



CONTINUUM AUDIO
INTERVIEW AVAILABLE
ONLINE

Myelitis and Other Autoimmune Myelopathies

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ABSTRACT

PURPOSE OF REVIEW: This article provides an update on the clinical diagnosis and management of immune-mediated myelopathies, including the relevance of imaging, ancillary testing with an emphasis on autoantibody biomarkers, recognition of myelitis mimics, and therapeutic approach.

RECENT FINDINGS: The imaging characterization of immune-mediated myelopathies and the discovery of neural autoantibodies have been crucial in improving our ability to accurately diagnose myelitis. The identification of autoantibodies directed against specific central nervous system targets has led to major improvements in our understanding of the mechanisms underlying inflammation in myelitis. It has also allowed distinction of these myelopathy etiologies from noninflammatory etiologies of myelopathy and from multiple sclerosis and provided insight into their risk of recurrence, treatment response, and long-term clinical outcomes. Prompt recognition and appropriate testing in the setting of acute and subacute myelopathies is critical as timely administration of immunotherapy can help improve symptoms and prevent permanent neurologic disability. A patient should not be classified as having “idiopathic transverse myelitis” without a comprehensive evaluation for a more specific etiology. Achieving the correct diagnosis and learning to recognize noninflammatory myelitis mimics is crucial as they have therapeutic and prognostic implications.

SUMMARY: Identifying the clinical and radiographic features of immune-mediated myelitis and recognizing mimics and pitfalls will help clinicians treat confirmed autoimmune myelitis appropriately.

CITE AS:

CONTINUUM (MINNEAP MINN)
2021;27(1, SPINAL CORD DISORDERS):
62–92.

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RELATIONSHIP DISCLOSURE:

Dr Lopez Chiriboga reports
no disclosure. Dr Flanagan
has received research/
grant support from
MedImmune/VielaBio.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Drs Lopez Chiriboga and
Flanagan discuss the
unlabeled/investigational use of
azathioprine, corticosteroids,
cyclophosphamide, IV
immunoglobulin, methotrexate,
mycophenolate mofetil, plasma
exchange, and rituximab for the
treatment of myelitis and other
autoimmune myelopathies.

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INTRODUCTION

The differential diagnosis of immune-mediated myelopathies is broad and includes noninflammatory myelopathies from compressive, vascular, neoplastic, metabolic, nutritional, infectious, toxic, and inherited causes.¹ Age, sex, ethnicity, risk factors, and comorbidities can help narrow the differential diagnosis, but careful attention to the clinical history with focus on the temporal profile of symptom onset, neuroimaging features, and comprehensive serologic and CSF evaluation is necessary to distinguish immune-mediated myelopathies from other causes and achieve a definitive diagnosis.^{2,3} This article focuses on recent advances

regarding the clinical, imaging, and serologic features and contemporary treatment of immune-mediated myelopathies.

TRANSVERSE MYELITIS DEFINITION AND TERMINOLOGY

Myelitis refers to inflammation of the spinal cord; the inflammation can result from infectious, immune-mediated, or other causes. The term *transverse myelitis* has become synonymous with immune-mediated myelitis; however, “transverse” myelitis implies inflammation across the entire transverse section of the spinal cord, and many causes of myelitis (eg, multiple sclerosis [MS]–associated myelitis) cause inflammation of only a segment of the spinal cord on cross section. Although such cases are often termed partial transverse myelitis and those with inflammation across the entire cross section of the cord are referred to as complete transverse myelitis, the clinical accompaniments of partial and complete transverse myelitis can overlap. The presence of bilateral symptoms and signs is often used to distinguish complete from partial transverse myelitis, but involvement of just the hemicord may still result in bilateral symptoms and signs (eg, as in Brown-Séquard syndrome).

Whereas clinical definitions have been problematic, radiologic discriminators have proved more useful. The length of the T2-hyperintense lesion seen on sagittal spinal cord imaging is a very useful discriminator between MS (less than three vertebral segments) and aquaporin-4 (AQP4) IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) (three or more vertebral segments). Transverse myelitis is generally classified into disease-associated (ie, related to a specific infectious or immune-mediated etiology) and idiopathic forms. Diagnostic criteria for idiopathic transverse myelitis were established in 2002 in an effort to identify homogeneous groups of patients for clinical studies. The criteria define idiopathic transverse myelitis as bilateral (although not necessarily symmetric) symptoms/signs of spinal cord dysfunction (sensory, motor, or autonomic) evolving over 4 hours to 21 days, a sensory level on the trunk, and evidence of inflammation (MRI gadolinium enhancement or CSF pleocytosis/elevated IgG index) with appropriate exclusion of alternative etiologies.⁴ Thus, idiopathic transverse myelitis should be considered a diagnosis of exclusion, with a comprehensive evaluation for both specific inflammatory and noninflammatory etiologies before assigning the diagnosis. This is further emphasized by recent studies highlighting that up to 70% of patients with a suspected diagnosis of idiopathic transverse myelitis have an alternative specific cause of myelopathy found.^{2,3} Significant advances in the field of autoimmune neurology, including the discovery of neural autoantibodies (eg, AQP4-IgG and myelin oligodendrocyte glycoprotein [MOG] IgG), have assisted in identifying a specific cause for patients previously classified as having idiopathic transverse myelitis.^{2,5} Better radiographic characterization of immune-mediated myelopathies and their mimics has improved our ability to diagnose patients with myelopathies of uncertain etiology.⁶ These advances highlight the need for updated diagnostic criteria for myelitis and for potentially removing *transverse* from the terminology as it often leads to confusion and fails to capture the frequently encountered focal spinal cord inflammation.

DEMOGRAPHICS AND EPIDEMIOLOGY

Immune-mediated myelopathies are more commonly encountered in females and can affect all ages. MOG-IgG-associated disorders and myelitis occurring as

KEY POINTS

- The differential diagnosis of immune-mediated myelopathies is broad and includes noninflammatory myelopathies from compressive, vascular, neoplastic, metabolic, nutritional, infectious, toxic, and inherited causes.
- The length of the T2-hyperintense lesion seen on sagittal spinal cord imaging is a very useful discriminator between multiple sclerosis (less than three vertebral segments) and aquaporin-4 (AQP4) IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) (three or more vertebral segments).
- Idiopathic transverse myelitis should be considered a diagnosis of exclusion, with a comprehensive evaluation for both inflammatory and noninflammatory etiologies before assigning that diagnosis.
- Significant advances in the field of autoimmune neurology, including the discovery of neural autoantibodies, have assisted in identifying a specific cause for patients previously classified as having idiopathic transverse myelitis.
- Better radiographic characterization of immune-mediated myelopathies and their mimics has improved our ability to diagnose patients with myelopathies of uncertain etiology.

a component of acute disseminated encephalomyelitis (ADEM), up to 50% of which is MOG-IgG seropositive, are more common in children; acute flaccid myelitis associated with outbreaks of enterovirus also occurs predominantly in children.⁷ A paraneoplastic myelopathy is more common in older adults, in whom the cancers (breast and lung) most associated with this disorder more commonly occur.^{8,9} Dural arteriovenous fistulas predominantly affect older males and should be strongly considered as a myelitis mimic when thoracic myelopathy occurs in this demographic.

Race is important to consider when evaluating patients with immune-mediated myelopathies. Neurosarcoidosis is more common in African Americans,¹⁰ and the prevalence of AQP4-IgG-seropositive NMO/NMOSD appears to be higher in Asians, Hispanics, Native Americans, and Africans.¹¹ MS is more frequent in Whites and in regions farther from the equator.

Few studies exist on the incidence and prevalence of idiopathic transverse myelitis, but a 2019 population-based US study (Olmsted County, Minnesota) showed that the incidence of idiopathic transverse myelitis was 8.6 per million person-years and the prevalence was 7.9 per 100,000.⁵

CLINICAL FEATURES

When evaluating patients with suspected myelitis, a detailed clinical history with focus on the temporal evolution is one of the most important aspects that can help narrow the differential diagnosis.

Time to Nadir

The time from onset to maximal neurologic deficit is the most important feature to determine when evaluating a myelopathy as it helps narrow the differential diagnosis (**TABLE 3-1**).^{2,3}

The time to nadir can be classified as hyperacute (<12 hours), acute/subacute (1 to 21 days), or chronic progressive (progression beyond 21 days). In spinal cord infarction, the rapid onset of severe deficits reaching nadir within a few hours (up to 12 hours) is typical and occurs in approximately 80% of patients with spinal cord infarction.¹² Most patients with idiopathic or disease-associated myelitis reach nadir in 1 to 21 days. Symptoms that progress beyond 21 days are more suggestive of an alternative etiology, such as spondylotic myelopathy, dural arteriovenous fistula, metabolic myelopathy, paraneoplastic myelopathy, neoplasms, or primary progressive MS.

Presenting Features

The classic clinical feature of myelitis is the development of sensorimotor deficits in one or more extremities. Ascending numbness, often accompanied by a sensory level across the trunk, is a characteristic presentation. Autonomic dysfunction is frequent, with a combination of neurogenic bladder (usually urinary retention), neurogenic bowel, and sexual dysfunction potentially encountered; these features are particularly common with MOG-IgG-associated disorder, perhaps reflecting conus involvement radiologically. Clinical features supportive of a demyelinating etiology include the Lhermitte phenomenon (an electrical sensation that radiates down the spine and to the extremities on neck flexion) and the Uhthoff phenomenon (transient worsening of neurologic symptoms from excessive heat). Tonic spasms (recurrent short-lived episodes of involuntary painful flexor contractions lasting 30 seconds to a few minutes) are

another clinical feature. They can appear dystonic-like, usually follow a myelitis episode, and can be triggered by movement or hyperventilation. Ephaptic transmission is thought to be the mechanism underlying tonic spasms. The spasms often respond well to carbamazepine. Tonic spasms are particularly frequent in AQP4-IgG-seropositive NMOSD. Neuropathic pruritus can be the initial manifestation of myelitis with AQP4-IgG-seropositive NMOSD.

