An Approach to the Diagnosis of Acute Transverse Myelitis

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ABSTRACT

The differential diagnosis of acute inflammatory transverse myelitis (ATM) is broad. Therefore, physicians must be aware of the many potential etiologies for acute myelopathy, and should pursue an ordered, efficient, and cost-effective approach to the diagnosis based on the patient's clinical history, examination, and magnetic resonance imaging (MRI) findings. Clinical, immunological, and radiological findings of non-compressive myelopathies are reviewed, as are how these findings can be used to distinguish between demyelinating, infectious, other inflammatory, vascular, neoplastic, and paraneoplastic etiologies. We also review predictors of further episodes of ATM in patients with demyelinating disorders. We discuss the diagnostic clues and pitfalls of the not uncommon clinical scenario of a presumed "myelopathy with normal MRI." Finally, we suggest an algorithm for the diagnosis and management of acute myelopathies.

KEYWORDS: Myelitis, neuromyelitis optica, multiple sclerosis

Acute transverse myelitis (ATM), an inflammatory myelitis, is one of the causes of acute transverse myelopathy. The three main categories in the differential diagnosis of ATM are demyelination, including multiple sclerosis (MS), neuromyelitis optica (NMO), and idiopathic transverse myelitis; infections such as herpes zoster and herpes simplex virus; and other inflammatory disorders such as systemic lupus erythematosus (SLE) and neurosarcoidosis. However, whether the cause of the acute myelopathy is inflammatory or not is not self-evident; therefore, the clinical and diagnostic workup for ATM requires that other causes of acute myelopathies be excluded.

When faced with a patient with an acute myelopathy, excluding an acute compressive cause is of utmost priority. A magnetic resonance imaging (MRI) scan is invaluable in this regard. Having excluded a compressive cause and having found an intrinsic spinal cord lesion on MRI, a detailed history and an examination followed by focused investigations are needed. In the following sections, clinical presentations of myelopathies are discussed followed by diagnostic categories of acute myelopathy. Only the classical presentations of the diseases are covered here. The predictors of relapses in demyelinating myelopathies are included, followed by an algorithm on diagnosis and treatment. Although we have used available literature and guidelines throughout, there may be instances where our personal clinical practice and experience have influenced our opinions and approach.

CLINICAL PRESENTATION OF SPINAL CORD DISORDERS

Spinal cord disorders are conventionally classified as "syndromes" due to the typical signs and symptoms produced because of the location of the lesion and specific tract involvement. The Brown-Séquard hemicord

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Table 1 Clinical Presentation of Acute Spinal Cord Disorders

Type of Lesion	Tracts Involved	Clinical Signs	Examples
Complete	All tracts	Pyramidal, sensory, and autonomic dysfunction* below lesion	Trauma or acute necrotizing viral myelitis
Brown-Séquard hemicord syndrome	Ipsilateral corticospinal, posterior columns; contralateral spinothalamic	Ipsilateral pyramidal weakness and loss of posterior column function; contralateral spinothalamic loss	Multiple sclerosis, compression
Anterior cord syndrome	Bilateral anterior horn cells corticospinal tracts, spinothalamic and autonomic	Acute bilateral flaccid weakness, loss of pain temperature and sphincter/ autonomic dysfunction; preservation of dorsal column modalities such as joint position sense	Anterior spinal artery occlusion
Posterior cord	Bilateral posterior columns	Bilateral loss of light touch, vibration and joint position	B_{12} or copper deficiency (usually chronic)
Central	Crossing spinothalamic, corticospinal, and autonomic fibers	Dissociated sensory loss (loss of pain and temperature with preserved vibration and joint position); pyramidal distribution weakness below lesion; autonomic dysfunction below the lesion	Syrinx, neuromyelitis optica
Conus medullaris	Autonomic outflow and sacral spinal cord segments	Early sphincter dysfunction, sacral sensory loss and relatively mild motor dysfunction	Post viral myelitis
Cauda equina	Spinal nerve roots of the cauda equina	Early often asymmetric flaccid weakness of the lower limbs, sensory loss in root distribution followed by autonomic dysfunction	Acute cytomegalovirus polyradiculitis, compression
Tractopathies	Selective tract involvement	Selective pyramidal, posterior column involvement	B_{12} deficiency, paraneoplastic myelopathy, multiple sclerosis

*Autonomic dysfunction: bladder, bowel, and sexual.

syndrome is an example. Table 1 summarizes the clinical presentation of acute spinal cord disorders.

Myelopathies with selective tract involvement are characteristic of metabolic or degenerative myelopathies (which are usually chronic) rather than inflammatory or infectious disorders (e.g., corticospinal and posterior columns in B_{12} deficiency, adrenomyeloneuropathy, and Friedreich's ataxia). However, paraneoplastic myelopathies, which are rare, often produce tract-specific involvement and should be considered when investigations to exclude a metabolic or degenerative myelopathy are negative in acute symmetric "tractopathy." Occasionally, inflammatory demyelinating syndromes may present with a very selective tractopathy due to discrete lesions (e.g., the classical acute "sensory useless hand syndrome" with acute proprioceptive loss due to posterior column involvement in patients with MS).

NONCOMPRESSIVE CAUSES OF ACUTE MYELOPATHIES

The five groups of disorders that present as acute myelopathy are: demyelination, infections, other inflammatory disorders, vascular, and neoplastic and paraneoplastic. The first three are considered inflammatory disorders. Among these, demyelinating disorders are the most common. The initial task of the clinician is to determine which of these is most likely. In general, inflammatory disorders have an inflammatory cerebrospinal fluid (CSF) manifested by either pleocytosis, raised IgG index or both. Fig. 1 is an algorithm on the diagnosis and management of acute noncompressive myelopathies.

Demyelinating Disorders

Typically, the onset of neurological symptoms in myelitis due to demyelination occurs over days with sensory motor symptoms and bladder and bowel disturbances, although occasionally necrotizing demyelinating myelopathies, including NMO, may progress over hours. They usually occur in individuals who are otherwise in good health and may be preceded by a nonspecific viral illness. Table 2 provides the differential diagnoses of demyelinating myelopathies and their clinical-radiological features.

