been shown to have a conspicuously low risk of developing MS.

**Neuromyelitis Optica**

NMO is diagnosed on the basis of the revised Wingerchuk criteria requiring the presence of optic neuritis and TM as well as 2 of 3 of the following: NMO antibodies, LETM, and/or brain MRI lesions inconsistent with MS. NMOSDs include Asian optic-spinal MS, recurrent LETM, recurrent AON, and AON or TM in the context of certain organ-specific and non–organ-specific autoimmune disease. The article on NMO by Sahraian, MA, elsewhere in this issue discusses this disease in detail. Here, we underscore the important features of NMO that give rise to diagnostic confusion.

Diagnostic confusion may arise with SAIDs, as patients with NMO/NMOSD often have accompanying autoimmune diseases and multiple non–organ-specific autoantibodies. Autoimmune diseases observed to coexist with NMO include SS, SLE, autoimmune thyroid disease, type 1 diabetes mellitus, ulcerative colitis, idiopathic
Box 5
Summary of reported causes of TM

1. Acquired demyelinating disorders
   a. Multiple sclerosis
   b. NMO
   c. ADEM

2. Systemic inflammatory autoimmune disorders
   a. SLE
   b. SS
   c. Antiphospholipid syndrome
   d. Behcet disease
   e. Vogt-Koyanagi Harada disease
   f. Ankylosing spondylitis
   g. Mixed connective tissue disease
   h. Others: systemic sclerosis, anti-Jo-1 antibody, urticarial vasculitis, psoriatic arthritis, perinuclear ANCA systemic vasculitis, graft-versus-host disease, common variable immunodeficiency, celiac disease

3. Neurosarcoidosis

4. Parainfectious TM
   b. Bacterial: Mycoplasma pneumoniae, Campylobacter jejuni, Borrelia burgdorferi, Acinetobacter baumanii, Coxiella burnetii, Bartonella henselae, Chlamydia psittaci, Leptospira, Chlamydia pneumoniae, Legionella pneumoniae, Orientia tsutsugamushi (scrub typhus), Salmonella paratyphi B, Mycobacterium tuberculosis, Treponema pallidum, Brucellosis melitensis, and groups A and B streptococci
   c. Fungal: Actinomyces, Blastomyces, Coccidioides, Aspergillus, Cryptococcus, and Cladophialaphora bantiana
   d. Parasitic: Toxocara species, Schistosoma species, Gnathostoma spinigerum, Echinococcus granulosus, Taenia solium, Toxoplasma gondii, Acanthamoeba species, Paragonimus westermani, and Trypanosoma brucei

5. Paraneoplastic syndromes
   a. Anti-Ri (ANNA-2) antibody
   b. CRMP-5-IgG antibody
   c. Anti-amphiphysin IgG antibody
   d. Anti-GAD65 antibody
   e. NMDAR antibody

6. Atopic myelitis

7. Drugs and toxins
   a. Tumor necrosis factor-alpha inhibitors
thrombocytopenic purpura, myasthenia gravis, rheumatoid arthritis, polymyositis, celiac disease, and Raynaud phenomenon.\textsuperscript{52,53} We propose that all patients with a known SAID (eg, SS or SLE) who present with TM undergo serologic testing for NMO-IgG. The high specificity of NMO-IgG seropositivity\textsuperscript{31,54} will establish the additional diagnosis of NMO coexisting with the systemic autoimmune disorder. In patients with NMO or TM, the isolated presence of systemic non–organ-specific antibodies should not be used to make a diagnosis of any particular rheumatic disease; instead, these assays can lend support in corroborating such conditions, when the established clinical criteria for each respective disorder has been fulfilled.

\textbf{Sj\o rgren Syndrome}

SS is a chronic, protean, progressive, systemic autoimmune disorder characterized by mononuclear infiltration and destruction of the salivary and lacrimal glands, leading to keratoconjunctivitis sicca, typically affecting middle-aged to elderly women. SS may appear alone (primary SS) or exist with another autoimmune disease (secondary SS).\textsuperscript{55–57}

A wide range of central nervous system (CNS) manifestations may occur, including AON and TM.\textsuperscript{56,58,59} The precise prevalence of neurologic manifestations in SS is unclear, and has been reported to range from 8.5\% to 70.0\%\textsuperscript{57}; this large discrepancy may be related to the inclusion or exclusion of psychiatric and cognitive impairment. Neurologic deficits may be the initial presentation in as many as 57\% of patients with SS.\textsuperscript{57} Spinal cord involvement (either acute TM or progressive myelopathy) may occur in 20\% to 35\% of patients with SS and may constitute the initial presentation of the disease in up to about 20\%.\textsuperscript{55,57} The lesions tend to affect the cervical cord and may be longitudinally extensive.\textsuperscript{57,60}

CSF typically reveals pleocytosis, mildly increased protein, and a mildly elevated IgG index.\textsuperscript{56,60} Cytologic analysis may reveal small round lymphocytes, reactive lymphoid cells, plasma cells, and atypical mononuclear cells.\textsuperscript{56} OCBs have been reported in about 30\% of patients with SS.\textsuperscript{57} SS-A or SS-B antibody seropositivity is not mandatory for the diagnosis of SS, because only 21\% of patients with primary SS and neurologic manifestations demonstrate such seropositivity.\textsuperscript{57}

Although other CNS manifestations of SS are corticosteroid-responsive,\textsuperscript{56} spinal cord involvement is often refractory to steroids.\textsuperscript{60} Intravenous (IV) cyclophosphamide is effective\textsuperscript{56,57}; there is anecdotal evidence supporting the use of plasmapheresis\textsuperscript{61} and IV gammaglobulin.\textsuperscript{62} Maintenance immunosuppressive therapy with monthly pulse IV cyclophosphamide may be considered.\textsuperscript{56} Rituximab is another promising agent\textsuperscript{63} and may be a suitable agent for patients with coexisting NMO or MS, or where there is diagnostic confusion with these diseases.
Careful longitudinal follow-up is important in SS, as recurrent attacks of TM or AON can culminate in substantial disability, and may ultimately lead to a confirmed diagnosis of NMO or MS.

Systemic Lupus Erythematosus

SLE is a chronic, systemic, autoimmune disease. The diagnosis of SLE requires at least 4 of 11 features, as outlined by the American College of Rheumatology. Although neuropsychiatric manifestations of SLE are common, TM accounts for only 1% to 2% of patients, but constitutes the most devastating complication of SLE and one that often portends a poor prognosis. SLE-related TM tends to occur within the first 5 years from diagnosis, is the initial clinical manifestation in almost half of patients, and recurs in 21% to 55% of cases. AON and brainstem manifestations may accompany TM in SLE, mimicking MS and representing a significant source of diagnostic confusion.

A short period of prodromal symptoms (eg, headache, fever, nausea) typically heralds the onset of thoracic myelopathy with prominent bladder dysfunction. In a large series of SLE-related TM, 2 different clinical patterns at presentation were observed: gray and white matter myelitis. Gray matter myelitis demonstrated lower motor neuron (LMN) features, urinary retention, and a more devastating but monophasic course. White matter myelitis demonstrated upper motor neuron (UMN) features and a more indolent but recurrent course. An earlier study suggested that EMG evidence of anterior horn cell dysfunction in patients with TM predicts a poor prognosis for recovery. The features of gray and white matter myelitis are summarized in Table 4.

Although low-titer positive antinuclear antibodies (ANA) in idiopathic TM (ITM) cases are similar to that of the general population, much higher serum ANA titers, anti–double-stranded DNA antibodies, and hypocomplementemia are found in SLE-related TM. The presence of antiphospholipid antibodies (APLA) in SLE has been suggested to increase the risk of developing TM but this association has been challenged. CSF pleocytosis with elevated protein and intrathecal IgG synthesis are typically detected, particularly in LETM; interestingly, OCBs, although unusual, have been observed in APLA-seropositive patients.

The most common MRI finding in SLE-related TM is a longitudinally extensive, T2-hyperintense lesion (accompanied by cord swelling). In severe cases, the lesion involves the entire spinal cord and extends into the medulla. Radiologic findings may not correlate with the clinical course. Almost a third of patients with SLE-related TM do not have any detectable MRI abnormalities at presentation. On brain MRI, subcortical lesions predominate in APS and SLE, whereas periventricular and callosal lesions are more common in MS.

In a randomized controlled trial, IV cyclophosphamide was found to be more efficacious in treating neuropsychiatric manifestations of SLE compared with IV methylprednisolone. The combination of high-dose IV methylprednisolone and IV cyclophosphamide may be effective in SLE-related TM if instituted promptly, resulting in improvement in a few days to 3 weeks. Relapses are common (50%–60%) during corticosteroid dose taper, emphasizing the need for maintenance immunosuppression. Plasmapheresis has been used in severe cases. There is anecdotal evidence for using intravenous immunoglobulin and rituximab. Anticoagulation therapy is indicated only in those with a history of thrombotic phenomena. Long-term aspirin use has anecdotal support.