The clinical severity of myelitis at nadir is usually mild with MS and moderate to severe with AQP4-IgG-seropositive NMOSD and MOG-IgG-associated disorder (often requiring a gait aid); however, recovery is better with MOG-IgG-associated disorder than AQP4-IgG-seropositive NMOSD. Rarely, respiratory failure requiring mechanical ventilation may ensue from a severe cervical myelitis accompanying MOG-IgG-associated disorder or AQP4-IgG-seropositive NMOSD. The natural evolution of attacks of myelitis associated with central nervous system (CNS) inflammatory demyelinating diseases (MS, AQP4-IgG-seropositive NMOSD, MOG-IgG-associated disorder) is subacute development reaching nadir within 21 days with potential plateau, followed by subsequent improvement that may be sped up by intervening with treatment. Back-to-back attacks may occur, particularly with AQP4-IgG-seropositive NMOSD. Primary progressive MS has a more insidious onset and slow progression beyond 1 year and usually manifests as a progressive myelopathy. Rarely, patients may have a single MS lesion and develop insidious motor progression from that lesion if located in an eloquent location (eg, spinal cord lateral columns). These patients are classified as having progressive solitary sclerosis as they follow a course similar to primary progressive MS but lack the dissemination in space required to fulfill MS criteria.¹³ It is also recognized that a subset of patients with progressive MS fulfilling MS diagnostic criteria may have isolated unilateral motor progression despite having bilateral demyelinating lesions in many CNS regions. The worsening in such cases is often attributable to a single severe lesion located along the lateral columns of the spinal cord (usually accompanied by atrophy). This highlights the potential important contribution of focal lesions in eloquent locations to motor disability in MS.¹⁴

An encephalomyelitis accompanied by glial fibrillary acidic protein (GFAP) antibodies or glycine receptor antibodies may develop subacutely or insidiously and often progresses beyond 21 days. Autoimmune GFAP astrocytopathy rarely manifests as isolated myelitis, and cerebral involvement at the time of myelitis is almost universal.¹⁵ Paraneoplastic myelopathy can be necrotizing with a fulminant or slowly progressive course.^{9,16} Asking about a prior history or assessing for the concurrent presence of CNS demyelinating episodes (eg, optic neuritis) is useful to indicate a CNS inflammatory demyelinating disease as the cause. A preceding vaccination or a viral-like prodrome may suggest MOG-IgG-associated disorder or GFAP antibody-associated encephalomyelitis.¹⁷ An area postrema syndrome manifested by intractable nausea and vomiting with or without hiccups should raise the suspicion for AQP4-IgG-seropositive NMOSD and may occur in isolation or immediately precede an episode of myelitis.¹⁷ A smoking history, unintended weight loss, or known cancer should raise concern for a paraneoplastic myelopathy, which often manifests before the detection of cancer.¹⁸ Asking about symptoms suggestive of systemic autoimmune disorders (eg, oral or genital ulcers in Behçet disease) or sicca symptoms and looking for the presence of arthritis or skin changes that may suggest systemic sarcoid involvement are

KEY POINTS

- The time from onset to maximal neurologic deficit is the most important feature to determine when evaluating a myelopathy as it helps narrow the differential diagnosis.
- The time to nadir in myelopathy can be classified as hyperacute (<12 hours), acute/subacute (1 to 21 days), or chronic progressive (progression beyond 21 days).
- In spinal cord infarction, the rapid onset of severe deficits reaching nadir within a few hours (up to 12 hours) is typical and occurs in approximately 80% of patients.
- Most patients with idiopathic or disease-associated transverse myelitis reach nadir in 1 to 21 days.
- The natural evolution of attacks of myelitis associated with central nervous system inflammatory demyelinating diseases is subacute development reaching nadir within 21 days with potential plateau, followed by subsequent improvement that may be sped up by intervening with treatment.

TABLE 3-1 Differential Diagnosis of Myelopathies

Onset and etiologies	Clinical/MRI clues
Acute	
Vascular	
Spinal cord infarct (anterior or posterior spinal artery)	Vascular risk factors
Fibrocartilaginous embolism	Valsalva, disk adjacent to lesion
Hematoma (hematomyelia, epidural hematoma)	Bleeding diathesis, trauma
Structural/trauma	
Surfer's myelopathy	Novice surfer
Spinal cord contusion	Recent trauma
Subacute	
Inflammatory demyelinating disease	
Multiple sclerosis	Short peripheral T2 lesions in dorsal/lateral columns
Aquaporin-4 antibody–seropositive neuromyelitis optica spectrum disorder (NMOSD)	Longitudinally extensive T2 lesion
Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disorder	Long or short T2 lesion; conus involvement; nonenhancing
Acute disseminated encephalomyelitis (ADEM)	Coexisting deep gray brain lesions
Inflammatory, confirmed etiology	
Spinal cord sarcoidosis	Milder deficit despite large lesion, linear dorsal subpial/trident enhancement
Connective tissue disease associated (Behçet disease, lupus, Sjögren syndrome)	Systemic features of connective tissue disease
Paraneoplastic	Known cancer; cancer risk factors; tract-specific lesion, especially gadolinium enhancing
Immune checkpoint inhibitor associated	Recent use of checkpoint inhibitor
Infectious	
Bacterial (Lyme disease, syphilis, tuberculosis)	Recent tick bite/rash; high-risk behavior
Viral (varicella-zoster virus, herpes simplex virus type 1, herpes simplex virus type 2 [may be associated with lumbar myeloradiculitis, Elsberg syndrome], cytomegalovirus, West Nile virus, enterovirus-associated acute flaccid myelitis; human immunodeficiency virus [HIV])	Zoster rash, genital herpes, endemic region for enterovirus/West Nile virus; high-risk behavior
Parasitic (schistosomiasis)	Endemic region
Idiopathic	Extensive investigations should be undertaken to assess for specific cause before assigning this diagnosis

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Onset and etiologies	Clinical/MRI clues
Chronic progressive (may have subacute onset/worsening)	
Vascular	
Dural arteriovenous fistula	Clinical worsening after exertion or steroids, thoracic longitudinally extensive lesion, flow voids
Cavernous malformation/arteriovenous malformation	Popcorn appearance for cavernous malformation ^a
Inflammatory or demyelinating	
Progressive solitary sclerosis	Single multiple sclerosis lesion in lateral columns or pyramids of medulla
Primary progressive multiple sclerosis	Multiple short T2 lesions in cord
Spinal cord sarcoidosis	Milder deficit despite large lesion, linear dorsal subpial/trident enhancement
Paraneoplastic	Known cancer, smoking
Infectious	
Bacterial (syphilis, tuberculosis); epidural abscess	High-risk behavior, endemic region, IV drug use
Viral (HIV, human T-cell lymphotropic virus 1 [HTLV-1])	High-risk behavior, endemic region, dorsal/lateral column signal abnormality
Neoplastic	
Primary spinal cord gliomas (astrocytoma, ependymoma)	Prior radiation, expansile, mass effect, cap sign ^b
Primary intramedullary spinal cord lymphoma	Expansile lesion; persistent enhancement (>3 months), steroid responsive, immunosuppressed
Metastatic disease (intramedullary, extramedullary compressive)	Known solid organ cancer
Structural	
Spondylotic myelopathy	History of trauma, neck osteoarthritis
Hereditary	
Adrenomyeloneuropathy	Neuropathy, progressive cord atrophy, adrenal involvement
Hereditary spastic paraplegia	Spasticity disproportionate to weakness; progressive spinal cord atrophy
Mitochondrial disorders (eg, <i>DARS2</i> gene)	Dorsal/lateral signal abnormality; elevated lactate
Other genetic	
Toxic/metabolic	
Nutritional deficiency (vitamin B ₁₂ , copper, vitamin E)	Gastric bypass, zinc supplements, malabsorption
Toxic (intrathecal methotrexate, heroin, vitamin B ₆)	Toxic exposure
Iatrogenic	
Radiation	Prior radiation exposure

IV = intravenous.

^a Popcorn appearance: mixed intensity at the center of the lesion from vascular components with a T2 hypointense rim from blood products.^b A cap of T2 hypointensity secondary to hemosiderin is present at the top or bottom of the lesion.

useful; such symptoms can suggest a myelopathy associated with a connective tissue disorder. It is important to recognize that AQP4-IgG-seropositive NMOSD can coexist with systemic autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, and antiphospholipid syndrome, and testing for AQP4-IgG in such cases is prudent as a seropositive result confirms a coexisting autoimmune neurologic disorder rather than a neurologic manifestation of a systemic connective tissue disease (refer to the discussion on autoantibodies below).

In the authors' experience, patients with spinal cord sarcoidosis often present with a myelopathy before they are diagnosed with systemic sarcoidosis; the presentation may be subacute in onset (mimicking transverse myelitis) or chronic and progressive, reaching nadir after 21 days.¹⁹ Systemic or primary CNS vasculitis involving the spinal cord has been reported.²⁰ Inflammatory myelopathies have been described in patients with rheumatoid arthritis, scleroderma, mixed connective tissue disease, and IgG4-related disease.²¹

It is also helpful to assess for clues to nonimmune myelopathies that commonly cause or mimic transverse myelitis. The absence of sensory symptoms with flaccid muscle tone in a child is strongly suggestive of the acute flaccid myelitis associated with enterovirus D68, whereas the presence of genital herpes (Elsberg syndrome) or vesicular rash (varicella-zoster virus) may suggest an infectious-related myelitis. For more information on infectious myelopathies, refer to the article "Infectious Myelopathies" by Michel Toledano, MD,²² in this issue of *Continuum*. Worsening with exercise, Valsalva maneuver, or corticosteroids is suggestive of dural arteriovenous fistula, and onset after Valsalva maneuver is also seen with fibrocartilaginous embolism. For more information on vascular myelopathies, refer to the article "Vascular Myelopathies" by Nicholas L. Zalewski, MD,²³ in this issue of *Continuum*. The presence of constitutional symptoms (eg, fevers, chills, night sweats) suggests epidural abscess, whereas a history of cancer should raise suspicion of metastatic spinal cord compression. MRI will usually readily distinguish these conditions from an immune-mediated myelopathy.

Typical findings of myelitis on neurologic examination include a sensory level across the trunk and an upper motor neuron pattern of weakness, hyperreflexia, spasticity, and extensor plantar responses, but these may take time to develop.^{1,4,24} The McArdle sign (rapidly reversible pyramidal weakness induced by neck flexion) is suggestive of MS myelitis.²⁵ The presence of an inverted brachioradialis, triceps, or biceps jerk is suggestive of a myeloradiculopathy (most commonly cervical spondylosis). For more information on spinal cord localization, refer to the article "Spinal Cord Anatomy and Localization" by Todd A. Hardy, PhD, MBBS, FRACP,²⁶ in this issue of *Continuum*. Acute spinal cord syndromes can present with spinal shock (flaccid limb weakness with areflexia and mute plantar reflexes) mimicking lower motor neuron disorders, such as Guillain-Barré syndrome.

NEUROIMAGING IN MYELITIS

MRI with and without gadolinium is the imaging modality of choice in the evaluation of myelopathies; in those with contraindications for MRI, CT myelography can be considered to exclude extrinsic compression. Diffusion-weighted images should be requested in hyperacute and acute myelopathy, which are not part of the usual MRI spine protocol. Confirmation of

lesions on multiple planes can improve specificity to avoid false-positive findings due to artifacts and false-negative results. Detailed evaluation of the gadolinium enhancement pattern is critical as it can provide clues to determine specific etiologies (TABLE 3-2). Persistent enhancement beyond 3 months should prompt strong consideration of noninflammatory etiologies, including neoplastic causes or dural arteriovenous fistula. Once extrinsic compression is excluded and if an inflammatory myelopathy is suspected, imaging the entire spine (cervical and thoracic spine) and brain is often useful to assess for other lesions (eg, MS or ADEM) that can help narrow the differential diagnosis. Repeat imaging can be considered in patients with a severe definitive myelopathy as the initial MRI may be negative and subsequent MRIs may detect the lesion in spinal cord infarct and MOG-IgG-associated disorder myelitis.^{12,27}

Length of the T2-Hyperintense Lesion on Sagittal Images

The length and location of lesions are helpful in the differential diagnosis of myelitis as they can provide clues to the specific etiology.

