Acute Transverse Myelitis: Demyelinating, Inflammatory, and Infectious Myelopathies

Timothy W. West, M.D. [1] Christopher Hess, M.D., Ph.D. [2] Bruce A. C. Cree, M.D., Ph.D., M.C.R. [3]

[1] Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, Nevada
[2] Division of Neuroradiology, UCSF Department of Radiology and Biomedical Imaging, San Francisco VA Medical Center, San Francisco, California
[3] Division of Clinical Neurology, Department of Neurology, Multiple Sclerosis Center, University of California, San Francisco, California

Address for correspondence and reprint requests Timothy W. West, M.D., Lou Ruvo Center for Brain Health, Cleveland Clinic, 888 W Bonneville Ave., Las Vegas, NV 89106 (e-mail: westt3@ccf.org).

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Abstract

Acute transverse myelitis is a rare neurologic condition that has an estimated incidence of up to 3 per 100,000 patient years (0.003%). Although rare, acute transverse myelitis can have devastating neurologic effects with up to two-thirds of patients having a moderate to severe degree of residual disability. The term *acute transverse myelitis* was previously reserved for idiopathic cases, but currently is used to encompass the general clinical syndrome, whether or not the cause is known. Once adequate neuroimaging has ruled out a compressive etiology, and a lumbar puncture has demonstrated signs of inflammation within the cerebrospinal fluid, a workup of causes for an acute transverse myelitis must be undertaken. Determining the etiology of transverse myelitis can be challenging because there are autoimmune, inflammatory, and infectious diseases associated with acute transverse myelitis. The authors discuss an approach to acute transverse myelitis including clinical symptoms, neuroimaging, and biomarkers that may aid the clinician in diagnosis.

Keywords
- myelitis
- myelopathy
- demyelinating
- inflammatory

Epidemiology

Acute transverse myelitis has been estimated to have an incidence of 1.34 to 4.6 per million.[1,2] In a recent study from the Northern California Kaiser system, this rate was reportedly much higher at 3.1 per 100,000 patient years.[3] A recent study from New Zealand found the incidence of myelitis to be 24.6 (18.2–31.1, 95% confidence intervals) per million; however, this study included patients who had brain lesions found on magnetic resonance imaging (MRI) consistent with multiple sclerosis (MS) as well as patients presenting with partial myelitis.[4] After excluding patients whose MRI scans were consistent with MS and patients with partial myelitis, the incidence of idiopathic acute transverse myelitis was estimated to be 6.2 (2.9–9.6, 95% confidence intervals) per million.

There seems to be no familial or ethnic predisposition for acute transverse myelitis and there is no evidence of geographic variation in its incidence.[5] Two recent studies did find a higher incidence in females,[3,6] but an important caveat to one of these studies is that the proportion of cases that later were diagnosed as multiple sclerosis (MS) was not specified.[3] MS is known to be more common in women and if a significant proportion of the cases were later diagnosed with MS, this may partially explain the higher incidence rate.[5]

Based on two older case series of acute transverse myelopathy, it was estimated that approximately one-third of patients recover with little to no sequelae, another one-third retain a moderate degree of residual disability and one-third remain severely disabled.[1,7,8] In one of these case series, 17 out of 62 patients failed to improve, including three who died.[1] In a recent large cohort of 170 patients with a heterogeneous mix of acute and subacute myelopathies, 38.2% ($n = 65$) had a poor recovery with 8.8% ($n = 15$) deaths.[9] This case series included 25 patients with spinal cord infarction, seven of whom died. In a more recent case series of 45

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patients with idiopathic transverse myelitis, there was one death and 15 (33%) had a poor outcome with an inability to walk at 3 months of follow-up.[10] Prognostic indicators that may portend a poorer outcome in acute transverse myelitis include rapid progression of symptoms, back pain, and spinal shock, as well as absent central conduction on somatosensory evoked potential testing.[7,10]

Clinical Presentations of Acute Transverse Myelopathy

Acute transverse myelopathy can present in a variety of ways and involve pyramidal, sensory, and autonomic dysfunction to varying degrees. The pattern of functional loss can help determine the etiology of the injury. A complete loss of spinal cord function may be due to trauma, an acute compressive lesion (abscess, hematoma or tumor), or an acute necrotizing myelitis.[11] Isolated dorsal column involvement may be associated with Vitamin B_{12} deficiency, copper deficiency, and nitrous oxide toxicity (►**Fig. 1**).[12] In contrast, an anterior spinal cord syndrome with acute flaccid weakness, loss of pain and temperature sensation but preserved dorsal column dysfunction, may be caused by an anterior spinal artery occlusion (►**Fig. 2**). Isolated tract involvement other than the dorsal columns may suggest a paraneoplastic etiology.[13]

A central cord lesion can present as pyramidal distribution weakness below the level of the lesion, autonomic dysfunction and spinothalamic deficits and may be due to a syrinx or possibly neuromyelitis optica.[11] Brown-Sequard syndrome is due to a unilateral lesion involving the hemicord that presents as ipsilateral corticospinal and dorsal column dysfunction with contralateral spinothalamic deficits and may be due to

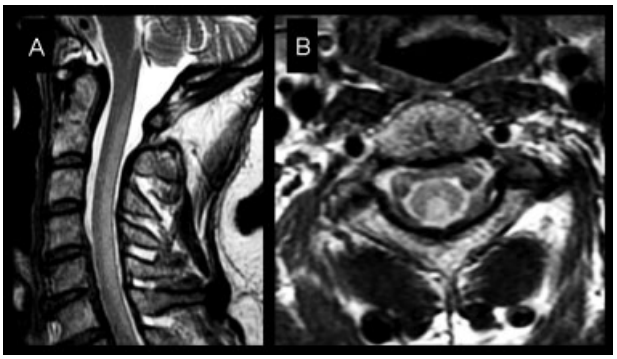

Figure 1 Vitamin B12 deficiency. A woman presents with tingling and cramping sensations in both arms and legs, and low serum B12. Sagittal (A) and axial (B) T2-weighted magnetic resonance images show well-defined, confluent T2-signal abnormality in the dorsal cervical cord without cord expansion.

MS or a compressive etiology.[11] Another more rare presentation that is suggestive of MS is the sensory "useless hand of Oppenheim" phenomenon. This presents as a functionally useless hand with fairly intact motor function and is usually caused by a lesion in the posterior column of the cervical cord leading to a deafferented hand.[14] Cauda equina syndrome presents as flaccid weakness in the lower extremities (that is often asymmetric at presentation), sensory loss in a nerve root distribution, and possibly autonomic involvement resulting in loss of bowel and bladder control. This syndrome can be caused by a viral or bacterial polyradiculitis, but is often associated with a compressive lesion requiring emergent surgical intervention. A conus medullaris injury presents

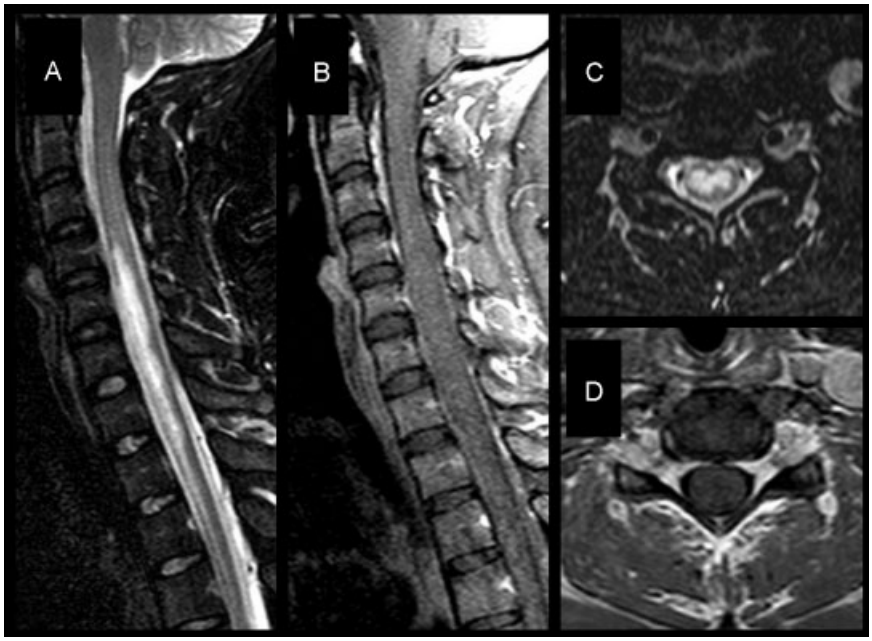

Figure 2 Anterior spinal artery infarct. This is a 33-year-old woman with acute onset of quadriparesis. Sagittal short T1-inversion recovery (STIR) (A) and fat-suppressed gadolinium-enhanced T1-weighted magnetic resonance images (MRIs) (B) show confluent signal abnormality spanning from C4–T1, without corresponding enhancement. Axial STIR (C) and axial gadolinium-enhanced T1-weighted MRIs (D) show signal largely confined to gray matter, with preservation of the normal flow voids within the codominant vertebral arteries.

