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Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Acute Transverse and Flaccid Myelitis in Children

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Abstract

Purpose of review The etiologies of myelitis in children are broad, and our understanding of inflammatory myelopathies in the pediatric population continues to evolve. Acute flaccid myelitis (AFM), increasingly linked to enterovirus infections, has risen in incidence over recent years. As with other infectious myelopathies, AFM can be challenging to distinguish from inflammatory causes of acute transverse myelitis (ATM) at initial presentation. This review outlines an approach to the treatment of children presenting with myelopathy of suspected inflammatory etiology, with attention to how management may differ in the specific case of acute flaccid myelitis.
Recent findings Although high-quality evidence is limited, intravenous corticosteroids, intravenous immunoglobulin, and plasma exchange have important roles in the acute management of ATM. Spinal cord injury in AFM, though similar to ATM in clinical presentation, is largely mediated by direct infection as opposed to a primary inflammatory process, and treatment with corticosteroids may worsen outcomes.
Summary Awareness of the distinguishing clinical features of AFM and the underlying inflammatory conditions that commonly manifest with ATM is essential to judicious selection of appropriate acute (and potentially chronic) therapies in children presenting with myelitis.

Introduction

The differential diagnosis for children presenting with signs and symptoms of acute myelopathy is broad and includes compressive, neoplastic, vascular, infectious, inflammatory, and toxic/metabolic etiologies. Magnetic resonance imaging (MRI) of the brain and spinal cord can help narrow the differential, but discerning inflammatory from infectious causes of myelitis remains a particular challenge due to the significant overlap in

clinical and paraclinical features. Given the turn-around time needed to obtain confirmatory test results, clinicians must often make acute treatment decisions on an empiric basis. Identifying patterns from the clinical history, neurologic examination, imaging, and early laboratory results can help formulate diagnostic considerations and inform time-sensitive management. This review will focus on the distinguishing clinical characteristics and treatment paradigms of acute transverse myelitis (ATM) and acute flaccid myelitis (AFM).

Acute transverse myelitis is an immune-mediated, inflammatory attack of the spinal cord that comprises approximately 20% of all pediatric acquired demyelinating syndrome (ADS) cases [1•]. ATM may represent a monophasic demyelinating disorder, the initial presentation of a chronic, relapsing demyelinating syndrome, or a neurologic manifestation of a systemic autoimmune condition [2••]. Our understanding of both monophasic and relapsing demyelinating conditions associated with ATM has evolved substantially, particularly with the identification of antibodies mediating these diseases. Specifically, detection of antibodies against aquaporin-4 (AQP4) or myelin oligodendrocyte protein (MOG) facilitates diagnoses of neuromyelitis optica spectrum disorders (NMOSD) and MOG-associated demyelinating disorders in the appropriate clinical context. Although this evolving diagnostic stratification does have implications for optimizing long-term treatment planning, the current mainstays of acute treatment for ATM remain high-dose intravenous corticosteroids, intravenous immune globulin (IVIg), and/or plasma exchange (PLEX) [3].

One form of pediatric myelitis, which has come to the forefront in recent years, is acute flaccid myelitis (AFM). This condition, though resembling ATM in many respects, is characterized by injury to the anterior horn cells of the spinal cord [4]. The emergence of clusters of AFM in the late summer to early fall of 2014 coincided with outbreaks of respiratory infections caused by Enterovirus D68 (EV-D68), and evidence implicating this virus (among other non-polio enteroviruses, such as Enterovirus A71) as a causative agent of AFM continues to grow. Although both inflammation and infection likely contribute to neuronal injury in AFM, experimental mouse models have confirmed the presence of active infectious virus in the spinal cord [5]. This suggests a primary mechanism of direct infection of motor neurons as seen in poliomyelitis rather than a para-infectious autoimmune response as can be seen in idiopathic transverse myelitis. This distinction may have important implications for the treatment approach of AFM.