SHORT LESIONS (LESS THAN THREE VERTEBRAL SEGMENTS). A lesion extending less than three vertebral segments (a short lesion) is most suggestive of MS (FIGURE 3-1), and multiple peripheral short T2 hyperintensities within the spinal cord with or without typical brain lesions is strongly suggestive of MS. Indeed, it is not uncommon for primary progressive MS to have predominantly or exclusively spinal cord lesions. Lesions are usually wedge-shaped on axial images and involve the periphery of the cord in either the lateral or dorsal columns (FIGURE 3-1B), although, less frequently, the central gray and anterior white matter can also be affected. When imaged with higher field strengths, lesions are hypointense on T1-weighted sequences.²⁸ Spinal cord edema is typically seen in the acute phase of MS myelitis, potentially mimicking neoplastic myelopathies; as edema resolves, chronic MS T2-hyperintense spinal cord lesions may appear smaller but typically do not resolve completely. Enhancement is present in most acute lesions; the pattern is variable, usually homogeneous or patchy, but ring enhancement²⁹ is seen in about one-third of enhancing cord lesions in MS (FIGURES 3-1C and 3-1D)³⁰ and the enhancement usually resolves within 8 weeks.³¹ On sagittal imaging in patients with chronic MS, the coalescence of multiple short lesions can mimic longitudinally extensive transverse myelitis (LETM),³² but true LETM is a red flag in MS and should prompt evaluation for an alternative etiology.³⁰ In some patients with unilateral progression or progression in the setting of a single lesion (ie, progressive solitary sclerosis), focal lesional atrophy may develop over time and is usually located in the eloquent spinal cord lateral columns (FIGURE 3-2) or in the medullary pyramids/anterior cervicomedullary junction.¹³ These critical lesions likely have an important role in the development of motor progression in patients with MS. Short lesions are less common with AQP4-IgG-seropositive NMOSD, occurring in about 15%; African American ethnicity, tonic spasms, coexisting systemic autoimmunity, central lesions and lesions extending two or more vertebral segments, absence of MS brain lesions, and lack of oligoclonal bands are factors that help identify those at highest risk, in whom AQP4-IgG should be tested.³³ One or more short lesions occur in one-third to one-half of cases of myelitis with MOG-IgG-associated disorder, and the presence of a coexisting longitudinally extensive lesion and the central location of lesions help distinguish it from MS.³⁴ Spinal cord sarcoidosis may also be

KEY POINTS

- AQP4-IgG-seropositive NMOSD can coexist with systemic autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, and antiphospholipid syndrome. Testing for AQP4-IgG in such cases is prudent as a seropositive result confirms a coexisting autoimmune neurologic disorder rather than a neurologic manifestation of a systemic connective tissue disease.

- Typical findings of myelitis on neurologic examination include a sensory level across the trunk and an upper motor neuron pattern of weakness, hyperreflexia, spasticity, and extensor plantar responses, but these may take time to develop.

- Detailed evaluation of the gadolinium enhancement pattern on MRI is critical in the evaluation of myelopathies as it can provide clues to determine specific etiologies.

- A lesion extending less than three vertebral segments (a short lesion) is most suggestive of multiple sclerosis, and multiple peripheral short T2 hyperintensities within the spinal cord with or without typical brain lesions is strongly suggestive of multiple sclerosis.

- Multiple sclerosis lesions are usually wedge-shaped on axial images and involve the periphery of the cord in either the lateral or dorsal columns.

associated with short T2-hyperintense lesions, but longitudinally extensive lesions are more typical.^{20,35}

LONGITUDINALLY EXTENSIVE T2-HYPERINTENSE LESIONS (THREE OR MORE VERTEBRAL SEGMENTS). A myelitis episode accompanied by an isolated longitudinally extensive T2-hyperintense lesion that extends over three or more vertebral segments is typical of AQP4-IgG-seropositive NMOSD (FIGURES 3-1E and 3-1F)

TABLE 3-2 MRI Findings in Autoimmune Myelopathies and Mimics

	Typical spinal location	Number of T2 lesions	Length on sagittal T2-weighted images ^a	Appearance on axial T2-weighted images	Postcontrast pattern	Other feature(s)
Inflammatory/autoimmune						
Multiple sclerosis	Cervical or thoracic	Multiple	Short	Peripheral (dorsal or lateral columns)	Ringlike, homogeneous	
Aquaporin-4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD)	Cervical or thoracic	Single	Long 85%; short 15%	Central (gray and white matter)	Ringlike, patchy	Bright spotty T2 ^b , prominent swelling
Myelin oligodendrocyte glycoprotein-IgG-associated disorder	Cervical or thoracic	Multiple	Long 70%; short 30%	Central (30% gray matter restricted/H sign ^c)	Faint or no enhancement	Conus
Sarcoidosis	Cervical or thoracic	Single or, less often, multifocal	Usually long	Central	Almost universal: dorsal subpial ^d or axial trident ^e	Swelling, may see enlarged lymph nodes in carina or hilum on thoracic MRI
Paraneoplastic	Cervical or thoracic	Single	Long	Tract-specific signal (dorsal/lateral column)	Tract-specific enhancement (usually lateral columns)	MRI normal in up to 50%

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and supports this diagnosis over MS; AQP4-IgG-seropositive NMOSD is the most common cause of both monophasic (50%) and recurrent (93%) LETM.³⁶ AQP4-IgG-seropositive NMOSD myelitis lesions may also have pockets of signal intensity similar to the CSF, which are called bright spotty lesions. Contrast enhancement is detected in the vast majority of myelitis associated with AQP4-IgG-seropositive NMOSD and is usually patchy, although ringlike lesions are found in one-third, often forming a ring around the bright spotty T2

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	Typical spinal location	Number of T2 lesions	Length on sagittal T2-weighted images ^a	Appearance on axial T2-weighted images	Postcontrast pattern	Other feature(s)
Most common mimics of inflammatory/autoimmune myelopathy						
Spondylosis	Cervical	Single	Long or short	Central owl eye ^f	Sagittal: pancakelike ^g ; axial: circumferential sparing gray matter	Cervical canal stenosis, other spondylotic changes; slow resolution of enhancement after surgery (1-2 years)
Spinal cord infarct	Cervical or thoracic	Single	Long or short	Owl eye ^f	Linear strip ^h ; owl eye ^f	Diffusion restriction; vertebral body infarct; adjacent artery dissection
Dural arteriovenous fistula	Thoracic	Single	Long	Central	Patchy, missing piece, ⁱ enhancing large veins; 40% no enhancement	Flow voids dorsal to cord
Nutritional (vitamin B ₁₂ deficiency, copper deficiency)	Cervical or thoracic	Single	Long	Tracts (dorsal/lateral columns)	None	
Intramedullary metastases	Cervical or thoracic	Single or multiple	Long or short	Central or peripheral	Rim and flame or dot sign ^j	

MRI = magnetic resonance imaging.

^a Short: less than three vertebral segments; long: three or more vertebral segments.

^b Very bright T2 hyperintensity similar in consistency to CSF (syrinxlike) spotted within less bright T2-hyperintense lesion.

^c T2 signal abnormality restricted to gray matter on axial image forming an H shape.

^d Parenchymal enhancement extending inward from the dorsal surface of the cord.

^e Dorsal subpial enhancement combined with central canal enhancement creates a three-pronged appearance on axial sequences resembling a trident.

^f Bilateral anterior horn cell involvement with the appearance of owl eyes (or snake eyes).

^g Transverse band of enhancement in which the width is equal to or greater than the height that appears squashed like a pancake.

^h A linear strip of enhancement in the anterior cord on sagittal images.

ⁱ Area of absent enhancement within a long segment of homogeneous enhancement appearing as if the enhancement has a missing piece.

^j A rim of enhancement around a less enhancing central region of milder enhancement with a flame appearance at the top or the bottom of the lesion; may have an accompanying dot of enhancement in the center on axial or sagittal images.



FIGURE 3-1

Comparison of acute myelitis MRI findings in multiple sclerosis, aquaporin-4 (AQP4) IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein autoantibody (MOG-IgG)-associated disorder. Sagittal MRI of an adult patient with multiple sclerosis shows a short T2 hyperintensity at C2 extending 1.5 vertebral segments in length (A, arrow). Axial image shows the lesion is located peripherally in the right lateral column (B, arrow). Sagittal (C) and axial (D) images show accompanying ring enhancement of the spinal cord lesion (C, D, arrows) on postcontrast T1-weighted images. Sagittal (E) and axial (F) images of AQP4-IgG-seropositive NMOSD-associated myelitis show a longitudinally extensive T2 hyperintense lesion extending more than three vertebral segments (E, F, arrows). Accompanying ring enhancement of the cord lesion is seen on sagittal (G, lower arrow) and axial (H, arrow) postcontrast T1-weighted images along with more homogeneous enhancement (G, upper arrow). In myelitis accompanying MOG-IgG-associated disorder, a longitudinally extensive T2-hyperintense lesion extending more than three vertebral segments is seen on sagittal imaging (I, arrows). On axial images, the lesion involves predominantly gray matter, forming an H sign (J, arrow). No postcontrast enhancement is seen on postcontrast T1-weighted images (K, L).

hyperintensity.³⁷ Long segments of atrophy extending over more than three vertebral segments may also be encountered as the sequelae of one or more myelitis attacks (FIGURES 3-2C and 3-2D).⁶ MOG-IgG-associated disorder myelitis can occur in isolation but is more commonly seen with concomitant involvement of the brain and brainstem as part of ADEM or concurrently with an episode of optic neuritis. Myelitis is considered a core clinical feature of MOG-IgG-associated disorder.^{38,39}



FIGURE 3-2

Comparison of chronic myelitis MRI findings in multiple sclerosis, aquaporin-4-IgG (AQP4-IgG)-seropositive neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-associated disorder. Sagittal T2-weighted cervical spine MRI of a patient with multiple sclerosis with progressive left hemiparesis attributable to a severe critical demyelinating lesion showing evidence of prominent “apple-core” atrophy on sagittal images (A, arrow) and focal left lateral cord atrophy on axial image (B, arrow). Sagittal T2-weighted cervical spine MRI of a patient with multiple prior episodes of myelitis from AQP4-IgG-seropositive NMOSD who has a residual paraplegia, showing a long segment of atrophy (C, arrows) extending over more than three vertebral segments, with residual T2 hyperintensity centrally on axial image (D, arrow; corresponding to level of upper arrow in panel C). Sagittal T2-weighted cervical spine MRI of a patient in remission after multiple episodes of MOG-IgG-associated disorder myelitis, without residual motor deficits, showing no residual T2 hyperintensity and minimal atrophy on sagittal (E) and axial (F) images.

Similar to AQP4-IgG-seropositive NMOSD, MOG-IgG-associated disorder myelitis is frequently associated with LETM (lesions extending for three or more vertebral segments) (FIGURE 3-1I), although often multifocal cord lesions are seen rather than the solitary lesion typical of AQP4-IgG-seropositive NMOSD.⁴⁰ Patients with MOG-IgG-associated disorder often have conus involvement.^{40,41} On axial sequences, lesions are usually central; in about one-third of patients, they are restricted to the gray matter in an H pattern and accompanied by a sagittal T2-hyperintense line (FIGURE 3-1J) (CASE 3-1). Recurrent isolated LETM is rare with MOG-IgG-associated disorder.³⁶ Gadolinium enhancement is less frequent (<50% of cases) than in AQP4-IgG-seropositive NMOSD or MS (FIGURE 3-1K and 3-1L).^{30,34,40} In MOG-IgG-associated disorder, T2 lesions often resolve completely (FIGURES 3-2E and 3-2F). In AQP4-IgG-seropositive NMOSD, T2 lesions markedly reduce in size with mild residual T2 hyperintensity in most (FIGURE 3-2C), whereas in MS, lesions lead to a persistent residual T2 hyperintensity that is only mildly reduced from the acute lesion (FIGURES 3-2A and 3-2B).