as early sphincter dysfunction, sacral sensory loss, and relatively mild motor deficits.

Initial Diagnostic Evaluation

Although the clinical presentation of acute myelopathy will lead the clinician to recognize that the spinal cord has sustained injury, the signs and symptoms of myelopathy do not provide insight into etiology and the differential diagnosis is broad (►**Table 1**). When faced with acute myelopathy, the first step in the diagnostic workup is to evaluate for a compressive or structural etiology. MRI with gadolinium contrast should be obtained without delay; however, if an MRI cannot be obtained emergently, computed tomography (CT) myelography is a reasonable alternative. The main disadvantage of this imaging modality is the limited ability to visualize the spinal cord.[7] Determining the region of the spinal cord to image based on clinical features in some cases can miss a compressive lesion just superior to the field of imaging that could be surgically decompressed.[15] This is especially the case if the suspected lesion is near the cervicothoracic or thoracolumbar junction because cord lesions can cause clinical deficits that localize to a lower spinal cord segment. For this reason, it is always best to image the region where the clinical signs and symptoms localize, as well as the superior spinal cord, possibly using a sagittal survey. It is important not to miss a compressive myelopathy as this can, and ought to be treated by emergent surgical decompression.[16]

Once neuroimaging has excluded a compressive etiology, the next step in the diagnostic workup is a lumbar puncture (LP) to determine if there are signs of inflammation within the cerebrospinal fluid (CSF). If the CSF is noninflammatory, then vascular, toxic/metabolic, neurodegenerative, or neoplastic myelopathies become much more likely and the subsequent workup should focus on these etiologies. If the

Table 1 Differential Diagnosis of Noninflammatory Myelopathy[125,126]

Traumatic/compressive	*Toxic/metabolic*
Trauma (fracture or central cord syndrome)	Vitamin deficiency (B12, B1, E, folate)
Disk herniation	Nitrous oxide abuse
Cervical spondylosis with stenosis	Abetalipoproteinemia
Epidural abscess or hematoma	Medication induced (amiodarone,
Extramedullary and extradural tumors	methotrexate, amphotericin, etc.)
Cyst (synovial or arachnoid)	Organophosphates
Congenital spinal stenosis	Konzo (cassava ingestion)
Posterior longitudinal ligament ossification	Lathyrism (legume ingestion)
Epidural lipomatosis	Heroin/hepatic myelopathy
Arnold-Chiari malformation	Fluorosis
Rheumatoid arthritis or ankylosing	*Neoplastic*
Spondylitis associated subluxation	Lymphoma (Primary CNS or metastatic)
Osteomyelitis	Glioma
Paget's disease	*Vascular*
Diffuse idiopathic skeletal hyperostosis	Thromboembolic infarct
Extramedullary hematopoiesis	Arteriovenous (AV) fistula
Hereditary/neurodegenerative	Fibrocartilaginous embolism
Spinocerebellar ataxia	Hypoperfusion injury
Spinal Muscular atrophy	Prothrombotic disorders (infection,
Hereditary spastic paraplegia	neoplasm, vasculitis, DIC, etc.)
Friedrich's ataxia	Arteriovenous malformation
Leukodystrophies	Decompression sickness (Caisson's disease)
Motor neuron disease (ALS, PLS)	*Other*
Mitochondrial	Syringomyelia
Krabbe's disease	Radiation myelopathy
	Superficial siderosis
	HIV vacuolar myelopathy

ALS, amyotrophic lateral sclerosis; CNS, central nervous system; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; PLS, primary lateral sclerosis.

CSF shows signs of inflammation (pleocytosis, elevated protein concentration, oligoclonal bands, or elevated IgG index), then the subsequent workup should focus on demyelinating, infectious, or other inflammatory causes of acute myelitis.

Differential Diagnosis of Inflammatory Myelopathies

Transverse myelitis typically presents acutely, however, subacute presentations are also described (►**Table 2**).[7,17] In acute transverse myelitis, symptoms typically develop over hours to days and then worsen over days to weeks. The first symptoms are often paresthesias ascending from the feet, or back pain at the level of the myelitis coupled with weakness and sphincter dysfunction.[18] Motor, sensory, and autonomic pathways are injured resulting in weakness and sensory disturbance below the level of the lesion. Autonomic involvement is also common and can manifest as paroxysms of hypertension and sweating, urinary retention, bladder incontinence, and loss of bowel function.[5,18] The term *transverse myelitis* is somewhat misleading in that the deficits are not necessarily bilateral. The term was first used in a case report of myelitis complicating a pneumonia.[19] The addition of the term *transverse* reflected the common clinical finding that patients reported a "band like" horizontal area of altered sensation on the neck or torso.[20] It did not refer to the breadth or extent of spinal cord involvement on pathology or imaging studies.

Additional symptoms, signs, and aspects of the patient's history may suggest an infectious etiology. For example, the presence of fever, meningismus, rash (zoster, enterovirus), concurrent systemic infection (e.g., pneumonia or diarrheal), an immunocompromised state (herpes zoster, cytomegalovirus), a history of recent travel (tuberculosis, parasitic infections), recurrent genital infection (herpesvirus), radicular burning pain with or without vesicles suggestive of zoster radiculitis, or adenopathy may suggest specific infectious etiologies.[7,17] Infectious etiologies of myelitis can be viral, bacterial, fungal, and rarely parasitic. It is always important to consider treatable infections such as syphilis, herpesviruses, human immunodeficiency virus (HIV), and tuberculosis.[17]

Table 2 Differential Diagnosis of Acute Transverse Myelitis[11,18]

Demyelinating	***Viral–herpes viruses (DNA)***
Multiple sclerosis*	Herpes simplex virus type-2 (HSV)*
Neuromyelitis optica*	Varicella-zoster virus (VZV)*
Idiopathic transverse myelitis*	Cytomegalovirus (CMV)*
Acute disseminated encephalomyelitis (ADEM)*	Epstein-Barr virus (EBV)
Postvaccinal*	***Viral–paramyxoviruses (RNA)***
Inflammatory/Autoimmune	Measles
Systemic lupus erythematosus (SLE)*	Mumps
Primary Sjögren's syndrome*	***Viral–orthomyxoviruses (RNA)***
Neurosarcoidosis	Influenza A virus (including H1N1)
Behçet's disease	***Viral–picornaviruses (RNA)***
Mixed connective tissue disease (MCTD)	Coxsackie viruses A and B
Systemic sclerosis	Enterovirus-70 and 71
Paraneoplastic	Echoviruses
Anti-amphiphysin (breast carcinoma)	Hepatitis A and C
Anti-CRMP-5 (small cell lung cancer)	Poliovirus 1, 2, and 3
Bacterial	***Viral–flaviviruses (RNA)***
Treponema pallidum (Syphilis)	West Nile virus
Mycobacterium tuberculosis (TB)	Japanese encephalitis virus
Borrelia Burgdorferi (Lyme)	Tick-borne encephalitis virus
Fungal	St. Louis encephalitis virus
Actinomyces	Dengue virus
Coccidioides immitis	***Parasitic***
Aspergillus	Neurocysticercosis
Blastomyces dermatitidis	Schistosoma
	Gnathostoma angiostrongylosis

*Indicates common causes for transverse myelitis.

