Evaluation and Management of Acute Myelopathy

Elia Sechi, MD[1] Eoin P. Flanagan, MD[1,2]

[1] Department of Neurology, Mayo Clinic, Rochester, Minnesota
[2] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

Address for correspondence Eoin P. Flanagan, MD, Department of Neurology and Laboratory Medicine and Pathology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905 (e-mail: flanagan.eoin@mayo.edu).

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Abstract

Acute myelopathies are spinal cord disorders characterized by a rapidly progressive course reaching nadir within hours to a few weeks that may result in severe disability. The multitude of underlying etiologies, complexities in confirming the diagnosis, and often unforgiving nature of spinal cord damage have always represented a challenge. Moreover, certain slowly progressive myelopathies may present acutely or show abrupt worsening in specific settings and thus further complicate the diagnostic workup. Awareness of the clinical and magnetic resonance imaging characteristics of different myelopathies and the specific settings where they occur is fundamental for a correct diagnosis. Neuroimaging helps distinguish compressive etiologies that may require urgent surgery from intrinsic etiologies that generally require medical treatment. Differentiation between various myelopathies is essential to establish timely and appropriate treatment and avoid harm from unnecessary procedures. This article reviews the contemporary spectrum of acute myelopathy etiologies and provides guidance for diagnosis and management.

Keywords

- spinal cord
- myelitis
- differential diagnosis
- misdiagnosis
- treatment

Acute myelopathies are a heterogeneous group of neurologic disorders characterized by rapidly evolving spinal cord dysfunction of multiple etiologies that may result in severe acute and long-term disability. The timing of symptom onset and progression to nadir has important etiological implication, as most myelopathies have a preferential timing of presentation (e.g., inflammatory myelopathies typically present acutely within days, while hereditary myelopathies tend to progress slowly over months). However, certain chronic myelopathies may present acutely or manifest with rapid deterioration in the setting of a previously slowly progressive course.[1] The severity is mainly dependent on the type (e.g., ischemic vs. inflammatory) and extent (e.g., partial vs. complete) of spinal cord damage. Among inflammatory myelopathies, the myelitis associated with multiple sclerosis (MS) classically affects only part of the spinal cord parenchyma on a transverse section (partial transverse myelitis), while the myelitis associated with autoantibodies against aquaporin-4 (AQP4-IgG) and myelin oligodendrocyte glycoprotein (MOG-IgG) generally results in bilateral/complete transverse spinal cord dysfunction.[2] The term "idiopathic transverse myelitis (ITM)" defines an acute, bilateral spinal cord dysfunction of unclear etiology that is assumed to be inflammatory. This relies on indirect evidence of spinal cord inflammation and is a common "diagnostic guess" among clinicians when there is uncertainty given the high relative frequency of inflammatory myelopathies in the population and potential for reversibility with immunotherapy. Although diagnostic criteria have been proposed for ITM in 2002,[3] the risk of misdiagnosis is high and noninflammatory myelopathies (e.g., vascular, neoplastic, infectious) can sometimes show laboratory/magnetic resonance imaging (MRI) characteristics typically seen with spinal cord inflammation.[4] Neuroimaging with MRI is crucial for diagnosis and to help distinguish extrinsic compressive from intrinsic myelopathy etiologies. Differentiation between various myelopathies is fundamental as an incorrect diagnosis may lead to unnecessary procedures (e.g., spinal cord biopsy in patients with severe inflammatory myelopathy misdiagnosed as neoplasm), or

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inappropriate treatments that may worsen the spinal cord deficit (e.g., corticosteroids in patients with spinal arteriovenous fistulas [AVFs]). In this article, we will review the main causes of acute myelopathy and provide clues for diagnosis and treatment. Traumatic spinal cord injury, the most common cause of spinal cord dysfunction, will be mentioned only briefly, as it is not generally cared for by neurologists in the acute setting; its management is mostly by trauma physicians including orthopaedic surgeons and neurosurgeons.[5] ►**Table 1** summarizes the typical demographics, presentation, timing, and clinical/MRI diagnostic clues for myelopathies that can present acutely/subacutely.

Epidemiology

The epidemiology of myelopathies varies worldwide, and comparison between studies is limited by ethnic and environmental differences that may favor specific etiologies. Traumatic spinal cord injury is the most common cause of acute myelopathy, with an estimated incidence in the United

Table 1 Demographic, clinical, and MRI characteristics of different myelopathy etiologies

Myelopathy etiology	Typical onset	Age and sex (if any)	Clinical, laboratory, and MRI characteristics
Mechanical injury			
Contusion/transaction (traumatic)[5]	Abrupt	Bimodal age distribution: 15–30 and >60 y of age, 80% men	Recent trauma, vehicle accident
Decompression sickness (scuba diving myelopathy)[45,103,145]	Acute; possible delayed onset in a minority of cases	Age 40–50; 80% men	Recent body-decompression (e.g., diving, flying). MRI: SCI-like/hemorrhagic changes; can be normal
Spondylotic[75]	Chronic, a fall/trauma may lead to acute worsening	Age 50–60; 70% men	Degenerative disc disease. MRI: long or short T2-lesion at narrowing level; "pancake" enhancement; spinal cord sarcoidosis may coexist
Surfer's myelopathy[41,146,147]	Hyperacute	Age 20–40; mostly men	Novice surfer/recent history of back hyperextension; MRI: similar to SCI
Iatrogenic			
Chemotherapy[59,63,148]	Variable, can be acute	Variable	Recent drug exposure: intrathecal cytarabine, methotrexate, or other chemotherapies. MRI: tractopathy (dorsal/lateral column signal abnormalities), nonspecific or normal
Immune checkpoint inhibitors[62]	Variable, often acute	Age 60–70; vary with cancer type	Recent treatment with immune checkpoint inhibitors; any immune-mediated myelitis may potentially occur
Post spinal/aortic surgery[66]	Hyperacute	Age 60–80	Recent surgery (e.g., spine degenerative disease, aortic)
Radiation myelopathy[10]	Generally chronic but rapid deterioration is possible	Age 30–40; men more affected	After spinal cord radiation; transient Lhermitte's symptom (>2 mo) or severe myelopathy (>6 mo). MRI: T2-hyperintensity ± enhancement; concomitant vertebral body changes
TNF-α inhibitors[64]	Acute	Variable	MRI: single or multiple nonspecific CNS demyelinating lesions
Inflammatory demyelinating			
AQP4-IgG associated[37,83]	Acute	Age 45–55; 90% women	Concomitant/preceding ON. MRI: long T2-lesion "bright spotty lesions," elongated ring/patchy enhancement

Table 1 (*Continued*)

MOG-IgG associated[2,21]	Acute	Age 10–30	Concomitant/preceding ON/encephalitis; preceding infection/vaccination. MRI: long T2-lesion: "sagittal line" + "H-sign"; common conus involvement; initially normal MRI in 10%
MS myelitis[78]	Acute	Age 20–40; 70% women	Most common myelitis. MRI: short-peripheral T2-lesions, mostly on dorsal/lateral columns; ring/nonspecific enhancement
Other immune mediated			
Connective tissue disease associated (e.g., Behçet's, lupus, Sjögren's)[32–34]	Acute	Age 30–50; women more affected	Systemic/laboratory features of connective tissue disease. MRI: "Bagel sign" in Behçet's disease; SCI-like with vasculitis
GFAP-IgG associated[25,38]	Chronic, acute presentation is possible	Age 40–50	Concomitant meningoencephalitis, optic disc edema, and/or tremor; common viral-like prodrome. MRI: faint long T2-lesions; punctate/leptomeningeal enhancement
Neurosarcoidosis[37,52]	Chronic; acute presentation in 20% of cases	Age 40–50	Occurs with/without systemic sarcoid. MRI: long T2-lesion in 50%; dorsal subpial enhancement, axial "trident" sign of enhancement, persistent enhancement
Paraneoplastic[53]	Chronic; acute presentation is possible	Age 60–70; slight female predominance	Known cancer/cancer risk factors (e.g., smoking); MRI: tract-specific signal abnormality/enhancement (dorsal/lateral column); normal in 35%
Infectious (see ►Table 2)			
Neoplastic			
Primary spinal cord neoplasms (astrocytoma and ependymoma account for 70% of the total)[74]	Chronic; acute onset is possible with high-grade tumors/hemorrhage	Age 30–40; 60% men; astrocytoma most common in children	MRI: expansile mass with cystic changes and syringomyelia, cap sign in ependymoma
Primary intramedullary spinal cord lymphoma[28]	Chronic; acute onset is possible	Age 60–70; 70% men	Immunocompromised patients; MRI: persistent enhancement (>3 mo)
Metastatic disease (epidural, intramedullary)[93,94]	Acute (nadir within 1 mo in 75% of cases)	Age 40–65, slight male predominance	Epidural enhancing mass; Known solid-organ cancer (lung and breast cancer most common); MRI: "rim and flame" and "central dot" sign
Toxic/Metabolic			
Biotinidase deficiency[58]	Variable, can be acute/subacute	Age 5–20	Vision loss frequently coexists; lactate elevation in serum and CSF; MRI: long T2-lesions that can enhance
Vitamin B12, vitamin E, or copper deficiency[24,98]	Chronic; acute presentation may occur with N_2O, zinc, or inborn errors of B12 metabolism	Age 30–40; 67% men	Gastric bypass, zinc supplements, pernicious anemia, malabsorption; recent anesthetic/N_2O exposure; MRI: dorsal/lateral column T2-lesions ("inverted V" sign)
Toxic (e.g., cocaine, heroin)[40,44]	Hyperacute with cocaine, acute with heroin	Variable	Recent toxic exposure