Factors associated with severe neurologic deficits include extensive cord MRI lesions, LMN features and sphincteric dysfunction at onset, APLA, and delayed (>2 weeks) initiation of therapy.
Antiphospholipid Syndrome

APS is a systemic, autoimmune disorder characterized by recurrent thrombotic events and/or miscarriages, as well as APLA seropositivity (2 or more occasions at least 6 weeks apart) (ie, anticardiolipin, lupus anticoagulant, and anti-beta-2-glycoprotein 1 antibodies).90 In secondary APS, the disease coexists with another autoimmune disorder. TM is an unusual complication of APS, with a prevalence of less than 1%.91–93 Although typically monophasic, recurrent corticosteroid-responsive LETM has also been observed.92 Characteristically, acute thoracic cord dysfunction occurs with sphincter involvement.93 Spine MRI may be normal on presentation in up to 40% of patients, underscoring the importance of repeat imaging in suspected cases.94 It is hypothesized that interactions between APLA and spinal cord phospholipids are responsible for APS-related TM,95 explaining the efficacy of and justifying the use of early high-dose corticosteroid therapy.93 In corticosteroid-refractory patients, cyclophosphamide, plasmapheresis, and rituximab may be needed.93

A higher prevalence of APLA seropositivity has been reported in patients with MS and appears to rise with disease duration.96–100 Although diagnostic confusion may

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The differences between gray and white matter myelitis in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gray Matter Myelitis</td>
</tr>
<tr>
<td>Present</td>
<td>Lower motor neuron features with urinary retention</td>
</tr>
<tr>
<td></td>
<td>(urinary retention always heralds paraplegia)</td>
</tr>
<tr>
<td>Prodrome (fever, nausea, vomiting)</td>
<td>Very frequent</td>
</tr>
<tr>
<td>Clinical course</td>
<td>More rapid deterioration; more severe weakness at nadir.</td>
</tr>
<tr>
<td></td>
<td>Lower motor neuron features persist beyond the time expected for spinal shock.</td>
</tr>
<tr>
<td></td>
<td>More aggressive immunosuppression needed.</td>
</tr>
<tr>
<td>Long-term Disability</td>
<td>Greater</td>
</tr>
<tr>
<td>CSF</td>
<td>Neutrophilic pleocytosis; higher protein; hypoglycorrachia</td>
</tr>
<tr>
<td>MRI</td>
<td>Cord swelling; frequent LETM; less frequent gadolinium-enhancement</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Very rare</td>
</tr>
<tr>
<td>Prior optic neuritis</td>
<td>Absent</td>
</tr>
<tr>
<td>Coexisting NMO and/or NMO-IgG seropositivity</td>
<td>None</td>
</tr>
<tr>
<td>Higher SLE disease activity</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; LETM, longitudinally extensive transverse myelitis; NMO, neuromyelitis optica; NMO-IgG, aquaporin-4-antibody; SLE, systemic lupus erythematosus.


Antiphospholipid Syndrome

APS is a systemic, autoimmune disorder characterized by recurrent thrombotic events and/or miscarriages, as well as APLA seropositivity (2 or more occasions at least 6 weeks apart) (ie, anticardiolipin, lupus anticoagulant, and anti-beta-2-glycoprotein 1 antibodies).90 In secondary APS, the disease coexists with another autoimmune disorder. TM is an unusual complication of APS, with a prevalence of less than 1%.91–93 Although typically monophasic, recurrent corticosteroid-responsive LETM has also been observed.92 Characteristically, acute thoracic cord dysfunction occurs with sphincter involvement.93 Spine MRI may be normal on presentation in up to 40% of patients, underscoring the importance of repeat imaging in suspected cases.94 It is hypothesized that interactions between APLA and spinal cord phospholipids are responsible for APS-related TM,95 explaining the efficacy of and justifying the use of early high-dose corticosteroid therapy.93 In corticosteroid-refractory patients, cyclophosphamide, plasmapheresis, and rituximab may be needed.93

A higher prevalence of APLA seropositivity has been reported in patients with MS and appears to rise with disease duration.96–100 Although diagnostic confusion may
arise in APLA-positive patients with TM, the presence of CSF OCBs and the absence of prior miscarriages or thrombotic phenomena would favor MS rather than APS.

**Behçet Disease**

BD is a relapsing multisystem inflammatory disorder of unclear etiology resulting in oral aphthous ulcers, genital ulcers, uveitis, cutaneous manifestations, and involvement of other organ systems.101

Neurologic involvement in BD (neuro-BD) may follow or precede the onset of systemic manifestations.102 Neuro-BD typically occurs in the third to fourth decade of life, is more common in men, and is usually associated with ocular involvement.102–104 The frequency of neuro-BD varies greatly, from 1.3% to 59.0%, with a pooled average of 9.4%.102,104 Neuro-BD can be classified as parenchymal or non-parenchymal (vascular). Parenchymal neuro-BD commonly manifests as a meningoencephalitic syndrome with headaches and focal neurologic deficits.102 The manifestations of vascular BD stem from cerebral venous thrombosis (often with subsequent increased intracranial hypertension) and/or rarely, arterial infarctions.105 Spinal cord involvement ranges between 2.5% and 30.0%, with a predilection for the cervical and thoracic cord segments (in particular the posterolateral cord), and carries a poor prognosis.102,103,106–109 Isolated TM in neuro-BD is distinctly unusual.102,105

Spinal cord lesions are usually longitudinally extensive and involve multiple noncontiguous segments, or even involve the entire cord. Cord swelling and T2-hyperintense, nonenhancing lesions are present in the acute or subacute phase.106,107,109–114 An unusual report of TM (extending from T9 to the conus) following CT-guided L2 nerve root injection, may be a florid demonstration of the pathergic reaction in the spinal cord.115

Brain MRI may reveal T1-hypo/isointense and T2-hyperintense lesions that may or may not show gadolinium enhancement acutely. Characteristically, an upper pontomesencephalic lesion with thalamic, hypothalamic, and basal ganglial extension on one side is seen.102,105,107,109,116,117 Interestingly, the red nucleus is almost always spared.107,109 Striking brainstem atrophy, as well as the rarity of periventricular lesions, optic neuropathy, cortical atrophy, and gray matter lesions in neuro-BD,102,109,117,118 distinguish it from MS.

CSF typically reveals normal glucose, increased protein, and neutrophilic pleocytosis; the IgG index may be elevated, and OCBs are rare.103–106,108,117

Acutely, administration of high-dose corticosteroids results in improvement in most patients103,104,108,110,111,113,119; corticosteroid therapy also improved pleocytosis.117 Infliximab, cyclophosphamide, and intravenous immunoglobulin have been used with some success.104,120

No randomized controlled trials have been conducted into the treatment of neuro-BD. Azathioprine, mycophenolate mofetil, and methotrexate have been used as initial immunosuppressive therapy. In more aggressive disease, tumor necrosis factor-antagonists or monthly infusions of cyclophosphamide have been used. Colchicine, thalidomide, and pentoxifylline may be used for mucocutaneous lesions.102–104 Cyclosporin A has been used to treat ophthalmic manifestations but may be neurotoxic and worsen neurologic manifestations.121–124

**TM in Other Rheumatologic Diseases**

TM has been reported in AS, psoriatic arthritis, mixed connective tissue disease, and systemic sclerosis (please refer to Table 5).
Neurosarcoidosis

Sarcoidosis is a multisystem granulomatous disease with protean manifestations that may affect any organ. Neurologic involvement (neurosarcoidosis) is reported in 5% to 13% of patients with sarcoidosis but may be as high as 26%. The usual age of onset is the fourth decade. Spinal cord neurosarcoidosis appears to be more common in men.

CNS features are the initial manifestation of neurosarcoidosis in up to 70% of patients. Although unusual, spinal cord involvement portends a poor outcome, and may be related to intramedullary, intradural extramedullary, or extradural lesions; cauda equina syndrome; or arachnoiditis. Although isolated myelopathy has been observed, half of patients with spinal cord neurosarcoidosis demonstrate systemic manifestations.

Neurosarcoidosis has a predilection for the cervical and thoracic cord and is frequently associated with back pain and radicular symptoms.

### Table 5

Other dysimmune disorders associated with TM

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>Neurologic involvement is rare and is almost always attributable to compressive myelopathy. Noncompressive myelopathy is exceptionally rare with only 2 clearly documented cases of TM.</td>
<td>368–370</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td></td>
<td>371</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Female preponderence; predilection for the thoracic cord.</td>
<td>372–377</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Rare and typically compressive in etiology. Progressive myelopathy, subacute TM, and NMO-IgG positive LETM have been reported.</td>
<td>378–381</td>
</tr>
<tr>
<td>Anti-Jo-1 antibody</td>
<td>A single report of TM preceding the development of polymyositis and pulmonary fibrosis in a patient with anti-Jo-1 antibody.</td>
<td>382</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td>Urticarial vasculitis may be primary disorder or coexist with other autoimmune diseases.</td>
<td>383</td>
</tr>
<tr>
<td>pANCA seropositivity</td>
<td>Perinuclear antineutrophil cytoplasmic antibody (pANCA) seropositivity has been reported to cause TM associated with CSF pleocytosis and increased protein with typically absent OCBs.</td>
<td>384,385</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Celiac disease is an immune-mediated disorder characterized by intolerance to dietary gluten.</td>
<td>386</td>
</tr>
<tr>
<td>Thymic follicular hyperplasia</td>
<td>Recurrent multifocal TM associated with thymic follicular hyperplasia that resolved following thymectomy.</td>
<td>387</td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td>TM may be a rare manifestation of graft-vs-host disease following hematopoietic cell transplantation.</td>
<td>388–390</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>A primary immune deficiency disorder characterized by hypogammaglobulinemia, antibody deficiency, and recurrent infections.</td>
<td>391,392</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; LETM, longitudinally extensive transverse myelitis; NMO-IgG, aquaporin-4-antibody; OCB, oligoclonal bands; SLE, systemic lupus erythematosus.