Gadolinium Enhancement Pattern

MS lesions may have homogeneous enhancement or ring enhancement or may not enhance.²⁹ AQP4-IgG-seropositive NMOSD can have ring enhancement that may be elongated or ellipsoid in appearance, extending over multiple segments (FIGURE 3-1G and 3-1H),³⁷ although patchy nonspecific enhancement is most common. With MOG-IgG-associated disorder, mild patchy enhancement or no enhancement is typical, and ring enhancement is not usually encountered. Paraneoplastic autoimmune myelopathies may reveal a characteristic tract-specific enhancement along the lateral columns (or, less commonly, the dorsal columns) (FIGURE 3-4) but can also be normal. Linear dorsal subpial enhancement extending inward from the posterior aspect of the cord and spanning over multiple vertebral segments is seen in approximately 60% of cases of spinal cord sarcoidosis and can distinguish it from AQP4-IgG-seropositive NMOSD or other causes of LETM.^{10,19,42} When this dorsal subpial enhancement is accompanied by central canal enhancement, an axial trident sign⁴² can be seen, which is very suggestive of spinal cord sarcoidosis (CASE 3-2). Despite a longitudinally extensive T2 hyperintense lesion with prominent swelling, the accompanying neurologic deficit is often mild in neurosarcoidosis (mild weakness or sensory deficit), unlike in other etiologies (eg, AQP4-IgG-seropositive NMOSD) in which a longitudinally extensive T2-hyperintense lesion is typically accompanied by a severe deficit (eg, paraplegia).¹⁰ Ventral subpial enhancement can also be encountered in a braid pattern.⁴³ Sarcoid myelitis lesions may occur around sites of mechanical stress from spondylosis, potentially implicating the breakdown of the blood-spinal cord barrier in its pathogenesis.¹⁰ Leptomeningeal enhancement may coexist with dorsal subpial enhancement, but the dominant pattern in spinal cord sarcoidosis is a parenchymal dorsal subpial enhancement. In Behçet disease, myelitis lesions seen on MRI can be longitudinally extensive, short, or a combination of both and may show a T2 lesion with a hypointense core and hyperintense rim with or without enhancement of the rim in a bagel-like pattern.⁴⁴ The gadolinium enhancement pattern can also assist with identifying noninflammatory myelopathies that are associated with enhancement (TABLE 3-2).

Other MRI features

Patients with glycine and glutamic acid decarboxylase 65 (GAD 65) autoantibodies may present with a myelopathy as a component of encephalomyelitis or stiff person syndrome; in such cases, MRI of the spine is often normal. With GFAP-antibody-associated encephalomyelitis, MRI shows poorly demarcated longitudinally extensive T2-hyperintense lesions with central canal enhancement in approximately 20% of cases, and meningeal involvement can be encountered, including along the cauda equina.⁴⁵

MRI BRAIN. Obtaining an MRI of the brain is standard in the evaluation of autoimmune myelopathy, and the features of the lesions detected can help suggest the underlying diagnosis (FIGURE 3-6). The presence of characteristic MS lesions (peripheral brainstem, inferior temporal pole, ovoid periventricular, ring/open-ring enhancement [FIGURES 3-6D, 3-6G, and 3-6J]) may allow patients to meet MS diagnostic criteria, whereas the absence of brain lesions predicts a low risk of MS over the next 15 years (<20%). With MS optic neuritis, optic nerve enhancement tends to be short, involving less than 50% of the length of the optic nerve (FIGURE 3-6A) versus AQP4-IgG-seropositive NMOSD or MOG-antibody-associated disorder, in which enhancing lesions tend to extend more than half the length of the nerve. With AQP4-IgG-seropositive NMOSD, the presence of brain lesions adjacent to the third (FIGURE 3-6H) or fourth ventricle (area postrema region [FIGURE 3-6E]), internal capsule, and splenium of the corpus callosum (in a bridge arch pattern) and linear ependymal enhancement have all been reported as suggestive (FIGURE 3-6K), although in the majority, a normal MRI head is found. Optic nerve lesions frequently involve the chiasm (FIGURE 3-6B). With MOG-IgG-associated disorder, cerebral manifestations can reveal ADEM-like lesions, including multifocal white matter lesions, deep gray matter lesions, and large fluffy brainstem lesions, and leptomeningeal enhancement may be encountered (FIGURES 3-6F, 3-6I, and 3-6L). Parenchymal lesions may or may not enhance, and a novel syndrome with unilateral cortical encephalitis accompanied by fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions in MOG-associated encephalitis with seizures (FLAMES) has been reported with MOG-IgG-associated disorder.^{46,47} Optic nerve lesions with MOG-IgG-associated disorder tend to be longitudinally extensive and often involve the anterior optic pathway, sparing the chiasm (FIGURE 3-6C).⁴⁸ ADEM can be associated with lesions similar to those mentioned with MOG-IgG-associated disorder, and up to 50% of patients with ADEM are MOG-IgG seropositive. With GFAP antibody-associated encephalomyelitis, a characteristic radial enhancement extending out from the ventricles has been reported. The presence of basilar leptomeningeal enhancement may suggest sarcoidosis, although often brain MRI is normal with spinal cord sarcoidosis. With Behçet disease, brainstem and internal capsule lesions can be encountered, as can cerebral venous sinus thrombosis.

NEURAL AND NON-NEURAL AUTOANTIBODIES

Serum and CSF biomarkers of myelitis discovered in the past 2 decades have aided in the diagnosis and understanding of the pathogenesis of myelitis. AQP4-IgG is an antibody that binds to a water channel on the end feet of astrocytes, whereas MOG-IgG binds the MOG protein on the surface of oligodendrocytes. AQP4-IgG and MOG-IgG are two important antibody

KEY POINTS

- Short lesions are less common with AQP4-IgG-seropositive NMOSD, occurring in about 15% of patients.
- An isolated longitudinally extensive T2-hyperintense lesion that extends over three or more vertebral segments is typical of AQP4-IgG-seropositive NMOSD and supports this diagnosis over MS.
- Similar to AQP4-IgG-seropositive NMOSD, MOG-IgG-associated disorder myelitis is frequently associated with longitudinally extensive transverse myelitis, although often multifocal cord lesions are seen rather than the solitary lesion typical of AQP4-IgG-seropositive NMOSD.
- Patients with MOG-IgG-associated disorder often have conus involvement.
- Linear dorsal subpial enhancement extending inward from the posterior aspect of the cord and spanning over multiple vertebral segments is seen in approximately 60% of cases of spinal cord sarcoidosis. When this dorsal subpial enhancement is accompanied by central canal enhancement, an axial trident sign can be seen, which is very suggestive of spinal cord sarcoidosis.
- Obtaining an MRI of the brain is standard in the evaluation of autoimmune myelopathy, and the features of the lesions detected can help suggest the underlying diagnosis.

CASE 3-1

A 20-year old right-handed woman developed a sore throat, rhinorrhea, and headache 5 days after receiving the injectable influenza vaccine. Over the subsequent 3 to 4 days, she developed ascending numbness and weakness in her lower extremities with difficulty urinating and the Lhermitte phenomenon. At her neurologic nadir 7 days from onset, she had weakness in both legs (resulting in wheelchair dependence), bilateral numbness from her knees to toes, and urinary retention that required an indwelling urinary catheter.

Neurologic examination at that time revealed a moderately severe paraparesis with brisk reflexes in the lower extremities but downgoing plantar responses. MRI of her spine revealed a multifocal T2 hyperintensity within the cervical and thoracic spine (FIGURE 3-3) predominantly involving the gray matter and forming a sagittal line (FIGURE 3-3A) and H sign (FIGURES 3-3B and 3-3F) with minimal enhancement (FIGURES 3-3C, 3-3D, 3-3G, and 3-3H). Brain MRI revealed some mild hazy central brainstem T2 hyperintensity without enhancement (not shown) and was otherwise normal. CSF analysis revealed an elevated white blood cell count of 101 cells/mm³, elevated protein of 68 mg/dL, normal glucose, and negative oligoclonal bands. Serum aquaporin-4 (AQP4)-IgG was negative, but serum myelin oligodendrocyte glycoprotein (MOG)-IgG was positive at high titer of 1:1000 (normal <1:20). She was diagnosed with MOG-IgG-associated disorder and treated with 1 g IV methylprednisolone once daily for 5 days followed by an oral prednisone taper over 3 weeks. She had an excellent recovery over the subsequent 2 months and returned to running, although she had mild residual bladder dysfunction. A watchful waiting approach was taken without empiric attack-prevention immunosuppressant treatment.

COMMENT

In this patient, the subacute onset of myelopathy reaching its nadir between 1 and 21 days is suggestive of transverse myelitis, and the positive MOG-IgG confirmed MOG-IgG-associated disorder, which can follow vaccination. The MRI findings were very suggestive of MOG-IgG-associated disorder, with a longitudinally extensive T2 hyperintensity with mild swelling (FIGURE 3-3A), multifocal T2 hyperintensity in the cord (FIGURES 3-3A and 3-3E), conus involvement (FIGURE 3-3E), predominantly gray matter T2 hyperintensity (FIGURES 3-3A, 3-3B, and 3-3F), and minimal gadolinium enhancement (FIGURES 3-3C, 3-3D, 3-3G and 3-3H), compared to AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD), which usually has a solitary longitudinally extensive T2 hyperintensity, more severe swelling, and more avid enhancement. The severity of the episode at nadir (requiring a wheelchair), longitudinally extensive T2 hyperintensity, absence of oligoclonal bands, and elevated white blood cell count (>50 cells/mm³) favored MOG-IgG-associated disorder over multiple sclerosis. The excellent recovery with acute treatment is typical of MOG-IgG-associated disorder, which responds to treatment better than AQP4-IgG-seropositive NMOSD. As the disease can be monophasic, empiric attack-prevention immunosuppression is typically reserved for cases that relapse.