(*Continued*)

Table 1 (*Continued*)

Tropical (e.g., lathyrism, konzo)[149,150]	Acute/subacute	Variable	Malnutrition/ingestion of Cassava or *Lathyrus sativus* grass pea in endemic areas
Vascular			
Spinal AVF[54,92]	Chronic; acute presentation in 22% of cases	Age 50–70; 70% men	Clinical worsening after exertion or steroids. MRI: long thoracic T2-lesion; perimedullary flow voids, "missing-piece" sign
Other spinal vascular malformations (e.g., arteriovenous malformations, cavernous malformations)[151,152]	Variable based on malformation type and spinal location (e.g., intradural more commonly acute)	Age 40–50; more common in men	Presentation ranges from acute bleeding to incidental detection. MRI: variable; "popcorn" appearance in cavernous malformation (heterogenous intralesional T2-signal due to multiple microhemorrhages)
Spontaneous epidural hematoma[153]	Acute	Age 40–50; 60% men	Bleeding diathesis, trauma, postsurgical
Spontaneous SCI[14]	Hyperacute	Age 60–70; 60% men	Vascular risk factors. MRI: ventral T2-lesions, "snake/owl eye" sign, DWI restriction, vertebral body edge infarction; initially normal MRI in 24% of cases
Fibrocartilaginous embolism[39]	Hyperacute	Age 40–50; possible female predominance	Approximately 5% of spontaneous SCI; Triggering event often identifiable (e.g., Valsalva, heavy lifting); disc adjacent to lesion

Abbreviations: AQP4, aquaporin-4; AVF, arteriovenous fistula; CNS, central nervous system; CSF, cerebrospinal fluid; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; ON, optic neuritis; SCI, spinal cord infarction; TNF, tumor necrosis factor.

States of 40 to 55 cases per million.[6,7] Inflammatory myelopathies are the second most common cause, but their overall incidence is unknown. One study conducted in New Zealand reported an incidence of acute myelitis of any etiology of 24.6 cases per million, but cases of partial transverse myelitis were excluded.[8] Among inflammatory myelopathies, MS myelitis represents the most common cause, accounting for approximately one-third of MS cases at onset,[9] followed by idiopathic myelitis, myelitis associated with specific autoantibodies (e.g., AQP4-IgG, MOG-IgG), spinal cord sarcoidosis, and other less frequent etiologies. In a recent study conducted in Olmsted County (Minnesota), the incidence of ITM by 2002 diagnostic criteria was 8.6 cases per million, while isolated myelitis associated with AQP4-IgG and MOG-IgG had an incidence of approximately 2 cases per million.[10] A similar incidence of 8.8 cases per million is reported for spontaneous epidural abscess.[11] Robust epidemiological estimates for spinal cord infarction (SCI) are lacking, but in our experience its incidence may approximate that of AQP4-IgG- and MOG-IgG-associated myelitis. The frequency of infectious myelopathies is dependent on the types of infections endemic to each region. Outbreaks of diseases such as enterovirus D68 may occasionally impact the incidence of infectious/parainfectious myelitis worldwide. Certain myelopathies have a predilection for specific age ranges, sex, and ethnicities (e.g., AQP4-IgG-associated myelitis is more common among women and Asian or African American patients, while no sex or ethnic predominance is seen with MOG-IgG-associated myelitis),[12,13] which can provide clues for diagnosis (►**Table 1**).

Diagnostic Approach

When faced with convincing clinical symptoms/signs of myelopathy, the first step is gathering a thorough history for possible predisposing factors. For example, a person with a history of metastatic cancer who presents with new symptoms/signs of spinal cord dysfunction is likely to have metastatic compressive myelopathy, while acute onset paraplegia occurring immediately after aortic aneurysm surgery suggests iatrogenic SCI. In addition, a comprehensive assessment of the timing of onset of myelopathy symptoms, imaging, and laboratory findings is crucial. The following stepwise approach may help:

1. *Localization*:
   - Do the clinical signs/symptoms localize to the spinal cord?
   - If so, is there concomitant evidence of extraspinal neurologic/systemic involvement (e.g., isolated myelopathy vs. encephalomyelopathy/myeloneuropathy)?
2. *Setting*:
   - Are there clues in the demographics and history that help narrow the differential diagnosis?

Table 2 Main causes of intramedullary infection, preferred test, and diagnostic clues[26]

Pathogen	Typical timing of presentation; at-risk geographic area (GA), if any	Preferred diagnostic test	Clinical and MRI clues for diagnosis
Bacterial			
Intramedullary abscess (e.g., *Staphylococcus*, *Streptococcus*, *Enterococcus faecalis*, *Escherichia coli*)[154]	Acute	Blood culture or surgical drainage cultures (CSF culture can be negative)	Recent surgical/dental procedure. MRI: ring enhancement with core DWI restriction; leptomeningeal enhancement and/or spondylo-discitis may coexist
Borrelia burgdorferi	Acute; GA: United States, Europe	Serum and CSF serology	Tick-borne, erythema migrans, polyarthritis. MRI: nonspecific or polio-like
Mycobacterium tuberculosis	Chronic; can be acute/subacute	Mycobacterial culture, CSF PCR	MRI: leptomeningeal enhancement, cauda equina, and vertebral body involvement
Treponema pallidum[155]	Acute; chronic in tabes dorsalis	Serum rapid plasma reagin, CSF VDRL	Can manifest as myelitis or spinal cord infarction (meningovasculitis). MRI: nonspecific; dorsal column T2-hyperintensity in tabes dorsalis
Viral			
Cytomegalovirus	Acute	CSF PCR	Almost exclusively seen in immunocompromised patients. MRI: root/cauda enhancement, normal MRI in 50%
Enterovirus (A71, D68, D70, coxsackie A/B, echovirus)	Acute	CSF PCR	Common in children or immunocompromised adults; common brainstem involvement in acute flaccid paralysis. MRI: ventral or central gray matter-restricted; normal in 5% of cases
Epstein–Barr virus	Acute	PCR + serology on both serum and CSF	Preceding/concomitant mononucleosis. Meningo-encephalo-radiculitis may coexist. MRI: long T2-lesion, centrally located ± enhancement
Herpes simplex virus 1/2[95]	Acute	CSF PCR	Myelitis, radiculitis, or both (myeloradiculitis), common lumbosacral involvement (Elsberg's syndrome [HSV-2 accompanied by genital herpes]). MRI: multiple, discontinued, central/ventral lesions sparing the distal conus; nerve root enhancement
HIV	Acute/Chronic	CSF PCR, serology	May occur acutely during seroconversion or chronically in advanced AIDS, other opportunistic causes need to be excluded. MRI: non-enhancing T2-lesions along the dorsal columns
Human herpesvirus 6/7	Acute	CSF PCR	May occur in transplanted patients; generalized pruritus may coexist.
JC virus[156]	Acute	CSF PCR	Only few cases of spinal cord involvement reported in immunocompromised patients
Poliovirus	Acute; GA: Some African countries	CSF serology, stool culture	May occur in underdeveloped countries where the vaccine is not available; acute flaccid myelitis, bulbar/autonomic dysfunction may occur. MRI: ventral or central gray matter involvement

(*Continued*)

Table 2 (*Continued*)

Pathogen	Typical timing of presentation; at-risk geographic area (GA), if any	Preferred diagnostic test	Clinical and MRI clues for diagnosis
Rabies	Acute	CSF and blood serology	Recent animal bite/contact; severe course. MRI: long T2-lesion, central cord restricted
Varicella zoster virus[97]	Acute	CSF serology > PCR	The myelitis can occur with/without rash. MRI: dorsal or gray matter restricted T2-lesions (single or multiple, long or short) at the level of the affected ganglion, enhancement is possible
West Nile virus	Acute	CSF PCR, serology on both serum and CSF	Myelitis in 5–10% of neurological cases; acute flaccid paralysis, meningoencephalitis may coexist. MRI: predominant ventral cord involvement, can be normal
Zika virus	Acute; GA: Central South America, Asia, Africa	CSF PCR	Guillain–Barre syndrome or acute myelitis has been reported. MRI is nonspecific
Parasitical/fungal			
Cryptococcus (*neoformans*/*gattii*) and other fungi[157,158]	Chronic	CSF and blood serology, CSF antigen, India ink staining	*Cryptococcus*, *Candida*, *Aspergillus*, and Zygomycetes are common; meningoencephalitis most common manifestation
Taenia solium (neurocysticercosis)	Chronic; GA: America, Central South Asia, Africa, Eastern Europe	CSF and blood serology	Spinal cord involvement is rare compared with brain involvement, MRI: intraspinal cord or leptomeningeal enhancing cysts with cystic content (T2-signal isointense to the surrounding CSF)
Schistosoma mansoni/*haematobium*	Acute; GA: South America, Middle East, Africa, Asia	Histopathology, serology, stool culture	Recent swimming in fresh water; myelitis or myeloradiculitis. MRI: multinodular enhancement mass in the lower thoracic cord
Toxoplasma gondii	Acute	Serology and PCR in both CSF and blood	Raw/undercooked meat ingestion; MRI: nonspecific enhancing, expansile mass

Abbreviations: AIDS, acquired immunodeficiency syndrome; CSF, cerebrospinal fluid; DWI, diffusion-weighted image; GA, geographic area; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

3. *Timing*:
   - Is the clinical presentation hyperacute (<12 hours), acute/subacute (~1–21 days), or acute-on-chronic (over weeks/months)?
4. *Spine imaging*:
   - Does MRI confirm the spinal cord involvement?
   - Are there signs of extrinsic compression?
   - Is the intrinsic spinal cord lesion longitudinally extensive (≥3 vertebral segments)?
   - Is there any recognizable sign or gadolinium enhancement pattern that can suggest a specific etiology?
5. *Additional tests*:
   - Is the brain MRI abnormal?
   - Do other investigations provide a clue (e.g., blood/cerebrospinal fluid [CSF] findings)?

