A cute transverse myelitis is a rare, focal immune-mediated disease that affects the sensory and motor pathways of the spinal cord. It is characterized by a sudden clinical onset of neurological motor dysfunction associated with sensory loss and autonomic disturbances.

The following tetrad of symptoms has been classically described in acute transverse myelitis (ATM): 1) weakness in the arms/legs; 2) sensory symptoms such as numbness or tingling; 3) pain and discomfort; and 4) bladder dysfunction and/or bowel motility problems.

The etiology of ATM is diverse and includes infectious, post-infectious, vascular, collagen/autoimmune, neoplastic, and paraneoplastic causes. Clinical interview and careful neurological examination are essential in making an ATM diagnosis. In addition to the clinical evaluation, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) testing are common diagnostic tools used as a first step in diagnosis.

Children with ATM undergo different therapeutic modalities such as corticosteroids, plasma exchange (PLEX), intravenous immunoglobulin (IVIG), cytotoxic drugs, and other immunomodulatory agents; however, the use of steroids followed by PLEX is the most widely accepted treatment regimen. ATM is commonly a monophasic ill-
expressed concern about her daughter’s increased drooling and trouble swallowing.

Initial clinical evaluation revealed a child with normal mental status and severe truncal hypotonia. Her lower extremity muscle strength was markedly decreased bilaterally with no antigravity movement (grade: 2/5) and her upper extremity strength was also decreased but to a lesser degree (grade: 3/5). Otherwise, vital signs and physical examination were unremarkable. Pertinent diagnostic work-up included lumbar puncture revealing normal CSF indices, and brain and spine MRI that demonstrated swelling and marked T2 signal prolongation of the spinal cord from approximately C2 to T2-T3 suggestive of an active inflammatory process (see Figures 1 and 2). No optic nerve or brain demyelinating lesions were observed. She was admitted with the diagnosis of ATM for further diagnostic testing and treatment. A comprehensive infectious and autoimmune work-up was obtained, with the only pertinent finding being a positive parainfluenza virus type 3 on nasopharyngeal polymerase chain reaction (PCR) swab.

The patient was started on high-dose intravenous corticosteroids followed by PLEX therapy per neuroimmunology recommendations. After completing five PLEX sessions, she had significant recovery of muscle strength, and was able to sit and stand unassisted. Upon follow-up visit 1 month after discharge, she was reported to have a normal neurological exam.

**SPECTRUM OF NEUROIMMUNOLOGICAL DISORDERS**

The term neuroimmunological disorder refers to a group of illnesses that are the result of acquired dysregulation of both the immune system and the central nervous system (CNS)\(^1\) (see Sidebar 1, page 479).

Historically, the CNS has long been considered an immunologically “privileged” organ. This old concept was based on four principles: (1) the presence of the blood–brain barrier; (2) the lack of constitutive expression of major histocompatibility complex (MHC); (3) the absence of lymphatic drainage; and (4) the lack of T cell immune surveillance.

However, it is now evident that most of these assumptions were not valid. Recent studies have shown that activated T lymphocytes can penetrate the blood–brain and the blood–nerve barriers and release cytokines that will engineer an immune-response.\(^2\) Also, it has been demonstrated that the nervous system microglial cells have the potential to act as antigen presenters and regulate T-cell activity.\(^3\)

Current research intends to elucidate the role of immune cells and immunomediators in the initiation and progression of these neurological disorders.\(^2\)

**HISTORY OF ATM**

In 1882, H.C. Bastain, MD, reported pathologic findings of several autopsies from patients who died of “acute myelitis” and divided the cases into those that he thought were due to “thrombotic events to blood vessels supplying the spinal cord” and those that were due to acute inflammation. The “inflammatory” cases were postulated to be due to an infectious or an allergic mechanism.\(^4\)

In the early 1920s, health care providers in England and Holland reported multiple cases of “inflammation of the spinal cord and brain” after smallpox immunization. At the time, clinical findings were interpreted as an “allergic” post-vaccine complication.\(^5\)

Several years later in 1928, Dr. Ford theorized that many cases of acute myelitis were post-infectious rather than infectious in nature.\(^6\) A new terminology was introduced in 1948 by A.I. Suchett-Kaye, MD, who described a case with a “band-like” horizontal area of altered sensation of the neck and torso. He

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**CASE SCENARIO**

A 1-year-old, previously healthy Hispanic female presented to the emergency department (ED) with acute generalized weakness. The sudden neurological clinical picture was preceded by a 3-day history of fever (Tmax: 38.8°C) and a 2-week history of rhinorrhea and cough.