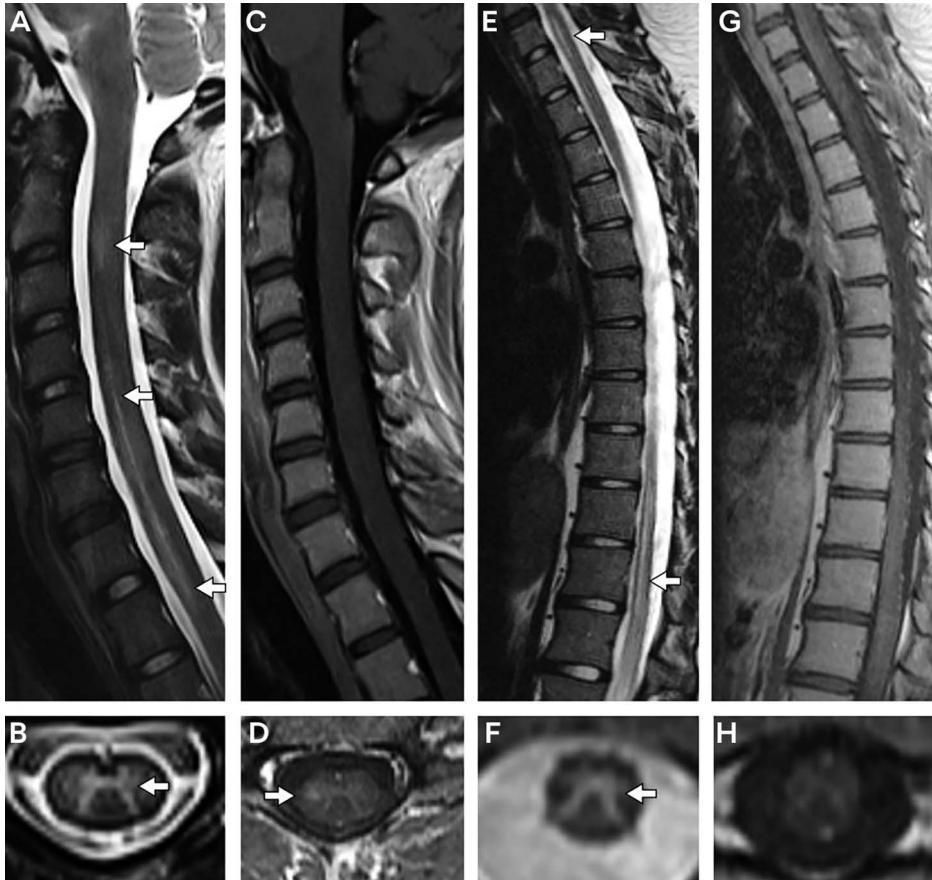
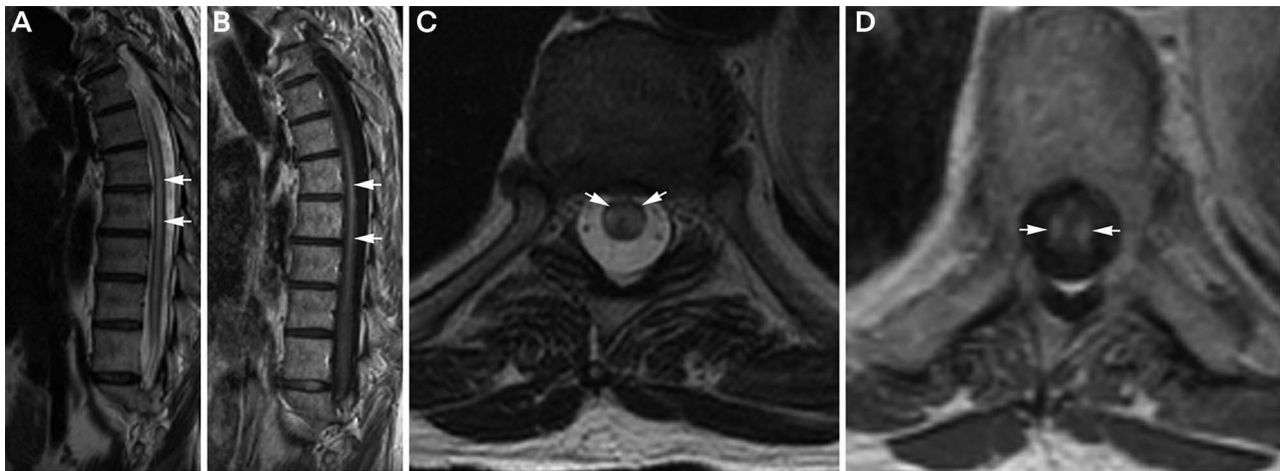


FIGURE 3-3

Imaging of the patient in **CASE 3-1**. Sagittal T2-weighted cervical spine MRI shows a longitudinally extensive T2 hyperintensity that forms a sagittal line (A, lower two arrows) with additional T2 hyperintensity above (A, upper arrow). Axial T2-weighted image shows predominantly gray matter T2 hyperintensity that forms an H sign (B, arrow). No gadolinium enhancement is appreciable on sagittal postcontrast T1-weighted image (C), and minimal gadolinium enhancement is seen on axial postcontrast T1-weighted image (D, arrow). Sagittal T2-weighted MRI of the thoracic spine reveals a short T2 hyperintensity in the upper thoracic/lower cervical cord (E, upper arrow) and a separate T2 hyperintensity in the conus (E, lower arrow). Axial T2-weighted image shows the lesion to be central, forming an H sign (F, arrow); no definitive accompanying enhancement is seen on sagittal (G) or axial (H) postcontrast T1-weighted images.

**FIGURE 3-4**

MRI findings in paraneoplastic myelopathy. Sagittal T2-weighted thoracic spine image shows longitudinally extensive T2 signal abnormality (A, arrows) extending over seven spinal segments with associated gadolinium enhancement (B, arrows) on sagittal postcontrast T1-weighted image. Axial T2-weighted image shows symmetric tract-specific T2 signal abnormality (lateral columns) (C, arrows) that enhances after gadolinium administration on axial post contrast T1-weighted image (D, arrows).

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biomarkers of transverse myelitis that should be tested in patients in whom the clinical and paraclinical findings are not suggestive of MS (eg, LETM). AQP4-IgG–seropositive NMOSD is found in up to 50% of patients with LETM and 90% of patients with recurrent LETM, and it may occur in conjunction with or be preceded by optic neuritis or area postrema syndrome.³⁶ The myelitis of MOG-IgG–associated disorder may occur in isolation, as a component of ADEM, or in conjunction with optic neuritis and accounts for 20% to 30% of NMOSD syndromes negative for AQP4-IgG.⁴⁰ For detection of AQP4-IgG and MOG-IgG, serum yields the optimal sensitivity (more so than CSF) and cell-based assays are the most reliable; CSF can be considered in highly suspicious cases if serum is negative. Rare cases of isolated MOG-IgG CSF positivity have been reported.⁴⁹ Testing before immunotherapy (eg, plasma exchange) is important to reduce the risk of false negatives. Low-positive MOG-IgG results should be viewed with caution as false positives can occur, particularly when ordered in low-probability situations (eg, patients with classic clinical, radiologic, and CSF features of MS), and the positive MOG-IgG test result should not replace clinical judgment. With AQP4-IgG cell-based assays, false positives are extremely rare, although with older-generation techniques (eg, enzyme-linked immunosorbent assay [ELISA]), false positives at low titer can be found.⁵⁰ Detection of AQP4-IgG in a patient with transverse myelitis predicts substantial risk of further relapses (>90%) and warrants lifelong immunotherapy; repeat AQP4-IgG titers are generally not useful. Repeating MOG-IgG serology may help predict the risk of recurrence as transient seropositivity is more associated with a monophasic course.^{39,40} AQP4-IgG may coexist with other neural autoantibodies (or their respective syndromes), including *N*-methyl-D-aspartate (NMDA) receptor-IgG (anti-NMDA receptor encephalitis) and GFAP-IgG (meningoencephalomyelitis), often with an accompanying teratoma. Muscle

acetylcholine receptor-binding antibodies and a clinical syndrome of myasthenia gravis may also occur.¹⁷ However, AQP4-IgG coexisting with MOG-IgG is exceedingly rare (0.06%).⁵¹ MOG-IgG and NMDA receptor-IgG also coexist more frequently than expected. Several neural autoantibodies are associated with paraneoplastic myelopathies, and the most commonly encountered are amphiphysin⁵² and collapsin response mediator protein-5 (CRMP-5)-IgG/anti-CV2.

GFAP-IgG appears to be a marker of a meningoencephalomyelitis, and CSF analysis yields optimal sensitivity and specificity. Glycine receptor α_1 subunit (GlyR α_1)-IgG, GAD 65-IgG (neurologic disease is usually associated with high titers and detection in CSF), and adaptor protein-3B2 (AP3B2)-IgG are also associated with autoimmune or paraneoplastic myelopathies.^{53,54}

Myelitis has been recently described accompanying a cerebellitis and brainstem encephalitis in a patient with neurochondrin-IgG.⁵⁵ Myelitis has also been reported in patients with autoantibodies specific for the neuronal (type 1) isoform of the ubiquitously expressed inositol trisphosphate receptor (ITPR1),⁵⁶ typically accompanying cerebellitis and neuropathy and rarely in isolation. Myelopathy has also been reported coexisting with encephalopathy and cerebellar ataxia in patients with neuronal intermediate filament NfL-IgG.⁵⁷

Testing serum for antinuclear antibody, double-stranded DNA antibodies, Sjögren syndrome A (SSA)/Sjögren syndrome B (SSB), cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA), other antibodies to the extractable nuclear antigen, C3/C4 complement, antiphospholipid antibodies, β_2 glycoprotein-1 autoantibodies, and lupus anticoagulant should be considered as part of laboratory testing in a patient with suspected myelitis. Although inflammatory myelitis has been reported in patients with systemic lupus erythematosus and Sjögren syndrome or with serologic markers of those disorders, it is crucial to test such patients for AQP4-IgG. It is now recognized that AQP4-IgG-seropositive NMO/D may coexist with these disorders, and seropositivity for AQP4-IgG confirms the NMO/D diagnosis rather than the myelitis being a manifestation of the connective tissue disease; such patients require specific treatment for NMO/D.⁵⁸ Indeed, antiphospholipid antibodies frequently coexist with AQP4-IgG-seropositive NMO/D, and patients may be at higher risk of deep venous thrombosis.⁵⁸

CSF ANALYSIS

The basic parameters of CSF (white and red blood cell counts, protein, glucose, and oligoclonal bands/IgG index) are helpful to show evidence of inflammation. The majority of autoimmune/inflammatory myelitis episodes will be accompanied by an elevated CSF white blood cell count, and its absence should at least raise consideration of alternative etiologies (eg, vascular myelopathies). A normal cell count with a markedly elevated CSF protein may suggest a spinal block, which can occur with spondylosis or tumor but should also lead to reconsideration of a peripheral cause (eg, Guillain-Barré syndrome). With MS myelitis, the CSF white blood cell count is usually less than 50 cells/mm³ and 85% of patients will have elevated oligoclonal bands or IgG index. With MOG-IgG-associated disorder, AQP4-IgG-seropositive NMO/D, and GFAP antibody-associated encephalomyelitis, the range in CSF

KEY POINTS

- AQP4-IgG and MOG-IgG are two important antibody biomarkers of transverse myelitis that should be tested in patients with transverse myelitis in whom the clinical and paraclinical findings are not suggestive of MS.

- For AQP4-IgG and MOG-IgG, serum yields the optimal sensitivity (more so than CSF) and cell-based assays are the most reliable.

- Care is needed with low-positive MOG-IgG results as false positives can occur, particularly when ordered in low-probability situations, and the positive MOG-IgG test result should not replace clinical judgment.

- With AQP4-IgG cell-based assays, false positives are extremely rare, although with older-generation techniques, false positives at low titer can be found.

- Several neural autoantibodies are associated with paraneoplastic myelopathies, and the most commonly encountered are amphiphysin and collapsin response mediator protein-5 (CRMP-5)/anti-CV2.