Clinical Manifestations

Myelopathies can manifest with different combinations of signs/symptoms of motor, sensory, or autonomic dysfunction affecting one or more limbs and trunk (face-sparing), with predominant involvement of certain functional systems being sometimes suggestive of specific etiologies.

The motor weakness is typically accompanied by spasticity and hyperreflexia with Hoffman or Babinski's signs below the level of the lesion. Weakness generally follows an upper motor neuron pattern distribution with more severe involvement of flexor muscles in the lower limbs and extensor muscles in the upper limbs. A severe motor impairment requiring gait aid is unusual in MS but common with other acute myelitis etiologies (e.g., AQP4-IgG/MOG-IgG associated).[2] Anterior spinal artery infarction is characterized by hyperacute onset of bilateral and severe weakness with

sparing of the dorsal columns, although this clinical pattern is not always present and sensory disturbances can appear after the first hours/days due to expanding edema surrounding the ischemic area.[14] MS myelitis is characterized by mild, sensory-predominant deficits that resolve spontaneously over days or weeks. Reduced or absent reflexes can be seen after abrupt severe spinal cord insults (spinal shock), with extensive involvement of the anterior horns (common with SCI and viral myelitis),[14,15] or with concomitant peripheral neuropathy.[16] Acute compression of the cauda equina below the L1–L2 level (cauda equina syndrome) is characterized by flaccid paraparesis/plegia, loss of sensation below the groin/saddle region, and early incontinence that may resemble spinal shock, although spinal shock is often accompanied by spinal cord abnormalities on MRI.[17]

Sensory disturbances may vary from positive (e.g., burning/itchy sensation) to negative (e.g., hypo-/anesthesia) manifestations that are often nonspecific and difficult to distinguish from those of peripheral neuropathies. Predominant involvement of pain and temperature with relative sparing of vibration sense and proprioception can be seen with predominant central cord damage (e.g., syringomyelia).[17] When present, a sensory level on the trunk (reported by the patient or detected on examination) or a Lhermitte phenomenon (i.e., an electrical sensation along the back sometimes extending to the extremities triggered by neck flexion) is highly suggestive of a spinal cord localization, and the latter is most suggestive of a demyelinating etiology. An intense back pain heralding myelopathy symptom onset is also common with acute myelopathies.[14] Dysmetria predominantly affecting the lower limbs may occur due to damage of the spinocerebellar tracts.[18] Tonic spasms (i.e., paroxysmal, unilateral, stereotyped episodes of painful tonic posturing of the limbs of 1–3 minutes of duration, triggered by movement, and typically responsive to low-dose carbamazepine) are commonly seen with inflammatory/demyelinating myelopathies, especially AQP4-IgG associated.[19] The McArdle sign (a rapidly reversible weakness induced by neck flexion) is characteristic of MS.[20]

Bladder dysfunction (incontinence or retention) is common, but is nonspecific when it occurs in isolation. Neurogenic bowel may manifest as constipation or fecal incontinence. Erectile dysfunction is a common accompaniment in males. Cardiovascular and other autonomic instability and respiratory failure can be seen with upper cervical cord involvement.

Acute inflammatory demyelinating polyneuropathy may sometimes mimic acute myelopathies, particularly those with a flaccid paraparesis from spinal shock, or myelopathies that can initially present without findings on MRI.[21] The presence of a sensory level on the trunk, an upper motor neuron pattern of weakness on examination, and urinary retention (more than incontinence) favors a myelopathy over a peripheral nervous system disorder.

Demonstrating signs/symptoms of extraspinal neurologic involvement is helpful to narrow the differential. The concomitance of peripheral neuropathy and myelopathy (myeloneuropathy) can be seen with some inflammatory etiologies,[22,23] but is more common in inherited[18] and nutritional myelopathies.[24] Encephalopathy/cognitive impairment or seizures are common with glial fibrillary acidic protein (GFAP)-IgG,[25] inherited/nutritional disorders,[18] certain infections,[26] neurosarcoidosis,[27] dual spinal cord and cerebral involvement of lymphoma,[28] and less frequently AQP4-IgG.[29] Acute disseminated encephalomyelitis (ADEM) is a clinicoradiologic phenotype characterized by encephalopathy and multifocal central nervous system (CNS) demyelination frequently seen with MOG-IgG.[30] Patients with MS myelitis may have focal brain symptoms but rarely encephalopathy. Optic neuritis can be seen with AQP4-IgG and MOG-IgG (typically bilateral and/or severe) and MS myelitis (typically unilateral and less severe). Intractable nausea, vomiting, or hiccups due to involvement of area postrema are seen with AQP4-IgG,[31] while meningitis can be seen with MOG-IgG, GFAP-IgG, sarcoidosis, or infections. Optic disc edema (often asymptomatic) and tremor are common with GFAP-IgG.[25]

Systemic manifestations accompanying the myelopathy are common with infections or rheumatologic disorders that can affect the spinal cord. It is important to enquire about a history of oral/genital ulcers (Behçet's disease),[32] dry eyes/mouth (Sjögren's disease),[33] or skin rash (e.g., malar rash in systemic lupus erythematosus),[34] while the presence of skin ulcers, purpura, or other cutaneous lesions suggest vasculitis,[35] infections,[36] or sarcoidosis.[37] Viral-like prodromes (e.g., fever, weight loss) preceding the myelopathy are common with rheumatologic disorders and infections, but can also be seen with MOG-IgG,[2] GFAP-IgG,[38] or neoplasms.

Presentation Timing and Setting

In acute myelopathies, patients are generally able to identify the exact day of symptom onset, while more vague descriptions are often reported by patients with chronic or subacute myelopathies.

Hyperacute Onset

A hyperacute onset within 12 hours is characteristic of spontaneous SCI, although symptom progression more than 12 hours is seen in approximately 25% of cases, typically in a stuttering/stepwise fashion.[14] In a minority of patients with spontaneous SCI (especially young patients), a triggering event can be identified, including (1) Valsalva maneuver, heavy lifting, or a new/intense physical activity suggestive of fibrocartilaginous embolism[39]; (2) cocaine use[40]; or (3) rapid back hyperextension (typical of novice surfers).[41] SCI can also be caused by vasculitis in the context of systemic rheumatologic disorders (e.g., ANCA associated, lupus, giant cell arteritis),[35,42,43] prothrombotic disorders (antiphospholipid syndrome), or infections (e.g., syphilitic or varicella zoster virus vasculopathy).[26] A hyperacute presentation may also occur with heroin exposure, particularly with heroin reuse after a period of abstinence,[44] rapid body decompression among scuba divers,[45] and spinal hemorrhage. Nontraumatic intramedullary hemorrhages (hematomyelia) are generally secondary to vascular malformations (cavernous

malformations, arteriovascular malformations, high-flow AVFs), neoplasms (primary or metastases), anticoagulation treatment, or hereditary bleeding disorders.[46] Similar causes can be identified in patients with spontaneous spinal epidural hematoma, which can also occur after spine surgery, although the majority of cases are idiopathic.[47] AQP4-IgG- and MOG-IgG-associated myelitis may sometimes reach maximal severity within 12 to 24 hours, but rarely in a sudden, "stroke-like" fashion.