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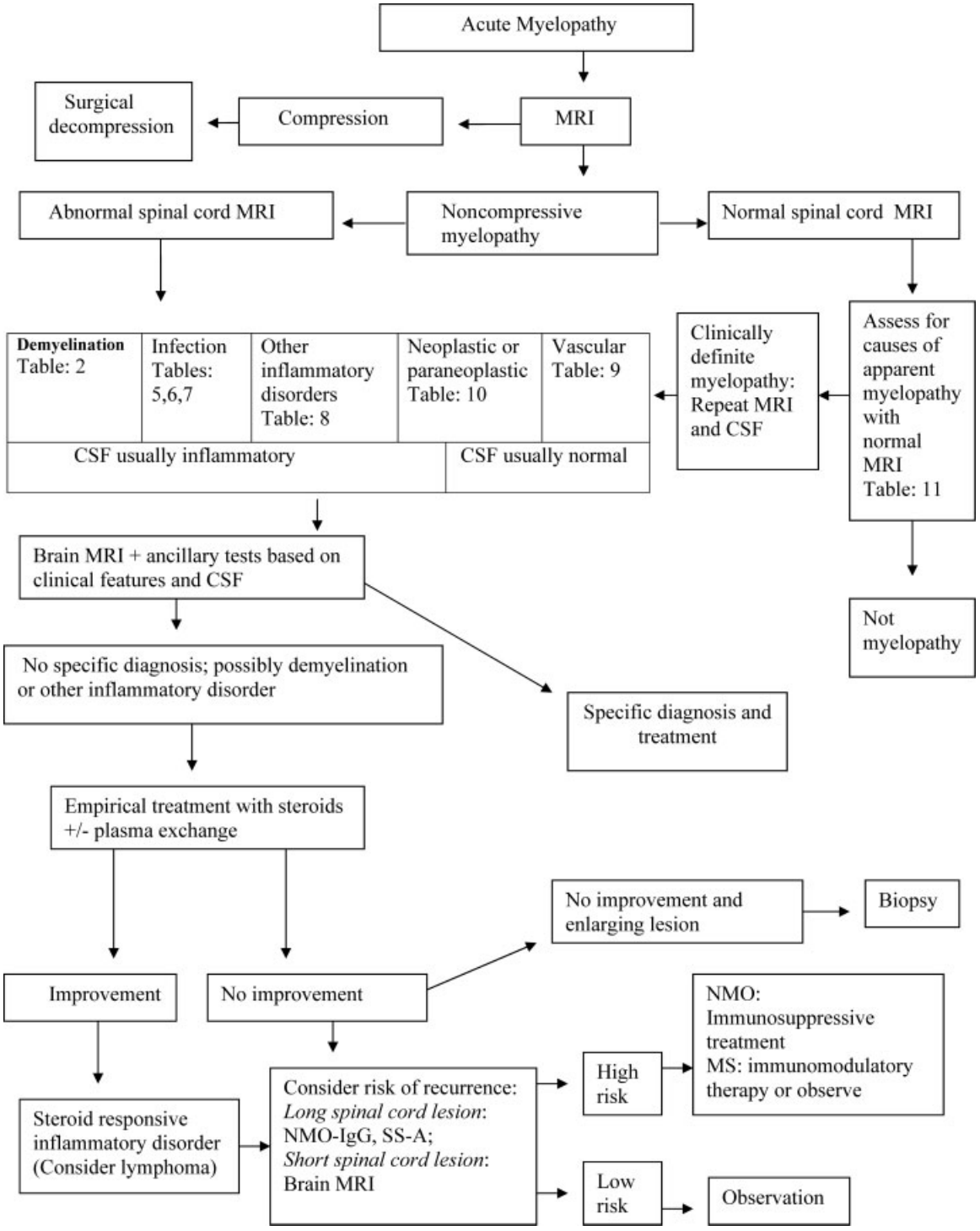

Figure 1 Diagnostic approach to acute myelopathy. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; NMO, neuromyelitis optica; MS, multiple sclerosis; IgG, immunoglobulin G; SS-A, Sjögren's syndrome antibody (anti-Ro).

MULTIPLE SCLEROSIS

In MS, lesions are usually small (< 2 vertebral segments in length) and peripheral, and therefore cause asymmetric symptoms and signs (Fig. 2). Lhermitte's sign (paresthesias spreading down the spine, often into the legs, on neck movement) is typical for a demyelinating lesion of the cervical posterior columns, but can be, although rarely, seen in other conditions that involve the same site. Other characteristic syndromes include isolated proprioceptive loss of an upper extremity ("sensory useless hand syndrome"),[1] Brown-Séquard syndrome, or, more commonly, incomplete versions thereof. Early in

Table 2 Causes of Acute Demyelinating Myelopathies and Diagnostic Clues

Condition	Clinical Presentation	MRI Spinal Cord	MRI Brain	CSF
Multiple sclerosis	Partial myelopathy, e.g., Brown-Séquard; previous episodes of neurological dysfunction with recovery	Lesion less than 2 spinal cord segments, usually peripherally located; predilection for lateral and posterior funiculi	White matter lesions; Dawson's fingers; periventricular, juxtacortical, infratentorial lesions	OCB and raised IgG index
Neuromyelitis optica	90% women; typically severe deficits; may have experienced previous myelitis or optic neuritis	Long cord lesion >3 segments; cord swelling and gadolinium enhancement in acute lesions	Lesions present in up to 60% of patients, often subtle, usually periventricular; occasionally hypothalamic or brainstem lesions	Prominent CSF pleocytosis, occasionally with neutrophilic /eosinophilic predominance during acute attacks; no OCB in $>80\%$; usually normal or transiently elevated CSF IgG index
Acute disseminated encephalomyelitis	Monophasic; most commonly children; fever; encephalopathy; infectious (usually viral) prodrome	Variable lesion length	Large, often confluent white matter lesions; lesions of the same/similar duration (lacking evidence for ''old'' lesions)	Pleocytosis; OCB and IgG index that may be abnormal, often transiently
Postvaccinial	Monophasic; recent vaccination (preceding 3 wk)	Variable lesion length	Brain lesions possible	Pleocytosis; OCB and IgG index that may be abnormal, often transiently
Idiopathic transverse myelitis (Table 4)	Monophasic; no cause after investigations; diagnosis of exclusion	Variable lesion length	No brain lesions	Pleocytosis OCB and IgG index that may be abnormal, often transiently

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; OCB, oligoclonal bands; IgG, immunoglobulin G.