The most commonly implicated viruses are varicella zoster (VZV), enteroviruses, herpes simplex type-2 (HSV-2), and cytomegalovirus (CMV).[11]

Similarly, the presence of other findings on general physical examination may suggest a systemic autoimmune disease, such as systemic lupus erythematosus (SLE), Sjögren's syndrome, antiphospholipid antibody syndrome (APLS), sarcoidosis, or mixed connective tissue disease (MCTD). Sign and symptoms of a systemic autoimmune disease include dry eyes, dry mouth, malar or discoid rash, oral or genital ulcers, arthritis, synovitis, Raynaud's phenomenon, sclerodactyly, uveitis, or lung or kidney disease. The association of myelitis with collagen vascular diseases underscores the need for a detailed history and examination (both general and neurologic), including a full review of systems when evaluating a patient with transverse myelitis.

Within demyelinating and inflammatory myelopathies, the differential diagnosis includes MS, neuromyelitis optica (NMO), other systemic inflammatory diseases (SLE, Sjögren's disease, sarcoidosis), idiopathic transverse myelitis, acute disseminated encephalomyelitis, and postvaccinial myelitis.

Neuroimaging

Once the MRI excludes compressive etiology (►**Table 1**), a closer look at the imaging may further assist in narrowing the differential diagnosis, particularly the appearance and pattern of the lesion(s). ►**Table 3** describes the imaging patterns associated with some of the more common causes of acute transverse myelitis. Following review of the spinal imaging, a brain MRI should be performed to determine if other demyelinating lesions within the central nervous system (CNS) are present.[7] Patients with MS and NMO are much more likely to have lesions on the brain MRI. In addition, MS-associated spinal cord lesions tend to be asymmetric, peripherally located within the cord axis and tend to extend over fewer than two spinal cord segments (►**Fig. 3**).[7,12] Patients with NMO are more likely to have lesions that extend over three or more spinal cord segments and tend to be centrally located.[12] Approximately 25% are associated with cord swelling,[21] and may have patchy gadolinium enhancement (►**Fig. 4**).[22]

Cerebrospinal Fluid Studies

CSF is an essential component of the evaluation of every patient with suspected myelitis. After measuring the opening pressure, it is essential that routine CSF studies include cell count with differential, protein, and glucose concentrations. In addition, measurements of intrathecal immunoglobulin synthesis with oligoclonal bands and an IgG index or synthesis rate (►**Table 4**). This requires drawing a serum sample at the time of the lumbar puncture for comparative analysis of gammaglobulin and should be performed on every patient with suspected myelitis. In addition, cytology for evaluation of neoplasm should be included. The evaluation of common infectious causes of myelitis includes the Venereal Disease Research Laboratory test, and polymerase chain reaction (PCR) studies for VZV, HSV-2, CMV, EBV, West Nile virus, and tuberculosis (►**Table 5**). In addition, bacterial, fungal, and acetate-free biofiltration cultures should be considered. Lyme disease rarely causes an encephalomyelitis, and more typically causes a lymphocytic meningitis, cranial neuritis, and/or polyradiculitis. One milliliter of acellular supernatant should be sent for interleukin-6 (IL-6; see section on biomarkers). Lastly, several ccs of frozen CSF sample should be reserved for additional PCR studies. As in neuroimaging, certain CSF patterns or findings may be helpful in narrowing the differential diagnosis.

A low CSF glucose concentration (less than 60% of serum glucose) generally suggests an infection (fungal, bacterial, or mycobacterial), especially when associated with an elevated CSF white blood cell count (WBC). However, an isolated low CSF glucose concentration can occur in neurosarcoidosis, leptomeningeal carcinomatosis, subarachnoid hemorrhage, and even systemic lupus erythematosus (SLE) with CNS involvement.[23] An elevated protein concentration is the most common CSF abnormality in patients with spinal cord disease and is present in ~50% of patients with transverse myelitis.[24] An elevated CSF protein concentration is associated with spinal cord tumors, paraneoplastic myelopathies, radiation myelopathies, vascular malformations, infection, syringomyelia with spinal block, and spinal cord trauma.[23] Elevation in the CSF WBC count defines inflammatory myelitis. The WBC differential can be very helpful in understanding whether an infectious or autoimmune process is the etiology. The presence of eosinophils can suggest NMO,[25] parasitic or fungal infection, or the presence of a foreign material, such as surgical hardware following a spinal operation. The presence of neutrophils in the CSF (especially a predominance) is highly suggestive of bacterial or mycobacterial infection, but can also be seen in sarcoidosis, NMO, or other autoimmune causes of transverse myelitis, as well as acute viral infections.[26] The presence of eosinophils in the CSF, >5% neutrophils in the CSF, or a pleocytosis of >50 cells/cm^3 is atypical for MS, and increases the suspicion for other diagnoses.[27] If infection is likely, the use of CSF cultures and PCR analysis is invaluable for identifying the cause. ►**Table 5** shows some of the common tests that are sent, including their reported sensitivity and specificity.

The presence of two or more OCBs in the CSF that are not found in the corresponding serum sample is considered indicative of intrathecal synthesis of gammaglobulin. OCBs are present in >95% of patients with clinically definite MS,[28] and can be a confirmatory test for this diagnosis once systemic inflammatory and infectious etiologies have been excluded. This is not the case at an initial demyelinating event, otherwise known as clinical isolated syndrome (CIS). When a patient presents with CIS (including a transverse myelitis), the rate of OCB positivity may be closer to 50 to 60%.[29] That being said, although not confirmatory, the presence of OCBs has been shown to confer up to a 1.7 increase in risk of developing clinical definite MS over 4 years (hazard ratio = 1.7; confidence interval = 1.1–2.7) that is independent of the baseline MRI findings.[29] In a study of 112 patients with CIS, the presence of OCBs showed a sensitivity of 81% with a specificity of 43% in predicting conversion to clinically

Table 3 Imaging in Acute Myelitis

Etiology of Myelitis	Location	Lesion Length	Pattern of T2 Involvement	Pattern of Contrast Enhancement	Cord Swelling (Enlargement)	Other Characteristics
MS	60–75% cervical[22]	≤2 cord segments[12]	Peripheral, ovoid, paracentral[7,12,22]	~15% of cord plaques enhance[127]	Atypical (atrophy more common)[22]	>50% have multiple lesions,[22] of which ~50% are clinically silent.[127]
NMO	~80% cervical[32]	≥3 cord segments[12]	Centrally located,[12] but can be dorsal[32]	Patchy[22]	~25%[21]	~25% will have an average of 3–4 brain lesions.[32]
Idiopathic TM	Usually thoracic[22]	≥3 cord segments[22]	Diffuse, patchy or peripheral[22]	Variable (diffuse, patchy, peripheral)[22]	Variable[22]	Many infectious etiologies have same profile (diagnosis of exclusion).
ADEM	Usually thoracic[114]	Variable	Multifocal flame-shaped,[22] can be large[128]	Variable[128]	Common[128]	Myelitis occurs in 11–28% of cases[89] meningeal enhancement is unusual.[128]
Sarcoidosis	Cervical ≈ thoracic[81]	Variable	Central (62%) > anterior, lateral, posterior[81]	Usually patchy, but can be (diffuse, nodular, multifocal, leptomeningeal)[22,81]	Up to 35%[81]	May involve the intradural nerve roots. Thickening of the roots may occur.[76] About 25% with >1 lesion[81]
VZV	Usually thoracic[129]	Variable	Typically posterior[129]	Patchy or focal at dermatomal level[22]	Common[22,129]	Enhancement may involve the dorsal root.[22]
CMV	Cauda equina and conus medullaris[22]	Variable	Thickened cauda equina[130]	Leptomeningeal, dorsal root and diffuse nerve enhancement[130]	Can cause a focal space occupying lesion[130]	Usually a polyradiculitis[22]
HSV		Variable	Can be >1 lesion[131]	Diffuse[22]	Can occur[22]	HSV-2 >> HSV-1 causes myelitis. Can have associated hemmorhage.[131]
Poliomyelitis		Variable	Increased signal in anterior horns[22]	Anterior horns[133]	Focal[133]	Can also be seen in postvaccinal poliomyelitis,[132] West Nile virus,[134] enterovirus-71[135]
Paraneoplastic		Variable[136]	Variable, can be holocord,[136] or highly specific symmetric tract involvement[13]	Patchy[136]		Antiampiphysin[13]

CMV, Cytomegalovirus; HSV, Herpes simplex virus; MS, multiple sclerosis; NMO, neuromyelitis optica; TM, transverse myelitis; VZV, varicella-zoster virus.