Acute to Subacute Onset

Most inflammatory myelopathies present within days to a few weeks (acute/subacute presentation; ►**Table 1**), with MS myelitis being the most common. Major red flags that suggest a non-MS myelitis are (1) a longitudinally extensive lesion on spinal cord MRI and (2) a particularly severe disabling myelopathy.[2] The myelitis associated with AQP4-IgG and MOG-IgG is almost always acute/subacute,[2] along with most idiopathic myelitis.[10] Infectious myelitis frequently presents acutely and should be particularly suspected in immunosuppressed patients, intravenous drug users, or patients with a recent history of travel to at-risk areas, although certain pathogens are typically associated with a slowly progressive course such as HTLV-1.[26] ►**Table 2** summarizes the major causes of acute infectious myelitis and their characteristics. Acute necrotizing myelopathy is characterized by intralesional necrosis, hemorrhage, and cavitation generally occurring after viral infections, including most recently SARS-CoV-2.[48] A characteristic syndrome of acute flaccid myelopathy and sometimes cranial nerve dysfunction has been reported in association with viral infections by poliovirus, enterovirus D68, D70, A71, coxsackievirus A and B, and echovirus.[15] West Nile virus myelitis can present similarly. A specific association between a predominantly sensory acute myelopathy with noninflammatory CSF and elevated serum IgE levels directed against mite antigens (atopic myelitis) has also been described, predominantly in Asia.[49] Spinal cord metastases typically have an acute presentation, while primary spinal cord tumors may sometimes present acutely when high grade or in the setting of an accompanying hemorrhage, but generally have a subacute to chronic course. Myelopathies due to toxic agents or drugs typically present acutely/hyperacutely in close temporal relation to the exposure. Spinal cord compression from extrinsic causes (e.g., epidural hematoma/abscess, vertebral disk herniation) can also manifest acutely.

Acute-on-Chronic Onset

Among the chronic myelopathies, spondylotic myelopathy is the most common, and an acute worsening may occur after trauma or vertebral disk herniation.[50,51] Other chronic myelopathies have an acute presentation in a minority of cases, including spinal cord sarcoidosis (acute presentation in 20%),[52] paraneoplastic myelopathies,[53] and spinal AVF (acute presentation in 22%).[54] Subacute combined degeneration is a typically chronic myelopathy, but acute presentations have been reported.[55] An acute onset is also seen with rapid B12 inactivation from nitrous oxide intoxication[24,56] or in patients with an underlying inborn error of cobalamin metabolism/adsorption (often with normal serum B12 levels).[57] Biotinidase deficiency may mimic neuromyelitis optica.[58] Hereditary myelopathies and progressive MS typically present insidiously over months to years.

Iatrogenic Etiologies

Myelopathy occurring with a cancer history may suggest spinal cord metastasis, a paraneoplastic etiology, or an iatrogenic cause such as intrathecal cytarabine or methotrexate toxicity or radiation myelopathy.[59] Radiation myelopathy is a rare complication of radiation exposure to the spinal cord, typically for the treatment of spinal or abdominal/thoracic malignancies. A mild radiation myelopathy characterized by Lhermitte phenomenon and spontaneous resolution may develop 2 to 4 months after the exposure, while a more severe, frequently irreversible form may present from 6 months to years after treatment.[60] In patients with a history of spine radiation, the diagnosis relies on the exclusion of other possible etiologies, especially cancer recurrence.[61] Cancer treatment with immune checkpoint inhibitors may trigger neurologic immune-mediated disorders, including myelitis,[62] while tumor necrosis factor (TNF)-α inhibitors may trigger CNS demyelinating lesions in the brain and/or the spinal cord.[63,64] Neurological autoimmunity has also been described in patients receiving immunosuppression following organ transplantation.[65] Other common iatrogenic causes include spine surgery, anesthesia, and aortic surgery, which may lead to SCI in up to 1% of cases.[66,67] Spinal cord involvement has also been reported in cases of posterior reversible encephalopathy syndrome,[68] sometimes associated with AQP4-IgG.[69]

Spine Imaging

Spinal cord MRI is the gold standard to confirm the clinical suspicion of myelopathy, although certain myelopathies may manifest clinically but without associated findings on initial MRI.[21] An optimal imaging protocol for acute myelopathy should include both sagittal and axial T2-weighted sequences, short-tau inversion recovery (STIR) sequences, pre- and postgadolinium T1-weighted sequences, and sagittal diffusion-weighted images (DWIs) with apparent diffusion coefficient (ADC) maps. Postgadolinium images are particularly important, as they may reveal specific enhancement patterns.[70] Computed tomography (CT) is often preferred to MRI acutely in the setting of trauma due to its greater sensitivity for detecting vertebral fractures and blood.[71] CT and CT-myelography can complement MRI in case of structural spine disorders or in patients with contraindications to MRI.[72]

Extrinsic Causes of Myelopathy

MRI should first exclude extrinsic causes of acute spinal cord compression that may require surgical intervention. In general, acute spinal cord compression may be due to bony structures (e.g., spondylosis, trauma, fractures), intervertebral disk disorders (e.g., disk herniation, calcification, cysts), or masses that can originate in or invade the epidural, subdural, or

subarachnoid space.[73] The epidural space is rich in venous plexuses and fat that predispose to abscesses, metastases, or hematomas that can then compress the spinal cord.[1]

Imaging of the entire spine is important to detect compression at multiple levels or distant spinal cord abnormalities. At the level of the compression, the spinal cord can be normal or show parenchymal T2 abnormalities. MRI characteristics of common compressive masses include the following:

- *Epidural abscess/hematoma*—A longitudinally extensive collection of T2-hyperintense/T1-hypo- or isointense fluid in the dorsal or ventral epidural space is typical (►**Fig. 1A**). A rim of gadolinium enhancement around the epidural mass is frequent with epidural abscess and may extend to the leptomeninges. Adjacent vertebral osteomyelitis with T1-hypointensity and loss of cortical bone margins and/or T2-hyperintensity of the intervertebral disk indicating discitis are also common (e.g., Pott disease in tuberculous infection), although epidural abscesses may occur in isolation from direct hematogenous dissemination.[1,73] Epidural and subdural spinal hematomas typically lack gadolinium enhancement.[71]
- *Neoplastic mass*—The MRI characteristics vary with the tumor type, but gadolinium enhancement is generally more homogeneous than epidural abscess and not confined to the margins of the mass. Concomitant vertebral metastases are common. In patients with multiple myeloma, spinal cord compression is generally due to vertebral collapse, while lymphomas commonly grow in the epidural space on either side of the spinal cord (►**Fig. 1B**).[74]
- *Spondylotic myelopathy*—A flat, intramedullary, transverse band of contrast enhancement just below the level of maximal stenosis on sagittal images ("pancake" enhancement), which involves the white matter and spares the central gray matter axially, is characteristic.[75] A rapid worsening in these patients can be seen after a trauma or acute disc extrusion (►**Fig. 1C**). When cervical spondylotic myelopathy is not overt, dynamic spinal cord MRI with flexion and extension views may help confirm the diagnosis.[76]

Intrinsic Causes of Myelopathy

Once compressive insults have reasonably been ruled out, assessing the length of the spinal cord lesion on sagittal T2-weighted images (the longest if multiple lesions are present) further assists the diagnostic workup. Short T2-hyperintense lesions (<3 contiguous vertebral segments on sagittal images), particularly when multiple, are typical of MS. The lesions are generally peripherally located in the dorsal or