After picking her up from daycare at midday, the mother noticed that she refused to pull up or walk. The child had previously been walking independently for 6 weeks. The mother tried repeatedly to get her to sit-up alone, but she was unable to do so. Also, the patient’s mother expressed concern about her daughter’s...
named this entity “acute transverse myelitis.”

**PATHOGENESIS/PATHOLOGY**

ATM is a heterogeneous inflammatory disorder of the spinal cord. Using immunohistochemistry techniques, spinal cord histopathology of ATM patients has demonstrated perivascular infiltration by T lymphocytes (+CD3 stain) and focal infiltration by macrophages (+HLA-Dr stain). These immunopathological observations substantiate that ATM is an immune-mediated inflammatory disease.

ATM is often preceded by an infectious process, which has led to the hypothesis of microbial superantigen-mediated immune response. Molecular “mimicry” by infectious agents has been acknowledged as a pathogenic mechanism in neurological disease (eg, Guillain-Barré syndrome). In ATM, this idea of cross-reactive immune activation against self-tissue is also embraced.

In addition, the humoral reaction to microbial molecular “mimicry” could trigger the production of autoantibodies. This autoimmune response against neuronal surface proteins could induce neural injury by altering cellular signaling and/or metabolism.

Recent identification of novel CSF biomarkers associated with ATM (eg, interleukin-6 and protein 14-3-3) might lead to better understanding of the spectrum of this disease. In the future, detection of these biomarkers could grant potential therapeutic targets and give prognostic value.

**CLINICAL PRESENTATION AND EPIDEMIOLOGY**

ATM is an inflammatory disorder of the spinal cord, characterized clinically by signs and symptoms of neurologic dysfunction that result in motor weakness, sensory loss, and autonomic dysfunction with acute or subacute onset.

There are four classic symptoms of ATM: 1) weakness in the arms/legs; 2) sensory symptoms such as numbness or tingling; 3) pain and discomfort; and 4) bladder dysfunction and/or bowel motility problems.

The distribution of these symptoms may be either symmetric or asymmetric, affecting either legs, arms, or both.

There is often a clearly defined rostral border of sensory dysfunction, and spinal MRI and lumbar puncture often show evidence of acute inflammation. Autonomic symptoms are variable, consisting of bowel or bladder incontinence, increased urinary urgency, difficulty or inability to void, incomplete evacuation, or constipation.

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. There may be a third peak involving children aged younger than 3 years, as evidenced by a recent study of 47 pediatric cases of ATM, with 38% of their patients being younger than the age of 3. It is estimated that 20% to 30% of ATM cases occur in children. The number of affected male and female children is approximately equal among cases of pediatric ATM.

**DIAGNOSTIC CRITERIA**

A diagnosis of ATM requires evidence of inflammation within the spinal cord, as determined by spinal MRI and CSF analysis. Diagnosis should require that all of the inclusion criteria and none of the exclusion criteria are fulfilled (see Sidebar 2, page 480).

**DIAGNOSTIC EVALUATION OF ACUTE MYELOPATHIES**

Differentiating ATM resulting from an underlying disease from the idiopathic form is essential. Many systemic inflammatory disorders (eg, SLE, sarcoidosis, Behçet’s disease, Sjogren’s syndrome) may also involve the CNS, and ATM may be one of the potential presentations of disease. Accordingly, all patients presenting with ATM should also be investigated for the presence of systemic inflammatory disease.

