

CME

Proposed diagnostic criteria and nosology of acute transverse myelitis

Transverse Myelitis Consortium Working Group*

Abstract—Acute transverse myelitis (ATM) is a focal inflammatory disorder of the spinal cord, resulting in motor, sensory, and autonomic dysfunction. A set of uniform diagnostic criteria and nosology for ATM is proposed to avoid the confusion that inevitably results when investigators use differing criteria. This will ensure a common language of classification, reduce diagnostic confusion, and lay the groundwork necessary for multicenter clinical trials. In addition, a framework is suggested for evaluation of individuals presenting with signs and symptoms of ATM. Best treatment often depends on a timely and accurate diagnosis. Because acute transverse myelopathies are relatively rare, delayed and incomplete work-ups often occur. Rapid and precise diagnosis will ensure not only that compressive lesions are detected and treated but also that idiopathic ATM is distinguished from ATM secondary to a known underlying disease. Identification of etiologies may suggest medical treatment, whereas no clearly established medical treatment currently exists for idiopathic ATM. Establishment of a diagnostic algorithm will likely lead to improved care, although it is recognized that the entire evaluation may not be performed for each patient.

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Epidemiology and natural history of acute transverse myelitis. Acute transverse myelitis (ATM) has an incidence of one to four new cases per million people per year, affecting individuals of all ages with bimodal peaks between the ages of 10 and 19 years and 30 and 39 years.¹⁻⁴ There is no sex or familial predisposition to ATM. It is characterized clinically by acutely or subacutely developing symptoms and signs of neurologic dysfunction in motor, sensory, and autonomic nerves and nerve tracts of the spinal cord. There is often a clearly defined rostral border of sensory dysfunction, and spinal MRI and lumbar puncture often show evidence of acute inflammation. When the maximal level of deficit is reached, approximately 50% of patients have lost all movements of their legs, virtually all patients have bladder dysfunction, and 80 to 94% of patients have numbness, paresthesias, or band-like dysesthesias.¹⁻⁶ Autonomic symptoms consist variably of increased urinary urgency, bowel or bladder incontinence, difficulty or inability to void, incomplete evacuation, or bowel constipation.⁷

Longitudinal case series of ATM reveal that approximately one third of patients recover with little to no sequelae, one third are left with moderate degree of permanent disability, and one third have severe disabilities.^{1,4,5} Rapid progression of symptoms, back pain, and spinal shock predict poor recovery.^{6,8-10} Paraclinical findings such as absent central conduction on evoked

potential testing and the presence of 14-3-3 protein, a marker of neuronal injury, in the CSF during the acute phase predict a poor outcome.¹¹

ATM can be the presenting feature of MS. Patients who are ultimately diagnosed with MS are more likely to have asymmetric clinical findings, predominant sensory symptoms with relative sparing of motor systems, MR lesions extending over fewer than two spinal segments, abnormal brain MRI, and oligoclonal bands in the CSF.^{9,12-16} A patient with monofocal CNS demyelination (transverse myelitis or optic neuritis) whose brain MRI shows lesions consistent with demyelination¹⁷ has an 83% chance of meeting clinical criteria for MS over the subsequent decade compared with 11% of such patients with normal brain MRI.¹⁸

Background and review of previous diagnostic criteria. Several cases of “acute myelitis” were described in 1882, and pathologic analysis revealed that some were due to vascular lesions and others to acute inflammation.¹⁹ Subsequently, the occurrence of >200 cases of postvaccinal encephalomyelitis was reported in 1922 to 1923 in England, a complication of smallpox and rabies vaccination.²⁰ Pathologic analyses of fatal cases revealed inflammatory cells and demyelination rather than the vascular pathology noted in earlier reports. Acute transverse myelopathy (which includes noninflammatory causes) and

*See the Appendix for a complete listing of the members of the Transverse Myelitis Consortium Working Group.

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Table 1 Criteria for idiopathic acute transverse myelitis

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10 y
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord c/w AVM
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or 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. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria	CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, <i>Mycoplasma</i> , other viral infection (e.g. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*
Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	Brain MRI abnormalities suggestive of MS*
	History of clinically apparent optic neuritis*

*Do not exclude disease-associated acute transverse myelitis.

