



## Review

## Transverse myelitis

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## ABSTRACT

Acute transverse myelitis (ATM) is an etiologically heterogeneous syndrome with acute or subacute onset, in which inflammation of the spinal cord results in neurologic deficits, manifesting as weakness, sensory loss and autonomic dysfunction. It is frequently associated with infectious or systemic autoimmune diseases, but its etiology remains unknown in a substantial portion of cases, which are classified as idiopathic. Unifying diagnostic criteria for idiopathic and disease-associated ATM were proposed in 2002. Although they have been applied to a few cohorts of patients, the limited information provided in the relevant publications has not yet yielded many new insights on the clinical characteristics, disease course, and outcome of adult patients with idiopathic ATM compared to older studies that did not always distinguish between the various etiologies of ATM. There is, however, some new epidemiological data indicating that the incidence of idiopathic ATM is considerably higher, and the female preponderance greater, than previously recognized. In addition, new data on children with ATM show that the prognosis in pediatric patients is not always as benign as previous studies had indicated. The combination of ATM and optic neuritis characterize Devic's syndrome or neuromyelitis optica (NMO). A seminal discovery was the identification of an antibody that is a specific marker not only for NMO, but also of some of its characteristic manifestations in isolation, including longitudinally extensive TM. This has resulted in the proposal that all of the disorders that are associated with NMO-IgG positivity constitute part of an NMO spectrum of disorders. This antibody recognizes aquaporin-4, which represents the most abundant water channel of the central nervous system. There is growing evidence that the antibodies targeting this channel protein have pathogenic potential, thereby providing insights into the possible pathogenetic mechanisms of at least one type of ATM.

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## 1. Introduction

### 1.1. Definitions and diagnostic criteria

Acute transverse myelitis (ATM) refers to the inflammatory subtype of transverse myelopathy, which is an acute or subacute clinical syndrome in which injury to the spinal cord results in neurologic deficits, manifesting as weakness, sensory loss and autonomic dysfunction. The etiologies of myelopathies are varied and can be subdivided into compressive and non-compressive causes. While compressive myelopathies stem from trauma and intra- or extra-spinal tumors, the etiologies of non-compressive myelopathies can be classified as delayed radiation effects, ischemic, paraneoplastic, infectious or parainfectious, or systemic autoimmune diseases. Among the latter, ATM can be associated with systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), sarcoidosis, Behçet's disease, other connective tissue diseases, and the antiphospholipid syndrome (APS), either primary or secondary to SS. In addition, ATM can be the first manifestation of multiple sclerosis (MS) and of neuromyelitis optica (NMO), also called Devic's syndrome, which is

defined as the combination of ATM with optic neuritis (ON). Despite extensive work-up, an etiology of ATM cannot be identified in a significant portion of cases, and these are classified as idiopathic. Previously proposed diagnostic criteria for acute transverse myelopathies generally excluded those resulting from spinal cord compression, but differed in their inclusion of disease-associated etiologies. In 2002, the Transverse Myelitis Consortium Working Group (TMCWG) proposed diagnostic criteria and nosology of ATM [1]. Mostly for prognostic reasons, it decided to classify ATM as either idiopathic or disease-associated (see Table 1). It is suggested that patients who fulfill the clinical criteria of idiopathic ATM, but lack evidence of inflammation, be classified as possible idiopathic ATM.

By excluding patients with a history of clinically apparent ON from the diagnosis of idiopathic ATM, these criteria classify ATM in NMO as disease-associated. Note, however, that there is a major difference in the nature of the association between ATM and systemic autoimmune or infectious diseases on the one hand and its association with NMO on the other hand. NMO itself, like ATM, can occur in the context of various systemic autoimmune diseases. More importantly, ATM may or may not occur at any time in the course of autoimmune diseases and may or may not be a neurological manifestation of infectious diseases. In contrast, ATM is one of the defining features of the NMO, the other one being ON. This is not obvious in the currently most widely used diagnostic criteria, which only require "acute myelitis" [2], but is specifically stated in the NMO diagnostic criteria proposed by an international Task Force on Differential Diagnosis in MS [3] (see Table 2). Of note, the Task Force criteria specify that the TM in NMO can be clinically complete or incomplete. Clinically complete TM is characterized by moderate to severe bilateral neurologic dysfunction associated with a lesion located centrally and occupying most of the cross-sectional area of at least one spinal segment. Incomplete, or partial, TM manifests as milder and often markedly asymmetric neurological deficits usually in association with involvement of less than half of the cross-sectional area of the cord. The TMCWG criteria for ATM do not specifically address this issue but, by requiring bilateral signs or symptoms, are more likely to identify patients with complete TM.

Acute TM along with isolated ON and NMO are part of a spectrum of inflammatory demyelinating disorders, which also includes acute disseminated encephalomyelitis and MS. These disorders differ in their spatial distribution of inflammation and their recurrence rates, but the factors determining the spatial and temporal disease patterns remain unknown. Both idiopathic ATM and NMO were originally considered to be monophasic disorders. In Devic's syndrome this meant that the two index events (TM and ON) occurred simultaneously or in close temporal association. Recurrent forms were diagnosed as MS. However, it is now widely accepted that ATM can be recurrent in up to 25% of cases. It is also recognized that the two index events of NMO can occur months, years or even decades apart and that the disease takes a recurrent or relapsing/remitting course in >80% of patients. This makes NMO difficult to distinguish clinically from MS, but it is increasingly obvious that the immunological, pathological, laboratory and imaging characteristics of NMO are distinct.

**Table 1**  
TMCWG criteria for idiopathic ATM [1].

| 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 years                                                                                           |
| 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 days following symptom onset meet criteria | CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, Mycoplasma, other viral infections (e.g., HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*      |
| Progression to nadir between 4 h and 21 day 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*<br>History of clinically apparent optic neuritis*                                                                   |

#### Abbreviations:

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

\* Do not exclude disease-associated ATM.

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