Key historical information should be obtained regarding the presence of rashes, oral or genital ulcers, night sweats, shortness of breath, sicca symptoms, pleuritic pain, or hematuria. Physical examination should include evaluation for oral or genital ulcers, uveitis or retinitis, skin rashes, lymphadenopathy, hepatosplenomegaly, or pericardial friction rub. Laboratory studies should include complete blood count with differential

**SIDEBAR 1.**

**Spectrum of Neuroimmunologic Disorders**

- Central Nervous System
  - Brain acute disseminated encephalomyelitis (ADEM)
  - Multiple sclerosis (MS)
  - Acute transverse myelitis (ATM)
  - Neuromyelitis optica (NMO)
  - Optic neuritis (ON)
  - Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)
  - Hashimoto’s encephalitis
  - Paraneoplastic encephalomyelitis
  - Rasmussen’s encephalitis
  - Tropical spastic paraparesis
  - stiff person syndrome
  - Vasculitis

- Peripheral Nervous System
  - Peripheral nerve chronic inflammatory demyelinating polyneuropathy
  - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)

- Neuromuscular Junction
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome

- Muscle
  - Polymyositis
  - Dermatomyositis

Source: Adapted from Krishnan et al

**FEATURE**

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and smear, antinuclear antibody, SS-A and SS-B antigens, erythrocyte sedimentation rate, and complement levels.

The first step in diagnostic evaluation is to rule out a compressive lesion. If a myelopathy is suspected, a gadolinium-enhanced MRI of the spinal cord should be obtained as soon as possible. If there is no structural lesion such as a spinal mass or spondylolysis, then the second step is to identify the presence or absence of spinal cord inflammation with lumbar puncture. The absence of pleocytosis would lead to the consideration of noninflammatory causes of myelopathy such as arteriovenous malformation (AVM), fibrocartilaginous embolism, radiation, epidural lipomatosis, or possibly early inflammatory myelopathy (ie, a false-negative CSF).

In the presence of an inflammatory process, as evidenced by gadolinium enhancement on MRI, CSF pleocytosis, or elevated CSF immunoglobulin index, one needs to determine whether there is a possible infectious cause. The third step is to define the area and distribution of demyelination within the CNS, since there are several disorders (eg, multiple sclerosis or acute disseminated encephalomyelitis) that may present with ATM as the initial presentation of disease or in the setting of multifocal disease. To check for these entities, a gadolinium-enhanced brain MRI should be ordered. The absence of multifocal areas of demyelination would suggest the diagnosis of isolated ATM and lead to appropriate treatment measures.

**DIFFERENTIAL DIAGNOSES**

There are five groups of disorders that present as acute myelopathy: demyelination, infections, other inflammatory disorders, vascular, and neoplastic/paraneoplastic. The first three are considered inflammatory disorders.

In demyelinating disorders (eg, MS, NMO, ADEM), typically the onset of neurological symptoms occurs over days, with both sensory and motor symptoms and bladder and bowel disturbances. They usually occur in individuals who are otherwise healthy and are sometimes preceded by a nonspecific viral illness.

In multiple sclerosis, lesions are usually small (<2 vertebral segments in length) and peripheral, and therefore cause asymmetric signs and symptoms. CSF oligoclonal bands are present in more than 90% of patients, and a raised immunoglobulin IgG index is seen in more than 60%.8

Early in relapse, symptoms usually resolve in a few weeks to months. Neuromyelitis optica is most commonly a relapsing demyelinating condition of the CNS affecting primarily the optic nerves and spinal cord. Lesions are typically long (>3 vertebral segments), centrally located, and necrotic, leading to more systemic signs and symptoms, greater disability than multiple sclerosis, and less complete recovery.

ADEM is a monophasic disorder that affects the brain and occasionally the spinal cord. Often, there is a history of a preceding viral or other infectious illness. The brain and spinal cord show demyelinating lesions that are generally of the same age. ADEM may evolve over the course of up to 3 months and is more common in children.

Viral, bacterial, fungal, and parasitic infections can also cause acute myelitis. Patients typically are systemically ill with fever and meningeal signs. Common organisms include HSV, VZV, CMV, EBV, HHV-6, enteroviruses, influenza, dengue, West Nile, mycoplasma, Lyme, and syphilis.113

Connective tissue disorders may present with acute or subacute myelitis.
SLE, Behçet’s, Sjogren’s, scleroderma, mixed connective tissue disorder, and sarcoidosis have all been associated with myelitis; however, it is uncommon for myelitis to be the presenting symptom. Invariably, classic systemic features of the disease will be present before the development of myelitis.