AVM = arteriovenous malformation; SLE = systemic lupus erythematosus; HTLV-1 = human T-cell lymphotropic virus-1; HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein-Barr virus; CMV = cytomegalovirus; HHV = human herpes virus.

ATM have often been used interchangeably throughout the published literature. One report established the following criteria for transverse myelopathy: bilateral spinal cord dysfunction developing over a period of ≤ 4 weeks with a well-defined upper level, no antecedent illness, and exclusion of compressive etiologies.⁸ Subsequently, these criteria were altered to include only those patients who developed motor, sensory, and sphincter dysfunction acutely over ≤ 14 days, whereas patients with other neurologic disease or underlying systemic diseases were excluded.³ Other authors then defined ATM as acutely developing paraparesis (no specification of a time to maximum deficit) with bilateral sensory findings and impaired sphincteric function, a spinal segmental level of sensory disturbance, a stable nonprogressive course (to distinguish from progressive spastic paraparesis), and no clinical or laboratory evidence of spinal cord compression.¹ Patients were excluded if they had progressive spastic paraparesis, a patchy sensory deficit or hemicord syndrome, syphilis, severe back trauma, metastatic cancer, or encephalitis. To further separate diseases with distinct etiologies, suggested criteria for ATM were revised to include only those patients who progressed to maximum deficit within 4 weeks and to exclude other known diseases including arteriovenous malformations of the spinal cord, human T-cell lymphotropic virus-1 (HTLV-1) infection, and sarcoidosis.² With use of these criteria, cases of ATM were classified as parainfectious, related to MS, spinal cord ischemia, or idiopathic.

Most recently, acute noncompressive myelopathies were classified according to an etiologic scheme¹²: 1) those related to MS, 2) systemic disease (e.g., systemic lupus erythematosus [SLE], anti-phospholipid syndrome, Sjögren disease), 3) parainfectious, 4) delayed radiation myelopathy, 5) spinal cord infarct, and 6) idiopathic myelopathy. The presence of MS or systemic disease was determined by standard criteria,²¹⁻²³ whereas parainfectious myelopathies were diagnosed on the basis of positive IgM serology

or a fourfold or greater increase in IgG levels on two successive tests to a specific candidate/infectious agent. Delayed radiation myelopathy was diagnosed according to clinical history, and spinal cord infarction was diagnosed on the basis of appropriate clinical and imaging findings in the absence of other likely etiologies. Idiopathic transverse myelopathy was defined in those individuals that could not be otherwise categorized and constituted 16.5% of this series.

Proposed diagnostic criteria for ATM. The diagnostic criteria for idiopathic ATM are listed in Table 1. A diagnosis of idiopathic ATM should require that all of the inclusion criteria and none of the exclusion criteria are fulfilled. A diagnosis of disease-associated ATM should require that all the inclusion criteria are met and that the patient is identified as having an underlying condition listed in the disease-specific exclusions.

As the clinical syndrome of acute transverse myelopathy may have noninflammatory causes (i.e., vascular causes), ATM represents a subset of acute myelopathies. A diagnosis of ATM requires evidence of inflammation within the spinal cord. Because spinal cord biopsy is not a practical option in the routine evaluation of these patients, spinal MRI and CSF analysis are the only tools currently available to determine the presence of inflammation within the involved lesion. Enhanced spinal MRI and a lumbar puncture are mandatory in the evaluation of suspected ATM, and we propose that abnormal gadolinium enhancement of the spinal cord or CSF pleocytosis or elevated CSF IgG index be required for a diagnosis of ATM. 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 should be performed to determine if these criteria are met. IgG synthesis rate is a less specific indicator of CNS inflammation than

is CSF IgG index^{24,25} and should not be utilized in the diagnosis.