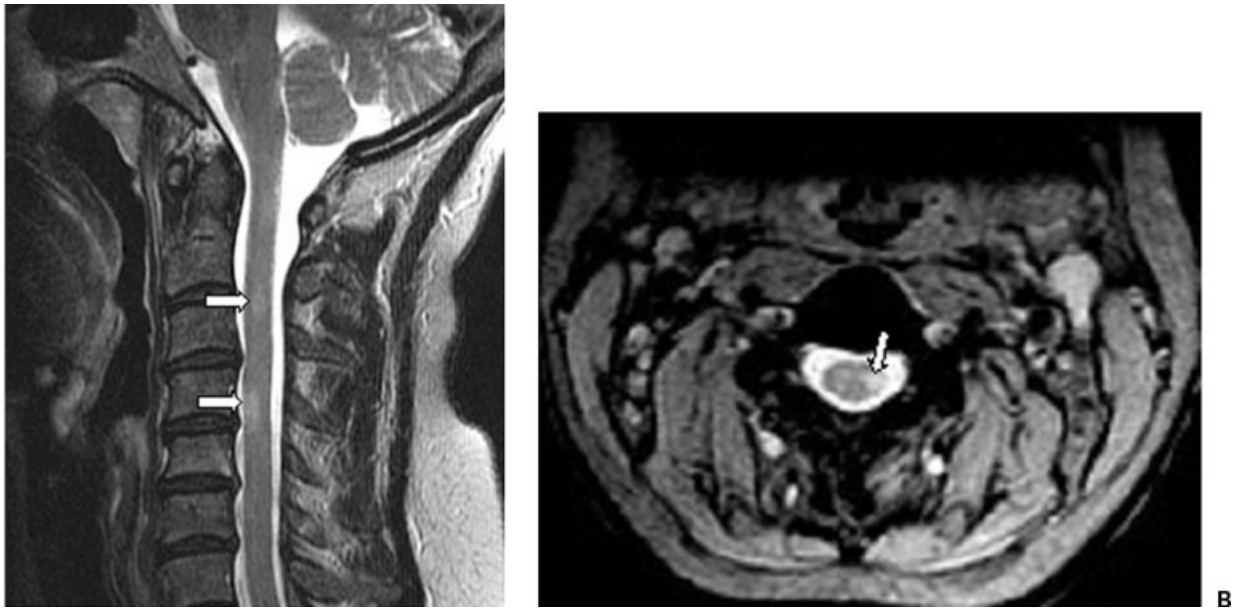

Figure 2 Cervical cord magnetic resonance imaging (MRI) from a 36-year-old woman with multiple sclerosis (MS). (A) Sagittal T2-weighted image shows discrete lesions without cord swelling. (B) Axial sections through the lower lesion show that the lesion is peripherally located within the cord.

the relapsing phase of MS, before the development of fixed gliotic scars, symptoms usually resolve in a few weeks to months. CSF oligoclonal bands (OCBs) are present in more than 90% of patients, and a raised immunoglobulin (Ig)G index is seen in more than 60%. Subclinical optic nerve involvement may be evident on visually evoked response testing. At the first occurrence of a partial myelitis, the presence of two or more brain lesions indicates an 88% chance of conversion to MS in the next 20 years. With a normal MRI, the risk is only 19%.[2–4]

NEUROMYELITIS OPTICA

Neuromyelitis optica is most commonly a relapsing demyelinating condition of the central nervous system (CNS) affecting predominantly the optic nerves and spinal cord. Table 3 lists the recently revised criteria for NMO. Lesions are centrally located and necrotic leading to more symmetric symptoms and signs, greater disability than seen in MS, and less complete recovery. The lesions in the cord are typically long (>3 vertebral segments) (Fig. 3). A history of severe optic neuritis should raise suspicion of NMO. NMO is relatively more common in Asian and African individuals, although the majority of patients with this condition in western countries are white. A variety of autoimmune conditions including SLE, Sjögren's syndrome, and thyroid autoimmune disorders may coexist with NMO. NMO-IgG is a recently identified serum antibody that is highly specific ($>90\%$) and sensitive ($>70\%$) for NMO.[5] It is also present in NMO spectrum disorders, including limited forms of NMO such as relapsing optic neuritis and relapsing myelitis. When identified at the first attack, NMO-IgG also predicts future episodes of myelitis or optic neuritis. In a prospective study, the risk of developing recurrent myelitis or new onset optic neuritis in patients with an isolated longitudinally extensive transverse myelitis was more than 50% among those who were NMO-IgG seropositive, compared with 0% in those who were NMO-IgG seronegative.[6] Brain MRI can be abnormal in NMO. Typically, lesions are periventricular, especially in regions of high concentration of aquaporin-4, the target antigen for the NMO-IgG.[7]

ACUTE DISSEMINATED ENCEPHALOMYELTIS

Acute disseminated encephalomyelitis (ADEM) is a monophasic disorder that affects the brain and occasionally the spinal cord.[8] Often there is a history of preceding viral or other infectious illness. The brain and spinal cord

Table 3 Diagnostic Criteria for Neuromyelitis Optica

Optic neuritis
Acute myelitis
And at least two of three supportive criteria:
1. Contiguous spinal cord MRI lesion extends over 3 vertebral segments.
2. Brain MRI does not satisfy diagnostic criteria for multiple sclerosis.
3. NMO-IgG is seropositive.

MRI, magnetic resonance imaging; NMO, neuromyelitis optica; IgG, immunoglobulin G.
From Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66(10):1485–1489.

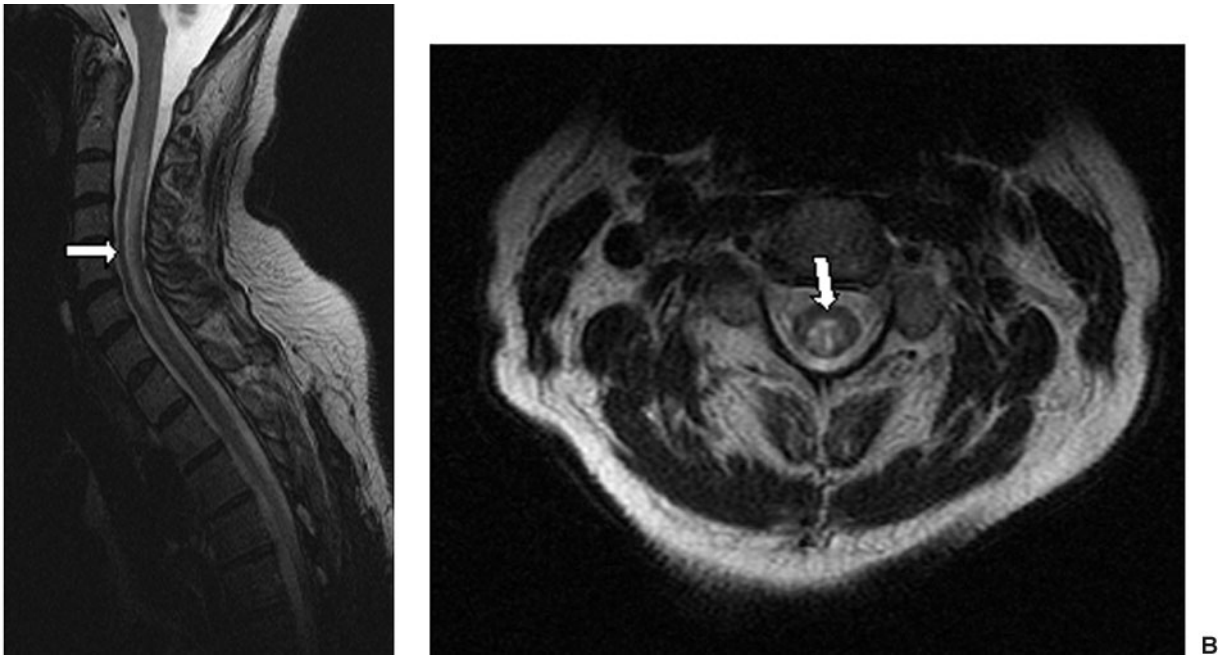

Figure 3 Cervical cord magnetic resonance imaging (MRI) from a 56-year-old woman with neuromyelitis optica (NMO). NMO-immunoglobulin (Ig)G was positive. (A) Sagittal T2-weighted MRI scan shows a longitudinally extensive T2 hyperintense lesion. (B) Axial image shows that the lesion is central within the cord.

show demyelinating lesions that are generally of the same age, although gadolinium enhancement may not be seen in all, and, occasionally, not in any of the lesions. ADEM may evolve over the course of up to 3 months. ADEM is more common in children, and is only reliably diagnosed in individuals who have concomitant encephalopathy. Follow-up of individuals with a clinical diagnosis of ADEM reveals that ~25% of cases