- The majority of autoimmune/inflammatory myelitis episodes will be accompanied by an elevated CSF white blood cell count, and its absence should at least raise consideration of alternative etiologies (eg, vascular myelopathies).

CASE 3-2

A previously healthy 38-year-old man presented with numbness affecting the trunk and painful dysesthesia involving both upper extremities, which were followed by urinary retention, with symptoms worsening over the course of 6 weeks. He had no other systemic symptoms.

Neurologic examination revealed a mild upper motor neuron pattern of weakness affecting both upper extremities and abnormal proprioception in the hands bilaterally but was otherwise normal. MRI of the cervical spine showed a longitudinally extensive T2-hyperintense abnormality in the cervical spine from C3 through T1 (FIGURES 3-5A and 3-5B), with dorsal subpial (FIGURE 3-5C) and central canal (FIGURE 3-5C) gadolinium enhancement forming a trident pattern on axial sequences, suggestive of spinal cord sarcoidosis (FIGURE 3-5D). CSF analysis showed 67 total nucleated cells/mm³ (normal 0 cells/mm³ to 5 cells/mm³) of which 89% were lymphocytes, a mildly elevated protein at 50 mg/dL, a normal glucose, and no oligoclonal bands. Testing for aquaporin-4 (AQP4)-IgG, myelin oligodendrocyte glycoprotein (MOG)-IgG, antinuclear antibodies, angiotensin-converting enzyme, vitamin B₁₂, copper, and syphilis and Lyme serologies were negative. CT of the chest was reported as negative for malignancy or other abnormalities but fludeoxyglucose positron emission tomography (FDG-PET) with CT showed increased glucose uptake in the subcarinal, precarinal, and bilateral hilar nodes (FIGURE 3-5E), and biopsy revealed non-necrotizing granulomatous inflammation. Extensive testing for fungal and bacterial etiologies, including tuberculosis, were negative.

The patient was treated with IV methylprednisolone (1 g/d for 5 days) and transitioned to a prolonged oral steroid taper for 12 weeks. After 36 months of follow-up, no recurrence of enhancing lesions was seen and the patient's urinary retention had resolved, but he continued to have residual allodynia in the upper limbs that responded poorly to multiple neuropathic pain medications.

COMMENT

The yield of PET-CT imaging may be higher than CT alone and should be considered in the evaluation for neurosarcoidosis as it can help identify potential sites for biopsy. The presence of gadolinium enhancement involving the central canal and the dorsal subpial region forming a trident pattern on axial images should raise suspicion for neurosarcoidosis. Chronic neuropathic pain may be refractory to neuropathic medications and is a common residuum of spinal cord sarcoidosis.

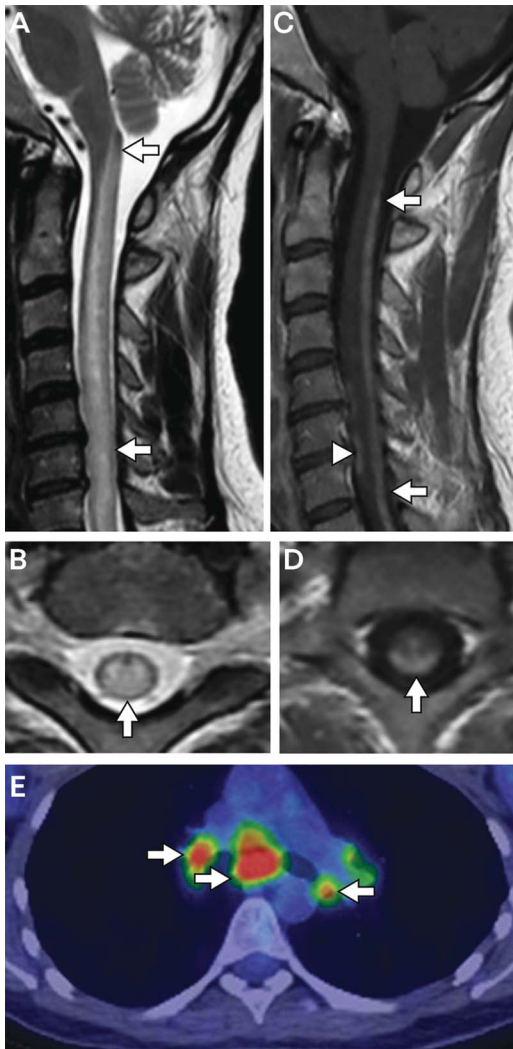


FIGURE 3-5
 Imaging of the patient in **CASE 3-2**. **A**, Sagittal T2-weighted cervical spine MRI shows a longitudinally extensive T2 hyperintensity (arrows). **B**, Axial T2-weighted image shows T2 hyperintensity in the central aspect of the cord with edema (arrow). **C**, Sagittal postcontrast T1-weighted image shows central (arrowhead) and dorsal (arrows) subpial enhancement. **D**, Axial postcontrast T1-weighted image shows a characteristic trident sign (arrow). **E**, Increased fludeoxyglucose positron emission tomography (FDG-PET)/CT shows uptake in the subcarinal nodes, precarinal nodes, and bilateral hilar nodes (arrows).

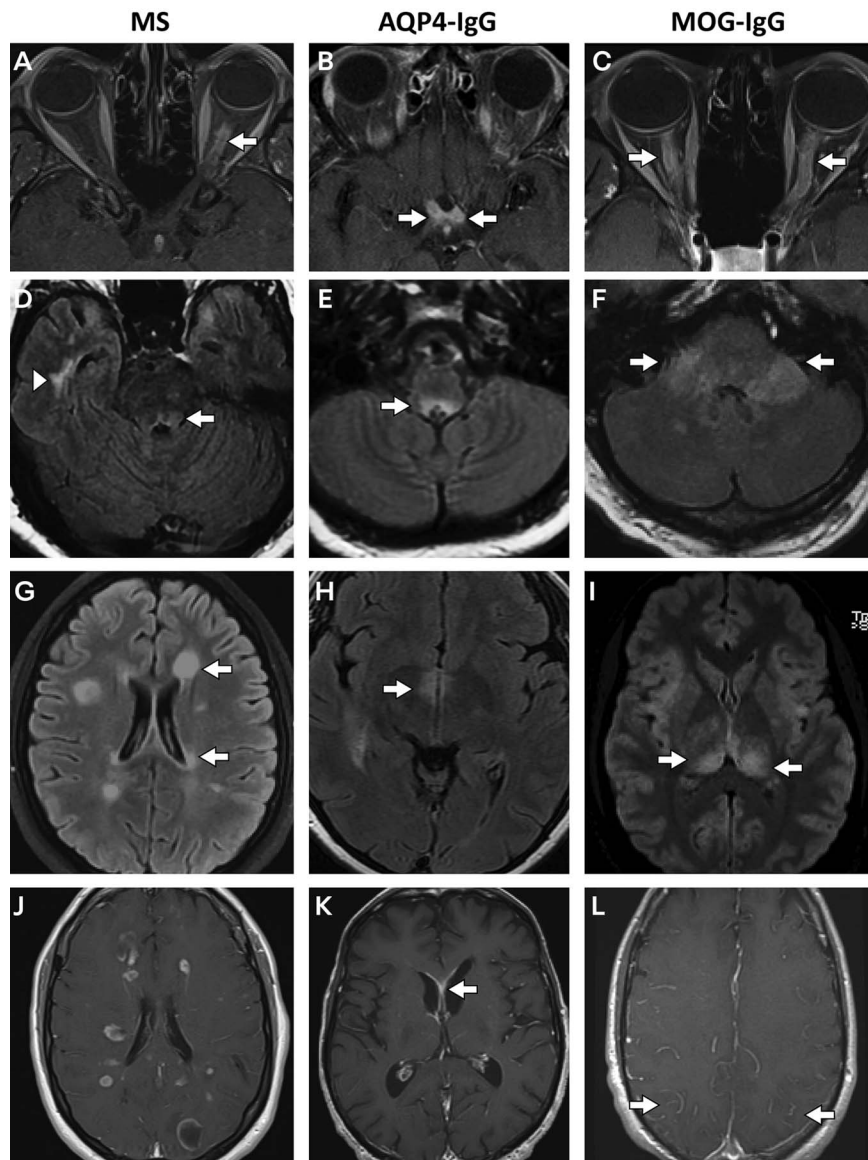


FIGURE 3-6

Comparison of brain MRI in multiple sclerosis (MS), aquaporin-4-IgG (AQP4-IgG)-seropositive neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-associated disorder. Axial postcontrast T1-weighted MRIs show optic nerve enhancement extending less than half the length of the nerve in a patient with MS (A, arrow), whereas AQP4-IgG-seropositive NMOSD has a predilection for the optic chiasm (B, arrows) and MOG-IgG-associated disorder is typically associated with bilateral anterior optic nerve pathway enhancement extending more than half the length of the optic nerve (C, arrows). Axial fluid-attenuated inversion recovery (FLAIR) images reveal peripheral small T2-hyperintense lesions in the dorsal pons typical of MS (D, arrow); an additional characteristic inferior temporal pole lesion of MS is also noted (D, arrowhead); a peri-fourth ventricle/area postrema T2-hyperintense lesion is seen in the patient with AQP4-IgG-seropositive NMOSD (E, arrow), whereas bilateral fluffy middle cerebellar peduncle T2-hyperintense lesions are typical of MOG-IgG-associated disorder (F, arrows). Axial FLAIR MRIs reveal typical ovoid periventricular lesions in MS (G, arrows), a peri-third ventricle hyperintense lesion in AQP4-IgG-seropositive NMOSD (H, arrow), and characteristic deep gray matter (bithalamic) hyperintense lesions in MOG-IgG-associated disorder (I, arrows). Axial postcontrast T1-weighted images show multiple enhancing lesions typical of MS (J), linear ependymal enhancement occasionally encountered with AQP4-IgG-seropositive NMOSD (K, arrow), and prominent enhancing vessels in MOG-IgG-associated disorder (L, arrows).

white cell count is wider and can be between 0 cells/mm³ and 1000 cells/mm³. Most inflammatory/autoimmune myelitis episodes are accompanied by a lymphocytic predominance. AQP4-IgG-seropositive NMOSD can be associated with a neutrophilic or eosinophilic predominance, whereas neutrophilic predominance is associated with Behçet disease. Oligoclonal bands are uncommon with AQP4-IgG-seropositive NMOSD (<30% of patients) and very rare with MOG-IgG-associated disorder (<10% of patients). Spinal cord sarcoidosis is almost always associated with an elevated white blood cell count, although low glucose is rare; if present, low glucose suggests a coexisting sarcoid meningitis. Experimental studies have shown that CSF GFAP is elevated (reflective of astrocytic damage) in AQP4-IgG-seropositive NMOSD, whereas elevated myelin basic protein (reflective of oligodendrocyte damage) is recognized with MOG-IgG-associated disorder.^{59,60} A lymphocytic pleocytosis is encountered in approximately two-thirds of paraneoplastic myelitis.⁹ CSF angiotensin-converting enzyme lacks sensitivity and specificity for sarcoidosis diagnosis and is of limited use.

Occasionally, mild elevations in white blood cell count may be encountered in noninflammatory/autoimmune myelopathies (eg, spinal cord infarct), perhaps from secondary inflammation or breakdown of the blood-spinal cord barrier, and should not dissuade from those diagnoses in the correct clinical context.