To further assist in the identification of patients with acute vascular myelopathies for whom other intervention strategies may be appropriate, patients whose symptoms reach maximal severity in <4 hours from onset should be presumed to have an ischemic etiology. We believe this is justified because the temporal course of vascular lesions (especially arterial thrombotic events) usually progresses to nadir very rapidly. If these diagnostic criteria are going to be used to identify patients for prospective therapeutic trials, it will be critical to exclude patients with ischemic myelopathies for whom anti-inflammatory strategies may not be indicated.

Differentiating idiopathic ATM from ATM attributed to an underlying disease is also important. Many systemic inflammatory disorders (SLE, Behçet disease, Sjögren syndrome, and so on) are associated with vasculitides that can result in ATM. As these conditions occur along a similar pathophysiologic spectrum and most have established treatment regimens, ATM associated with these disorders must be distinguished from idiopathic ATM. Thus, two diagnostic categories of “idiopathic ATM” and “disease-associated ATM” (i.e., SLE-associated ATM) are proposed, provided that other criteria are met (see below). This distinction will aid in the conduct of therapeutic clinical trials where uniform comparison groups are required.

Likewise, ATM may be the first presentation in patients who will be ultimately diagnosed with MS. Because there are potential treatment options for patients with definite MS and for those at high risk for developing clinically definite MS,²⁶ it is important to identify these individuals. We propose that brain MRI findings suggestive of multifocal inflammation define a patient as having disease-associated ATM rather than idiopathic ATM. This criterion will serve an important role in the identification of cases likely to represent MS or acute disseminated encephalomyelitis (ADEM).

Limitations of the proposed criteria. There are limitations to these proposed criteria that require further discussion. There may be cases that fulfill all of the proposed criteria with the exception of objective documentation of inflammation within the spinal cord. Thus, a situation in which spinal MRI shows an appropriately located high signal intensity lesion on T2-weighted sequences but no clear-cut enhancement of the abnormality following gadolinium administration could be envisioned. If the CSF were normal, then a diagnosis of ATM would not be possible under the proposed criteria. Further, the clinical findings present in such an individual may not be consistent with a vascular myelopathy either. Nevertheless, labeling such a situation as “possible ATM” may be the best option at the moment.

Likewise, although the exclusion of cases based on the interval between symptom onset and maximal

deficit is arbitrary, this criterion is felt to be valid based on the authors' clinical experience and review of the literature. We remain committed to distinguishing ATM from a rapidly evolving vascular myelopathy (<4-hour progression), a slowly progressive or stuttering hereditary myelopathy, spinal cord tumor, myelopathy due to a dural arteriovenous fistula, and a chronic progressive form of MS (all longer than 21 days of progression). Nevertheless, some vascular myelopathies will still undoubtedly fall within the current ATM criteria, whereas some patients who may have inflammatory “true” ATM may be excluded based solely on their rapid progression of symptoms. Additionally, for clinical management and research study inclusion of patients with suspected ATM, it may not be prudent to wait until the nadir is reached. Rather, treatment may be initiated with continued observation to determine if the patient ultimately meets all the criteria.

Though patients with a spinal tumor (such as a glioma) usually will have symptoms lasting for weeks to months, there may be occasions where the clinical history will not completely distinguish ATM from a spinal tumor. Additionally, patients with a tumor may have an enhancing lesion in the spinal cord and therefore will meet criteria for “inflammation.” This is not a truly inflammatory disorder, and the enhancement is merely a reflection of breakdown of the blood–brain barrier. Such patients will usually not have CSF pleocytosis, and this and the temporal course may be the only way to distinguish ATM from spinal glioma unless biopsy is considered. Short of that, in cases in which the distinction remains unclear, it may be appropriate to initiate a course of steroids followed by reimaging of the spinal cord. If significant enhancement with gadolinium persists, a spinal cord biopsy could be considered.

