Pediatric transverse myelitis

ABSTRACT

Pediatric acute transverse myelitis (ATM) is an immune-mediated CNS disorder and contributes to 20% of children experiencing a first acquired demyelinating syndrome (ADS). ATM must be differentiated from other presentations of myelopathy and may be the first presentation of relapsing ADS such as neuromyelitis optica (NMO) or multiple sclerosis (MS). The tenets of the diagnostic criteria for ATM established by the Transverse Myelitis Consortium Working Group can generally be applied in children; however, a clear sensory level may not be evident in some. MRI lesions are often centrally located with high T2 signal intensity involving gray and neighboring white matter. Longitudinally extensive ATM occurs in the majority. Asymptomatic lesions on brain MRI are seen in more than one-third and predict MS or NMO. The role of antibodies such as myelin oligodendrocyte glycoprotein in monophasic and relapsing ATM and their significance in therapeutic approaches remain unclear. ATM is a potentially devastating condition with variable outcome and presents significant cumulative demands on health and social care resources. Children generally have a better outcome than adults, with one-half making a complete recovery by 2 years. There is need for standardization of clinical assessment and investigation protocols to enable international collaborative studies to delineate prognostic factors for disability and relapse. There are no robust controlled trials in children or adults to inform optimal treatment of ATM, with one study currently open to recruitment. This review provides an overview of current knowledge of clinical features, investigative workup, pathogenesis, and management of ATM and suggests future directions.

GLOSSARY

ADS = acquired demyelinating syndrome; AFM = acute flaccid myelitis; AQP4 = aquaporin-4; ASIA = American Spinal Injury Association; ATM = acute transverse myelitis; GBS = Guillain-Barré syndrome; IL = interleukin; IVIg = IV immunoglobulin; LEM = longitudinally extensive TM; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMO = neuromyelitis optica; PLEX = plasmapheresis; SLE = systemic lupus erythematosus; TMCWG = Transverse Myelitis Consortium Working Group.

Pediatric acute transverse myelitis (ATM) is an immune-mediated CNS disorder classically described as demyelinating. ATM comprises a subgroup of the noncompressive transverse myelopathies. It is a potentially devastating condition with variable outcome. ATM must be differentiated from other, rarer presentations of noncompressive myelopathy. ATM may be the first presentation of relapsing acquired demyelinating syndromes (ADS) such as neuromyelitis optica (NMO) or multiple sclerosis (MS). A PubMed search using the terms “pediatric or paediatric transverse myelitis” revealed that more than 200 articles have been published in English on the topic between 1976 and 2015. In this article we discuss current knowledge on clinical features, pathogenesis, and investigative and management strategies in ATM and propose future directions.

DEMOGRAPHICS AND CLINICAL FEATURES

Active surveillance studies from Canada and the UK have estimated that the incidence of ATM in children under 16 years of age is 2/million children/year. ATM accounts

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for one-fifth of children experiencing a first ADS.6,7 TM is more common in adults, but children account for 20% of cases.8 Although males are more likely to present with ATM (male:female ratio 1.1–1.6:1), a female preponderance is seen among teenagers in regions at high risk for MS and NMO (United States, Canada, Europe, and parts of Australia).6–12 A bimodal age distribution is observed in children under 5 and older than 10 years of age.5,8,9,11–13 There is no difference in ethnicity prevalence. A range of prodromal infections are reported in the preceding 30 days in up to 66% of ATM cases.8,11,12 The tenets of the diagnostic criteria for TM established by the Transverse Myelitis Consortium Working Group (TMCWG) are applicable in pediatric cases with appropriate modifications to account for the difficulty in defining a clear sensory level in the younger child (usually under 5 years old).3,12 ATM can present with back pain as the first symptom, followed by motor and sensory deficits or bladder/bowel dysfunction.8,12,14 Sensory symptomatology can be either positive (burning paresthesia, hyperesthesia, allodynia) or negative (numbness).8,12,14

Most children develop urinary retention and need catherization.5,8,12 Establishing the level of involvement by assessing dermatomes and myotomes is an important component of the American Spinal Injury Association (ASIA) scale and helps track progression to nadir and later recovery.15 However, this can be challenging because a clear sensory level may not be evident in up to 40% of children.5,8,12 A complete ATM describes bilateral motor and sensory deficits with bladder dysfunction, whereas in a partial cord syndrome there are patchy motor or dissociated sensory deficits of at least one spinal segment with occasional bladder involvement.12,13,16