### Neurosarcoidosis

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CNS features are the initial manifestation of neurosarcoidosis in up to 70% of patients. Although unusual, spinal cord involvement portends a poor outcome, and may be related to intramedullary, intradural extramedullary, or extradural lesions; cauda equina syndrome; or arachnoiditis. Although isolated myelopathy has been observed, half of patients with spinal cord neurosarcoidosis demonstrate systemic manifestations.

Neurosarcoidosis has a predilection for the cervical and thoracic cord and is frequently associated with back pain and radicular symptoms.
Intramedullary disease typically appears as a longitudinally extensive, T1-hypointense, T2-hyperintense, heterogeneously enhancing lesion with fusiform cord enlargement or myelomalacia. Spinal cord lesions may be multifocal; gadolinium enhancement may be nodular or predominate at the periphery of the lesion. Neurosarcoïdosis should be suspected in any infiltrating intramedullary cord lesion with leptomeningeal enhancement. Half of patients with spinal neurosarcoïdosis have concomitant intracranial lesions.

The diagnosis of spinal cord neurosarcoïdosis is challenging, particularly if systemic manifestations are absent. When clinical suspicion is high, even in the absence of systemic symptoms, it is worthwhile performing a high-resolution chest CT, positron emission tomography, ophthalmic examination, or a gallium-67 scan to identify extraneural granulomas that may be amenable to biopsy.

CSF findings reveal elevated protein, lymphocytic pleocytosis, occasional hypoglycorrachia, and infrequent OCBs. CSF angiotensin-converting enzyme levels are normal in more than half of patients. Hypoglycorrachia is specific and can distinguish neurosarcoïdosis from other inflammatory etiologies.

Early corticosteroid therapy results in remarkable recovery but delayed treatment leads to only partial resolution of myelopathic manifestations. A high index of suspicion for the diagnosis is required because early intervention is associated with a favorable outcome.

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada syndrome (VKH), also known as uveomeningoencephalitis, is a systemic inflammatory disorder affecting the melanin-forming cells in different organs. TM is an infrequent complication of VKH, and bilateral AON with papillitis has been reported. These manifestations may mimic MS or NMO. CSF pleocytosis can provide early evidence of disease activity, therefore allowing early treatment with corticosteroids.

Acute Disseminated Encephalomyelitis

ADEM is a monophasic disorder that occurs following infections or vaccinations, is associated with multifocal demyelinating lesions, and may include encephalopathy, coma, and/or seizures. TM occurs in about 24% of patients and, in unusual cases, may be the sole manifestation of ADEM. It is possible that some cases of TM represent limited forms of ADEM. Unlike MS and NMO, ADEM may be associated with demyelinating peripheral neuropathies.

ADEM may occur at any age but is most common in the pediatric population (mean age of onset of 5.7 years). Postvaccination ADEM incidence is variable, and the most frequently implicated vaccine is the non-neural measles, mumps, and rubella vaccine. An initial attack consistent with a demyelinating event with acute or subacute onset, a stable to stuttering course (evolving over 1 week to 3 months), characteristic MRI features, and concomitant encephalopathy and meningismus, suggests a diagnosis of ADEM.

Radiologically, acute, multiple, symmetric, supratentorial and infratentorial lesions, with one at least 1 cm in diameter are observed; symmetric basal ganglial and thalamic involvement is common. The lesions should be of the same age and demonstrate homogeneous gadolinium enhancement, as ADEM is typically monophasic. The typical spinal cord lesion is swollen, enhancing variably, and predominantly affects the thoracic cord. It may take up to 14 days from the onset of symptoms for the MRI to show abnormalities. CSF in ADEM typically reveals marked pleocytosis, elevated protein, normal IgG index, and no OCBs.
Treatment with high-dose IV corticosteroid therapy may help diminish inflammation and restore the blood-brain barrier integrity. Early initiation of plasmapheresis (within 15 days of onset) has been shown to result in clinical improvement and should be offered to those who fail steroid therapy.\textsuperscript{161–165}

\textbf{Parainfectious TM}

Parainfectious TM (PITM) refers to TM associated with an antecedent infection. It is unclear if it shares the same pathophysiological underpinnings as ADEM (and represents different ends of a spectrum) or if they are separate entities. Both are preceded by typically monophasic, steroid-responsive events preceded by infections. It is difficult to determine if PITM is caused by direct microbial invasion (causing myelitis by either the direct pathogenic destruction, or from the pathogen-triggered immune reaction), or a consequence of immune-mediated, inflammatory mechanisms induced by a remote infection. The antecedent infection has typically resolved before the onset of TM and it is difficult to demonstrate the offending organism in the spinal cord parenchyma.

The hepatitis viruses may cause TM via postinfectious, immune-mediated, inflammatory mechanisms.\textsuperscript{166} Hepatitis A virus and Hepatitis B virus infection have been associated with immune-mediated TM.\textsuperscript{166} Hepatitis C virus (HCV) is the most commonly implicated hepatitis virus in TM. HCV has been associated with recurrent, corticosteroid-responsive, demyelinating TM (even without hepatic involvement).\textsuperscript{166–171} There is a single report of hepatitis E–virus associated TM.\textsuperscript{172}

Viruses associated with PITM\textsuperscript{155,173–186} are listed in Box 5.

CNS manifestations are the most common extrapulmonary complication of \textit{Mycoplasma pneumoniae} infection.\textsuperscript{155,187–189} Although encephalitis is the most frequent complication,\textsuperscript{189} TM is the most severe and debilitating manifestation.\textsuperscript{190} Acute to subacute thoracic myelopathy typically arise 2 to 4 weeks after the antecedent respiratory infection and progress to a nadir in about 3 days; it may be accompanied by meningoencephalitis and/or polyradiculopathy.\textsuperscript{190} LETM has been reported.\textsuperscript{191–193} A predominantly mononuclear pleocytosis with increased protein and normal glucose levels are frequently found.\textsuperscript{190} Serologic detection of anti-\textit{Mycoplasma} antibodies supports the diagnosis. Positive \textit{M pneumoniae} CSF polymerase chain reaction provides reliable diagnostic evidence of preceding infection.

Antecedent \textit{Campylobacter jejuni} infection has been classically associated with GBS, presumably because of molecular mimicry between bacterial lipopolysaccharides and human gangliosides. It has been associated with TM,\textsuperscript{194–196} ADEM,\textsuperscript{197–199} and 1 case of biopsy-proven CNS vasculitis.\textsuperscript{200} In patients with TM with a recent diarrheal illness, stool cultures for \textit{C jejuni} and serologic studies for antiganglioside antibodies should be considered.

Bacteria reported to cause PITM\textsuperscript{155,195,201–214} are listed in Box 5.

Fungal and parasitic causes of PITMs\textsuperscript{215–223} are rare; these are listed in Box 5. These microbes most likely cause myelopathy by direct pathogenic effects. One noteworthy parasite is the pinworm (\textit{Enterobius vermicularis}), which has been reported to cause TM associated with anti-GM1 antibodies (which are also seen in \textit{C jejuni} infection) via molecular mimicry.\textsuperscript{224}

Pathogens associated with parainfectious LETM\textsuperscript{167–170,186,192,193,201,209,212,213,225–239} are listed in Box 3.

It is imperative to remember that the occurrence of TM following an infection does not automatically implicate ADEM or a parainfectious autoimmune response. Longitudinal follow-up is needed and further evaluation may be warranted because infections may trigger TM that heralds the diagnosis MS or NMO. Diagnostic confusion may arise
in cases in which concomitant parainfectious AON\(^{240,241}\) and TM may mimic the appearance of a demyelinating disease. As such, longitudinal follow-up is required to ascertain the nature of the disease.

**Paraneoplastic TM**

Collapsin response-mediator protein-5 (CRMP-5-IgG) antibodies, observed in small-cell lung cancer, is the paraneoplastic antibody most commonly associated with TM; LETM has also been observed. CRMP-5-IgG–related AON is a recognized manifestation of this paraneoplastic syndrome. A clinical picture resembling MS or NMO may arise.\(^{242,243}\) Patients demonstrate a subacute, progressive, predominantly motor myelopathy as well as increased CSF protein, elevated IgG index, and mild pleocytosis.\(^{242,244}\) MRI demonstrates T2-hyperintense lesions with occasional gadolinium enhancement. In more than 40% of patients, LETM may be demonstrated.\(^{242}\) Other paraneoplastic antibodies associated with TM are listed in Table 6.