Vascular disorders can also lead to spinal cord infarction, imitating myelitis. Arterial occlusions are rare and develop acutely over minutes. AVMs usually progress slowly due to gradual ischemia resulting from venous congestion.

Metastatic disease and compressive tumors (eg, neurofibromas and meningiomas) are common causes of acute or acute-on-chronic myelopathy. Several paraneoplastic antibodies are also associated with subacute myelopathies. Radiation-induced myelopathies are usually slowly progressive but may occur up to 15 years after the completion of radiation treatment.

**TREATMENT OPTIONS**

ATM is a rare disease; randomized placebo-controlled studies to support evidence-based management are not available. Decision-making is often guided by clinical experience and treatment of related disorders. At the Johns Hopkins Transverse Myelitis Center, high-dose methylprednisolone (1 g IV daily for 3-7 days) is typically first-line treatment. The decision to extend steroids or provide additional treatment modalities is based both on the clinical course and MRI findings after completion of steroids.

PLEX is often added to the regimen if a patient shows little clinical improvement after the standard steroid course. PLEX can be considered as initial treatment if a patient has moderate to severe ATM symptoms on presentation (eg, is unable to ambulate, sensory loss in lower extremities, or significant autonomic dysfunction).

Other therapeutic options include immunomodulatory and cytotoxic drugs such as rituximab, azathioprine, and cyclophosphamide, although there is not sufficient evidence in the literature to support their routine use. In one large retrospective study of adult patients with ATM, patients with the most severe level of disability at nadir, and those with a history of autoimmune disease did show some benefit from IV cyclophosphamide after corticosteroids.

In that same study, another subgroup of patients receiving IV corticosteroids followed by PLEX fared better than those who received IV corticosteroids alone, further supporting the use of steroids followed by PLEX as the widely accepted standard of care. In terms of preventing recurrence, there is insufficient evidence to warrant the use of immunosuppressive medications at this time.

In addition to pharmacologic therapies, the importance of physical and occupational therapy in the care of patients with ATM cannot be overlooked and should be included as early as possible in their care.

**NATURAL HISTORY AND PROGNOSIS**

The progression of symptoms in ATM often slows within 2 to 3 weeks of onset, with a corresponding improvement in CSF and MRI abnormalities.
expected to begin within 6 months; most patients show some improvement in neurologic function within 8 weeks, although recovery can take a more prolonged course of up to 2 years. About one-third of patients will show minimal (eg, mild urinary symptoms, minimal sensory deficits and upper motor neuron signs) to no permanent effects. Another one third will have a moderate degree of disability (eg, mild spasticity, but still ambulating independently, urinary urgency +/- constipation, some sensory symptoms). The remaining one third will be left with severe disabilities (eg, inability to walk or severe disturbance in gait, lack of sphincter control).1

The majority of patients with ATM have monophasic disease without recurrence.4 It is generally accepted that pediatric outcomes are better in adults, with children often regaining complete function.10 Studies in adults and children have identified several risk factors for unfavorable outcomes at presentation, including rapid progression to maximal neurologic deficit (<24 hours), severe motor weakness, spinal shock, back pain as the initial complaint, and sensory disturbances at the cervical level.1,10

In terms of recurrence, findings of multifocal lesions within the spinal cord, demyelinating lesions in the brain, oligoclonal bands in CSF, evidence of mixed connective tissue disorders, and serum autoantibodies (especially SS-A) all seem to be significant predictors of a possible multiphasic disease course.1,10

CONCLUSION

ATM is a rare, but serious acute inflammatory neurological disorder of the spinal cord characterized by four classic symptoms: 1) weakness in the arms/legs; 2) sensory symptoms such as numbness or tingling; 3) pain and discomfort; and 4) bladder dysfunction and/or bowel motility problems.

Early systemic corticosteroids +/- PLEX are the current treatment modality of choice. Pediatric outcomes are better than in adults, with children often regaining complete function.1

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