Spinal cord symptomatology in childhood ATM usually evolves over 2–4 days to peak at 5–6 days.5,8,12 Following immunotherapy, pain is the first symptom to resolve, followed by an improvement in motor deficits. Bladder function and sensory deficits may take longest to improve.12 Patients with ATM may also develop a persisting flaccid motor weakness during the course of their illness. Spinal nerve root or cauda equina enhancement may be clearly delineated on MRI, suggesting a simultaneous CNS and peripheral nerve inflammatory disorder (i.e., an “ATM-plus syndrome”) or a secondary event from cellular damage to the anterior and ventral horn. A patchy axonal motor and sensory polyneuropathy is seen on EMG in ATM-plus syndromes.14 There are no systematic studies investigating the prevalence of ATM-plus syndromes. A prospective cohort of adults with myelitis or encephalomyelitis following an infectious event showed that 29/176 (16%) had axonal peripheral nervous system involvement.17 During the summer of 2014, there was an apparent increase in the number of pediatric patients with a variant of TM termed acute flaccid myelitis (AFM).18 This condition was noteworthy for significant involvement of the spinal cord gray matter with resulting flaccid, polio-like patterns of weakness. The number of cases in 2014 brought this to the attention of public health officials.

DIFFERENTIAL DIAGNOSIS AND EVALUATION

Because ATM is a diagnosis of exclusion, deliberate consideration should be given to the differential diagnosis. Disorders intrinsic and extrinsic to the spinal cord should be considered. A clear history of significant trauma before onset of myelopathic symptoms would not typically pose a diagnostic dilemma. Extrinsic injuries include vertebral body compression, intervertebral disk herniation, and epidural hematoma. Uncommon posttraumatic intramedullary disorders include ischemic myelopathy from arterial compromise or venous hypertension from fibrocartilagenous embolus.19 Patients with anterior spinal artery occlusion present with deficits localized to the territory of the anterior two-thirds of the cord.

Spinal cord tumors typically present with subacute symptoms of unremitting pain that may awaken the child at night along with myelopathic symptoms. Extramedullary tumors causing cord compression include meningioma, nerve sheath tumors, and drop metastasis from medulloblastoma, whereas intramedullary tumors are typically astrocytomas and ependymomas. Arteriovenous malformations of the spinal cord classically present with fluctuating symptoms from a vascular steal phenomenon. Bruits may sometimes be heard with auscultation of the back.

Aside from an infectious abscess, direct infectious myelitis can be difficult to discern from an idiopathic etiology because the clinical presentation (fever and constitutional symptoms) and CSF findings can be similar. CSF isolation of a pathogen, positive PCR results, or demonstration of acute and convalescent serum antibody titers provide the best evidence for direct infection. A variety of pathogens have been reported to cause infectious myelitis (table 1). Enteroviruses have most recently been implicated in AFM, which typically presents with primary motor symptoms possibly caused by direct infection of spinal cord motor neurons.18

Guillain-Barre syndrome (GBS) is often the first alternative consideration for patients presenting with acute weakness. Clinical features mimic ATM with depressed reflexes, bowel and bladder dysfunction, autonomic dysregulation, and transient sensory...
disturbances. The latter is not a predominant feature and a clear sensory level is not expected in GBS. ATM may occur with acute disseminated encephalomyelitis or represent an initial attack of a relapsing demyelinating syndrome, such as MS, NMO, or an autoimmune rheumatologic disorder (e.g., systemic lupus erythematosus [SLE], Sjögren syndrome, and sarcoidosis). Comorbid clinical, imaging, and laboratory findings can help to discern the presence of such conditions.

Myelopathic symptoms are a neurologic emergency because prompt diagnosis and treatment may lessen the severity of neurologic sequela. Emergent spinal imaging with contrast-enhanced spine MRI rapidly discerns etiologies requiring surgical intervention. CSF analysis and serum studies are required to distinguish specific etiologies. CSF protein and white blood cell counts may be normal in 20%–50% of children with definite ATM.5,9,11,12 Qualitative tests for intrathecal oligoclonal bands are positive in up to one-third of children, many of whom will eventually have MS.5,8 In a UK pediatric NMO study, only 3/20 (15%) presented with isolated ATM, 2 of whom were aquaporin-4 antibody-positive. Nonetheless, aquaporin-4 antibody should be considered for all children presenting with ATM.20 Evaluating a broader repertoire of markers of CNS inflammation in the CSF, such as neopterin, may be helpful. CSF proteomics to identify neuronal and glial markers of injury and inflammation need further study.21