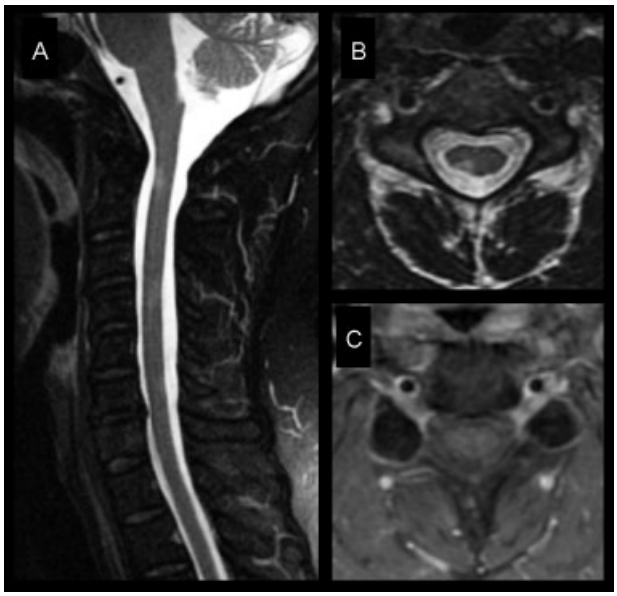

Figure 3 Multiple sclerosis. Sagittal (A) and axial (B) T2-weighted magnetic resonance images in a patient with clinically definite multiple sclerosis, without enhancement on gadolinium-enhanced T1-weighted images (C). Note the sharply marginated, short-segment plaque that is peripherally located within the cord axis and predominantly located within the white matter of the cervical spinal cord. The patient also had multiple plaques in the periventricular white matter (not shown).

definite MS with a mean follow-up of 31 months. Within that same cohort, the fulfillment of Barkhof criteria on brain MRI showed a sensitivity of 65% and a specificity of 70%.[30] A smaller cohort of 70 patients with MS-appearing demyelinating lesions on MRI, but no clinical manifestation (radiologically isolated syndrome) found that the presence of OCBs was only statistically significant in predicting conversion to CIS when associated with nine or more T2-hyperintense lesions on the first MRI.[31]

It is important to note that the presence of intrathecal synthesis of OCBs can be found in other conditions that cause inflammation in the CNS, including NMO,[32] paraneoplastic disorders, SLE, neurosarcoidosis, Behçet's disease, various forms of cerebral angiitis, and many CNS infections.[33] In patients with NMO, OCBs are positive in as many as 24 to 34% of cases.[21,32] Given these caveats, "it should be emphasized that the finding of oligoclonal bands by isoelectric focusing... reaches its maximal value in differential diagnosis only when other known causes of CNS inflammation have been excluded."[28]

The immunoglobulin G (IgG) index is calculated by the following equation: IgG Index = (CSF IgG/albumin)/(serum IgG/albumin). This ratio generally falls between 0.3 and 0.6 for normal patients depending on the laboratory. Like oligoclonal bands, this test assesses an abnormal intrathecal humoral response. Among MS patients, the IgG index is elevated 70 to 80% of the time.[28] Similar caveats to the interpretation of OCB also hold for interpreting the IgG index. Accurate calculation of the IgG index requires that the CSF sample not be contaminated by a significant amount of blood caused by a traumatic LP.

CSF IL-6 has been described as a biomarker to help predict disability in acute transverse myelitis. In a study that examined the CSF from six patients with acute transverse myelitis, all six patients showed a dramatic elevation in IL-6 levels.[34] Furthermore, a strong correlation between CSF IL-6 obtained

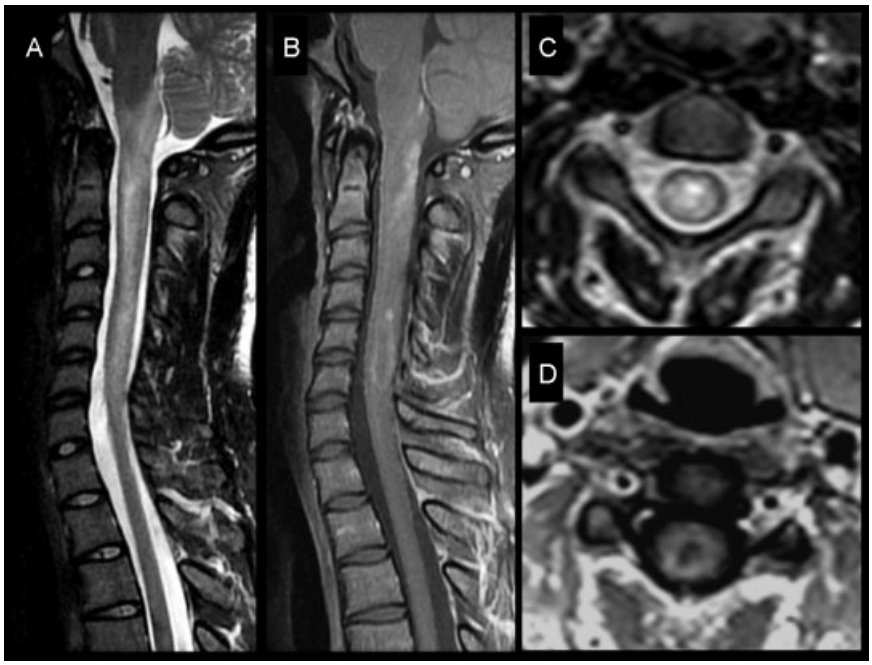

Figure 4 Neuromyelitis optica. Magnetic resonance images shown include sagittal T2 (A), sagittal gadolinium-enhanced T1 (B), axial T2 (C), and axial gadolinium-enhanced T1 (D). Longitudinally extensive T2 signal abnormality in the cervical cord (A,C), accompanied by patchy intramedullary enhancement on gadolinium-enhanced T1-weighted imaging (B,D). The patient subsequently developed monocular vision loss and was found to have a positive neuromyelitis optica antibody.

Table 4 Cerebrospinal Fluid (CSF) Studies Necessary for Evaluation of Possible Acute Transverse Myelitis

CSF Studies	Amount of CSF	Method	Special Considerations
Cell count with differential	1 mL	1. Hemocytometer for count 2. Wright-stained cytocentrifuge preparation for differential	CSF specimens should be transported at ambient temperature as soon as possible after collection. Cellular degeneration of CSF can begin within 1 h of collection.
Glucose	0.5 mL	Spectrophotometric (glucose oxidase)	Measure the serum glucose as well. CSF levels are usually >55% of serum glucose and >40 mg/dL. As serum glucose rises above 200 mg/dL the CSF/serum ratio falls from ~0.55 to a minimum of 0.31. Sample can be stable for up to 10 d if refrigerated.
Total protein	0.5 mL	Spectrophotometric (pyrogallol red)	Sample can be stable for up to 10 d if refrigerated.
Oligoclonal bands (OCBs)	2 mL (and 2 mL of blood)	Isoelectric focusing with immunoblotting,[137,138] preferably with antihuman IgG labeled with alkaline phosphatase.[139]	It is important to include a serum sample to test in parallel with the CSF. If serum collected the same day as the CSF is unavailable, a sample collected within 72 h of the CSF is acceptable. Isoelectric focusing is superior to immunofixation with sensitivity for detecting OCBs in excess of 95%.[137,138]
IgG Index	1 mL (and 1 mL of blood)	Rate nephelometry[140]	As with OCB, a serum sample must accompany the CSF sample. A bloody contamination of CSF due to a traumatic lumbar puncture can significantly elevate the IgG index.