Another condition, which may not be fully differentiated from idiopathic ATM based on the current criteria, is Devic neuromyelitis optica (NMO). Although the inflammatory pathologies of MS, ADEM, and NMO may exist on a continuum with ATM, only the spinal forms of MS and ADEM can be distinguished from suspected ATM based on brain MRI as part of the initial work-up. The consortium has not proposed that normal visual evoked potential responses be required, as even this finding does not absolutely preclude an eventual diagnosis of NMO.^{27,28} Furthermore, whereas an individual with ATM and a history of clinically apparent optic neuritis meets criteria for NMO and is more likely to have recurrent and/or progressive disease, this may not be true in individuals with subclinical optic nerve disease.²⁹ The diagnosis of ATM may be changed to NMO over time should a clinically apparent optic neuritis follow the acute spinal cord syndrome. We have recommended that visual evoked potentials be obtained in individuals with ATM, though it is not certain at present if this signifies a patient population at increased risk for recurrence or progression.

Though these criteria will need to be prospectively

validated to determine whether they appropriately categorize individuals and whether these categorizations are meaningful in terms of treatment strategies or long-term outcomes, they represent a useful framework for future studies. Although the criteria may be perceived as restrictive, we believe use of these criteria will lead to the identification of more homogeneous groups of individuals for clinical studies. At the very least, adoption of these criteria will aid in accurate description of individuals in published reports and provide the framework for subsequent classifications as better understanding of inflammatory myelopathies emerges.

Work-up and evaluation. Initial evaluation of an individual with an evolving myelopathy should determine whether a structural cause (e.g., herniated disk, pathologic vertebral fracture, tumor metastasis, or spondylolisthesis) can be identified (figure). Ideally, MRI with gadolinium contrast agent should be obtained within several hours of presentation. If, however, one cannot be obtained in a short time period, CT-myelography is a reasonable alternative, though this study has the distinct disadvantage of being unable to assess the spinal cord itself. If a structural cause is identified for the myelopathy, urgent neurosurgical evaluation is mandatory.

If no structural cause is identified, then a lumbar puncture should be performed to distinguish an inflammatory from a noninflammatory myelopathy. The CSF should be evaluated for routine studies (cell count, differential, protein and glucose levels) as well as for intrathecal antibody synthesis (oligoclonal bands and IgG index) and cytologic analysis. If no gadolinium enhancement is seen on spinal cord MRI and the CSF does not show pleocytosis or increased IgG index, then a noninflammatory myelopathy should be considered. Possible causes of a noninflammatory myelopathy include ischemia (arterial, venous, watershed, or that due to arteriovenous malformation), radiation, epidural lipomatosis, and fibrocartilaginous embolism.³⁰⁻³⁴ If an inflammatory myelopathy is identified, the extent of inflammation should be determined. Brain MRI with gadolinium and visual evoked potentials will determine if there is demyelination elsewhere in the neuraxis, therefore defining the process as multifocal. If the demyelination is limited to the optic nerve/tract, NMO is possible. If demyelination is seen beyond the optic nerve and tract, then the diagnosis is either ADEM or possible MS. Alternatively, individuals who have monofocal demyelination in the spinal cord (evoked potential and brain MRI do not show demyelination) and meet the criteria set forth above are defined as having ATM. Further evaluation should then determine if the ATM is primary or is disease associated.

Clinical features such as fever, meningismus, rash, concurrent systemic infection (e.g., pneumonia or diarrheal illness), immunocompromised state (e.g., AIDS or immunosuppressive medication), recurrent genital infection, radicular burning pain

with or without vesicles suggestive of zoster radiculitis, or adenopathy may suggest an infectious etiology for ATM (table 2). In those cases, serum rapid plasma reagin, CSF viral and bacterial cultures, CSF Venereal Disease Research Laboratory, CSF viral PCR studies, and serum acute titers for a variety of infectious agents should be obtained. Convalescent viral titers should then be drawn 4 to 8 weeks following the onset of symptoms.

Other clinical features (see table 2; for review of criteria, see Vitali et al.,²¹ Lockshin et al.,²² and Tan et al.,²³ and Statement on Sarcoidosis) may suggest a systemic inflammatory disease such as Sjögren syndrome, antiphospholipid syndrome, SLE, sarcoidosis, or mixed connective tissue disease. In these clinical settings, the following serum studies should be obtained: angiotensin-converting enzyme level, anti-nuclear antibodies, anti-double-stranded DNA antibody, SS-A (Ro), SS-B (La), anti-cardiolipin antibody, lupus anti-coagulant, β_2 -glycoprotein I, and complement levels. A urinalysis with microscopic analysis for hematuria should also be obtained. Depending on clinical level of suspicion, lip/salivary gland biopsy, chest CT scan with IV contrast agent, and Schirmer test should be considered.