**MRI IN CHILDREN WITH ATM** MRI is a major tool for diagnosis and prognosis in ATM. Lesions are often centrally located with high T2 signal intensity involving gray matter and neighboring white matter (figure).9 Lesions may be contiguous or patchy. Longitudinally extensive TM (LETM), defined as ≥3 vertebral segments, occurs in 66%–85% of ATM in children.5,9 Gadolinium enhancement is frequently observed, but the absence of gadolinium enhancement does not rule out ATM.5,6,9 LETM is not unique to ATM and can occur in NMO and rarely MS.6 Some adults with NMO may have short TM and the location of the lesion may be key; however, children with NMO appear to exclusively present with LETM.21 In childhood ATM, T1 hypointensity is also described and occurs in one-third of spinal lesions. Cervical and cervicothoracic lesions represent the majority of ATM lesions (64%–76%).5,8,9 In the context of ATM, brain MRI is expected to be normal. However, asymptomatic lesions on brain MRI are seen in more than 40% of children, indicating the need to include brain MRI in evaluation for ATM.5,15 Silent MRI brain lesions at first ADS predict an increased risk for developing MS or NMO.5 Approximately 66%–88% of children with a partial ATM and supratentorial MRI brain lesions develop MS.13,16 Clinical 1.5T and 3T MRI scanners will not show spinal cord lesions in up to 6% of patients with ATM.5,8 New MRI sequences (e.g., double inversion recovery, phase sensitive inversion recovery) may detect cord lesions.23 Although repeat spinal cord imaging after 5–7 days may reveal spinal cord atrophy, other novel techniques used in adult MS studies, such as magnetization transfer ratio and diffusion tensor imaging, may help to quantify and correlate with disability earlier in the disease.24 These novel

### Table 1 Investigations in ATM and diagnostic implications

<table>
<thead>
<tr>
<th>Investigation</th>
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<tr>
<td>MRI studies</td>
<td>Extrinsic compression, intrinsic cord disease</td>
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<tr>
<td>Entire spine with and without gadolinium contrast</td>
<td>McDonald MRI MS criteria support a diagnosis of MS; subclinical optic nerve involvement with LETM may suggest NMO</td>
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<tr>
<td>Brain and orbits</td>
<td>Leukodystrophy and other neurodegenerative disorders</td>
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<td>CSF analysis</td>
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<td>Protein, glucose</td>
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<tr>
<td>IgG index, oligoclonal bands (paired studies with serum)</td>
<td>Abnormal in MS; 30% abnormal in NMO and autoimmune TM</td>
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<td>Bacterial and viral culture</td>
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<td>PCR</td>
<td>Enterovirus; parechovirus; herpes simplex virus; cytomegalovirus; Epstein-Barr virus; human herpesvirus 6 and 7; varicella-zoster virus; influenza; hepatitis A, B, and C; human T-lymphotropic virus type 1; Mycoplasma pneumoniae; Bartonella henselae; Borrelia burgdorferi; mycobacteria; tuberculosis</td>
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<tr>
<td>Aquaporin-4 IgG</td>
<td>NMO (unlikely to be solely positive in CSF and negative in serum)</td>
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<td><strong>Serum</strong></td>
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<tr>
<td>ANA, ENA, double-stranded DNA, ANCA, anti-phospholipid antibodies, lupus anticoagulant</td>
<td>Systemic lupus erythematosus, Sjögren syndrome, antiphospholipid antibody syndrome, Behçet disease</td>
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<tr>
<td>Aquaporin-4 IgG</td>
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<td>MOG antibodies</td>
<td>MOG antibody-associated disease</td>
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<td>Acute and convalescent antibody titers for HIV, mycoplasma, arboviruses, cat-scratch, and Lyme disease</td>
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<td>Angiotensin-converting enzyme level</td>
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<td>Vitamin B12, folate, vitamin E, biotidinase, copper, plasma amino acids, ammonia, lactate</td>
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<td>Throat swab and stool for enterovirus PCR</td>
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Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophilic cytoplasmic antibody; ATM = acute TM; ENA = extractable nuclear antigens; LETM = longitudinally extensive TM; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMO = neuromyelitis optica; TM = transverse myelitis.
techniques may be challenging in young children because they involve increased imaging time and associated sedation.

PATHOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS OF IDIOPATHIC TM
Clinical and pathologic studies reveal features of inflammation and neuronal loss in idiopathic acute transverse myelitis (ATM). Nevertheless, significant differences in pathogenesis exist, and distinguishing among them is important for understanding disease biology and treatment implications. Neurosarcoid, for example, is pathologically associated with noncaseating granulomas within the spinal cord, whereas ATM associated with MS has lymphocytic cell infiltration. It is important to note that multiple mechanisms may coexist or occur independently within a disease spectrum, as in lupus-associated ATM in which vasculitis is identified in some and thrombotic infarction in others. There is limited information on immunopathogenesis of ATM in children; however, studies in adults are likely to be relevant. In childhood ATM, as in adult cases, immune-mediated mechanisms are implicated by radiologic findings and CSF reactivity. Histopathologic adult studies demonstrate focal infiltration of the spinal cord by monocytes and CD4+ and CD8+ T lymphocytes, accompanied by activation of astrocytes and microglia. Demyelination and axonal loss occur, often involving the gray matter, a finding that is supported by neuroimaging in adults and children. Necrosis and cavitation can result in severe disability, especially in NMO.

The mechanisms of cellular and humoral autoimmune responses contributing to spinal cord inflammation and degeneration remain unclear. Molecular mimicry, a mechanism whereby immune targeting of infection proteins cross-react with neuronal proteins that bear molecular similarity, or a less specific super-antigen effect are 2 proposed mechanisms.

In contrast to the large number of studies characterizing the abnormal cellular immune responses in MS, a paucity of similar evaluations are available in ATM. Studies to date interrogate the humoral response, identifying interleukin-6 (IL-6) levels to be markedly elevated in the CSF of adult patients with ATM compared to those with MS and controls. A recent pediatric study confirmed these results. IL-6 is secreted following activation of astrocytes and microglia, exerting its effect on oligodendroglia and axons and mediating cellular injury in spinal cord culture sections. There is a correlation between elevated IL-6 levels and disability in patients with ATM. Positive results from early-phase intervention studies with monoclonal antibodies to attenuate IL-6 responses in NMO have direct implications on patients with ATM with elevated IL-6.

Since the identification of aquaporin-4 (AQP4) antibody in NMO, recent studies have also reported the presence of other autoantibodies in ADS, including ATM. Myelin oligodendrocyte glycoprotein (MOG) antibodies have been found in childhood-onset ADS and may be an important early predictor of a non-MS course, although it remains unclear whether patients with recurrent demyelination associated with MOG antibodies warrant the same treatment as in AQP4 antibody disease. Because MOG antibody testing is still not universally available (as it is in the United States), the larger implications of this finding remain to be determined.

OUTCOMES, PROGNOSIS, AND MEASUREMENT
Since publication of the TMCWG criteria, several case series and cohort studies have been conducted to help understand risk of relapse at first presentation and risk of subsequent disability. Children with ATM have a better outcome than adults, with nearly one-half making a complete recovery by 2 years. However, in a single-center childhood ATM study (n = 47), 43% were unable to walk 30 feet at a median of 3 years follow-up. Mortality is
associated with respiratory failure and a high cervical cord lesion. The most common sequelae are sensory disturbances and bladder dysfunction (15%–50%). Approximately one-quarter are nonambulatory or require walking aids, and 10%–20% never regain mobility or bladder function. The influence of age, time to nadir of symptoms, and time to recovery from nadir in predicting clinical outcome varies between studies.

Studies in pediatric ATM have attempted to define risk factors for relapse and disability at onset of disease. A single-center study of 47 children identified younger age (less than 3 years old), longer time from symptom onset to treatment, higher spinal level, radiologic evidence of longer segmental involvement, presence of T1-hypointense lesions, and lack of white cells in the CSF as predictors of disability. A multicenter ATM study (n = 95) with retrospective ascertainment and longitudinal follow-up had a relapse frequency of 17% (n = 3 NMO and n = 13 MS). Risk factors for relapse were female sex and abnormal brain MRI, consistent with adult ATM data. Risk factors for disability included severe ASIA scale (A–C) at onset, absence of CSF pleocytosis, spinal lesion with gadolinium enhancement, female sex, and absence of cervicothoracic lesion. ATM may have a relapsing course, which could be categorized as relapsing ATM, a presentation of MS, part of a systemic autoimmune disease, or NMOSD in the setting of identified antibodies.