Table 4 Criteria for Idiopathic Acute Transverse Myelitis (modified from reference 17)

Inclusion Criteria	Exclusion Criteria
• Sensory, motor, or autonomic dysfunction attributable to the spinal cord	• History of previous radiation to the spine within the past 10 years
• Bilateral signs and/or symptoms (though not necessarily symmetric)	• Clinical deficit consistent with thrombosis of the anterior spinal artery
• Clearly defined sensory level	• Abnormal flow voids on the surface of the spinal cord consistent with AVFs
• Exclusion of extra-axial compressive etiology by neuroimaging (MRI, myelography; CT of spine not adequate)	• Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)*
• Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement	• Clinical or laboratory evidence for syphilis, Lyme disease, HIV, HTLV-1, *Mycoplasma*, other viral infection (e.g., HSV- 1, HSV-2, VZV, EBV, CMV, HHV-6, enterovirus)*
• If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 days following symptom onset	• Brain MRI abnormalities suggestive of MS*
• Progression to nadir between 4 hours and 21 days following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	• History of clinically apparent optic neuritis*

*Do not exclude disease-associated acute transverse myelitis.
AVFs, arteriovenous fistulas; MRI, magnetic resonance imaging; CT, computed tomography; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus; IgG, immunoglobulin G; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus 1; HSV, herpes simplex virus; VZV, varicella zoster virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus; HHV, human herpes virus.

eventually meet clinical criteria for MS.

POSTVACCINE MYELITIS

An acute transverse myelitis occurring in the 3 weeks following a vaccination has been linked to an immunological reaction to the vaccine, such as smallpox or rabies. In recent years vaccines such as hepatitis B, typhoid, influenza, rubella, and tetanus have been implicated,[9–14] but a causal relationship has not been established. Such cases may reflect chance occurrences of idiopathic transverse myelitis in patients who incidentally have had a vaccination.

ACUTE IDIOPATHIC TRANSVERSE MYELITIS

Inflammatory transverse myelitis (CSF inflammation with usual pleocytosis and occasionally elevated IgG index/OCBs) in the absence of a specific cause (such as MS, NMO, ADEM, connective tissue disease, etc.) is the most common cause of acute myelitis.[15,16] Criteria have been proposed for this entity[17] (Table 4). However, the idiopathic nature is a diagnosis of exclusion. The bimodal peaks in onset ages are 10 to 19 years and 30 to 39 years. A preceding nonspecific fever, nausea, or muscle pain, possibly indicating a prior viral infection, is common, although one or more of these symptoms may also precede attacks of MS and NMO. The lesion length varies from less than one segment to the entire cord. Many of these large series of patients were reported before NMO-IgG was identified, and it is possible that many such patients may have an NMO spectrum disorder. The proportion of "idiopathic" inflammatory transverse myelitis is likely to decline with the increasing availability of newer autoimmune markers, imaging techniques, and microbiological tests capable of defining a specific etiology.

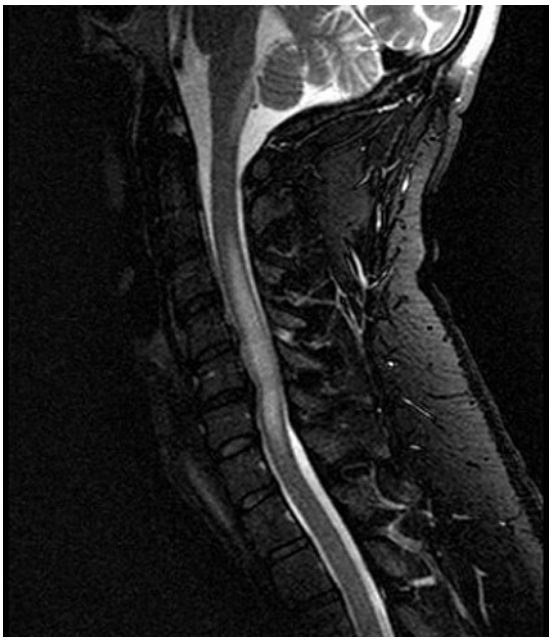

Figure 4 Sagittal T2-weighted magnetic resonance imaging (MRI) of the cervical cord in a 43-year-old man who developed herpes zoster in the upper limbs and simultaneously a longitudinally extensive cervical myelitis. (Image courtesy of Dr. Orhun Kantarci, Mayo Clinic, Rochester, MN.)

Assessment for Recurrence Risk in Demyelinating Myelopathies

After management of acute myelitis with steroids and/or plasma exchange, demyelinating myelopathies need to be evaluated for the risk of recurrence. The major decision point is whether a patient has complete or incomplete transverse myelitis (Fig. 1). Complete transverse myelitis usually has more or less symmetrical findings and involvement of motor, sensory, and sphincter function. Incomplete transverse myelitis usually has asymmetric findings that may involve a limited number of tracts and does not typically result in loss of all motor, sensory, and sphincter function. In general, complete transverse myelitis is associated with a long spinal cord lesion exceeding three vertebral segments in length, often central within the cord, and an incomplete transverse myelitis is associated with a short spinal cord lesion, typically one to two segments in length and peripheral. However, there are exceptions to this general rule.

Patients with Complete Transverse Myelitis

Complete transverse myelitis patients, in general, are at low risk for future development of MS. However, they could have recurrences consistent with relapsing myelitis or NMO. Two autoimmune markers that may predict recurrence are anti–Sjögren's syndrome antibody (SS-A) and NMO-IgG.[18] NMO-IgG predicted each case of recurrence in a Mayo Clinic series,

Table 5 Clinical Indications Suspicious of an Infectious Myelopathy

Fever
Confusion
Meningismus
Rash
• Vesicular rash in the buccal mucosa and on the hands and feet in enterovirus 71
• Herpes zoster rash in dermatomal distribution
• Erythema chronicum migrans of Lyme disease (rarely presents as acute myelitis)
Concurrent systemic infection
Immunocompromised state
Recurrent genital infection
Lymphadenopathy
Residence in area endemic for parasitic infections

Table 6 Causes of Acute Myelopathies Resulting from Infectious Agent

	Specific Agents	
Viruses	**DNA Viruses**	**RNA viruses**
	Herpesviruses	**Flaviviruses**
	Herpes simplex virus-2*	Dengue virus
	Varicella-zoster virus*	Japanese encephalitis virus†
	Cytomegalovirus*	St. Louis encephalitis virus
	Human herpes viruses 6 and 7	Tick-borne encephalitis virus†
	Epstein-Barr virus[36]*	West Nile virus†
		Orthomyxoviruses
		Influenza A virus
		Paramyxoviruses
		Measles virus
		Mumps virus
		Picornaviruses
		Coxsackieviruses A and B†
		Echoviruses
		Enterovirus-70 and -71†
		Hepatitis A, C[37]
		Poliovirus types 1, 2, and 3†
Bacterial	Spinal cord abscess due to hematogenous spread of systemic infection	
	Mycoplasma, *Borrelia burgdorferi* (Lyme), *Treponema pallidum* (syphilis)	
	Mycobacterium tuberculosis	
Fungal	*Actinomyces*, *Blastomyces dermatitidis*, *Coccidioides*, *Aspergillus*	
Parasites	Neurocysticercosis, *Schistosoma*, *Gnathostoma*, angiostrongylosis (eosinophilic myelitis)	