**Atopic Myelitis**

Atopic myelitis (AM) demonstrates a chronic persistent or fluctuating course of predominantly cervical myelitis, associated with marked hyper-IgEemia, allergen-specific IgE (most commonly to dust mites), and occasional coexistent atopic diseases (eg, atopic dermatitis, atopic rhinitis, asthma).\(^{245}\) The vast majority of reported cases occur in Japanese patients, but there are a few reports of AM in White patients.\(^{246,247}\) Sensory deficits are the predominant symptom, with infrequent motor and bladder involvement.\(^{248}\)

On MRI, the lesions are T2-hyperintense with variable gadolinium enhancement, appear to favor the posterior columns of the cervical cord, and are limited to 1 to 2 vertebral bodies.\(^{248,249}\) Because the clinical and radiologic picture resembles MS, it is imperative to obtain a brain MRI to look for lesions that would be suggestive of MS.\(^{250}\) CSF cell count and protein are typically normal and OCBs are not seen.\(^{249,250}\) VEP may be abnormal in more than 20% of patients with AM (and therefore may not help distinguish it from MS), as atopic AON has been reported to occur as well.\(^{250,251}\)

**TM in Other Dysimmune Disorders**

Table 5 lists various dysimmune disorders that have been associated with TM.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Paraneoplastic antibodies associated with TM aside from collapsin response-mediator protein 5 IgG antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic Antibody</td>
<td>Comment</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>Anti-Ri antibodies are usually associated with lung or breast carcinoma</td>
</tr>
<tr>
<td>Anti-amphiphysin IgG</td>
<td>Classically associated with breast cancer and stiff man syndrome</td>
</tr>
<tr>
<td>Anti-glutamic acid decarboxylase (GAD65)</td>
<td>Classically associated with stiff person syndrome, cerebellar ataxia, diabetes mellitus type 1, and limbic encephalitis</td>
</tr>
<tr>
<td>N-methyl-d-aspartate receptor (NMDAR)</td>
<td>Classically associated with limbic encephalitis, and related to ovarian teratomas.</td>
</tr>
</tbody>
</table>
Drug-induced and Toxin-related TM

Drugs and toxins associated with TM are listed in Table 7.

Idiopathic TM

The Transverse Myelitis Consortium Working Group has proposed a set of strict criteria for the diagnosis of ITM, which are summarized in Table 8. To make the diagnosis, all inclusion and no exclusion criteria should be present. The application of these criteria has resulted in a fairly homogeneous group of patients in terms of clinical and radiologic data. The reported proportion of patients with TM with ITM varies widely, from 16% to approximately 60%.

The overall mean age of disease onset appears to be between 35 and 40 years, with a female preponderance. The MRI typically demonstrates a centromedullary lesion, extending over 2 vertebral segments and involving more than two-thirds of the cross-sectional area of the spinal cord, with a predilection for the thoracic cord. Cord swelling is seen in half of cases. Gadolinium enhancement (which may be nodular, peripheral, heterogeneous, or moderately diffuse) occurs in approximately one-third to one-half of cases. CSF shows increased protein in most patients; pleocytosis and OCBs are sometimes seen. Interestingly, unlike other causes of TM, negative OCBs is correlated with recurrence.

ITM is typically monophasic but recurs in about one-quarter to one-third of cases (recurrence of initial insult, expansion of prior lesion, or a new lesion). Risk factors for recurrence seem to be the following: (1) male gender; (2) age older than 50 years; (3) severe motor weakness and sphincteric dysfunction; and (4) negative CSF OCBs, normal IgG index, and NMO-IgG seronegativity. Recurrences are associated with a poor outcome. Interestingly, Kim and colleagues and Alvarenga and colleagues both reported recurrences exceeding 60% in their respective studies despite the low rate of NMO-IgG seropositivity. There are several serologic, CSF, and radiologic differences among the patients with recurrent ITM in these studies and may represent distinct clinical entities that have yet to be characterized. A Korean study of 15 patients with recurrent ITM lends support to the hypothesis that recurrent ITM may represent a unique entity. More longitudinal studies are needed to clearly elucidate the characteristics of recurrent ITM.

### Table 7

<table>
<thead>
<tr>
<th>Drug/Toxin</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-alpha inhibitors</td>
<td>Reported to cause CNS demyelination and TM.</td>
<td>401,402</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
<td>403</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>Gemcitabine, cytarabine (cytosine arabinoside), and cisplatin.</td>
<td>404–408</td>
</tr>
<tr>
<td>General and epidural</td>
<td>The association between TM and general anesthesia is debatable.</td>
<td>409–415</td>
</tr>
<tr>
<td>anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>Although most of cases of myelopathy in heroin addicts result from anterior spinal artery infarction, there are reports of TM.</td>
<td>416–419</td>
</tr>
<tr>
<td>Benzene</td>
<td></td>
<td>420</td>
</tr>
<tr>
<td>Brown recluse spider bite</td>
<td>Incomplete TM (anterior spinal syndrome), responsive to corticosteroid therapy.</td>
<td>421</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; TM, transverse myelitis; TNF, tumor necrosis factor.
The response of ITM to corticosteroid therapy is usually disappointing. In general, one-third of patients with idiopathic acute transverse myelitis recover with little or no sequelae, one-third are left with a moderate degree of permanent disability, and one-third have severe disabilities. Spinal shock at presentation was highly predictive of a poor outcome. Interestingly, a higher CSF glucose level (related to higher serum levels) may portend a poorer outcome.

Pediatric TM

On the whole, the incidence of TM in children is much lower than that of the adult population. There appears to a bimodal distribution: toddlers younger than age 3, and children between 5 and 17 years. Males and females are equally affected. Antecedent infections (typically respiratory) or preceding vaccinations are common. Because of the association with respiratory infections, there is a clustering of TM cases in the winter months. Compared with adults, pediatric TM is more frequently postinfectious, thoracic, centromedullary, and longitudinally extensive. The risk of conversion to MS is lower and functional recovery is often better than in the adult population. Complete recovery appears to be the rule with poor outcome in only a minority of patients. The course in pediatric TM has been divided into 3 phases: onset, plateau, and recovery. The plateau may last up to 4 weeks; if recovery has not started by the end of this period, the likelihood of recovery diminishes. Beyond 6 months, any improvement is very improbable.

CSF analysis frequently reveals pleocytosis and elevated protein; OCBs and increased IgG indices are rare. Although the proportion of pediatric TM cases with LETM is higher than that of adults, the rate of NMO-IgG seropositivity is much lower. This low rate of NMO-IgG seropositivity, with the typically monophasic clinical course and benign outcome in pediatric LETM, suggests that the pathobiological underpinnings of LETM in the pediatric population is different from that in adults.
Age younger than 3 years, requirement for respiratory support, severe impairment at onset, flaccid paralysis at onset, a more rapid progression to the nadir of weakness, CSF pleocytosis, and MRI T1-hypointensity at the time of diagnosis were poor prognostic indicators for recovery.261,264,267,268 Early treatment with IV methylprednisolone had a significant positive effect on outcome.264 The most common long-term neurologic complication of TM in children is bladder dysfunction.261,264,266 As in adults, APTM, CSF OCBs, and the brain MRI lesions portend an increased risk for transition to MS; LETM carries a low risk of developing MS.262

Table 9 highlights the important CSF and MRI features of the different causes of TM.

**PSEUDOEXACERBATION**

Pseudoexacerbation is a phenomenon in which patients experience temporary worsening of previously suffered neurologic deficits. In demyelinating disorders, Uhthoff phenomenon is the most common underlying cause of pseudoexacerbation (authors’ personal experience). Any condition that increases the patient’s body temperature (eg, febrile illness, exercise, hot weather, hot baths, hot showers, stress, menses, dehydration) can cause a pseudoexacerbation. Any infection, particularly urinary tract infections (UTI) may result in pseudoexacerbation. In fact, any metabolic or physiologic derangements (eg, hyperglycemia, hypertension) has the potential to transiently worsen prior neurologic deficits. In conclusion, worsening of prior myelopathic symptoms in a patient with previous TM does not automatically implicate a recurrence or relapse. Pseudoexacerbation should be considered and investigations into the cause of pseudoexacerbation should be undertaken. Treatment of recurrent TM entails immunosuppressive therapy, but treatment of pseudoexacerbation involves addressing the underlying cause (eg, treating the UTI).

**MIMICS OF TRANSVERSE MYELITIS**

In making the diagnosis of TM, it is essential to remember that many noninflammatory etiologies may mimic the appearance of TM. Recognizing these entities is important, as the treatment and management strategies would be vastly different.

Entities important to recognize include vascular myelopathy, compressive myelopathy, metabolic/toxic myelopathy, neoplasms, and radiation myelitis. Selected etiologies are described in Table 10.