CSF testing is also useful to assess for mimics of autoimmune myelitis. Testing with polymerase chain reaction (PCR) in CSF for herpes simplex virus type 1, herpes simplex virus type 2 (associated with the lumbar myeloradiculitis of Elsberg syndrome), varicella-zoster virus, cytomegalovirus, and JC virus (rarely associated with myelopathy) or next-generation sequencing can be considered. CSF cytology and flow cytometry, and *MYD88* L265P mutation (L265P is a missense mutation changing leucine at position 265 to proline in *MYD88*, identified in approximately 90% of cases of Waldenström macroglobulinemia and in significant proportions of cases of activated diffuse large B-cell lymphomas and IgM monoclonal gammopathy of undetermined significance) are helpful in the evaluation of suspected lymphoproliferative disorders.⁶¹

OTHER TESTING

In cases of suspected neurosarcoidosis, chest x-ray is insensitive and CT chest is 73% sensitive; however, FDG-PET/CT has higher sensitivity (88%) and is useful in selected cases (**CASE 3-2; FIGURE 3-5E**).^{1,8,19} CT body is considered first line in assessing for malignancy accompanying a paraneoplastic myelopathy, but PET-CT offers better sensitivity if suspicion is high; mammogram is also useful.⁶² Searching for cancer is also recommended in older patients (≥50 years) with AQP4-IgG-seropositive NMOSD as it is recognized to occur occasionally in a paraneoplastic context.⁶³ Somatosensory evoked potentials may be helpful for patients who cannot undergo MRI. In patients with clinical and radiologic progression despite immunotherapy, the diagnosis of an autoimmune myelitis should be reconsidered. Spinal cord biopsy is considered a last resort; however, in one study at a tertiary referral center it helped guide specific treatment in 26% of patients with a morbidity of 21%, although permanent deficits were rare (<5%).⁶⁴

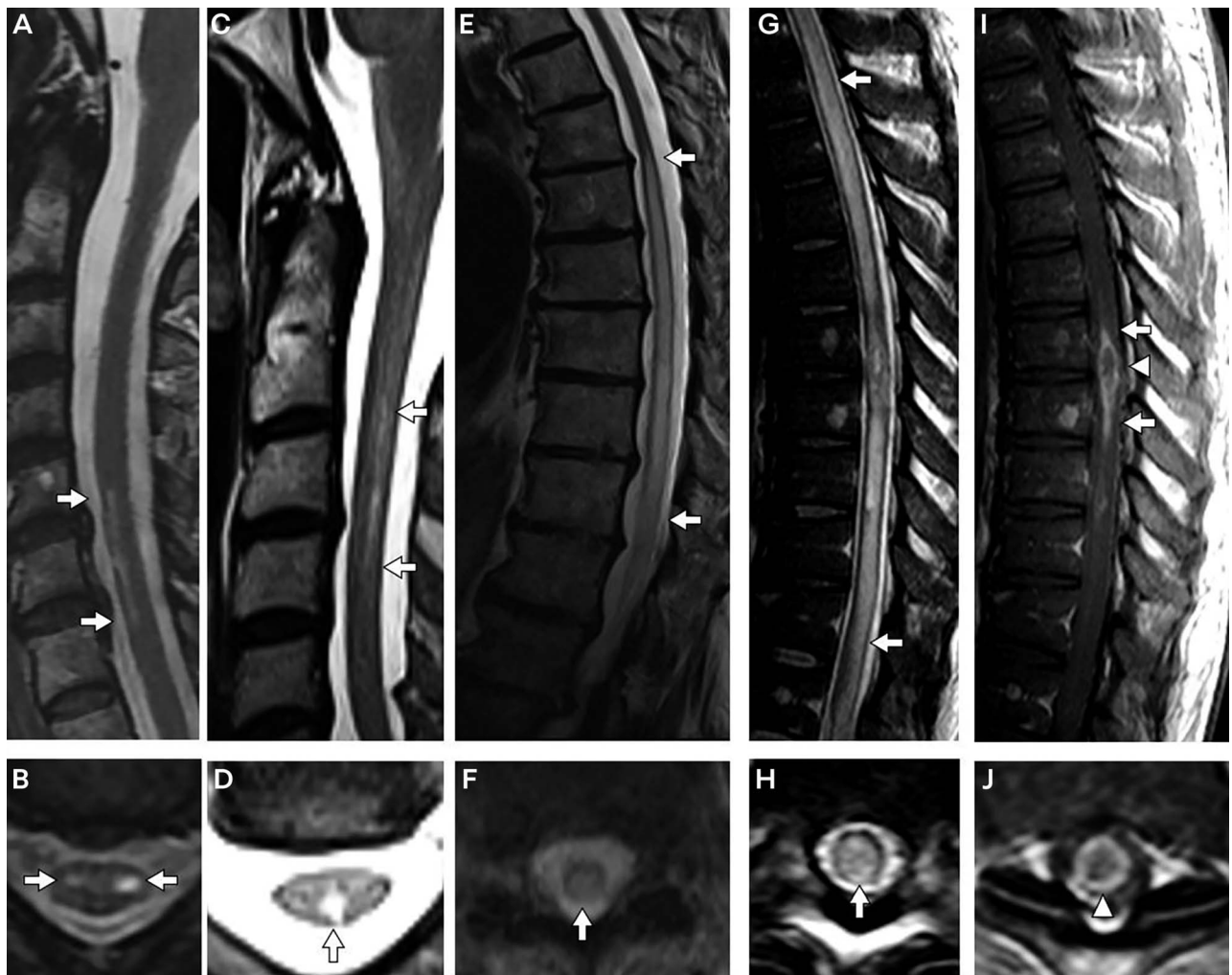


FIGURE 3-7

Mimics of inflammatory/autoimmune myelitis. Sagittal T2-weighted cervical spine MRI shows T2 hyperintensity extending from C5 through C7 in the anterior aspect of the cord (A, arrows); axial T2-weighted MRI shows involvement of the anterior horn cells in a snake-eye pattern (B, arrows), consistent with spinal cord infarct. Sagittal T2-weighted cervical spine MRI shows T2 hyperintensity in the dorsal cord extending from C2 through C4 (C, arrows); axial T2-weighted image shows involvement of the dorsal cord (D, arrow), consistent with vitamin B₁₂ deficiency. Sagittal T2-weighted thoracic spine MRI shows a longitudinally extensive T2 hyperintensity extending from the upper thoracic cord to the conus (E, arrows); axial T2-weighted image shows involvement of the central cord (F, arrow) that was eventually confirmed to be a dural arteriovenous fistula despite the lack of evident flow voids. Sagittal T2-weighted thoracic spine MRI shows a longitudinally extensive T2 hyperintensity in the thoracic cord (G, arrows); axial T2-weighted image shows that the lesion is central (H, arrow). Sagittal (I) and axial (J) postcontrast T1-weighted images show a rim of enhancement (I, J, arrowheads) around a less enhancing center with a flame pattern at the top and bottom of the lesion (I, arrow), a pattern that is highly characteristic of spinal cord intramedullary metastasis.

Panels A and B modified with permission from Flanagan EP, Pittock SJ, *Handb Clin Neurol*.²⁴ © 2017 Elsevier BV.

DIFFERENTIAL DIAGNOSIS

Understanding the differential diagnosis of autoimmune/inflammatory myelopathy is crucial as many diagnostic pitfalls can lead the clinician to the wrong diagnosis. As outlined previously, the time to nadir and speed of onset are crucial in narrowing the differential diagnosis. MRI attributes, particularly the gadolinium enhancement patterns, are also extremely useful in determining the cause of the myelopathy (TABLE 3-1, TABLE 3-2, and FIGURE 3-7). An example of a noninflammatory myelopathy mimicking an inflammatory myelopathy is outlined in CASE 3-3 and illustrated in the accompanying FIGURE 3-8. FIGURE 3-9 is a pictorial summary of the useful T2 signal and enhancement patterns accompanying myelopathies with longitudinally extensive lesions clinicians should be aware of.

ACUTE TREATMENT

For most autoimmune/inflammatory myelopathies, after reasonable exclusion of alternative etiologies such as extrinsic compression, spinal cord infarction, and infections, expert consensus recommends prompt administration of high-dose IV corticosteroids with 1 g IV methylprednisolone once daily for 5 days. Treatment should not be withheld while waiting for results of antibody testing. In patients with myelitis as a manifestation of CNS inflammatory demyelinating disease (eg, MS, AQP4-IgG-seropositive NMOSD, MOG-IgG-associated disorder, ADEM, idiopathic transverse myelitis) with severe neurologic deficits despite steroids, plasma exchange should be considered, as a randomized sham-controlled trial showed benefit of plasma exchange in patients with inflammatory CNS demyelinating disease with ongoing impairment after high-dose corticosteroids.⁶⁷⁻⁶⁹ In children with MOG-IgG-associated disorder, IV immunoglobulin (IVIg) has been used in the acute setting with good success, and a steroid taper over the course of 6 to 12 weeks may be considered after an acute MOG-IgG-associated disorder attack to prevent early relapse. Supportive care is focused on preventing complications, with early implementation of frequent bladder scans, intermittent catheterization or temporary indwelling catheter placement, and prevention of deep venous thrombosis and decubitus ulcers. Depending on the etiology of the myelopathy, chronic maintenance treatments may be implemented to prevent future relapses.

MAINTENANCE AND ATTACK-PREVENTION IMMUNOTHERAPY

A comprehensive review of all the medications used as maintenance therapies for autoimmune and inflammatory myelopathies, dosing, and side effects is beyond the scope of this article, but a brief summary is provided here. Several disease-modifying therapies are approved for relapsing-remitting and progressive forms of MS.⁷⁰ Long-term immunosuppression is recommended in all patients with AQP4-IgG-seropositive NMOSD, as attacks can be very severe. Historically, treatments included azathioprine and mycophenolate mofetil, but these lacked clinical trial evidence. Recently, four randomized controlled phase 3 clinical trials for relapse prevention in NMOSD (which included predominantly AQP4-IgG-seropositive cases) showed efficacy for four novel treatments in preventing attacks. The treatments tested included eculizumab, which targets the terminal complement component C5⁷¹; inebilizumab, which antagonizes CD19, depleting B cells and plasmablasts⁷²; rituximab, which blocks CD20, depleting B cells⁷³; and satralizumab, which

KEY POINTS

- Understanding the differential diagnosis of autoimmune/inflammatory myelopathy is crucial as many diagnostic pitfalls can lead the clinician to the wrong diagnosis.
- For most autoimmune/inflammatory myelopathies, after reasonable exclusion of alternative etiologies such as extrinsic compression, spinal cord infarction, and infections, expert consensus recommends prompt administration of high-dose IV corticosteroids with 1 g IV methylprednisolone once daily for 5 days.
- In patients with myelitis as a manifestation of central nervous system inflammatory demyelinating disease with severe neurologic deficits despite steroids, plasma exchange should be considered.