*Common causes.
†Can cause acute poliomyelitis-like syndrome due to preferential, rather than selective, destruction of anterior horn cells and other motor pathways.
Note: HTLV-1 (human T-lymphotropic virus 1) and HIV can cause a chronic myelitis without brain involvement.

whereas anti-SS-A did not.[6] Thirty-eight percent of patients with a first episode of transverse myelitis were seropositive for NMO-IgG in a recent Mayo Clinic series; more than 50% of those followed for 1 year had recurrent myelitis or optic neuritis, whereas none of the seronegative patients experienced recurrence.[6] We currently advise testing for NMO-IgG in patients who have experienced a first episode of longitudinally extensive transverse myelitis, and instituting immunosuppressive therapy in those positive for NMO-IgG. We believe that monophasic inflammatory demyelinating transverse myelitis in patients seropositive for NMO-IgG is a limited form of NMO with a high risk of relapse, or an NMO spectrum disorder, and should be managed accordingly.

Patients with Incomplete Transverse Myelitis

This group of patients is currently regarded as having a clinically isolated syndrome (CIS), which places them at risk for developing other symptoms that will lead to a definite diagnosis of MS. Cranial MRI is used to determine the degree of risk of MS. Those with lesions consistent with MS (two or more) are at high risk, currently estimated at 88% within 20 years. Those with a normal brain on MRI have a much lower risk, ~19% at 20 years.[2,4] Some experts advocate prophylactic treatment with disease-modifying therapy for high-risk patients.[19] The prognosis for MS attacks may be much better than for NMO attacks, and some would argue that it would be worth waiting to determine if further disease activity occurs, given the highly variable and often favorable prognosis of MS.[20] This is a major point of controversy regarding management of CIS. Other predictors of recurrence include CSF OCBs.[21,22] MRI remains the single most potent predictor, although it is subject to problems of specificity of MRI-identified brain lesions for demyelinating disease.

Acute Infectious Myelopathies

Viral, bacterial, fungal, and parasitic agents can cause acute myelitis (Fig. 4). Patients are systemically ill with

fever and meningismus. Prominent CSF inflammation (pleocytosis, often neutrophilic and raised protein concentration) must prompt investigation for a causative agent, especially a treatable one. This is in contrast to parainfectious or idiopathic inflammatory myelitis where patients have recovered from a recent infection, usually viral. Table 5 lists clinical clues to an infectious cause, Table 6 lists the infectious agents, and Table 7 provides diagnostic studies. However, in most cases of acute viral myelitis, a specific viral cause is never determined.[23]

Myelopathies Associated with Other Inflammatory Disorders

Connective tissue disorders and granulomatous disorders may present with acute or subacute myelitis. SLE, Sjögren's syndrome, scleroderma, mixed connective tissue disorder (MCTD), Behçet's disease, and sarcoidosis (Fig. 5) have all been associated with myelitis.[24–26] However, it is rare for myelitis to be the presenting symptom. Almost invariably, classical systemic features, brain, or meningeal involvement, at least on MRI, will be present before development of myelitis. In general, established criteria for these disorders should be satisfied before the myelitis is attributed to these disorders. CSF is usually inflammatory, and MRI of the spinal cord may show enhancing lesions. The significance of an autoantibody (e.g., antinuclear antibody [ANA]) in isolation without consistent systemic clinical features is suspect. Table 8 lists the conditions that could cause acute inflammatory myelopathy and criteria needed to diagnose them. Recent evidence suggests that the presence of autoantibodies in patients with acute myelitis may suggest that the myelitis is an NMO spectrum disorder. This is because NMO-IgG is present in approximately half such cases, whereas it is absent in patients with connective tissue diseases, such as SLE and Sjögren's syndrome, who do not have a history of myelitis or optic neuritis.

Table 7 Cerebrospinal Fluid Evaluation in Suspected Infectious Myelitis

Stains and cultures
• Gram's stain, bacterial culture
• Acid-fast bacilli smear and tuberculosis culture
• CSF India ink smear and fungal culture
• Viral cultures
CSF polymerase chain reaction
• Herpes simplex virus type 1
• Herpes simplex virus type 2
• Human herpesvirus 6
• Varicella-zoster virus
• Cytomegalovirus
• Epstein-Barr virus
• Enteroviruses
• Herpes simplex virus
• Varicella-zoster virus
• Human T-lymphotropic virus type 1
• *Borrelia burgdorferi* (Lyme)
Serology
• Herpes simplex virus
• Varicella-zoster virus
• HIV
• Human T-lymphotrophic virus type 1
• *B.* burgdorferi
• Syphilis
• Hepatitis A, B, C
• Mycoplasma
• Parasites
Blood cultures
Chest radiograph/CT

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; CT, computed tomography.

Vascular Disorders

The arterial supply of the spinal cord consists of a single anterior spinal artery and two posterior spinal arteries (that course vertically over the surface of the cord) and their penetrating branches.[27] Acute vascular occlusion can lead to spinal cord infarction mimicking myelitis (Fig. 6). Arterial occlusions are rare and develop acutely over minutes. However, arteriovenous fistulas (AVFs) usually progress slowly due to gradual ischemia resulting

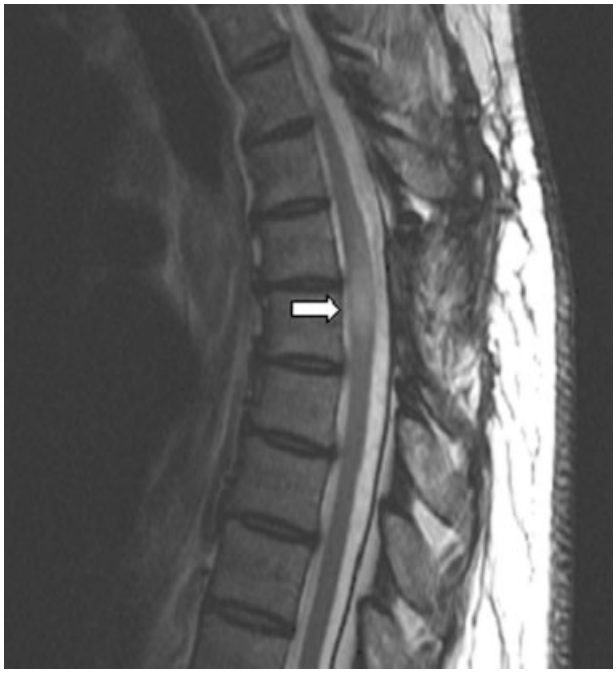

Figure 5 Sagittal T2-weighted magnetic resonance imaging (MRI) of the thoracic cord of a 45-year-old woman with sarcoidosis who presented with a subacute myelopathy.