Table 5 Infections Associated with Acute Myelitis and the Utility of Biomarkers Used in the Diagnosis of Their Most Commonly Associated Infections and Clinical Syndromes

	Sensitivity	Specificity	Associated CNS Infection
CSF Studies			
VDRL	71%	99%	Neurosyphilis[141]
Enterovirus PCR	>90%		Aseptic meningitis[142]
Herpes simplex virus (HSV-1) PCR	98%	94%	Encephalitis[143]
Herpes simplex virus (HSV-2) PCR	100%*	99%*	
Varicella Zoster Virus (VZV) PCR	80%*	98%*	Varied CNS infections (including myelitis)[144]
Cytomegalovirus (CMV) PCR	82–100%*	89–100%*	Encephalitis or polyradiculitis[142]
Epstein-Barr virus (EBV) PCR	88–100%*	89–100%*	Primary CNS lymphoma[142]
Serologic assays			
Rapid plasma reagin (RPR)	75%	99%	Neurosyphilis[141]

CNS, central nervous system; CSF, cerebrospinal fluid.
*Among human immunodeficiency virus-positive patients.

at the time of acute clinical evaluation and long-term disability was observed.[34] IL-6 levels in peripheral blood mononuclear cells were assessed in a larger cohort ($n = 50$, 37 with MS and 13 with acute transverse myelitis) and compared with healthy controls ($n = 16$). Mononuclear cell IL-6 levels were increased in patients with acute transverse myelitis relative to healthy controls and those with MS.[35] Another study found that CSF IL-6 levels in patients with NMO or acute transverse myelitis were significantly higher than those with optic neuritis, MS, and normal controls.[36] Furthermore, the CSF IL-6 levels correlated with disease severity of NMO patients.[36] Taken together,

these studies demonstrate that IL-6 levels can be very useful for distinguishing inflammatory from noninflammatory myelopathies and may be useful prognostically. For these reasons, CSF IL-6 should be measured in all patients presenting with acute transverse myelitis. Accurate measurement requires that the assessment be made prior to treatment with corticosteroids and that the assay be performed on an acellular CSF supernatant.

Serologic Studies

In the right clinical setting, serologic tests for autoimmune or inflammatory disease can help determine the underlying etiology of acute transverse myelitis. The NMO antibody (also known as anti-aquaporin-4 or NMO IgG) is a specific serum autoantibody that binds to the dominant CNS water channel protein aquaporin-4 (AQP4). The sensitivity of NMO-IgG is ~70% whereas the specificity approaches 100%.[37] This means that a seropositive result effectively establishes a diagnosis of NMO, or NMO spectrum disorder if the patient has not had a prior optic neuritis. However, because the sensitivity is ~70%, patients who test seronegative could still have NMO. Thus, a seronegative test for NMO-IgG does not rule out NMO. NMO remains a clinical diagnosis and although the NMO-IgG has improved diagnostic certainty, it is not required to establish the diagnosis.[38] Indeed, a recent publication of the largest NMO cohort to date (125 patients) showed that only 54% of patients tested seropositive for NMO IgG.[32] In addition, 5 to 10% of patients with MS may test seropositive for NMO-IgG,[39] and this antibody has been associated with other autoimmune disorders, including SLE, Sjögren's syndrome,[40,41] systemic sclerosis,[42] Hashimoto's thyroiditis,[43] and in paraneoplastic myelopathy.[44]

One useful application of this assay is to identify patients with a longitudinally extensive myelitis (LETM) who are at risk for recurrent myelitis or optic neuritis. A study of 29 patients found that 38% of patients ($n = 11$) presenting with a first-ever attack of LETM were seropositive for NMO-IgG.[45] Of the 23 that were followed up for at least one year, 55% (5 of 9) of the seropositive patients experienced a relapse of either transverse myelitis or optic neuritis during the 12-month period following their presenting attack. In contrast, none (0 of 14) of the NMO IgG-seronegative group experienced a second attack of any type over the same follow-up period.[45] Another autoimmune associated antibody, the anti-SS-A (Ro) antibody, also was associated with acute transverse myelitis and also has some mild predictive value for a relapsing myelitis course.[46] In a small retrospective study, 10 of 13 patients with recurrent myelitis were seropositive for the anti-SS-A (Ro) antibody, compared with 4 of 12 control patients.[46]

When evaluating a patient with acute transverse myelitis, it is important to screen for other autoimmune disorders, especially if there are any clinical characteristics present that might suggest another autoimmune disease, such as Sjögren's syndrome (xerostomia, xerophthalmia), antiphospholipid antibody syndrome (history of venous thrombosis or multiple miscarriages), SLE (malar rash, arthritis, pericarditis, anemia, nephropathy), sarcoidosis (uveitis, pulmonary symptoms), or mixed connective tissue disease (arthralgias, malaise, Raynaud's phenomenon, Sjögren's syndrome, sclerodactyly, and myopathy). ►**Table 6** lists the common available laboratories and their associated conditions. In addition to these studies, a urinalysis with microscopic analysis for hematuria may also be warranted and depending on the clinical level of suspicion, lip/salivary gland biopsy, chest CT scan with intravenous (IV) contrast agent, and a Schirmer test should be considered.[7] From an infectious point of view, the only serologic tests recommended for routine screening are the serum rapid plasma reagin (RPR) and lyme antibodies (in patients with radiculitis) (►**Table 4**).[7]

Multiple Sclerosis

Although acute transverse myelitis can be the heralding event of MS,[47] MS typically presents with a partial myelitis (►**Fig. 3**), meaning that either sensory or motor symptoms will be present and that bowel and bladder function is not compromised at the time of the myelitis. MS myelitis patients are more likely to have asymmetric clinical findings with a particular predilection for dorsal column impairment. Clinical patterns of spinal cord impairment commonly present in MS include the Brown-Sequard syndrome, and the sensory useless hand of Oppenheim as described previously. Although complete versions of these syndromes can occur, more commonly in MS, incomplete versions of these syndromes are found.[11,48]

A clinical sign referable to the cervical spinal cord often associated with MS is the Lhermitte symptom: the sensation of paresthesias in the spine or limbs elicited by neck flexion. A Lhermitte symptom is present in ~41% of MS patients.[49] This finding is not specific to MS and can be present in compressive as well as inflammatory spinal cord injuries. For example, the Lhermitte symptom was present in 35% of NMO patients.[48,50]

Patients presenting with a monofocal, demyelinating syndrome, such as myelitis, whose brain MRI studies show at least one lesion consistent with demyelination have an 82% chance of meeting clinical criteria for MS over the subsequent 20 years compared with 21% of patients whose brain MRI is normal.[47] For patients presenting with acute myelitis, the most recent MS diagnostic criteria according to an international panel require only one additional brain lesion for the dissemination in space criteria and a simultaneous asymptomatic gadolinium-enhancing lesion for the dissemination in time criteria, to establish a diagnosis of clinically definite MS.[51,52] These studies underscore the importance of obtaining a brain MRI following acute transverse myelitis.