**MANAGEMENT**

**Acute Management**

Once the diagnosis of TM is made, immunotherapy should be instituted to stop the inflammatory process and therefore allow recovery to commence. In a small open-label trial, high-dose IV methylprednisolone was shown to improve the outcome in pediatric TM.264 Despite the lack of randomized controlled studies, administration of high-dose IV corticosteroids (IV methylprednisolone 1 g daily for 3–7 days) should be started as early as possible in all patients with TM.13

In patients with poor or no response to corticosteroids, plasmapheresis should be offered,13 with the rationale of removing humoral factors inciting TM. The benefits of plasmapheresis have been proven in acute attacks of CNS demyelinating diseases.163–165,270 Early initiation of plasmapheresis (within 15 days of onset) is the best predictor of a favorable acute response and of improvement at 6 months.164,165 The typical regimen is exchanges of 1.5 plasma volumes for 5 treatments over 10 days.271 Plasmapheresis also has anecdotal support in various systemic autoimmune disorders (described previously).
Table 9
Highlighted CSF and MRI differences for various causes of TM

<table>
<thead>
<tr>
<th>Cause</th>
<th>CSF</th>
<th>MRI Features of Spinal Cord Lesion</th>
<th>MRI Features of Brain Lesions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>OCB</td>
<td>APTM</td>
<td>Periventricular plaques (Dawson fingers)</td>
<td>Juxtacortical lesions T1 black holes Cortical atrophy</td>
</tr>
<tr>
<td></td>
<td>Increased IgG index</td>
<td>Cigar-shaped</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>OCB rare</td>
<td>LETM</td>
<td>Periventricular lesions (not perpendicularly oriented), hypothalamic, lesions around 3rd and 4th ventricles, or brainstem lesions. Clinically silent lesions rare. “Cloudlike” gadolinium enhancement</td>
<td>NMO-IgG seropositivity</td>
</tr>
<tr>
<td>Neurosarcoïdosis</td>
<td>Lymphocytic pleocytosis</td>
<td>LETM</td>
<td>Leptomeningial enhancement</td>
<td>Cranial neuropathies Pulmonary manifestations</td>
</tr>
<tr>
<td></td>
<td>OCB rare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Pleocytosis OCBs infrequent</td>
<td>LETM</td>
<td>Subcortical lesions</td>
<td>Gray and white matter myelitis</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Pleocytosis OCBs in a third of patients</td>
<td>LETM</td>
<td>Basal ganglial lesions</td>
<td>Cochlear neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Corpus callosal lesions rare</td>
<td></td>
</tr>
<tr>
<td>Behcet disease</td>
<td>Mixed pleocytosis OCBs rare</td>
<td>LETM</td>
<td>Unilateral upper brainstem-diencephalic-basal ganglial Brainstem atrophy</td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>Marked pleocytosis</td>
<td>LETM</td>
<td>Acute, multiple, symmetric, supratentorial and infratentorial lesions, with one at least 1 cm in diameter Symmetric basal ganglial and thalamic lesions</td>
<td>Typically monophasic Antecedent infection or vaccination</td>
</tr>
<tr>
<td></td>
<td>Increased protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No OCB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgG index negative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
Although plasmapheresis may provide benefit beyond that obtained with steroids, patients with American Spinal Injury Association (ASIA) A level of disability may need IV cyclophosphamide as well.\textsuperscript{272} IV cyclophosphamide appears to be efficacious in active inflammatory MS\textsuperscript{273,274} and other autoimmune conditions. The major concern with cyclophosphamide is the adverse effect profile, which includes nausea, hemorrhagic cystitis, and malignancies.

In high cervical cord lesions extending into the medulla, respiratory failure may be fatal\textsuperscript{275}; therefore, in such patients, vital signs and respiratory function should be vigilantly monitored. Other acute issues that may arise include immobility (and the complications thereof), urinary retention, constipation, and gastroparesis. These are discussed later in this article.

In cases of TM attributable to systemic autoimmune disease or acquired demyelinating disease, commencement of long-term immunomodulatory therapies would help prevent future attacks.\textsuperscript{3} A discussion of these therapies is beyond the scope of this article.

### The Importance of a Multidisciplinary Approach to Neurorehabilitation

A very important aspect of managing TM focuses on the multiple complications arising from the disease. The main thrust of long-term management is neurorehabilitation, the active process by which those disabled by injury or disease achieve a full recovery or, if full recovery is not possible, realize their optimal physical, mental, and social potential and are integrated into their most appropriate environment.\textsuperscript{276} Successful neurorehabilitation is dependent on a multidisciplinary assessment that can develop goal-oriented programs tailored for the patient’s specific needs; therefore, early consultation with the physical medicine and rehabilitation physician, physical therapist, occupational therapist, and psychologist/psychiatrist is vital. In fact, there is evidence that a multidisciplinary comprehensive care center is a highly efficient and cost-effective care delivery system that minimizes adverse events, lowers rehospitalization rate, and improves patients’ perception.\textsuperscript{277}

### Mobility and Gait Impairment

#### Acute immobility

In the acute phase of TM, weakness may be severe and care should be taken to avoid the complications of prolonged immobility. Low molecular weight heparin or
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 deficiency</td>
<td>May present as an isolated myelopathy or in combination with neuropathy, encephalopathy, and/or behavioral changes. Dorsal column impairment is the most common manifestation, followed by pyramidal dysfunction (the classic subacute combined degeneration of the cord). Hematologic manifestations may be absent up to 30% of patients with neurologic manifestations. MRI reveals T2-hyperintense signal in the posterior columns (the “inverted V” or “inverted rabbit ear” sign on axial views). In severe cases, MRI shows the “anchor” sign (because of involvement of the posterior, anterior, and pyramidal tracts).</td>
<td>422–425</td>
</tr>
<tr>
<td>Vitamin E deficiency</td>
<td>May cause a predominantly dorsal column syndrome associated with a peripheral neuropathy because of axonal degeneration. Preferentially affects the cervical cord. Clinically and radiologically similar to B12 deficiency.</td>
<td>426–428</td>
</tr>
<tr>
<td>Copper deficiency</td>
<td>May cause both myelopathy and optic neuropathy. Causes of acquired copper deficiency include malnutrition, zinc toxicity, Menke disease, bariatric surgery, gastrectomy, malabsorption syndromes, and use of copper chelating agents. Clinically and radiologically indistinguishable from B12 deficiency.</td>
<td>429–433</td>
</tr>
<tr>
<td>Nitrous oxide (N2O) toxicity</td>
<td>Analgesic gas commonly abused because of euphoric effects. N2O inactivates vitamin B12 by irreversible oxidation of the cobalt center of methylcobalamine, thereby inhibiting the methionine synthesis pathway. In healthy subjects, this does not cause clinical manifestations. In subclinically B12-deficient individuals, N2O exhausts residual stocks of vitamin B12, leading to neurologic manifestations.</td>
<td>434–436</td>
</tr>
<tr>
<td>Neurolathyrism and neurocassivism</td>
<td>Neurolathyrism is caused by consumption of grass pea. Neurocassavism (konzo) is caused by bitter cassava root consumption. Both are found in malnourished populations, and are characterized by subacute paraparesis with prominent UMN features.</td>
<td>437</td>
</tr>
</tbody>
</table>

Table 10
Mimics of TM
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramedullary primary spinal cord tumors</td>
<td>May be ependymomas, astrocytomas, or hemangioblastomas. Typically cause an insidious, progressive myelopathy. Hemorrhage or infarction of the tumor may result in an acute presentation and radiologic appearance mimicking TM.</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>May give rise to a clinical and radiologic picture mimicking TM compounded by its corticosteroid-responsiveness. Congenital or acquired immunodeficiency is the only established risk factor. More common in middle-aged and older men. Insidious onset of myelopathy with back pain and constitutional symptoms. Serum lactate dehydrogenase may be elevated. CSF: lymphocytic pleocytosis, markedly elevated protein, and hypoglycorrachia. OCBs and IgG index are absent. Cytologic analysis may demonstrate malignant cells (large-volume CSF examination can increase the diagnostic yield). MRI: T2-hyperintensity, gadolinium enhancement, cord swelling, conus medullaris involvement, and concomittant brain lesions.</td>
</tr>
<tr>
<td>Intravascular lymphoma</td>
<td>Predominantly affects vessels in the skin and neurologic system. May mimic TM and even LETM. CSF: lymphocytic pleocytosis and increased protein, but no malignant cells. MRI: affects the conus medullaris (unlike TM).</td>
</tr>
<tr>
<td>Radiation myelitis</td>
<td>Early radiation myelopathy: begins 10–16 weeks after starting radiotherapy with predominantly sensory phenomena (including Lhermitte) and typically resolves spontaneously. Delayed radiation myelopathy: begins months or years following radiation exposure and manifests as a subacute or insidious myelopathy. Concurrent use of chemotherapeutic agents may cause widespread white matter necrosis owing to synergistic toxicity. Preexisting myelopathy from any cause may be risk factors for radiation myelitis. MRI: cord swelling on T1-weighted images, intramedullary T2-hyperintensity, ring-like gadolinium enhancement.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; CSF, cerebrospinal fluid; Ig, immunoglobulin; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; OCB, oligoclonal bands; TM, transverse myelitis; UMN, upper motor neuron.
Fondaparinux can be used to prevent venous thromboembolism. Respiratory therapy may prevent atelectasis. In severely weak patients, pressure sores are a serious complication. Addressing risk factors (e.g., malnutrition, impaired circulation), conscientious use of pressure-reducing measures (e.g., frequent and regular turning, pressure-distributing positioning aids, sheepskins), and early mobilization are critical.

*Long-term mobility*

Decreased mobility is a factor associated with diminished quality of life (QOL) following spinal cord injury (SCI). Improving mobility in an energy-efficient manner may thus improve health-related QOL following TM and should be a priority of rehabilitation.