Table 8 Disorders that Could Cause Acute Inflammatory Myelopathy and Criteria to Diagnose Them

Condition	Criteria
SLE	**The 1982 revised criteria; 4 of 11 needed for diagnosis:**[38] 1. Malar rash 2. Discoid rash 3. Photosensitivity 4. Oral ulcers 5. Arthritis 6. Serositis 7. Renal disorder 8. Neurologic disorder: (a) seizures or (b) psychosis (both not due to drugs or metabolic abnormalities) 9. Hematologic disorder 10. Immunologic disorder (positive LE cell preparation/Anti-DNA/Anti-Sm/false-positive serologic test for syphilis 11. Antinuclear antibody
Primary Sjögren's syndrome	**International consensus criteria; 4 of 6 any criteria or 3 of 4 objective criteria need to be present for diagnosis:**[39] 1. Dry eyes 2. Dry mouth 3. Objective evidence of dry eyes (at least one present): Schirmer test, Rose-Bengal, lacrimal gland biopsy 4. Histopathology of minor salivary glands focal lymphocytic sialoadenitis 5. Objective evidence of salivary-gland involvement (at least one present): Salivary-gland scintigraphy, parotid sialography, unstimulated whole sialometry (1.5 mL per 15 min) 6. Laboratory abnormality (at least one present): Anti-SS-A or anti-SS-B, ANA, IgM rheumatoid factor (anti-IgG Fc)
MCTD	**Diagnostic criteria:**[40] 1. Serological: High titer anti-U1RNP 2. Clinical: Edema of hands/synovitis/myositis/Raynaud's phenomenon/acrosclerosis 3. Serological criteria and at least three clinical criteria, including either synovitis or myositis required
Systemic sclerosis (Scleroderma)	**ARA Preliminary classification criteria 1980:**[41] Proximal skin scleroderma *or* two of the following three criteria: • Sclerodactyly (fingers or toes) • Digital pitting scars/pulp loss • Bibasilar pulmonary fibrosis
Neurosarcoidosis	**Proposed criteria for diagnosis:** **Definite:** Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of nervous system histology **Probable:** Clinical syndrome suggestive of neurosarcoidosis with: • Laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis) • Exclusion of alternative diagnoses • Evidence for systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging, elevated serum ACE) **Possible:** Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met
Behçet's Disease	**International Study Group for Behçet's Disease; 1990 criteria:**[42] Recurrent oral ulceration should occur at least three times in 1 y, accompanied by any two of the following: 1. Recurrent genital ulcers 2. Anterior or posterior uveitis or retinal vasculitis 3. Skin lesions (erythema nodosum, acneiform nodules, pseudofolliculitis, and papular lesions) 4. Positive pathergy test

SLE, systemic lupus erythematosus; LE, lupus erythematosus; SS-A, Sjögren's syndrome antibody A (anti-Ro); SS-B, Sjögren's syndrome antibody B (anti-La); ANA, antinuclear antibody; Ig, immunoglobulin; Fc, fragment, crystallizable (of immunoglobulin); MCTD, mixed connective tissue disorder; ARA, American Rheumatism Association; CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ACE, angiotensin-converting enzyme.

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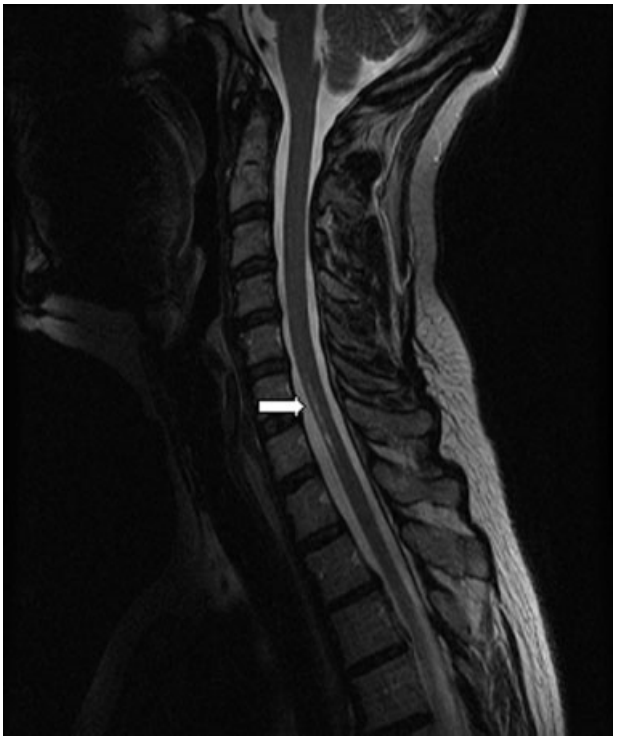

Figure 6 Sagittal T2-weighted cervical magnetic resonance imaging (MRI) of a 49-year-old woman who developed acute paraparesis and a thoracic sensory level to pain following heavy physical exertion. Arrow points to the linear lesion in the anterior cord–presumed anterior spinal artery occlusion. (Image courtesy of Mark Keegan, Mayo Clinic, Rochester MN.)

from venous congestion. Sudden decompensation of myelopathy caused by AVFs or bleeding into vascular malformations may also mimic myelitis (Fig. 7). CSF is usually normal, although spinal AVF can lead to elevated CSF protein concentration without pleocytosis. Causes of acute vascular myelopathies and diagnostic clues are listed in Table 9.

Neoplasia and Myelopathy

Intramedullary metastatic disease and intradural extramedullary compressive tumors (neurofibromas and meningiomas) are common causes of acute or acute-on-chronic myelopathy. Primary intramedullary cord tumors (ependymomas, astrocytomas, hemangioblastomas) or metastatic intramedullary tumors usually present over weeks. This is not a difficult diagnosis when there is an enhancing heterogenous lesion on MRI, especially with known systemic cancer. However, certain situations may cause diagnostic dilemmas.

ACUTE PRESENTATIONS OF SPINAL TUMORS

Hemorrhage or infarction of tumors resulting in acute swelling can mimic myelitis. Intramedullary cord lymphomas may respond symptomatically and radiologically to corticosteroids, which can further confuse the diagnosis. If serial imaging, CSF studies, and a search for a primary neoplasm are inconclusive, cord biopsy may be necessary. OCBs in CSF may be seen with tumors, but persistence of the bands is unusual.[28] Persisting gadolinium enhancement months after treatment of an acute myelitis should alert physicians to a potential neoplasm.[28]

RADIATION-ASSOCIATED MYELOPATHY

Radiation-induced myelopathies are usually slowly progressive but may occur up to 15 years after the end of radiation treatment, which may obscure the role of radiation therapy in causing the myelopathy. Early in