CASE 3-3

A 35-year-old man presented with subacute paresthesia initially affecting the right arm, which had spread over the course of 5 weeks to include the left arm symmetrically up to the midforearm. He had progressed despite treatment for presumed bilateral carpal tunnel syndrome. Six months later, he was involved in a motor vehicle accident and subsequently developed a progressive gait disorder, with right leg weakness and frequent falls. MRI of his cervical spine was abnormal, showing a longitudinally extensive T2 hyperintensity (FIGURE 3-8A) centrally located on axial imaging (FIGURE 3-8B), associated with a pancakelike transverse band of enhancement in which the width was equal to the height at C5-C6 (FIGURE 3-8C). On axial images, the enhancement involved the white matter and spared the gray matter (FIGURE 3-8D). Moderate to severe degenerative disk disease was also noted. CSF showed a normal white blood cell count, red blood cell count, and glucose; a mildly elevated protein of 66 mg/dL; and negative oligoclonal bands and IgG index. Extensive serologic testing for infectious and autoimmune causes of myelopathy were negative, including aquaporin-4 (AQP4)-IgG and myelin oligodendrocyte glycoprotein (MOG)-IgG. Brain MRI and optical coherence tomography were normal. The patient was diagnosed with seronegative neuromyelitis optica spectrum disorder (NMOSD) and received treatment with IV methylprednisolone daily for 5 days, but his sensory symptoms progressed, gait dysfunction worsened, and urinary frequency and erectile dysfunction ensued.

A second neurologic opinion was sought. Neurologic examination showed an upper motor neuron pattern of weakness affecting the right upper extremity and diffuse hyperreflexia, a positive Hoffman sign on the right, and bilateral extensor plantar responses. His gait was broad based, and a positive Romberg sign was noted. A diagnosis of cervical spondylotic myelopathy was established based on the characteristic presentation and imaging findings. The patient underwent cervical decompression surgery, after which his symptoms improved.

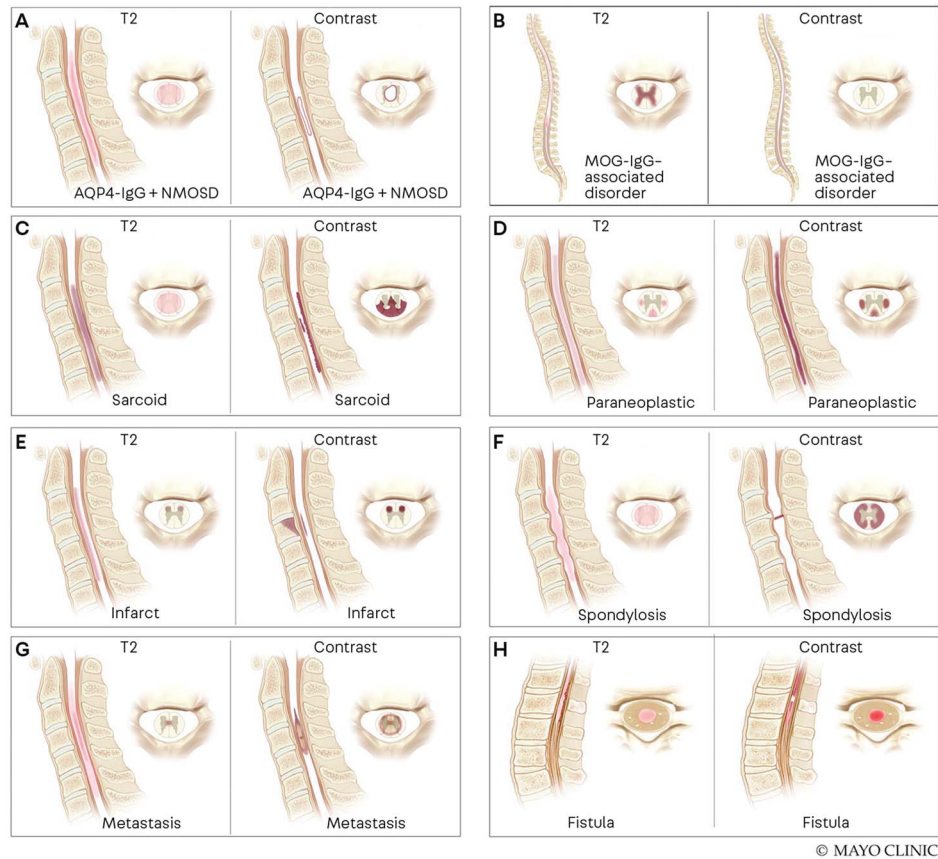
COMMENT

Spondylotic myelopathy can be associated with gadolinium enhancement in 7% of patients, and its presence often leads to diagnostic confusion and suspicion for a primary inflammatory or neoplastic etiology. The progressive myelopathy following trauma and absence of CSF inflammation were atypical for inflammatory myelopathy. The pattern of gadolinium enhancement characterized by a pancakelike transverse band of enhancement on sagittal images and sparing of the gray matter on axial images is highly suggestive of spondylotic myelopathy.⁶⁵ The accompanying stenosis may appear only moderate in the neutral position, and dynamic flexion-extension MRI views may help in selected cases as compression often becomes more apparent during extension.⁶⁶



FIGURE 3-8

Imaging of the patient in **CASE 3-3**. Sagittal T2-weighted cervical spine MRI shows a longitudinally extensive hyperintensity in the cervical cord (*A*, *arrows*), which on axial T2-weighted images is central (*B*, *arrow*). Sagittal postcontrast T1-weighted image (*C*) reveals evidence of a pancakelike transverse band of enhancement at the C5-C6 interspace where the width is equal to the height. Axial postcontrast T1-weighted image shows enhancement of the white matter sparing the gray matter (*D*, *arrows*), highly consistent with the specific pattern of enhancement seen with cervical spondylotic myelopathy.



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FIGURE 3-9

Distinctive imaging features and patterns of enhancement with myelopathies accompanied by longitudinally extensive T2 lesions. The sagittal and axial images depict the typical lesion patterns on T2-weighted images (shown in light red) and postcontrast T1-weighted images (enhancement after contrast is shown in dark red). For each panel, the T2 sequences are shown on the left and postcontrast T1 sequences are shown on the right. **A**, Aquaporin-4 (AQP4)-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) myelitis on sagittal cervical spine images typically reveals a solitary T2-hyperintense lesion that is central on axial sequences and extends over three or more vertebral segments, with contrast enhancement sometimes having a ringlike appearance. **B**, Myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disorder myelitis on cervicothoracic cord images typically shows multifocal T2-hyperintense lesions with one or more longitudinally extensive T2 lesions and a predilection for the conus. The T2 lesions are generally central on axial sequences and in about one-third of patients will be restricted to the gray matter, forming an H pattern. Contrast enhancement is infrequent; if present, it is usually faint. **C**, Neurosarcoidosis myelitis in the cervical spine shows a typical nonspecific longitudinally extensive T2-hyperintense lesion that is central on axial images. Postcontrast images show hallmark linear dorsal subpial enhancement with some accompanying central canal enhancement, with the combination forming an axial trident sign. **D**, Paraneoplastic myelopathy in the cervical spine shows the typical longitudinally extensive T2 signal abnormality with a tractopathy on axial images confirmed by the presence of symmetric tract-specific T2 hyperintensity and enhancement restricted to the dorsal columns or lateral columns, or both. **E**, Spinal cord infarction in anterior spinal artery territory reveals the typical pencillike linear anterior cord longitudinally extensive T2 hyperintensity with a partial linear strip of enhancement with contrast. On axial T2 and postcontrast images, the anterior horn cells are preferentially affected in an owl-eye or snake-eye pattern; occasionally (in approximately 10%), a vertebral body infarct can ensue, as shown here. **F**, Cervical spondylotic myelopathy with sagittal imaging showing spondylosis and a spindle-shaped T2 hyperintensity extending more than three vertebral segments, with a characteristic flat pancake-like transverse band of enhancement just below the site of maximum stenosis on postcontrast images. On axial images, the enhancement typically involves the white matter but spares the gray matter. **G**, Intramedullary spinal cord metastasis reveals a longitudinally extensive T2 hyperintensity with an enhancing intramedullary mass with the hallmark thin rim of more intense enhancement (the rim sign) accompanied by an ill-defined flame-shaped region of enhancement at its superior and inferior margins with a central dot (the dot sign) occasionally noted on postcontrast images, as shown here. **H**, Spinal dural arteriovenous fistula reveals the typical thoracic longitudinally extensive T2 hyperintensity extending to the conus with prominent flow voids and contrast enhancement and a characteristic “missing piece” of enhancement sometimes noted, as shown here.

targets interleukin-6, involved in the plasmablast pathway.⁷⁴ Transitional low-dose prednisone (10 mg to 20 mg orally daily) for up to 1 month is often used while the B-cell-depleting treatment takes effect. No randomized controlled trials have been conducted for MOG-IgG-associated disorder, and the role of immunotherapy after an initial episode of transverse myelitis related to MOG-IgG-associated disorder remains to be determined. As MOG-IgG-associated disorder may be monophasic, the current approach is generally not to treat after a single attack and generally to restrict maintenance immunotherapy to patients who relapse. Although the long-term outcome is generally favorable in MOG-IgG-associated disorder, the accumulation of mild disability with each attack supports the need for maintenance immunotherapies in this disease.⁷⁵ In the absence of clinical trial evidence in MOG-IgG-associated disorder, consideration can be given to empiric mycophenolate mofetil, azathioprine, rituximab, and intermittent IVIg.⁷⁶ For GFAP antibody-associated encephalomyelitis, a brisk response to steroids is characteristic, but relapses can occur, and prolonged administration of steroids or additional immunotherapy such as mycophenolate mofetil may be required in some cases.⁴⁵

Spinal cord sarcoidosis is usually treated with high-dose IV steroids followed by prolonged high-dose oral corticosteroids (eg, prednisone 1 mg/kg/d for 3 months followed by a prolonged taper over the subsequent 6 to 12 months); steroid prophylaxis with trimethoprim-sulfamethoxazole (one single-strength tablet daily or one double-strength tablet 3 times a week) is recommended in any patients on more than 20 mg/d prednisone for more than 5 weeks. In addition, calcium and vitamin D supplementation and monitoring of bone density are recommended and gastrointestinal prophylaxis should be considered. Administration of other medications, such as infliximab, may be considered in those with severe disease or those who are intolerant to steroids. Steroid-sparing medications, including methotrexate, azathioprine, and mycophenolate mofetil, have been used in patients with spinal cord sarcoidosis who relapse or develop recurrence on weaning off steroids but may also be considered from onset to reduce the risk of relapse.⁷⁷

CONCLUSION

Autoimmune myelopathies are a heterogeneous group of spinal cord disorders unified by their immune-mediated mechanism and potential for response to immunotherapy. The time course of development of neurologic symptoms is crucial in determining the likely etiology of a myelopathy, and autoimmune myelopathies are usually subacute in onset. Immune-mediated myelopathies may be monophasic or the initial manifestation of a relapsing disorder (eg, MS, NMO); ancillary testing, particularly MRI, serologic antibody biomarkers, and CSF analysis, can help determine a specific diagnosis and the correct treatment approach and assist with prognosis. Idiopathic transverse myelitis should be considered a diagnosis of exclusion and should only be assigned once a comprehensive search for alternative etiologies has been completed. Timely administration of acute treatment is critical to help stabilize and improve symptoms while maintenance immunotherapy decisions are based on the underlying etiology found.

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