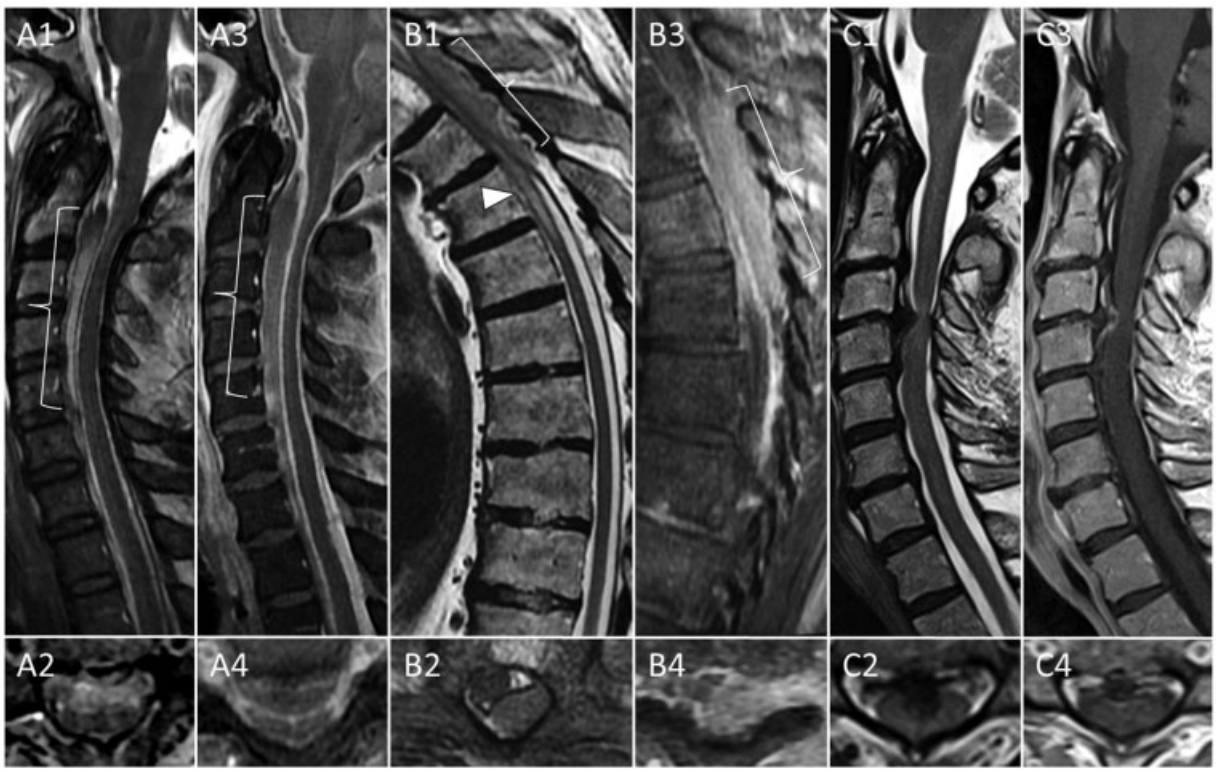

Fig. 1 Examples of compressive myelopathies. (**A**) Epidural abscess. A T2-hyperintense fluid collection in the anterior epidural space compressing the cervical spinal cord is appreciable on both sagittal (A1) and axial (A2) images. Enhancement of the abscess margins and leptomeninges is shown with extensive purulence of CSF noted on fat-saturated T1-weighted images after gadolinium (A3–A4). (**B**) Diffuse large B-cell lymphoma. A mildly T2-hyperintense mass compressing the thoracic spinal cord from the dorsolateral epidural space and accompanying increased T2-signal of the adjacent spinal cord parenchyma (arrow) is noted (B1–B2). The neoplastic mass shows intense gadolinium enhancement (B3–B4). (**C**) Spondylotic myelopathy. Anterior compression of the cervical spinal cord from intervertebral disk extrusion is shown. The hypointense extruded disk on T2-weighted images (C1–C2) is surrounded by a thin rim of enhancement at the level of the compression on postgadolinium images (C3–C4).

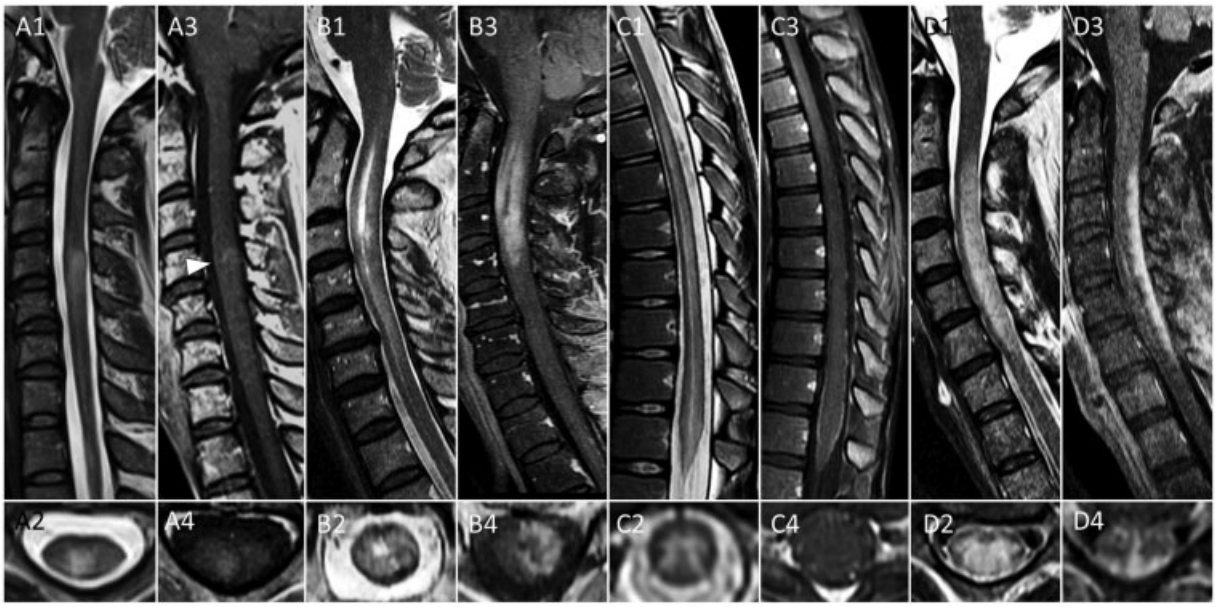

Fig. 2 Examples of inflammatory myelopathies. (**A**) Multiple sclerosis. A short (<3 contiguous vertebral body segments) T2-hyperintense lesion along the dorsal columns is noted on sagittal (A1) and axial images (A2), with corresponding nonspecific enhancement after gadolinium (A3–A4). (**B**) AQP4-IgG-associated myelitis. A longitudinally extensive (≥3 contiguous vertebral body segments) T2-lesion with associated swelling of the cervical spinal cord, and a focal area of higher T2-hyperintensity within the lesion ("bright spotty lesion") visible on both sagittal (B1) and axial (B2) images. After gadolinium there is marked enhancement of the periphery of the lesion (B3–B4). (**C**) MOG-IgG-associated myelitis. A longitudinally extensive T2-lesion involving the entirety of the thoracic spinal cord, more pronounced ventrally on sagittal images (C1) and gray matter-restricted axially (C2). No enhancement is noted after gadolinium (C3–C4). (**D**) Spinal cord sarcoidosis. A longitudinally extensive cervical T2-lesion (D1–D2) is noted with associated gadolinium enhancement along the dorsal subpial surface (D3), and anterior extension to the central canal resembling a trident ("trident sign") on axial images (D4).

lateral columns, and are often accompanied by either homogeneous or rim enhancement if acute (►**Fig. 2A**). Long T2-hyperintense lesions (≥3 contiguous vertebral body segments) are rarely seen in MS,[77] but are common with AQP4-IgG and MOG-IgG.[78] Rarely, multiple contiguous MS lesions may resemble a single longitudinally extensive lesion on sagittal images; in these patients, a careful evaluation of axial images helps demonstrate the presence of multifocal T2 abnormalities.[77] Linear dorsal column T2-lesions, with or without enhancement, can also be seen in patients with sensory ganglionopathy associated with specific paraneoplastic autoantibodies (e.g., antineuronal nuclear antibody-1),[79] connective tissue disorders (e.g., Sjögren's disease),[80] amyloidosis, and exposure to certain drugs (e.g., cisplatin).

Among intrinsic causes of myelopathy that commonly manifest with longitudinally extensive spinal cord lesions, several may show characteristic MRI signs and/or enhancement patterns:

- *AQP4-IgG associated*—Marked swelling and central/holocord involvement on axial images are common,[81] with intralesional foci of higher T2-hyperintensity similar to the surrounding CSF ("bright spotty lesions")[82]; gadolinium enhancement is present in more than 90% of cases acutely and can be patchy or ring-like ("elongated ring"; ►**Fig. 2B**).[83] Short myelitis T2-lesions are seen in 14% of cases,[84] and involvement of the conus is infrequent.[2]
- *MOG-IgG associated*—The T2 hyperintensity is frequently more pronounced along the ventral cord parenchyma on sagittal images ("ventral sagittal line") and gray matter restricted on axial images ("H-sign")[2]; conus involvement is common (►**Fig. 2C**).[85] Gadolinium enhancement is observed in approximately 50% of cases acutely and is usually faint and nonspecific; long and short myelitis lesions frequently coexist[2]; the initial MRI can be negative in 10% despite a severe myelitis.[21]
- *GFAP-IgG associated*—A faint, poorly demarcated T2-lesion, extending over the entire cord, occurs most frequently.[38] Punctate parenchymal enhancement, enhancement of the central canal, and/or leptomeningeal enhancement are common. This myelitis rarely occurs without concomitant clinical/MRI evidence of extraspinal neurologic involvement.[38]
- *Spinal cord sarcoidosis*—A very bright subpial enhancement is typical along the dorsal cord surface,[37] sometimes extending to the central canal and resembling a trident on axial images ("trident sign"; ►**Fig. 2D**)[86]; concomitant leptomeningeal/radicular involvement is common. Predominantly anterior abnormalities may be seen in association with spondylosis. Persistence of gadolinium enhancement over 6 months is characteristic. Nonlongitudinally extensive lesions or isolated meningoradiculitis are seen in 50% of cases.[52]
- *Behçet's myelitis*—Focal areas of T2-hypointensity are frequently noted within the lesions, with or without accompanying enhancement, and often resembling a bagel on axial images ("bagel sign"). It has a predilection for the midthoracic region.[32]