Bipedal locomotion is a complex phenomenon that requires intricate interactions between central pattern generators and peripheral reflexes that involve multiple neural networks, including the visual, vestibular, proprioceptive, and corticospinal systems. Walking parameters can be affected by age, weight, spasticity, lower limb strength, balance, pain, duration of rehabilitation, cord lesion level, and the presence of other comorbidities. Functional walking has several requisites, including safety (which dictates the need for walking aids), speed, comfort, and distance.

Velocity is one of the most important parameters in determining functional ambulation, particularly community ambulation; SCI patients have tremendous difficulty achieving the speed needed to cross an intersection safely. Following nontraumatic SCI, although inpatient rehabilitation may improve walking abilities, gait speed often remains impaired and insufficient to safely negotiate community environments.

*Table 11* describes concepts and strategies in managing mobility following TM.

The benefits of physical exercise extend beyond improvements in strength and functional capacity; mood, fatigue, balance, and QOL can also improve. Exercise also carries anti-inflammatory benefits.

*Spasticity*

Spasticity is the velocity-dependent increase in muscle tone owing to disruption of the descending corticospinal, vestibulospinal, and reticulospinal pathways. It often affects the patient by causing muscle stiffness, spasms, pain, and clonus. Paroxysmal tonic spasms are sudden, episodic, brief, painful, stereotypic, dystonic contractions that may occur following TM. Spasticity may result in pain, interrupted sleep, and impaired ambulation.

Although some degree of spasticity may protect against osteoporosis, and is needed for weight bearing to allow ambulation, excessive spasticity can disrupt activities of daily living (e.g., transferring, hygiene, sexual activity). Successful treatment of spasticity can be attained with an integrated multidisciplinary approach. *Table 12* summarizes management options for spasticity.

*Movement Disorders*

Movement disorders that may complicate TM include propriospinal myoclonus (PSM), periodic limb movement disorder (PLMS) and restless leg syndrome (RLS). PSM is an unusual movement disorder, sometimes seen after spinal cord lesions, characterized by myoclonic jerks arising in muscles corresponding to a myelomere (myoclonic generator) and spreading rostrally and caudally to the other myotomes. Drug therapy of PSM is disappointing but there are reports of treatment with benzodiazepines, zonisamide, and valproate.
PLMS and RLS have been reported as a consequence of spinal cord pathologies, including TM, and may be related to the emergence of spasticity. These disorders may impair sleep quality and, as such, should be treated. Serum ferritin levels should be ascertained, as iron-deficiency anemia is a common and treatable cause of RLS. Caffeine, alcohol, nicotine, and medications that may aggravate RLS should be avoided. The first-line choice for pharmacologic therapy is a dopaminergic agonist (eg, ropinorole, pramipexole). Other options include levodopa, opiates, gabapentin, lamotrigine, or clonazepam.

**Bladder Dysfunction**

Bladder dysfunction remains one of the most common and disabling consequences of TM; UTI is the most common medical complication in myelopathic patients.
Despite complete motor recovery following TM, bladder dysfunction often persists. In general, 3 forms of bladder dysfunction may be present: detrusor overactivity (failure to store), detrusor-sphincter dyssynergia (DSD), and detrusor hypocontractility (failure to empty).

In acute TM, urinary retention from a hypocontractile “shocked” bladder (detrusor areflexia or hyporeflexia) often necessitates placement of a urinary catheter. Similar to how UMN signs appear following spinal shock, detrusor hyperreflexia typically develops, characterized by frequency, urgency, urge incontinence, and the sensation of bladder spasms; in fact, the resolution of spinal shock and subsequent emergence of UMN signs may parallel similar changes in the bladder. Some patients experience DSD, where insufficient external urinary sphincter relaxation during detrusor contraction results in urinary retention, increasing the risk for vesicoureteral reflux, infection, and nephrolithiasis. Patients with DSD can also report urgency, frequency, incontinence, urinary hesitancy, and a sensation of incomplete bladder emptying after voiding. More infrequently, a hypotonic, overly compliant bladder (failure to empty) may present with frequency, overflow incontinence, and signs of incomplete emptying. Urinary symptoms are unreliable in differentiating poor bladder compliance from urinary retention.

Although ultrasonographic assessment of postvoid residual urine volume is useful, urodynamic studies (and hence, urologic consultation) and renal ultrasound are often required to properly characterize the nature of bladder dysfunction, plan management, and identify those at risk for future complications.

Table 13 summarizes the various problems of bladder dysfunction and management options.

**Gastrointestinal Dysfunction**

TM may result in gastrointestinal dysfunction following perturbation of the autonomic pathways of the spinal cord. In the setting of spinal shock, there is an increased risk for gastroduodenal ulceration and hemorrhage, paralytic ileus, acute gastric dilatation, and atypical presentations of acute abdominal pathology.
Table 13
Managing the urinary dysfunction following transverse myelitis

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor hyperreflexia (failure to store)</td>
<td>• Anticholinergic agents (eg, trospium, fesoterodine, oxybutynin, tolterodine)</td>
</tr>
<tr>
<td></td>
<td>• Selective M2- and M3-antimuscarinics (darifenacin and solifenacin)</td>
</tr>
<tr>
<td></td>
<td>• Intravesical atropine, oxybutynin, capsaicin, or resiniferatoxin</td>
</tr>
<tr>
<td></td>
<td>• Detrusor muscle botulinum toxin A injection</td>
</tr>
<tr>
<td></td>
<td>• Suprapubic vibration (“Queen Square bladder stimulator”)</td>
</tr>
<tr>
<td>Detrusor-sphincter dyssynergia</td>
<td>• Alpha-1 adrenergic antagonists (eg, tamsulosin)</td>
</tr>
<tr>
<td></td>
<td>• Clean intermittent catheterization (CIC)</td>
</tr>
<tr>
<td></td>
<td>• Suprapubic vibration (“Queen Square bladder stimulator”)</td>
</tr>
<tr>
<td></td>
<td>• Neuromodulation (InterStim)</td>
</tr>
<tr>
<td></td>
<td>• Intrasphincteric botulinum toxin</td>
</tr>
<tr>
<td></td>
<td>• Indwelling Foley catheter</td>
</tr>
<tr>
<td></td>
<td>• Suprapubic catheter</td>
</tr>
<tr>
<td>Frequent urinary tract infections</td>
<td>Appropriate antibiotics</td>
</tr>
<tr>
<td></td>
<td>Prophylactic antibiotic therapy</td>
</tr>
<tr>
<td></td>
<td>Cranberry preparations</td>
</tr>
<tr>
<td></td>
<td>Vitamin C supplementation</td>
</tr>
<tr>
<td>Painful bladder spasms</td>
<td>Pharmacotherapy</td>
</tr>
<tr>
<td></td>
<td>Timed voiding</td>
</tr>
<tr>
<td></td>
<td>Neuromodulation</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Behavioral measures</td>
</tr>
<tr>
<td></td>
<td>Pelvic floor exercises</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
</tr>
<tr>
<td></td>
<td>Desmopressin (DDAVP)</td>
</tr>
<tr>
<td></td>
<td>Bladder rehabilitation</td>
</tr>
</tbody>
</table>

Data from Refs.3,297,298,458–465

Gastroparesis
Gastroparesis (presenting with nausea, vomiting, pain, bloating, and/or early satiety) increases the risk of reflux and aspiration of gastric contents. It has been reported following cervical cord, thoracic cord, and cervico-medullary junction lesions.300-303
Gastroparesis may occur in the acute and chronic phases of TM. Table 14 summarizes the management of gastroparesis.

**Neurogenic bowel dysfunction**
Bowel dysfunction is a source of considerable psychosocial disability, limiting the ability to work and affecting patients’ QOL.³⁰⁴ It may manifest as either constipation or fecal incontinence. The exact pathophysiology of bowel dysfunction in TM is unclear, but may be caused by disruption of the extrinsic neurologic control of gut and sphincter function, pelvic floor musculature, autonomic dysfunction, and/or impaired anorectal sensation.³⁰⁴ Psychiatric disorders and medications also contribute to bowel dysfunction. For example, although opioid narcotics and anticholinergic drugs cause constipation, baclofen can theoretically alter the response to rectal distension and the threshold of conscious rectal sensation and cause fecal incontinence.³⁰⁴ Management strategies for neurogenic bowel dysfunction are summarized in Table 14. Transanal irrigation (TAI) can be carried out using either a rectal balloon catheter or a cone-shaped colostomy tip. In a retrospective study of 348 patients (either constipation or fecal incontinence) during a 10-year period, TAI showed benefit in treating neurogenic bowel dysfunction.³⁰⁵

**Miscellaneous gastrointestinal disorders**
Hemorrhoids (and hemorrhage) are more frequent in patients with bowel dysfunction and is likely a consequence of straining and the use of suppositories and enemas.²⁹⁹ Gallbladder disease is also more prevalent following SCI.²⁹⁹ Superior mesenteric artery syndrome (where the third part of the duodenum is intermittently compressed by the vessel) causes vomiting when supine. Rapid weight loss, prolonged supine positioning, and the use of spinal orthosis are predisposing factors.²⁹⁹

**Sexual Dysfunction**
Sexuality is a fundamental aspect of health at the core of individual identity and influences a person’s well-being.³⁰⁶ Sexual dysfunction is a frequent complication of spinal cord lesions and has been shown to increase the risk of suicide.³⁰⁷ As the incidence of TM is higher in the second and fourth decades of life, it affects adolescents or young adults who are sexually active.