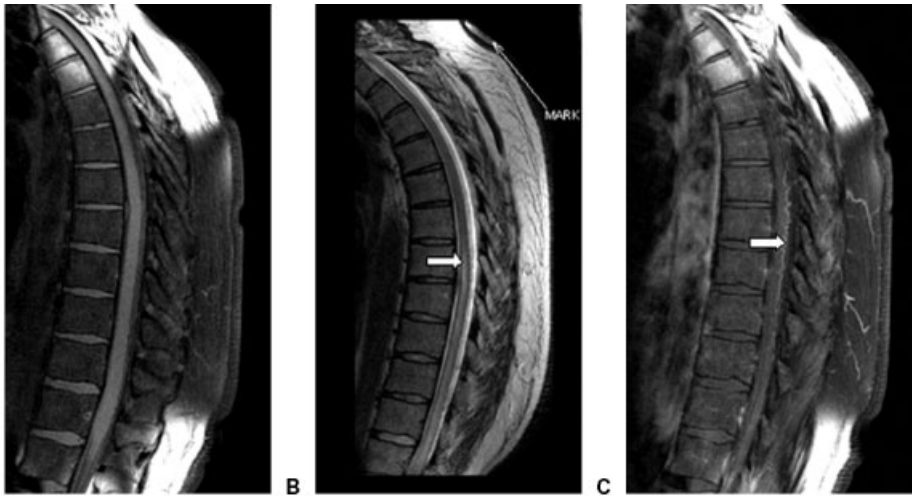

Figure 7 A 49-year-old man who presented with acute myelopathy. (A) T1-weighted image shows no definite abnormality. (B) T2-weighted image shows hyperintense longitudinally extensive lesion. (C) Gadolinium-enhanced T1-weighted image reveals dilated blood vessels on the surface of the cord.

Table 9 Causes of Acute Vascular Myelopathies and Diagnostic Clues[27,43,44]

Condition	Clinical Presentation	MRI Spinal Cord
Anterior spinal artery occlusion[27] (spinal radicular artery occlusion is clinically indistinguishable)	Anterior cord syndrome especially in the following settings: • Aortic surgery • Spinal angiography • Vasculitis • Embolic source (e.g., cardiac; cholesterol) • Aortic/vertebral dissection • Hypotension • Prothrombotic states (e.g., sickle cell; protein C or S deficiency; activated protein C resistance/Factor V Leiden; antiphospholipid syndromes)	Elongated ''pencil-like'' lesion in the anterior cord[43]
Posterior spinal artery occlusion	Posterior column dysfunction • Etiology as above	Triangular lesion in posterior cord
Sulcocommissural artery[27]	Brown Séquard syndrome • Etiology as above	Lateral cord lesion
Arteriovenous fistulas	• Stepwise progressive or recurrent episodes of weakness related to upright posture or walking, accompanied by upper motor neuron or lower motor neuron syndrome or both • Due to ischemia or congestion	Long spinal cord lesion often extending into the conus on T2 images; tortuous vessels seen on the surface of the cord; if highly suspected, despite normal MRI proceed to spinal angiogram
Hematomyelia	• Bleeding diathesis (coagulation/platelet) • Cavernomas • Arteriovenous malformations of the cord • Osler-Rendu-Weber syndrome (hereditary hemorrhagic telangiectasia)	Appearance of blood products (exact appearance depends on stage) Flow voids in the cord
Fibrocartilaginous disc embolism[45]	• Back pain and history of physical exertion • Features of anterior spinal artery occlusion	Loss of vertical intervertebral disc height and T2 signal abnormality in corresponding level cord; microfractures of the vertebral endplates

MRI, magnetic resonance imaging.

the course, cord swelling or enhancement may be seen, but later atrophy may be the only finding.[29] Myokymia may be evident on electromyography (EMG) in affected muscles. MRI may show cord lesions indistinguishable from inflammatory lesions, but the simultaneous involvement of the adjacent vertebrae (usually hyperintense on T2-weighted scans) in the same field of radiation is an important clue to the etiology (Fig. 8).

Paraneoplastic Disorders and Myelopathy

When paraneoplastic antibodies are identified in neurological syndromes, they usually predict an underlying cancer and not necessarily a specific neurological syndrome.[30] Several paraneoplastic antibodies are associated with subacute myelopathies, and a search for such antibodies and an underlying malignancy is

Table 10 Myelopathy Associated with Paraneoplastic Antibodies and Cancers

Cancers Associated with Possible Paraneoplastic Myelopathies	Paraneoplastic Antibodies Associated with Myelopathies
Small cell lung carcinoma	Amphiphysin-IgG
	CRMP-5 IgG
	GAD
	Cation channel antibodies*
Breast cancer	PCA 2
Ovarian cancer	ANNA 2
Non–small cell lung cancer	Neuronal and muscle AChR antibodies

*P/Q or N-type calcium channel, KC voltage-gated potassium channel. Ig, immunoglobulin; CRMP, collapsin response-mediator protein; GAD, glutamic acid decarboxylase; PCA, Purkinje cell antibody; ANNA, antineuronal nuclear antibodies; AChR, acetylcholine receptor.

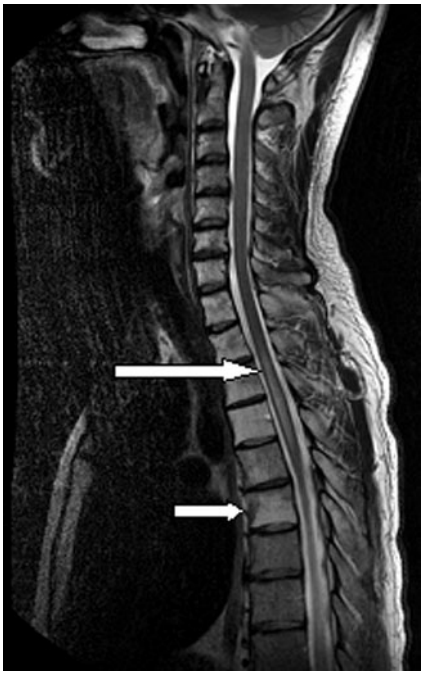

Figure 8 Radiation myelopathy. Sagittal T2-weighted image of the thoracic cord of a 34-year-old man with Hodgkin's lymphoma who received radiotherapy and presented 2 years later with subacute myelopathy and thoracic sensory level. Long arrow points to the longitudinally extensive T2 hyperintense intramedullary lesion. The short arrow points to the vertebral changes in the field of radiation. The vertebra immediately below seems normal. (Image courtesy of Dr Orhun Kantarci, Mayo Clinic, Rochester, MN.)