Neuromyelitis Optica

Patients presenting with simultaneous myelitis and optic neuritis should be evaluated for NMO; however, in the case of isolated acute transverse myelitis, some clinical clues can raise suspicion for NMO. Attacks of myelitis in NMO are more severe compared with MS and recovery is less complete.[48]

Table 6 Autoimmune and Inflammatory Diseases Associated with Acute Transverse Myelitis and the Utility of Common Biomarkers Used in Their Diagnosis

	Sensitivity	Specificity	Associated Diseases
CSF Studies			
Oligoclonal bands (performed by isoelectric focusing with immunoblotting)	>95%		MS[28]
	61%		CIS[29]
	24%		NMO[32]
Elevated IgG index	70–80%		MS[28]
Angiotensin converting enzyme (ACE)	24–55%	94–95%	Neurosarcoidosis[145]
Serologic assays			
Anti-aquaporin-4 antibody (NMO-IgG)	54–73%	91%	NMO[32,37]
Angiotensin converting enzyme (ACE)	~60%	80–95%	Sarcoidosis[83,84]
Antinuclear antibodies (ANA)	93%	57%	SLE[146]
	85%	54%	Systemic sclerosis[146]
	48%	52%	Sjögren's syndrome[146]
	44%		NMOSD[40]
Anti-double-stranded DNA (dsDNA)	66%	99.5%	SLE[147]
Anti-SSA (anti-Ro52)	63%		Sjögren's syndrome[148]
	35%		Myositis[148]
	19%		Systemic sclerosis[148]
	16%		NMOSD[40]
	5%		SLE[148]
Antiribonucleoprotein (when ANAs are also +)	34%	88%	SLE[149]
Anti-Smith (when ANAs are also +)	39%	84%	SLE[149]
Anti-scl70 (ELISA)	43%	90%	Systemic sclerosis[150]

CMV, Cytomegalovirus; CIS, clinical isolated syndrome; ELISA, enzyme-linked immunosorbent assay; HSV, herpes simplex virus; MS, multiple sclerosis; NMO, neuromyelitis optic; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus.

Furthermore, acute transverse myelitis associated with NMO usually affects bilateral motor and sensory pathways, often with near symmetry because the inflammatory attack affects most of the cross-sectional area of the cord.[50] Radiographically the lesions within the cord are usually longitudinally extensive extending over three or more spinal cord segments and tend to be centrally located (►**Fig. 4**).[12] Patients with recurrent LETM or recurrent optic neuritis are at risk for developing NMO and comprise an increasingly recognized group with an estimated prevalence as high as 1.5% of patients with demyelinating disorders in a recent retrospective review.[53] These patients are referred to as having an NMO spectrum disorder (NMOSD).[40,41]

A history of presentation with intractable hiccups or vomiting should raise suspicion for NMO. In one series, intractable hiccups occurred in 8 of 47 (17%) of cases with NMO compared with none of 130 patients with MS.[54] Another case series described 12 patients whose first symptom of NMO was intractable vomiting.[55] In this series, vomiting persisted for a median of 3 months prior to the onset of optic neuritis or acute transverse myelitis. On imaging, these symptoms are associated with involvement of the medulla oblongata affecting the area postrema and medial and lateral portions of the nucleus tractus solitarius.[55,56] Hiccups were seen in 23 of 35 patients (66%) and nausea was seen in 28 of 35 patients (80%). Intractable hiccups and nausea may portend a future exacerbation because these symptoms preceded an attack of NMO 54% of the time or accompanied an NMO attack 29% of the time.[54]

Another clinical symptom that can help distinguish MS from NMO is the presence of radicular pain, a symptom uncommon in MS that occurs in up to 33% of patients with NMO.[48,50] Paroxysmal tonic spasms may also suggest NMO because in one series these occurred in 35% of NMO patients during acute attacks of myelitis.[48,50] However, this symptom is generally associated with central demyelination and also occurs commonly in MS patients.

Idiopathic Acute Transverse Myelitis

In 2002, the Transverse Myelitis Consortium Working Group (TMCWG) proposed diagnostic criteria for idiopathic acute transverse myelitis based on expert opinion. The diagnostic criteria require clinical evidence of bilateral sensory, motor,

or autonomic dysfunction referable to the spinal cord, with a clearly defined sensory level that progresses to the nadir over 4 to 21 days from onset. Neuroimaging must eliminate structural etiologies. Evidence supporting an inflammatory etiology is also required either by MRI evidence of gadolinium enhancement within the cord or by CSF findings of pleocytosis or elevation of the immunoglobulin G (IgG) index. In addition, there must be no history of radiation near the spine for 10 years, no serologic evidence of connective tissue disease or infection, no brain MRI abnormalities consistent with multiple sclerosis, no history of optic neuritis, and no clinical evidence of an anterior spinal artery infarction. If all diagnostic criteria are met, this is considered to be definite idiopathic acute transverse myelitis. A diagnosis of possible idiopathic acute transverse myelitis can be made if the inflammatory criteria (MRI or CSF) are not met.[7] The intent of these criteria were to identify a relatively homogenous patient cohort for the purposes of forwarding research.[57]

When the Transverse Myelitis Consortium Working Group (TMCWG) proposed diagnostic criteria are applied to a cohort of patients with acute transverse myelitis, a relatively small proportion of patients meet criteria for idiopathic transverse myelitis. In one cohort of 288 patients with clinically diagnosed acute transverse myelitis, 45 patients (15.6%) met criteria for idiopathic transverse myelitis.[10] Another concern about these criteria is that despite these stringent, diagnostic criteria, some patients still go on to ultimately have another diagnosis. For example, in a retrospective study of 24 patients who met proposed TMCWG diagnostic criteria for acute transverse myelitis, and 21 patients who met diagnostic criteria for possible acute transverse myelitis, five patients (11%) developed MS during a mean follow up of 3.5 years.[58] In contrast, in a population-based study of acute transverse myelitis in New Zealand, 15 idiopathic acute transverse myelitis cases were identified by retrospective chart review using the definition of acute transverse myelitis developed by the TMCWG.[4] None of the 15 patients classified as definite or possible idiopathic acute transverse myelitis developed MS. Anti-AQP4 antibody serologic assessment was not available at the time this cohort was identified.

Systemic Lupus Erythematosus

Transverse myelitis is a rare but serious complication of SLE and has been estimated in rheumatologic reviews to occur in 1 to 2% of patients with SLE.[59–61] Over the past 10 years, several case series reported lupus patients with myelitis.[60–63] Aside from antinuclear antibodies (ANA), the most frequent antibody association reported with SLE myelitis is the antiphospholipid antibody that is positive in 43 to 73% among patients with myelitis.[60–62] However, the presence of antiphospholipid antibodies is not overrepresented in SLE patients with myelitis. Thus it is unclear if antiphospholipid antibodies have any pathologic role in SLE myelitis although some authors have speculated that antiphospholipid antibodies could cause venous infarcts resulting in thrombotic SLE myelopathy. In the most recent review of the case report literature of SLE-related myelitis, 22 patients with longitudinally extensive myelitis affecting four or more spinal segments were identified. In 23% of patients, myelitis was the first symptom of SLE. Among this group, 65% (11/17) were seropositive for anti-double-stranded DNA antibodies and 74% (14/19) had low levels of complement, whereas 60% (14/19) had both laboratory findings.[62] That myelitis can be a presenting manifestation of SLE was documented in a case series of 15 patients who all had systemic signs of SLE. At presentation only four of the 15 fulfilled the American College of Rheumatology criteria for SLE; however, 12 were confirmed as having SLE at follow-up, and the other three were described as having a "lupus-like disease."[61] In this case series, 54% of patients (6 of 11) were antiphospholipid antibody seropositive and all 15 were positive for ANA.[61]