- Spinal cord infarct—The ventral spinal cord T2-hyperintensity is typically affected in a sagittal "pencil-like" or axial "owl/snake eyes" pattern with involvement of the anterior horn cells, which are the most vulnerable region of the spinal cord to ischemia and are often injured in a watershed pattern. Abnormal gadolinium enhancement may appear a few days after symptom onset in 39% of cases (►**Fig. 3A**). An accompanying parenchymal DWI restriction is useful to assess for, but this imaging technique is limited by poor spatial resolution and artifacts when compared with analogous brain sequences. T2-/T1-post-gadolinium hyperintensity of the dorsal edge of an adjacent vertebral body (due to concomitant vertebral body infarct) can also be noted in the days to weeks following the infarct.[14,87] Dorsal cord infarction is possible and more commonly manifests with short nonspecific dorsal column lesions accompanied by an acute sensory ataxia.[14] The initial MRI in SCI is negative in 24% within the first 24 hours.[14] Lesion evolution to myelomalacia is common, and a small punched out T2-hyperintensity with T1-hypointensity of similar constituency to CSF may be encountered in the cord parenchyma in follow-up.
- *Hematomyelia*—The MRI signal of blood is heterogeneous and varies over days from the initial bleeding. The detection of precontrast T1-hyperintensity on MRI suggests the presence of blood in the subacute phase of a hemorrhage (►**Fig. 3B**), although it can also be seen with lipid content (e.g., lipoma), or melanoma metastasis (due to the paramagnetic properties of melanin).[88,89]
- *Spinal AVF*—Typically affects the lower half of the thoracic spinal cord, although the cervical spinal cord can be affected sometimes with an intracranial location of the fistula.[90] Paraspinal flow voids from venous congestion are often dorsal and are pathognomonic, but may be absent or subtle and difficult to appreciate in up to 50% of cases. Thus, any longitudinally extensive T2-hyperintense lesion in the thoracic spine should lead to strong consideration for a dural AVF. Gadolinium enhancement is common (up to 86% of cases) and may lead to misdiagnosis as an inflammatory/neoplastic etiology.[54,91] Occasionally, the MRI will reveal a focal nonenhancing area of spinal cord parenchyma within a region of diffuse enhancement ("missing piece sign"; ►**Fig. 3C**).[92]
- *Primary spinal cord tumors*—Intramedullary cystic T2-hyperintense lesions and syringohydromyelia are common with all tumor types, although some tumors have longitudinally extensive lesions isointense to the spinal cord parenchyma. Ependymomas are more often located centrally, and astrocytomas often have a more peripheral location, although there is some overlap. Gadolinium enhancement is observed in the majority of cases (►**Fig. 4A**). A T2-hypointense "cap" of hemosiderin due to previous hemorrhages above and/or below the expansile T2-mass ("cap sign") is seen in one-third of

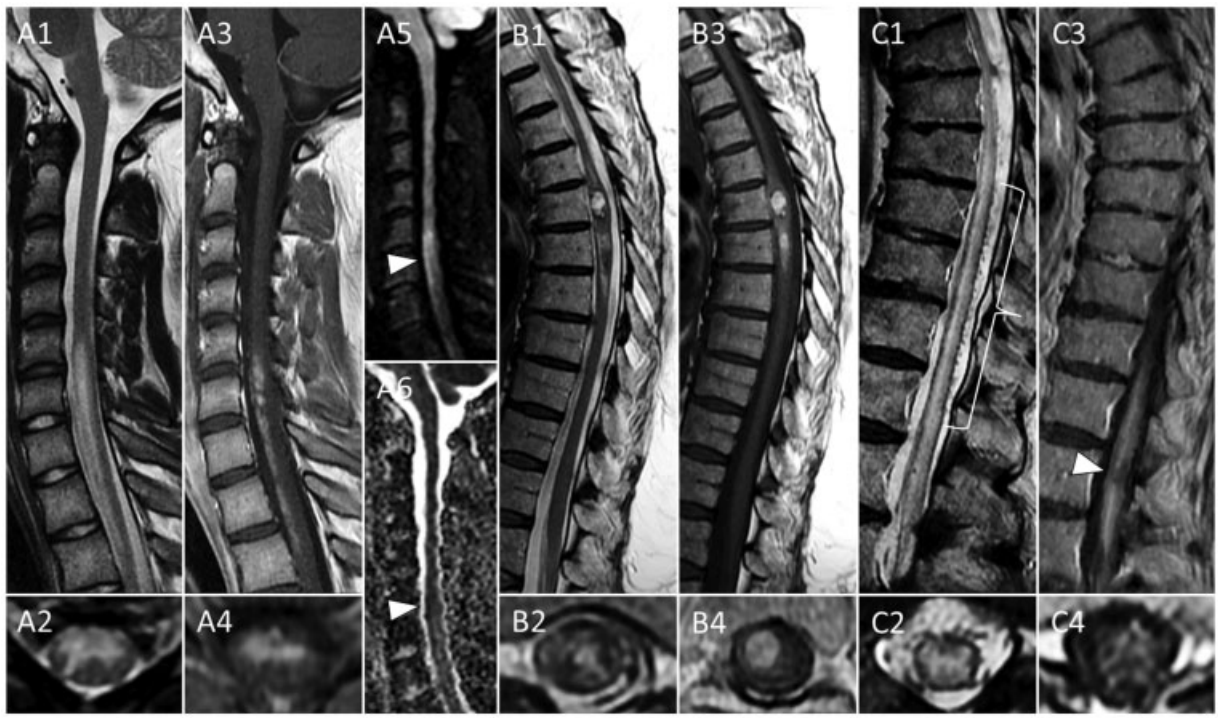

Fig. 3 Examples of vascular myelopathies. (**A**) Spinal cord infarction. A longitudinally extensive T2-lesion is noted along the anterior two-thirds of the lower cervical and upper thoracic spinal cord on both sagittal (A1) and axial (A2) images, with corresponding enhancement after gadolinium (A3–A4). On diffusion-weighted images, the ischemic lesion shows restricted diffusion (A5) and corresponding hypointensity on apparent diffusion coefficient map (A6). (**B**) Hematomyelia. In a case of intraparenchymal bleeding, the T2-lesion signal often appears heterogeneous due to the concomitant presence of blood products of different ages (B1–B2). On pregadolinium T1-weighted images of the blood often appears hyperintense (B3–B4). (**C**) Spinal dural arteriovenous fistula. The longitudinally extensive T2-lesion involving the distal thoracic spinal cord is accompanied by multiple dorsal hypointense areas (flow voids) from venous congestion (C1–C2). After gadolinium, the diffuse lesion enhancement is interrupted by a focal nonenhancing area ("missing piece sign"; arrowhead) of spinal cord parenchyma (C3–C4).

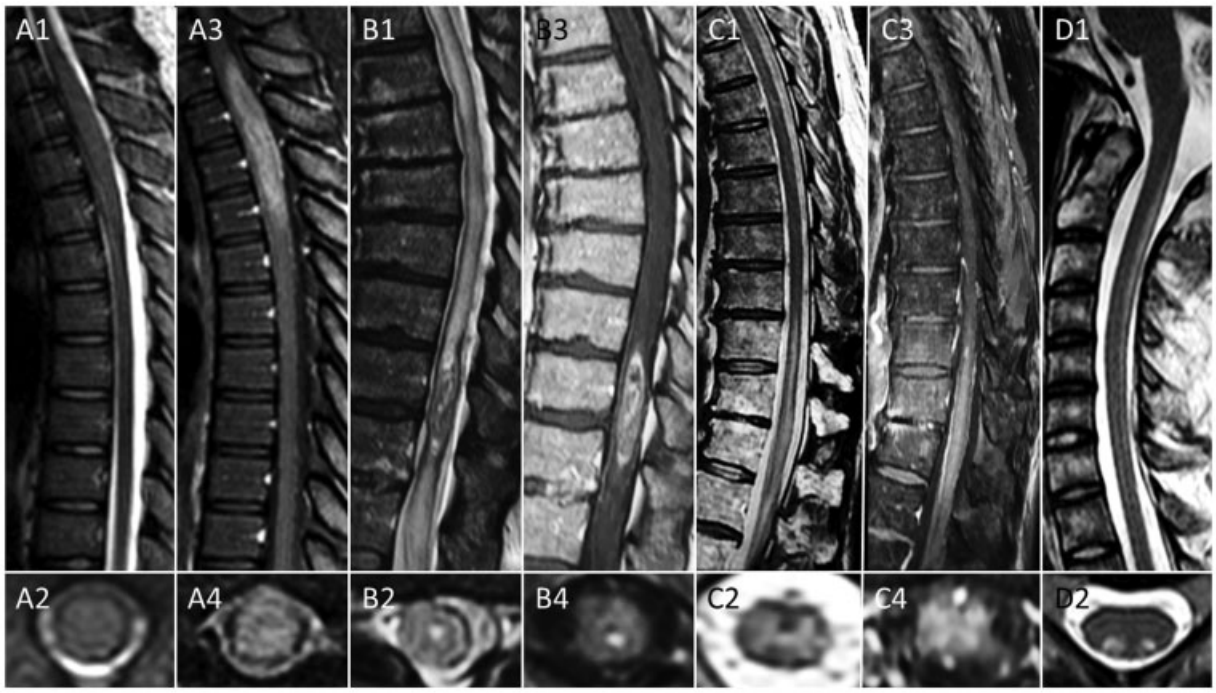

Fig. 4 Examples of other intrinsic causes of myelopathy. (**A**) High-grade spinal cord astrocytoma. A longitudinally extensive iso- to hyperintense lesion is evident in the upper thoracic spinal cord on T2-weighted images (A1–A2). Diffuse, nonspecific lesion enhancement is noted after gadolinium (A3–A4). (**B**) Spinal cord intramedullary metastasis. A highly heterogeneous T2-lesion is evident in the lower thoracic spinal cord (B1), with irregular, mostly peripheral enhancement after gadolinium (B3). A focal dotty area of hyperintense signal in the center of the spinal cord is evident on both T2-weighted (B2) and postgadolinium T1-weighted (B4) sequences axially ("central dot sign"). (**C**) West Nile virus myelitis. A longitudinally extensive T2-hyperintense lesion, predominantly affecting the central gray matter, is evident in the lower third of the thoracic spinal cord (C1–C2). Diffuse, nonspecific enhancement is noted after gadolinium in the affected spinal cord parenchyma and adjacent leptomeninges (C3–C4). (**D**) Myelopathy from intrathecal methotrexate infusion. A longitudinally extensive T2-hyperintensity is evident along the dorsal columns in the cervical and upper thoracic spinal cord on both sagittal (D1) and axial (D2) images. The lesion does not enhance after gadolinium (not shown).