Sexual dysfunction may be a direct consequence of damage to the autonomic and sensory pathways in the spinal cord following TM. Indirectly, complications of TM, including the psychological response to disability, spasticity, immobility, pressure ulcers, pain, and sphincter dysfunction, affect sexual function. Psychological dysfunction contributes more to sexual dysfunction than the actual physical disabilities.³⁰⁸ Comorbidities (eg, mood disorders, diabetes) and medications are other important contributors to sexual dysfunction.

An open, frank, and nonjudgmental discussion about sexual function, expectations, beliefs, preferences, and the potential complications from TM should be undertaken with the patient. Including the patient’s partner in such discussions is often helpful. A medical assessment of the reproductive system should be conducted as part of the multidisciplinary approach to TM.³⁰⁶ Skin, bladder, and bowel care before sexual activity is important.³⁰⁶ Autonomic dysreflexia (see later in this article) is a potentially dangerous consequence of sexual activity. Because of diminished or absent sensation, skin breakdown may occur from excessive friction, and in men, there is an increased risk of penile trauma.

Following spinal cord damage, most men can have some form of erection (psychogenic or reflexogenic) but these are often insufficiently predictable, rigid, or long
lasting to allow sexual intercourse. Only 25% of men with SCI have erections adequate for sexual intercourse; erectile dysfunction is a great source of distress in men with SCI, even more so than the loss of functional independence or sphincter dysfunction. A precise coordination of sympathetic, parasympathetic, and somatic

### Table 14: Management of gastrointestinal dysfunction in patients with transverse myelitis

<table>
<thead>
<tr>
<th>Problem</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastroparesis</strong></td>
<td>Stop drugs that inhibit gastrointestinal motility (eg, narcotics, calcium channel blockers, anticholinergics). Consultation with a gastroenterologist for endoscopy, gastric emptying studies, and investigations to characterize the nature of dysmotility. Gastric decompression with a nasogastric tube, bowel rest, intravenous fluids, and proton-pump inhibitors or gastric H2-receptor blockers should be considered. Prokinetic agents (eg, metoclopramide, macrolide antibiotics, bethanechol or pyridostigmine) may be used. Tardive dyskinesia is a risk of metoclopramide use. Gastric electrical stimulation (Enterra therapy) and endoscopic injection of botulinum neurotoxin may be of potential benefit. In refractory cases, surgical interventions like pyloroplasty may be needed.</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td><strong>General measures</strong>: high-fiber diet, bulking agents, increased fluid intake (at least 2 L daily), physical exercise, and establishing a regular toileting routine (best accomplished after breakfast to take advantage of the gastrocolic response, which peaks about 30 minutes after eating). Stimulant or osmotic laxatives (senna and bisacodyl) can be titrated to produce a satisfactory response (without producing liquid stool). Osmotic laxatives, although effective, can produce liquid stool with subsequent incontinence. Rectal stimulants have a predictable time of response. Begin with a glycerine suppository, progressing to bisacodyl, sodium citrate microenema, and ultimately a phosphate enema. Biofeedback may help, particularly in pelvic floor incoordination. Neostigmine in combination with glycopyrrolate has been shown to be effective. 4-aminopyridine may improve constipation. Digital stimulation of the anal canal serves to manually disimpact the rectum. Abdominal massage may be helpful. For refractory cases: colostomy, neuromodulation, Malone Antegrade Continence Enema. Transanal irrigation (TAI).</td>
</tr>
<tr>
<td><strong>Fecal incontinence</strong></td>
<td>Mild and infrequent: loperamide, codeine phosphate. Antidiarrheal drugs should be used with caution if incontinence and constipation coexist, and periodic checks for impaction may be required. Fecal impaction is a common complication and patients experience anorexia, nausea, and spurious diarrhea (liquid stool passing around the blockage). Biofeedback is another useful tool. Anal plugs or pads may be needed. Severe cases: surgical intervention (eg, dynamic graciloplasty, artificial bowel sphincter, and sacral nerve stimulation). TAI</td>
</tr>
</tbody>
</table>

Data from Refs.299,304,315,466,467
divisions of the nervous system is essential for normal antegrade ejaculation. This intricate neural network is easily disrupted following spinal cord damage, leading to ejaculatory dysfunction and, hence, infertility. Intact genital sensation is the most important positive predictive factor of male sexual function, whereas an important negative predictor of sexuality is the presence of spasticity.314

The effects of spinal cord lesions on female sexuality is much less studied than in males, mainly because of the preponderance of male patients with traumatic SCI and partly because female fertility is not affected.308,315 Manifestations include decreased libido, lack of arousal, vaginal dryness, dyspareunia, and decreased genital sensation.316

An important point to emphasize to all patients is that although genital sensation is diminished, individuals are more likely to develop new erogenous areas above the level of the lesion, or with time, learn to interpret altered autonomic input from genito-perineal stimulation317,318; it is, therefore, important to explore new methods of sexual expression. Also, access to programs for sexual rehabilitation that include a multidisciplinary spinal cord team, as well as support groups, may be a pivotal part of treatment. Table 15 summarizes some management strategies for sexual dysfunction.

### Autonomic Dysregulation

Autonomic dysfunction may occur in the acute or chronic phases of TM and appears to be present in lesions above the upper thoracic segments. Acute spinal cord lesions may cause neurogenic shock. In addition, cardiac dysrhythmias (eg, bradycardia and arrest) may occur.319 Initial management may require hemodynamic monitoring and management in an intensive care setting.

**Orthostatic hypotension**

Orthostatic hypotension (OH) may occur in both the acute and chronic phases of TM. OH is defined as a decrease in systolic blood pressure of 20 mm Hg or more or a decrease in diastolic blood pressure of 10 mm Hg or more when the subject moves from an upright to supine posture, regardless of whether symptoms occur.320 Clinical manifestations include pallor, diaphoresis, light-headed dizziness, syncope, anxiety, and nausea.

It is more common with lesions above the upper thoracic spinal segments.321 Loss of sympathetic nervous activity and reflex vasoconstriction lead to pooling of venous blood in the abdominal organs and lower limbs; ultimately, cardiac output (and arterial pressure) drops. The reflex tachycardia that occurs often cannot adequately compensate for this. Cerebral hypoperfusion from reduced cardiac output is responsible for its manifestations.

**Thermodyrsregulation**

Although classically reported following traumatic SCI, thermodyrsregulation is another potential complication of TM with lesions at T6 and above; it can be classified as poikilothermia, “quad fever,” and exercise-induced hyperthermia.319 Disruption of the interomediolateral columns of the spinal cord and hypothalamic lesions likely contribute to thermodyrsregulation following TM.322 Perturbed heat dissipation mechanisms, in particular defective sweating (possibly owing to disruption of the descending sudomotor pathways), is believed to be a major contributor to thermodyrsregulation. Urinary dysfunction following TM often leads to voluntary restriction of fluid intake; further exacerbating thermodyrsregulation.323

“Quad fever” can occur in the acute phase and patients often present with fever.319 Needless to say, a thorough workup should be undertaken to rule out infection, thromboembolism, inflammation, and atelectasis before attributing pyrexia to “quad fever.”
Exercise-induced hyperthermia as a result of Uhthoff phenomenon and heat-induced fatigue is important to recognize. Approximately 60% to 80% of patients with MS experience transient worsening of neurologic symptoms as a result of elevated body temperature (ie, Uhthoff phenomenon). In addition to defective sweating (hypohidrosis), profuse sweating (hyperhidrosis) can occur above the level of the lesion with little or no sweating below it. Episodic hyperhidrosis may be associated with episodes of autonomic dysreflexia.

Autonomic dysreflexia
Autonomic dysreflexia (AD) is a well-recognized chronic complication of SCI and may occur following TM. It usually occurs in subjects with lesions above the outflow to the splanchnic and renal vascular beds (T5-6). AD is characterized by paroxysms of excessive, uninhibited sympathetic output leading to hypertension, bradycardia

<table>
<thead>
<tr>
<th>Problem</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced libido</td>
<td>Stop any offending medication (particularly selective serotonin reuptake inhibitors). Consider using bupropion. Check free testosterone levels (in both men and women) - testosterone replacement therapy for deficient states.</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Phosphodiesterase 5 inhibitors (sildenafil, tadalafil, and vardenafil). If unresponsive to oral agents, intracavernosal alprostadil injection, intraurethral alprostadil pellet, penile tension rings, vacuum devices, implantable penile prostheses, and sacral neuromodulation (Sacral Anterior Root Stimulator Implants) may be considered.</td>
</tr>
<tr>
<td>Ejaculatory dysfunction (affecting fertility)</td>
<td>Strong afferent stimulation and intense activation of the autonomic nervous system is needed to trigger the ejaculatory reflex. Penile vibratory stimulation (PVS) is the first line of treatment. Midodrine may be used as an adjunct to PVS in men who failed PVS alone. Rectal probe electro-ejaculation may be used but frequently results in retrograde ejaculation and may cause significant discomfort. Surgical techniques for sperm retrieval (eg, Brindley reservoir, microsurgical aspiration of spermatozoa from the vas deferens, or testicular biopsy) may also be considered if other measures fail.</td>
</tr>
<tr>
<td>Female orgasmic dysfunction</td>
<td>Manual and vibratory clitoral stimulation (eg, Eroscillator). Clitoral vacuum suction device (Eros) is approved by the Food and Drug Administration for female orgasmic dysfunction.</td>
</tr>
<tr>
<td>Lubrication dysfunction</td>
<td>Lubricants Topical estrogen Clitoral vacuum suction device (Eros) Estrogen replacement therapy</td>
</tr>
</tbody>
</table>

A description of the various considerations and measures to improve sexual activity and function in patients with spinal cord lesions is beyond the scope of this article. An excellent resource is the clinical practice guideline published by the Consortium for Spinal Cord Medicine. Data from Refs. 306,317,465,468–472
(although tachycardia may occur), pounding headache, piloerection, nasal congestion, anxiety, nausea, chills and shivering, flushing, and profuse sweating above the level of the lesion; severe cases may result in myocardial ischemia, seizures, retinal detachment, intracranial hemorrhage, hypertensive emergency, reversible posterior leukoencephalopathy, and even death.