The main caveat to interpreting the findings is that none of these case series assessed NMO-IgG antibody status. There is a well-established association between NMO and antibodies associated with SLE.[40,41] In a recent study including 78 patients with NMO, the ANA was positive in 52.6% of patients ($n = 41$) and antibodies to extractable nuclear antigens (primarily anti-Ro/SSA and anti-La/SSB) were positive in 16.7% of patients ($n = 13$).[40,41] A case series evaluating 22 patients with SLE myelitis found that 11 had gray matter involvement, whereas 11 had only white matter involvement. Of those with only white matter involvement, 54.5% (6/11) had an associated optic neuritis and 45.5% (5/11) met criteria for NMO. When the NMO-IgG antibody was tested, five of the 22 patients were seropositive.[63] In addition, 50% (11 of 22) fulfilled criteria for an NMO spectrum disorder defined as a syndrome recognized to have a high risk of conversion to NMO (including recurrent LETM or recurrent optic neuritis).[40,63]

Sjögren's Syndrome

The CNS manifestations of Sjögren's syndrome are controversial. In the 1980s, two case series suggested that Sjögren's syndrome could mimic MS.[64,65] One case series found that 10 of 60 patients with primary progressive MS (PPMS) met criteria for Sjögren's syndrome, suggesting that Sjögren's syndrome might be a mimic for PPMS.[66] This hypothesis later was challenged by the observation that in large MS datasets Sjögren's syndrome was not found.[67–69] A recent review of CNS manifestations of primary Sjögren's syndrome found that the reported prevalence ranges between 0 and 62%.[70]

The association between Sjögren's syndrome and myelopathy is clearer. A recent large case series of 82 patients found that 35% (29 of 82) had spinal cord involvement. Of these 29, one had a progressive myeloradiculitis, 12 had acute transverse myelitis, and 18 had a chronic myelopathy that mimicked PPMS in 13 patients.[71] Of the 12 patients who had acute transverse myelitis, two also had a concomitant optic neuritis suggesting NMO. Similar to the SLE myelitis literature, most case series of Sjögren's syndrome myelopathy did not test for the NMO IgG. Although the association between primary Sjögren's syndrome and MS remains unclear, there is a definite association between Sjögren's syndrome and NMO.[40,41,72–74] As mentioned above in the SLE section, of

78 patients with NMO, 78% were seropositive for NMO-IgG ($n = 61$), and of these, 3% met the international criteria for the diagnosis of SLE or Sjögren's syndrome.[40] Also, 53% were seropositive for ANA and 17% were positive for antibodies to extractable nuclear antigens (primarily anti-Ro/SSA and anti-La/SSB).[40,41]

Sarcoidosis

The largest review of sarcoidosis included 5092 cases reported in the medical literature from 1941–1972. Within this group, the incidence of CNS involvement in sarcoidosis was estimated to be ~5% of cases.[75] In this review only 17 patients of the 5092 (0.3%) had spinal cord involvement. This review was conducted prior to the MRI era. In a more recent series of 2894 patients with systemic sarcoidosis from the Mayo Clinic, 83 (2.9%) were found to have neurologic involvement.[76] Within this subset, 18% (15 of 83 patients) presented with myelopathy (0.5% overall; 15 of 2894). The most common presentation was chronic meningitis in 65% (54 of 83) of patients; thus, it is not surprising that the most common finding on MRI was leptomeningeal enhancement (►**Fig. 5**).[76] Of the patients with myelopathy, 63% had an abnormal MRI with the typical pattern of linear T2 signal abnormality and patchy enhancement. Additional radiographic features include subpial enhancement, enhancement and thickening of the cauda equina, and enlargement of the spinal cord with T2 hyperintensity but without enhancement (►**Fig. 5**).[76] Two recent smaller case series supported these findings with 13 to 18% of neurosarcoidosis patients experiencing myelopathy. In both of these case series, the most commonly affected cranial nerve was the optic nerve, which was affected in 25 to 35% of patients.[77,78]

If neurosarcoidosis is suspected, plain films of the chest may be useful because in these two recent case series, 50 to 60% of patients had chest x-ray findings suggestive of pulmonary or mediastinal sarcoid.[77,78] There is evidence that a chest CT is superior to plain films at detecting pulmonary disease (especially mediastinal adenopathy and parenchymal infiltration),[79,80] but a chest x-ray is still the screening imaging study of choice.[80] In the largest case series of spinal cord sarcoidosis to date, 55% ($n = 17$) had abnormal findings on their initial chest x-rays.[81] An additional seven patients had abnormal results on bronchial alveolar lavage despite normal chest x-ray and high-resolution chest CT studies. Only 11 patients had a gallium scan, and 45% ($n = 5$) had abnormal results. Lastly, on spinal cord MRI, this group showed various patterns of involvement (anterior, posterior, lateral, and panmedullar), but the most common pattern was central cord (62%; 13 of 21 patients).[81]

Additional tests that may help identify sarcoidosis include ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scans, ^{67}Ga scintigraphy (gallium) scans, serum and CSF angiotensin converting enzyme (ACE), the Kveim-Siltzbach test, and 24-hour urine calcium. A recent study of 20 patients with sarcoidosis tested the sensitivity of ^{18}F-FDG PET/CT scan versus gallium scan at identifying biopsy proven sites of active sarcoidosis. Overall, gallium scans were 58% sensitive at identifying these sites compared with 79% sensitivity with the ^{18}F-FDG PET/CT scan.[82] Serum ACE is a very commonly used study to evaluate for the presence of sarcoidosis and has relatively good specificity at 80 to 95%; however, the sensitivity is ~60%.[83,84] The use of CSF ACE to diagnose neurosarcoidosis is controversial, but may be of some use. A study found that CSF ACE levels are insensitive (24–55%) for the diagnosis of CNS sarcoidosis, but if elevated, may be relatively specific (94–95%).[85] The Kveim-Siltzbach test involves injecting part of a spleen from a patient with known sarcoidosis into the skin of a patient with suspected sarcoidosis. If granulomas form within 4 to 6 weeks, the test is positive. The Kveim-Siltzbach test is rarely used in the diagnosis of sarcoidosis anymore, but does have a reported sensitivity of ~78%.[86] Lastly, serum hypercalcemia has been reported in as many at 63% of patients with sarcoidosis, but is likely to be closer to 10% with hypercalciuria being about three times more common.[87]

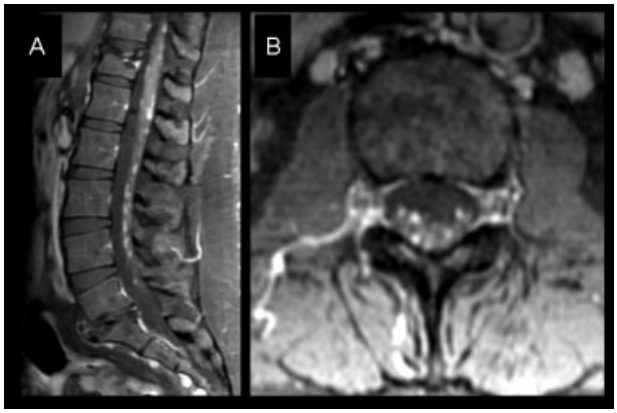

Figure 5 Sarcoidosis. Sagittal (A) and axial (B) gadolinium-enhanced T1-weighted magnetic resonance images in a man with gradual onset of weakness in both lower extremities and inflammatory cerebrospinal fluid. Note extensive nodular enhancement along the terminal cord and nerve roots of the cauda equina, consistent with sarcoid granulomatous disease in this patient with longstanding pulmonary sarcoidosis.

Postvaccinal and Acute Disseminated Encephalomyelitis

A recent review identified 37 cases of myelitis thought to be caused by an antecedent vaccination.[88] Among these cases, 73% occurred during the first month postvaccination. The cases included 18 children (age 0–18) and 19 adults, with an average age of 24.5 years old. The vaccines that were associated with myelitis were as follows: anti-HBV (13 cases), MMR (six cases), diphtheria–tetanus–pertussis or diphtheria–tetanus (four cases), rabies vaccine (four cases), oral polio virus (three cases), influenza (two cases), and one case each for typhoid vaccine, pertussis, and Japanese B encephalitis. Two cases were after multiple vaccine regimens.[88] Although it is tempting to speculate that vaccination can trigger myelitis, case reports cannot establish a cause–effect relationship. To date, no study has shown an increased incidence of myelitis in

those receiving vaccinations; therefore, based on the available data the proposed association between vaccination and myelitis is most likely coincidental.