ependymomas and other highly vascularized tumors.[74] Initial improvement with steroids and persistence of gadolinium enhancement over months is suggestive of spinal cord lymphoma.[28] The contrast enhancement patterns differ based on the tumor type (e.g., homogeneous enhancement in ependymoma, patchy enhancement in spinal cord astrocytoma).[74]

- *Intramedullary spinal cord metastasis*—The "rim" (i.e., a more intense thin rim of peripheral enhancement surrounding an enhancing lesion) and "flame" (i.e., an ill-defined flame-shaped region of enhancement at the superior or inferior lesion margin) sign, and the "central dot" sign (i.e., a singular intense, punctate focus of enhancement in/near the center of a less intensely enhancing intramedullary lesion) are characteristic and favor spinal cord metastasis over primary neoplasias or other etiologies (►**Fig. 4B**).[93,94]
- *Infectious myelitis*—MRI findings differ based on the specific pathogen (►**Table 2**). Most viral myelitides (e.g., West Nile, poliovirus) are characterized by predominant involvement of the ventral or central gray matter, sometimes accompanied by nonspecific gadolinium enhancement (►**Fig. 4C**). Elsberg syndrome is a lumbosacral radiculitis often accompanied by lower cord myelitis that may occur during or after HSV-2 infection. Multiple and discontinuous T2-hyperintensities in the conus medullaris that can enhance after gadolinium are often detected.[95] Varicella zoster virus myelitis typically affects the central gray matter or the dorsal columns, with single or multiple, long or short T2-hyperintense lesions at the level of the skin rash (when present).[96,97]

Patients with vitamin B12, vitamin E, or copper deficiency may show short or longitudinally extensive T2-hyperintensity along the dorsal and/or lateral columns ("inverted V" sign), with or without associated enhancement.[98–100] Resolution of MRI abnormalities with vitamin supplementation may precede clinical improvement.[101] Cognitive symptoms or optic neuropathy may coexist.[98] A tract-restricted T2-hyperintensity along the dorsal or lateral columns can also be observed in paraneoplastic myelopathies with corresponding tract-specific enhancement, and after intrathecal administration of certain chemotherapies (►**Fig. 4D**). For other longitudinally extensive myelopathies (e.g., myelitis associated with connective tissue disorders, radiation myelopathy,[102] genetic/inherited myelopathies,[18] surfer's/scuba diving myelopathy,[103] ITM), MRI findings are more nonspecific.

Laboratory Investigations

Serum and CSF analysis may reveal infections, inflammatory markers, or specific autoantibodies associated with

neurologic or systemic autoimmunity. When possible, samples should be collected acutely and before treatment to limit confounders (e.g., detection of antibodies will be limited after a course of plasma exchange [PLEX]). An optimal serum investigation panel for acute myelopathy includes complete blood cell count, liver and kidney function tests, erythrocyte sedimentation rate, C-reactive protein, antinuclear and extractable nuclear antigens, antineutrophil cytoplasmic antibodies, and specific nutrients/vitamins (B12, E, and copper). Increased serum white blood cell count, C-reactive protein, and erythrocyte sedimentation rate suggest infectious or systemic inflammatory disorders. Serum protein electrophoresis, immunofixation, and lactate dehydrogenase may help detect hematologic malignancies, while coagulation tests are important to rule out coagulopathies or a bleeding diathesis. More specific testing (e.g., biotinidase, long chain fatty acid, genetic testing) can be considered in selected cases.

For infectious etiologies, the optimal test varies based on the specific pathogen (►**Table 2**). Polymerase chain reaction (PCR) in CSF is generally the gold standard for viral infections, with exceptions like varicella zoster virus, for which serology yields higher sensitivity.[104] PCR may be negative early in the disease course. Testing both serum and CSF is recommended, especially for infections that begin systemically (e.g., Epstein–Barr virus, *Borrelia burgdorferi*), as an isolated CSF positivity with negative serum test should raise the suspicion of a false-positive result. Serology may be negative in immunocompromised patients or after B-cell-depleting agents (e.g., rituximab, ocrelizumab).[105]

In patients with epidural abscess, cultures may be unrevealing if preceded by empiric antibiotics. Serial blood cultures at admission increase the likelihood of identifying a pathogen. The most commonly identified organisms worldwide are *Staphylococcus aureus* and streptococcus, while *Pseudomonas* is common among intravenous drug users. Mycobacterium tuberculosis is frequent in endemic areas.[36]

CSF pleocytosis (>5 white blood cells per mm^3) and/or high IgG index are regarded as indicators of CSF inflammation, but they are not specific and mild elevations in CSF white blood cell count can be sometimes seen with noninflammatory myelopathies (e.g., vascular myelopathies).[106] Lymphocyte predominance is typically seen with inflammatory, viral, fungal, and TB etiologies, while polymorphonuclear cells predominate with bacterial infections, some viral infections (e.g., West Nile), and Behçet's disease, or early during an inflammatory myelitis.[107] Eosinophils and monocytes can be seen with parasitic and fungal infections, respectively.[26] In MS, the white blood cell count does not generally exceed 50 cells, and higher values should prompt consideration of other etiologies. CSF-restricted oligoclonal bands are typical with MS (present in 85–100%) and certain viral infections,[108] less common with sarcoidosis and GFAP-IgG (30–50%),[38,52] and uncommon with AQP4/MOG-IgG (15–20%), where they can be transiently detected during relapses.[2] Low CSF glucose (<40 mg/dL) suggests meningomyelitis with infections, neoplasms, or chronic inflammation (e.g., sarcoidosis).[109] Elevated CSF protein (>45 mg/dL) can be seen with obstruction of CSF flow,[110] while a high opening pressure is expected with bacterial/fungal infections.[26] CSF cytology and flow cytometry are useful to identify neoplastic cells.

Testing for specific autoantibodies associated with myelitis may confirm an autoimmune or paraneoplastic etiology. While serum testing is generally preferred for AQP4-IgG and MOG-IgG because of increased sensitivity,[111,112] isolated CSF MOG-IgG positivity has been reported on rare occasions.[113] GFAP-IgG is preferentially tested in CSF.[25] In patients with paraneoplastic myelopathies, antibodies against amphiphysin and collapsing response mediator protein-5 (anti-CRMP-5/anti-CV2), which are generally detectable in both serum and CSF, are the most common, although seronegative forms are possible.[53] When the suspicion is high, immunofluorescence or immunohistochemistry screening on mouse brain tissue on both serum and CSF in dedicated research laboratories can help identify unexpected or yet unclassified neural-specific autoantibodies.

Additional Investigations

Brain MRI abnormalities accompanying the myelopathy (either symptomatic or not) are common with MS myelitis (small juxtacortical, periventricular, or infratentorial ovoid-shaped lesions),[78] ADEM/MOG-IgG (large poorly defined "fluffy" lesions),[114] GFAP-IgG (radially oriented linear perivascular enhancement—"radial enhancement"),[38] sometimes AQP4-IgG (peri-third/fourth ventricles or large tumefactive white matter lesions),[29] and neurosarcoidosis (e.g., bright homogeneous subpial/basilar leptomeningeal enhancement).[27]

Whole-body CT scan can demonstrate systemic inflammatory foci for biopsy in patients with sarcoidosis or metastatic spinal cord lesion. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has a greater sensitivity and is helpful to demonstrate occult systemic involvement in patients with neurosarcoidosis or systemic malignancy.[115] In patients with active myelopathy, the detection of hypermetabolic activity in the spinal cord lesion favors neurosarcoidosis or spinal cord tumors versus other etiologies.[116] Focal FDG-uptake may be seen with acute/subacute disk herniation or Schmorl nodes associated with an inflammatory response and can mimic metastatic disease.[73] When paraneoplastic autoantibodies with strong cancer association are detected without known malignancies, a periodic cancer screening (every 6–12 months) is recommended, as paraneoplastic manifestations may precede cancer detection by months or years.[117] Cancer screening should include FDG-PET of the torso, mammography, and other specific investigations, as appropriate.[118] Electromyography study can demonstrate a myeloneuropathy or a pure peripheral deficit mimicking a myelopathy (e.g., cauda equina syndrome, Guillain–Barré syndrome). Somatosensory evoked potentials can confirm spinal cord dysfunction when the MRI is normal.[21] Traditional spinal angiography is the gold standard for the detection of vascular malformations, although MRI angiography is also accurate and can help localize the

malformation and guide formal angiography.[119] The sensitivity of angiography for AVF detection is operator-dependent and increases with repeated exams and experienced operators.[120] Spinal cord biopsy can be considered when clinical deficits are severe and diagnosis is uncertain and can be safely undertaken in specialized centers with low complication rates.[121]

Treatment and Management

The management of acute myelopathies encompasses (1) an initial general risk assessment, (2) identification of those who may need surgical intervention, and (3) treatment of the specific etiology.