Comparison between existing studies regarding disability outcomes presents a challenge because of inconsistent use of core outcomes. The ASIA scale is an internationally accepted scale for the measurement of disability in ATM but has rarely been used in pediatric studies. Previous studies used other measures such as the Expanded Disability Status Scale, WeeFIM II system, clinician-derived motor recovery ordinal measures, and Paine and Byers scale (poor, fair, and good recovery). The time of CSF sampling (if done at all) and imaging often varies. Patients with ATM should be followed up longitudinally, irrespective of initial outcome, in part to clarify the diagnosis and also to provide multidisciplinary rehabilitation interventions (motor disability, urinary/bladder management, psychological and schooling support).

**THERAPEUTIC CONSIDERATIONS**

Because of lack of controlled clinical trials, there are no US Food and Drug Administration–approved therapies for ATM. Medications are used based on experience and data from open-label studies and retrospective analyses, primarily from studies involving adults. Data suggest that certain conditions have preferential responses to certain therapeutic interventions. For example, SLE patients with ATM may respond to cyclophosphamide whereas patients with NMO benefit from plasmapheresis (PLEX). In patients without a prior history suggestive of a systemic condition, the treatment of TM has to be approached empirically.

In general, no data suggest that first-line therapies (i.e., corticosteroids) worsen the outcome of patients with mimics of TM, including infarcts or infections. Thus, clinicians should empirically treat cases of suspected or confirmed ATM. The potential benefit of earlier therapy outweighs the theoretical concerns of treating infectious or vascular etiologies with an anti-inflammatory therapy.

The standard empiric therapy for ATM consists of high-dose corticosteroids. Pediatric patients are usually treated with a 30 mg/kg/dose (maximum 1,000 mg) of methylprednisolone intravenously once a day for 3–5 days. Multiple studies have documented the efficacy and safety of corticosteroids in CNS inflammatory disorders, including ATM. The benefit to patients with ATM was observed in a retrospective study, suggesting better short- and long-term outcomes in patients treated with corticosteroids vs patients who did not receive steroids.

PLEX has been used to treat ATM. Some centers have used this intervention in patients who do not respond to corticosteroids, whereas other centers have used the therapy concurrent with corticosteroids if a patient had significant motor or respiratory deficits. Several studies support the use of PLEX in patients with ATM (table 2). PLEX protocols typically involve 5–7 treatment sessions, with each session exchanging 1.1–1.5 plasma volumes. Of note, American Academy of Neurology guidelines published in 2011 recognized the potential benefit of PLEX in patients with adult ATM. Anecdotal reports of IV immunoglobulin (IVIg) 2 gm/kg divided over 2–5 days have not provided conclusive evidence of benefit, but IVIg is often incorporated into the treatment regimen in fulminant disease. A UK randomized controlled trial to determine the benefit of additional treatment with IVIg in adults and children with TM is currently open to recruitment.

Although there is no consensus on how to handle patients with ATM-plus syndromes therapeutically,
there is no evidence to suggest a detriment to using the therapies traditionally used for patients with ATM.

CONCLUSIONS AND FUTURE DIRECTIONS ATM is a potentially devastating condition with variable outcome and presents significant cumulative demands on health and social care resources. There are no robust controlled trials in children or adults to inform optimal treatment of ATM, with one study in the UK currently open to recruitment.44 The following are proposed future directions in ATM:

1. Standardization of clinical assessment and investigation protocols will enable international collaborative studies to help define early therapy considerations and delineate prognostic factors for disability and relapse.
2. Defining a basic protocol of core MRI sequences for the evaluation of ATM. New MRI sequences should be investigated as surrogate markers for disability to facilitate early-phase clinical trials.
3. Establishing common outcome measures for use in ATM. The ASIA scale is an internationally accepted scale for the measurement of disability in ATM but requires adaptation and validation for young children.
4. The role of antibodies such as MOG in monophasic and relapsing ATM and their significance in therapeutic approaches remain unclear and require international collaboration.
5. Future clinical trials need to consider adaptive designs to include pediatric and adult populations with appropriate statistical considerations.

AUTHOR CONTRIBUTIONS

All authors contributed extensively to the writing, editing, and consensus-finding process of all sections of the manuscript.

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