If individuals have no features suggestive of disease-associated ATM and they meet the criteria for ATM set forth above, they are diagnosed with idiopathic or primary transverse myelitis. Evoked potentials, electromyographic studies, and CSF 14-3-3 levels should be considered optional studies that may determine the extent of neural injury and the prognosis for recovery.^{36,37}

Recommendations for treatment of individuals with ATM are outside of the scope of this report and will be considered elsewhere.

Whereas previous reports have provided a framework to define the syndrome of ATM, older diagnostic criteria have variably distinguished other etiologies for noncompressive myelopathy. As a result, it is likely that diseases with distinct pathology, epidemiology, and potential treatments were included in a common diagnostic term. This limitation, coupled with the role that modern neuroimaging techniques play in defining ATM, has prompted these revised diagnostic criteria. The proposed nosologic scheme differentiates individuals into idiopathic and disease-associated categories, both for the purposes of longitudinal natural history studies as well as for eventual recruitment into therapeutic clinical trials. We have further set forth a strategy for evaluating individuals with ATM. These criteria must now be evaluated in a longitudinal study of ATM.

Appendix

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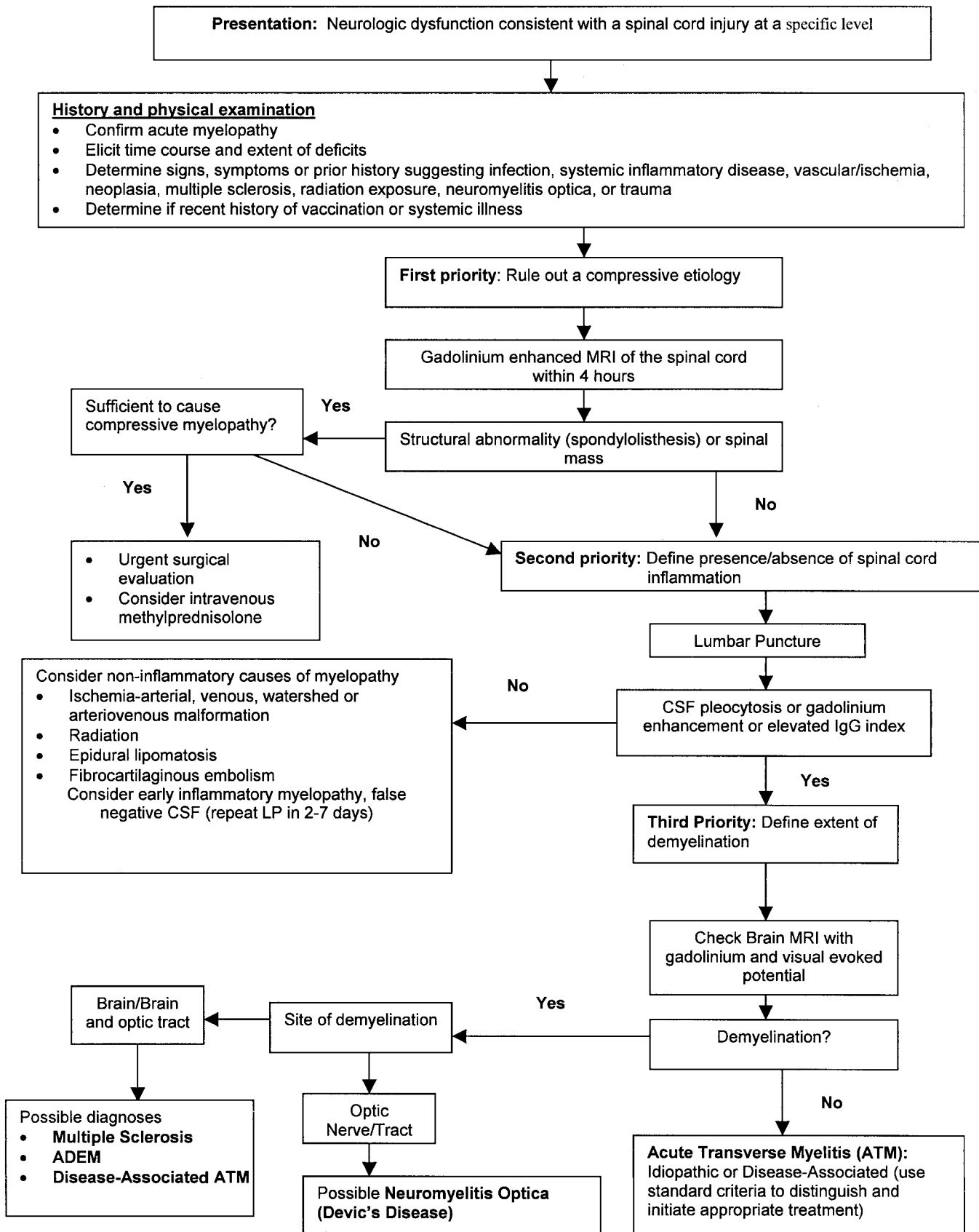