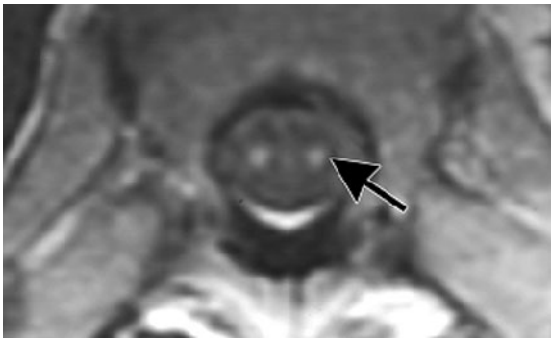

Figure 9 Paraneoplastic tractopathy. Axial T2 sections through the cord of a 69-year-old woman with melanoma and high titres of amphiphysin-immunoglobulin (Ig)G. Arrow points to hyperintensity in the region of the corticospinal tracts. (Reproduced with permission from Pittock SJ, Lucchinetti CF, Parisi JE, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 2005;58[1]:96–107.)

warranted if other etiologies for the myelopathy are not apparent (Table 10). Autoimmunity to CRMP5 may lead to myelopathy and optic neuropathy that may mimic NMO,[31] and when present, should spur a search for an underlying small cell lung carcinoma. Amphiphysin-specific antibodies raise the possibility of breast cancer. Detection of a longitudinally extensive tract-specific lesion, usually symmetrically involving both sides of the cord, may occur with diverse cancers. We have recently recognized this finding, particularly when accompanied by gadolinium enhancement, as a specific

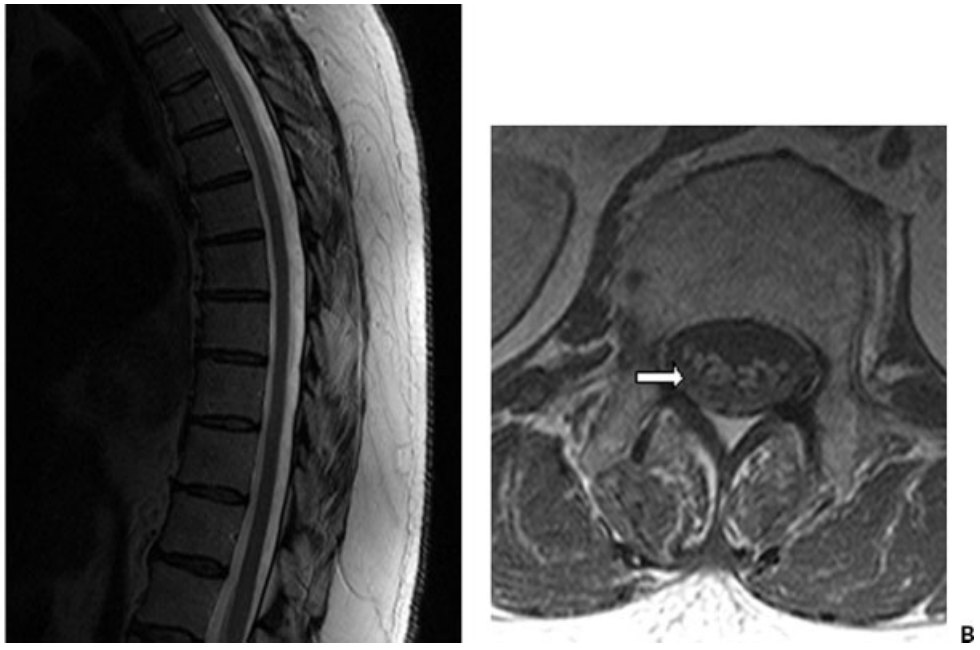

Figure 10 A 67-year-old woman with presumed acute myelopathy and markedly elevated cerebrospinal (CSF) protein. (A) T2-weighted sagittal magnetic resonance imaging is normal; (B) T1-weighted, gadolinium-enhanced axial section through the cauda equina with gadolinium showed enhancing nerve roots. Nerve conduction studies confirmed acute inflammatory demyelinating polyneuropathy.

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radiological sign of a paraneoplastic myelopathy (Fig. 9). Some paraneoplastic conditions may mimic a myelopathy, although they are more likely "neurochemical" (e.g., GAD65 autoimmunity and stiff man syndrome–associated spasms may mimic spasticity; amphiphysin and rigidity/myoclonus may mimic spasticity).[32–35]

Myelopathy with Normal Magnetic Resonance Imaging

Occasionally, the MRI is normal in the setting of an acute myelopathy. There are several potential explanations. First, the syndrome may not be a myelopathy. Guillain-Barré syndrome may be mistaken as myelitis, especially considering the abnormal CSF protein concentration and ascending symptoms that may mimic those seen in myelitis. Enhancing nerve roots on MRI may be a clue to an inflammatory radiculopathy (Fig. 10). It is uncommon to find an acellular CSF in acute inflammatory myelitis. Second, it may not be an acute problem. It is well known that trivial trauma or environmental or physiological stressors like viral illnesses may decompensate a longstanding myelopathy, making it symptomatic to the patient. Friedreich's ataxia, motor neuron disease, vitamin B_{12} or copper deficiency myelopathy, hereditary spastic paraparesis, human immunodeficiency virus (HIV), human T-lymphotropic virus 1 (HTLV-1)-myelopathy, and adrenomyeloneuropathy may all have such "pseudo-acute" presentations. MRI scans are more often normal than not in these disorders.

Imaging performed during the convalescent phase may miss a cord lesion. The quality of the images may

Table 11 Approach to 'Myelopathy' with Normal Magnetic Resonance Imaging

Alternative Explanations	Examples
Has a compressive cause been missed?	Epidural lipomatosis
	Dynamic compression on flexion extension only[46,47]
Is it really a myelopathy?	Ganglionopathy, e.g., Sjögren's, paraneoplastic, toxins
	Peripheral nerve disease, e.g., acute inflammatory polyradiculoneuropathy
	Plexopathy, e.g., neoplastic or idiopathic inflammatory
	Neuromuscular junction, e.g., myasthenia gravis
	Muscle, e.g., periodic paralysis
	Motor neuronopathy, e.g., ALS/primary lateral sclerosis
Is there a cerebral cause for the deficit?	Parasagittal meningioma
	Cerebral venous thrombosis
	Anterior cerebral artery thrombosis
	Normal pressure hydrocephalus
	Hydrocephalus
	Small vessel disease (vascular lower limb predominant parkinsonism)
	Other extrapyramidal disorders
Is it an acute presentation of an underlying chronic metabolic, degenerative, or infective myelopathy?	B_{12}, folate, copper deficiency
	Nitrous oxide inhalation
	HTLV-1
	HIV
	Syphilis
	Motor neuron disease (ALS)
	Adrenomyeloneuropathy
	Hereditary spastic paraplegia
	Friedreich's ataxia
	Lathyrism
Is the image quality adequate?	Motion artifact
	Low-strength magnet (0.5 T)
Were the images taken too early or too late in time and therefore ''missed'' the lesion (i.e., before it appeared or after it resolved)?	Long lesions of NMO may appear patchy or short, and hence nondiagnostic, if imaging is performed in the convalescent phase
Is the lesion too small to be seen on MRI?	
Is the weakness not organic (''functional'')?	

ALS, amyotrophic lateral sclerosis; HTLV-1, human T-lymphotropic virus 1; HIV, human immunodeficiency virus; NMO, neuromyelitis optica.

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have been suboptimal, especially in terms of resolution of an intramedullary lesion. Repeat imaging using sedation, if necessary, to prevent movement-related artifact may be needed if suspicion of myelopathy is high. Table 11 lists the various other possibilities for myelopathy with normal MRI.

CONCLUSION

Although inflammatory demyelinating etiologies account for a high proportion of acute myelopathies, other diagnoses need to be excluded. Once a demyelinating pathology is deemed likely, the chance of recurrence should be considered and, if appropriate, preventative treatments should be initiated. The proportion of idiopathic inflammatory myelitis is likely to decline with the increasing availability of newer autoimmune markers, imaging techniques, and microbiological tests capable of defining a specific etiology for an acute myelopathy.

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