General Risk Assessment

Patients with clinical and/or MRI evidence of high cervical spinal cord or bulbar involvement should be assessed for the risk of respiratory failure and hemodynamic instability, starting with physical examination maneuvers to detect early respiratory distress signs (e.g., the presence of paradoxical breathing, inability/difficulty to count out loud from 1 to 20 in a single breath).[122] Neurogenic shock may occur with severe acute neurologic damage from traumatic or nontraumatic myelopathies, and is characterized by systemic hypotension from sudden loss of sympathetic stimulation to the blood vessels below the level of the lesion, sometimes accompanied by reduced heart rate from unopposed vagal activity.

Baseline investigations should include electrocardiography, blood pressure, oxygen saturation, and arterial blood gas. The presence of hypoxic respiratory failure should prompt consideration of mechanical ventilation, while systolic hypotension ($\leq$90 mm Hg) and/or reduced heart rate ($\leq$40) should prompt hemodynamic stabilization with supportive fluids, inotropes, and vasoactive agents.[122] In cases of clinical/MRI evidence of severe spinal cord damage above the C5 level and normal baseline parameters, intensive care unit (ICU) monitoring for the first 24 to 36 hours can be considered.[122] A bedside swallow assessment is recommended with bulbar symptoms/signs, while an indwelling bladder catheter is often needed with severe myelopathies.

Surgical Indications

Acute nontraumatic myelopathies that may require surgical intervention include extrinsic compressive myelopathies of all causes or infarction due to aortic dissection. Compression from spinal epidural abscesses is a medical emergency generally treated with spinal decompression and drainage in combination with broad-spectrum antibiotic coverage while awaiting microbial cultures. Early surgical decompression is also the treatment of choice with epidural hematomas. Anticoagulants or antiplatelet agents should be discontinued or reversed as applicable.[123] In patients with spinal cord compression due to epidural metastases, dexamethasone (from 16 to 96 mg/day) in combination with surgery, radiation, or both can be considered and may depend on the radiosensitivity of the tumor and the patient's functional status. Most patients with spondylotic myelopathy stabilize with or without improvement after decompressive surgery. The residual T2-hyperintensity may persist, and gadolinium enhancement, when present, tends to resolve quite slowly (>6 months), which may lead to diagnostic confusion.[75]

Surgical ligation or endovascular embolization is indicated for spinal AVF and may be considered in other vascular malformations, but up to 13% of cases require further interventions due to incomplete treatment or fistula recurrence, particularly with embolization.[54] In patients with SCI of any type (iatrogenic or spontaneous), increasing parenchymal perfusion through collateral vessels by blood pressure augmentation and lumbar drainage remain of potential benefit in the absence of randomized controlled trials.[124] A spontaneous functional recovery occurs in about one-third of patients with SCI.[125]

Acute Pharmacological Treatment

Once infectious myelitis and spinal AVF have reasonably been ruled out, an empiric immunotherapy trial may be reasonable in uncertain severe cases given the high frequency of inflammatory myelopathies. An immunotherapy trial may be both therapeutic and diagnostic in case of response (although a transient initial response may also be seen with lymphoma).[28] One or more of the following treatments are generally considered:

- High-dose intravenous methylprednisolone (IVMP), 1 g/day $\times$ 3–5 days.
- PLEX, 1 exchange every other day for five to seven exchanges.

Intravenous immunoglobulins (IVIG: 0.4 g/kg/day $\times$ 5 days, then weekly for 6–12 weeks) can also be considered, especially in children. A similar approach is generally appropriate for every type of myelitis, including ITM. Corticosteroids are generally preferred given the easier accessibility and lower risk profile, although lack of response does not exclude an inflammatory etiology. In particular, steroids alone are often ineffective with AQP4-IgG-associated myelitis, where complete recovery is seen in only one-third of patients.[126] Early use of PLEX/immunoadsorption (alone or with corticosteroids) is recommended with AQP4-IgG,[127] with maximum improvement within 5 days from symptoms onset.[128] PLEX was proven to be effective for the treatment of severe demyelinating attacks of different etiologies in a randomized sham-controlled trial.[129] IVIG can also be considered as an alternative to PLEX.[130] The optimal treatment of MOG-IgG-associated myelitis is unknown, but most patients show complete or nearly complete recovery despite severe attacks, unlike AQP4-IgG-associated relapses, for which recovery is less complete.[2,131] In patients with MS myelitis, a single IVMP course of 3 to 5 days is usually sufficient, given the milder disability and that complete or nearly complete recovery is typical. Administration of an equivalent oral dose of methylprednisolone has been shown to be similarly effective and safe at 1 month.[132]

The specific treatment of infectious myelitis depends on the underlying pathogen, and with viral myelitis may vary from antiviral treatment (when available) to supportive therapy. Complete details of the treatments for infectious myelopathies are beyond the scope of this article and have been reviewed elsewhere.[26]

In patients with high suspicion for spontaneous SCI, empiric thrombolysis can be considered within the first few hours from onset and in the absence of major contraindications.[133] For drug-related myelitis, treatment withdrawal should be evaluated, with additional immunotherapy for the immune-mediated forms (e.g., TNF-α/immune checkpoint inhibitor-related). In patients with cancer who develop immune-mediated complications from checkpoint inhibitors, the risk/benefit of drug withdrawal should be carefully weighed. Improvement has been reported with corticosteroids alone while maintaining the immune checkpoint inhibitor in patients with mild-moderate forms.[62]

Maintenance Treatment

Long-term immunotherapy is particularly important in patients with myelitis that is prone to a relapsing course, especially AQP4-IgG/MOG-IgG-associated disorders and MS. Other disorders like sarcoidosis and Behçet's may also relapse or follow a steroid-dependent course.

In patients with AQP4-IgG-associated myelitis, several drugs have recently been proven effective for relapse prevention in phase 3 prospective randomized placebo-controlled clinical trials, including rituximab (anti-$CD20^+$ lymphocytes),[134] inebilizumab (anti-$CD19^+$ lymphocytes),[135] eculizumab (anti-C5 complement protein),[136] and satralizumab (anti-interleukin 6).[137] In patients with MOG-IgG-associated myelitis, the decision to begin long-term immunotherapy is often challenging, as up to 50% will be monophasic and thus not need immunotherapy. A slow steroid taper after the acute stage for a few months may reduce the risk of early relapse.[138] Furthermore, the long-term outcome in these patients is generally favorable with just mild to moderate residual disability despite a highly relapsing course.[139] Empiric attack-prevention immunosuppression is often utilized in relapsing disease, but randomized-controlled trials are lacking. Treatment options include mycophenolate mofetil,[140] azathioprine,[141] periodic IVIG,[141] and rituximab, although rituximab seems less effective than in AQP4-IgG-associated myelitis.[142] Prolonged high-dose oral steroids are utilized for spinal cord sarcoidosis, with 1 mg/kg × 3 months followed by a slow taper over the next 6 to 12 months, and can also be used with GFAP-IgG.[37,38] TNF-α inhibitors are an effective option for both sarcoidosis and Behçet's disease. Several disease-modifying agents are available for MS relapse prevention.[143]

In patients with spontaneous SCI, a thorough cardiovascular risk assessment is important to evaluate for the cause, and antiplatelet or anticoagulation therapy may be considered in addition to managing other risk factors. In patients with neurological complications from immune checkpoint inhibitors that improve after drug withdrawal, there is currently no evidence to support long-term immunosuppression, although relapse may occur.[62] Therapy rechallenge with the same or a different immune checkpoint inhibitor is not recommended in patients with moderate-severe neurological manifestations unless strictly necessary for cancer treatment.[144]

Conclusions

Acute myelopathies are crucial for neurologists to diagnose, as disability can accrue rapidly and irreversibly without treatment. Identifying extrinsic compressive myelopathies with the help of neuroimaging is the first step, as extramedullary etiologies often require early surgical intervention. For intramedullary myelopathies, advances in autoantibody biomarker discovery and identification of MRI patterns have allowed earlier and more accurate diagnosis. Early disease-specific treatment is essential to prevent irreversible disability.

Conflict of Interest
Dr Flanagan has served on advisory boards for Alexion, Genentech and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times. He received royalties from UpToDate. Dr Flanagan was a site primary investigator in a randomized clinical trial on inebilizumab in neuromyelitis optica spectrum disorder run by Medimmune/Viela Bio/Horizon Therapeutics. Dr Flanagan has received funding from the NIH (R01NS113828). Dr Flanagan is a member of the medical advisory board of the MOG project. Dr Flanagan is an editorial board member of the Journal of the Neurological Sciences and Neuroimmunology Reports.

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