The higher the level of the lesion, the more severe the cardiovascular dysfunction; complete SCI is associated with a higher incidence of AD compared with incomplete lesions. Any stimuli below the affected spinal level may precipitate AD, including bladder catheterization, manipulation of an indwelling catheter, DSD, UTI, bladder percussion, sexual activity, fecal impaction, ingrown toenails, sacral stress fracture, and use of devices for ejaculation. In most cases, AD is related to bladder distention or bowel impaction.

Table 16 summarizes the management strategies for AD.

### Pain and Sensory Complaints

Sensory phenomena are a common complication of TM. Early recognition and intervention may prevent chronic pain syndromes. TM-related pain may be classified as nociceptive or neuropathic. Nociceptive pain is related to musculoskeletal and visceral (eg, biliary colic) sources. Neuropathic pain may be related to complex regional pain syndromes, segmental deafferentation, radiculopathy, or cord damage. Two unique types of neuropathic pain are recognized: (1) a segmentally distributed radicular pain at the level of the lesion; and (2) a late-onset central dysesthesia syndrome below the level of the lesion, characterized by a stimulus-independent, continuous pain.

Treatments include oral tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory drugs, or narcotics. Lidocaine patches, topical capsaicin, and botulinum neurotoxin are other options. Anticonvulsants may be useful for Lhermitte phenomenon. Biofeedback, physical therapy, acupuncture, and transcutaneous electrical nerve stimulation are nonpharmacologic measures that can be considered. Dorsal root entry zone ablation is useful for radicular pain at the level of the lesion. Consultation with a pain management team may be needed.

A rare complication of TM is neurogenic pruritus, characterized by a dermatomal distribution of pruritus that is often associated with hypoesthesia or hyperesthesia; it responds poorly to medical therapy.

### Osteoporosis

Osteoporosis is a known complication of SCI and may be a consequence of both the cord lesion, subsequent immobilization, and neuroendocrinological dysfunction. The duration of paralysis correlates with the degree of bone loss. The pathobiological underpinnings of bone demineralization are unclear and, interestingly, its pattern differs from that seen in endocrine-related osteoporosis.

Bone loss begins immediately after SCI and is greater below the level of the lesion. In the first months, demineralization occurs exclusively in the sublesional areas and predominantly in weight-bearing skeletal sites. The largest decrease in bone mass occurs during the first 6 months after injury and stabilizes after 12 to 16 months, at which point approximately two-thirds of the original bone mass is close to the threshold for pathologic fractures. Hypercalcemia and hypercalciuria resulting from increased bony resorption may increase the risk of nephrolithiasis. Women are at greater risk of osteoporosis following SCI.

Supplementation with calcium and vitamin D is a cost-effective and easily implemented method of addressing bone loss. Physical exercise (weight-bearing activities,
verticalization, and aided-walking systems) has been shown to have an osteogenic influence in healthy subjects and in those with SCI. Functional electrical stimulator–induced mechanical loading has also been shown to conserve bone density, but this benefit is seen only if it is started as early as possible following spinal cord damage (less than 6 months postinjury). Bisphosphonates and salmon calcitonin are potentially beneficial therapies.339

Vitamin D Deficiency

Vitamin D deficiency is commonly found in patients with both acute and chronic SCI.342 It may lead to elevated parathyroid hormone levels that subsequently increase
bone loss.\textsuperscript{343} Aside from its role in osteoporosis, Vitamin D is important in the immunopathogenesis of TM.

Low vitamin D levels have been linked to TM\textsuperscript{344} as well as various autoimmune disorders, including MS,\textsuperscript{345,346} SLE,\textsuperscript{347} and AS.\textsuperscript{348} In MS, suboptimal vitamin D levels increase the relapse rate as well as the risk of developing the disease. Interestingly, low vitamin D levels have been shown to correlate with an increased risk for recurrent TM.\textsuperscript{349,350} The immunologic role of vitamin D is fascinating but remains unclear. Reductions in proinflammatory agents, such as interleukin (IL)-6, IL-1-beta, gamma-interferon, and IL-17 have been observed with vitamin D supplementation.\textsuperscript{351,352} Optimal vitamin D levels have been shown to suppress Th17-mediated autoimmunity\textsuperscript{353} and augment T-cell regulatory cell populations, providing a putative mechanism for preventing autoimmunity.\textsuperscript{354}

Factors contributing to vitamin D deficiency include inadequately dietary intake and sun exposure. The primary source of vitamin D in humans is sunlight.\textsuperscript{355} TM-related complications, including immobility and thermodynamics, as well as photosensitivity in some autoimmune disorders, limit sunlight exposure. Many patients also harbor the misconception that consuming foods with calcium and vitamin D causes nephrolithiasis.\textsuperscript{342} The use of hepatically metabolized anticonvulsants to treat various complications of TM further exacerbates vitamin D deficiency.\textsuperscript{356}

The “normal” value of 25-hydroxyvitamin D levels remains 10 to 20 ng/mL in many institutions and commercial laboratories.\textsuperscript{342} Unfortunately, recommendations about vitamin D intake from health agencies lags behind developments in the field.\textsuperscript{357} An amount of 5000 IU per day has been shown to reduce the number of MS relapses\textsuperscript{358} and intakes up to 10,000 IU per day appear safe.\textsuperscript{359} Vitamin D3 appears superior to vitamin D2\textsuperscript{360} and is available at all retail pharmacies in the United States for a low price. Patients seen at the neuroimmunologic disease clinic at our institution are encouraged to take between 5000 and 10,000 IU of vitamin D3 daily to achieve serum levels of between 60 and 80 ng/mL.

Adequate vitamin D levels have several other notable benefits, including a decreased risk of breast and colon cancer,\textsuperscript{361,362} improved muscle strength,\textsuperscript{363} decreased frequency of falls,\textsuperscript{364} and diminished musculoskeletal pain.\textsuperscript{365}

**Psychological Considerations**

In patients presenting for the first time with TM, consultation with a clinical psychologist or psychiatrist is valuable in addressing its understandably devastating impact on the patient’s QOL. Indeed, a recent study found that almost 90% of parents of children with TM perceive a need for psychiatric care but only a quarter receive it.\textsuperscript{277} The loss of functional independence, along with sphincter and sexual dysfunction, would be expected to negatively affect the patient’s psychological constitution and adversely affect future expectations. Mood disorders and emotional changes following TM may also be a consequence of the pathobiological changes engendered by the underlying disease process. Mood disorders, fatigue, and cognitive impairment are well-recognized sequelae of MS and autoimmune disorders like BD, SS, and SLE.\textsuperscript{56,102,103,105,366} Additionally, certain immunomodulatory drugs (eg, interferon-beta) may cause depression.\textsuperscript{367}

Recognition of the neuropsychiatric symptoms associated with TM is important because it affects the patient’s QOL. Formal neuropsychological testing may help identify the mood disorder or cognitive domain(s) affected. Consultation with a clinical psychologist and/or psychiatrist is useful in deciding if the patient can be managed with counseling, psychotherapy, group therapy, and/or pharmacotherapy. Cognitive
dysfunction may be treated with memantine or anticholinesterase inhibitors like donepezil.297

SUMMARY

TM constitutes a pathobiologically heterogeneous syndrome, with immune-mediated, inflammatory damage of the spinal cord at its core. A detailed history and thorough physical examination are indispensible. The most important investigation to undertake is an MRI of the entire spinal axis and the brain. The location and length of the lesion are important discriminators with etiologic and prognostic significance.

APTM is commonly attributable to MS. Although LETM is characteristic of NMO, longitudinally extensive lesions may occur in other diseases as well. The brain MRI and CSF OCBs are powerful predictors of conversion to MS. NMO-IgG seropositivity has a high specificity for NMO.

The epidemiologic, clinical, radiologic, and longitudinal data seen in pediatric TM suggests that the pathobiological underpinnings are distinct from TM in the adult population. As such, caution should be exercised when applying findings from studies in the adult population to children and vice versa.

Although the application of set criteria for diagnosing ITM has resulted in a fairly homogeneous group of patients (clinically and radiologically), it remains possible that recurrent ITM represents a unique disease entity. More longitudinal studies are needed to elucidate the nature of recurrent ITM.

REFERENCES