Acute disseminated encephalomyelitis (ADEM) is an uncommon inflammatory disorder of the CNS characterized by widespread demyelination that is often associated with an antecedent infection or vaccination.[22] Symptoms usually develop within 3 weeks following a prodromal phase of fever, myalgia, and malaise. One case series identified a preceding infection or vaccination in 70% of cases within the previous few weeks.[89] In that same series, spinal cord involvement was reported as the presenting symptom in 24% of patients and vaccinations were associated with 12% (10/84) of the cases. Of these 10 patients with ADEM, seven had received a measles vaccination (8%) and three had received pertussis vaccination (3.5%).[89] Postvaccination ADEM has been associated with several vaccines, including rabies, diphtheria-tetanus-polio, smallpox, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, H1N1, and human papillomavirus (HPV).[90–92] As with myelitis, the possible cause–effect association of ADEM with these various vaccinations, although commonly assumed, is speculative because an increased risk of ADEM following vaccination has not been conclusively demonstrated by prospective observational studies.

Lyme Myelitis

Assessment for Lyme disease is warranted in cases of myelitis occurring in endemic areas. The lymphocytic meningoradiculitis described by Garin, Bujadoux, and Bannwarth[93–95] is a familiar manifestation of the second stage of Lyme disease and is characterized by a painful, ascending polyradiculitis. An acute myelopathy may evolve from these cases.[96–98]

Lyme disease presenting as ATM is relatively rare.[99] The extent of clinical involvement is variable and presentations include isolated urinary retention with pyramidal signs on examination but without weakness or sensory changes,[100] back pain with spine tenderness,[101] a lower motor neuron poliomyelitis-like syndrome,[102,103] as well as partial[104] and transverse forms of myelitis.[105,106] CSF findings are variable and include cytoalbuminemic dissociation, elevated IgG synthesis, oligoclonal bands, and WBC counts that are typically lymphocytic predominant and typically $>100/mm^3$. Demonstration of intrathecal snythesis of anti-Borrelia antibodies by either Western blot or an elevated Lyme index is diagnostic. Oligoclonal bands specific to Borrelia antigens have been reported in some cases. Treatment with cephalosporins or doxycycline often results in alleviation of the neurological manifestations of Lyme myelitis.

Transverse Myelitis with Normal Magnetic Resonance Imaging

Rarely, a patient can present with a clinical picture consistent with ATM who has imaging of the spinal cord that is perplexingly normal.[11] In this setting, the quality of the imaging study must be evaluated. Motion degradation and studies performed on low field strength or open MRI scanners may be suboptimal in identifying spinal cord lesions. If the image quality is questionable, then repeat imaging with sedation, possibly with general anesthesia to reduce motion artifact, or by using a superior scanner can reveal missed lesions.[11] Despite the advances in spinal cord imaging, not all pathologic processes can be clearly visualized by MRI. For example, conventional imaging of the spinal cord may appear normal in patients with adrenomyeloneuropathy; however, lesions can be identified using nonconventional techniques such as magnetization transfer ratio (MTR).[107,108] On occasion, other neurologic processes, such as ascending inflammatory polyradiculopathy or acute demyelinating inflammatory polyneuropathy, can present with clinical symptoms suggestive of myelitis. Nerve conduction studies and somatosensory evoked potentials can help distinguish between peripheral and central etiologies. Furthermore, an acute decompensation can be superimposed on a subacute problem. Patients with longstanding myelopathy can decompensate in the setting of physiological stressors resulting in acute symptomatic worsening. In this setting, MRI scans can be normal and the differential diagnosis should broaden to consider Friedrich's ataxia, motor neuron disease, vitamin B12 or copper deficiency, hereditary spastic paraparesis, human immunodeficiency virus (HIV), human T-lymphotropic virus-1 (HTLV-1) associated myelopathy, and adrenomyeloneuropathy.[11] Lastly, if a comprehensive evaluation fails to identify an anatomic or physiologic correlate for the apparent myelopathy, especially if there are unexpected discrepancies present on the neurologic examination, psychogenic etiologies should be considered.

Initial Treatment

The initial treatment of acute transverse myelitis is determined by the presenting clinical symptoms, the appearance on MRI and the findings on CSF. Once an inflammatory etiology is identified by CSF analysis, the clinician must decide whether or not infection is a likely etiology. Any systemic symptoms suggestive of infection must prompt a thorough infectious workup (fever, chills, rash, etc.). If the CSF shows an elevated WBC count with a neutrophilic predominance, decreased glucose, and elevated protein concentrations, then the indicated cultures and serologies (►**Table 4**) should be sent and appropriate antibiotic or antiviral agents should be started as soon as possible. There is evidence that empiric corticosteroids may be of benefit in bacterial[109] and tuberculous meningitis,[110] and systemic corticosteroids have been used in a variety of systemic infections and been shown to be safe when used in tandem with empiric antibiotics.[111]

If the clinical symptoms, CSF profile, and appearance on MRI are indicative of an autoimmune or inflammatory myelitis, serologies looking for systemic autoimmune or inflammatory diseases should be obtained and IV corticosteroids initiated. Although corticosteroid treatment is clearly warranted in the setting of MS and NMO-associated myelitis, not all studies have found a benefit of IV corticosteroids for all causes of myelitis.[112,113] A study in sarcoidosis[81] and several small studies in pediatric patients found improved outcomes

with IV methylprednisolone.[114–116] A recent retrospective study looking at acute transverse myelitis treatment in adults also found IV methylprednisolone beneficial, but not in patients affected by complete loss of motor and sensory function.[117] In severely affected patients, this study found a trend favoring IV cyclophosphamide in combination with plasma exchange.[117] Plasma exchange was found to be helpful following failure of IV corticosteroid treatment, especially in patients with NMO or NMO spectrum disorders (independent of NMO-IgG positivity).[118,119] If there is still no improvement with plasma exchange, case reports suggest that IV immunoglobulin (ADEM),[120] cyclophosphamide (idiopathic TM, SLE),[61,117] rituximab (NMO),[121,122] or azathioprine (NMO)[123] might be helpful. In contrast to this escalation therapy, limited evidence in SLE supports early aggressive treatment. A case series in SLE myelitis and a clinical trial of neuropsychiatric SLE found improved outcomes from IV corticosteroids with cyclophosphamide compared with IV corticosteroids alone.[61,124]

Conclusions

The term *acute transverse myelitis* was initially applied to idiopathic cases. Acute transverse myelitis is now recognized as a clinical syndrome associated with multiple etiologies.[22] Idiopathic transverse myelitis remains the default diagnosis for unexplained noncompressive myelopathy with radiographic or imaging evidence of inflammation. In a recent large case series of 170 patients presenting with acute noncompressive myelopathy, 40.6% (69/170) of patients had an identifiable cause on initial evaluation; however, on follow-up, an etiology was secured in 71.2% (121/170) of cases (mean follow-up of 73.2 months). The most commonly identified causes were demyelinating disease (MS 27%, NMO 6%), infarction (15%), parainfectious myelitis (12%), and systemic inflammatory disease (8%, e.g., SLE and Sjögren's syndrome).[9]

Determining the etiology of transverse myelitis can be challenging. Effective interpretation of clinical symptoms and signs, high quality neuroimaging and biomarkers such as CSF IL-6 levels and the NMO-IgG can help identify the cause of the myelitis, and guide treatment. In the absence of a definitive diagnosis empiric treatment with IV corticosteroids, plasma exchange, and possibly immune suppression may be warranted. Validated diagnostic criteria, biomarkers, and improved imaging will enhance study of acute transverse myelitis, its idiopathic form, and its associated causes.[57] Hopefully, with improved understanding of acute transverse myelitis, treatments tailored to the underlying disease can be developed.

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