Figure. Immediate diagnostic approach to acute myelopathy. LP = lumbar puncture; ADEM = acute disseminated encephalomyelitis.

Table 2 Potential medical work-up for suspected acute transverse myelitis

Indicative signs and symptoms	Suggested evaluation
Infectious etiology	
Fever	CSF Gram's stain and bacterial culture
Meningismus	CSF PCR: HSV-1, HSV-2, HHV-6, VZV, CMV, EBV, enteroviruses, HIV
Rash	CSF viral culture
Concurrent systemic infection	CSF acid-fast bacilli smear and tuberculous culture
Immunocompromised state	CSF HSV, VZV, and HTLV-1 antibodies
Recurrent genital infection	CSF anti- <i>Borrelia burgdorferi</i> antibodies
Symptoms of zoster radiculopathy	CSF VDRL
Adenopathy	CSF India ink and fungal culture
Residence in area endemic for parasitic infections	Chest radiograph Serology for antibodies to HSV, VZV, HTLV-1, <i>B. burgdorferi</i> Serology for hepatitis A, B, C, and <i>Mycoplasma</i> Consider serology for parasites
Systemic inflammatory disease (vasculitis, collagen vascular diseases, mixed connective tissue disease)	
Rash	Serum ACE
Oral or genital ulcers	Auto-antibodies: ANA, ds-DNA, SS-A (Ro), SS-B (La), Sm (Smith), RNP
Adenopathy	Complement levels
Livedo reticularis	Urinalysis with microscopic analysis for hematuria
Serositis	Lip/salivary gland biopsy
Photosensitivity	Chest CT
Inflammatory arthritis	Schirmer's test
Erythema nodosum	Chest radiograph
Xerostomia	Anti-phospholipid antibodies (anti-cardiolipin antibodies, Russel viper venom time, partial thromboplastin time)
Keratitis	
Conjunctivitis	
Contractures or thickening of skin	
Anemia/leukopenia/thrombocytopenia	
Raynaud's phenomenon	
History of arterial and venous thrombosis	
MS	
Previous demyelination event	Brain MRI
Incomplete deficit clinically with MRI abnormality ≤ 2 spinal segments and $< 50\%$ of cord diameter	Evoked potentials
CSF oligoclonal bands	
Neuromyelitis optica (Devic's disease)	
Optic neuritis	Evoked potentials
Normal brain MRI	Brain MRI (usually negative) Presence of multiple autoantibodies, of the type listed above or others
Idiopathic transverse myelitis	
No clinical or paraclinical features suggestive of another diagnostic category	Evoked potentials Electromyography/nerve conduction velocity

HSV = herpes simplex virus; HHV = human herpes virus; VZV = varicella zoster virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HTLV-1 = human T-cell lymphotropic virus-1; VDRL = Venereal Disease Research Laboratory; ACE = angiotensin-converting enzyme; ANA = anti-nuclear antibodies; ds = double-stranded; RNP = ribonucleoprotein.

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