Epidemiology

The incidence of ATM in children is approximately 0.2 per 100,000 children per year [1•, 6, 7] and accounts for approximately 20% of all children experiencing an initial ADS [1•]. While ATM overall exhibits a slight male predominance, a female predominance is noted among those subjects at higher risk for multiple sclerosis (MS) [1•]. The median age of presentation is between 8 and 11 years [8•, 9, 10•, 11•, 12, 13].

An increase in cases of polio-like illness was first reported in California in 2012 [14, 15]. More widely distributed outbreaks were reported in subsequent years. The establishment of case definitions by the Centers for Disease Control (CDC) enabled more accurate surveillance for cross-country acute flaccid myelitis cases. AFM has an estimated overall incidence of 1.4 cases per 100,000 [16] and affects children from infancy into young adulthood, with a median age of presentation between 5 to 9 years of age [16, 17, 18••, 19, 20].

Clinical and diagnostic considerations

Acute transverse myelitis is frequently preceded by a non-specific illness, with up to two thirds of patients ascribing to an infectious prodrome in the weeks

preceding clinical onset [13, 21, 22]. Neurologic symptoms of ATM typically manifest with back pain followed by motor and sensory deficits. Autonomic impairment and/or bowel/bladder dysfunction may also be seen. The neurologic manifestations can evolve rapidly (over the course of hours) or more subacutely (over several days). Weakness in ATM is typically bilateral, though partial cord myelitis may result in asymmetric neurologic findings. Muscle tone and reflexes may be diminished initially; however, upper motor neuron signs (e.g., hyperreflexia, increased tone) become more apparent as the clinical course evolves. Sensory abnormalities may include numbness, paresthesias, or hyperesthesias. A spinal level may be apparent in some cases, though deficits may be patchy depending on the distribution of the cord lesions. Predictors of a relapsing demyelinating syndrome (e.g., MS, NMSOD) at the time of ATM include female sex and the presence of associated brain lesions in addition to the symptomatic spinal cord lesion(s) [8•]. ATM associated with persistent nausea, vomiting, or hiccups suggests involvement of the area postrema and is more suggestive of an NMOSD-associated myelitis [23].

Similar to ATM, the presentation of AFM almost always follows a mild respiratory or other febrile illness. AFM presents with predominately motor symptoms, though sensory changes can be seen. Distinguishing features of AFM include (1) asymmetric onset of flaccid limb weakness, commonly starting in a single arm, and (2) positive complaints of pain or paresthesia in the affected limb without an apparent sensory deficit [18••, 24]. Bowel and bladder dysfunction are less commonly seen in AFM compared to ATM. Flaccid tone and hyporeflexia/areflexia in the affected limb are hallmarks of AFM, but may also occur in the acute phase of ATM [2••]. Cranial nerve involvement, bulbar weakness, or other deficits localizing to the brainstem are seen in AFM, but altered mental status is rare and should raise suspicion for an alternative diagnosis [18••].

Cerebrospinal fluid (CSF) protein and white blood cell counts may be normal in a substantial proportion of children with ATM or AFM, though increased protein and a lymphocytic pleocytosis are the most common findings [7, 13, 18••, 19, 22]. The presence of unique intrathecal oligoclonal bands are typically seen in patients who will ultimately meet criteria for a diagnosis of MS [25]. Positive aquaporin-4 antibodies are consistent with a diagnosis of NMOSD in the appropriate clinical context and should be tested in serum, as CSF testing is less sensitive [26]. Serum MOG antibodies should be checked in all pediatric myelitis patients. MOG antibodies are found in monophasic (e.g., optic neuritis, transverse myelitis, acute disseminated encephalomyelitis) and relapsing demyelinating syndromes (e.g., NMOSD, multiphasic ADEM) [27••]. Angiotensin converting enzyme levels in the CSF and serum are not sensitive or specific for the diagnosis of sarcoidosis, and imaging to identify pulmonary or other systemic manifestations is warranted [28]. Screening for underlying rheumatologic conditions that can manifest with ATM (e.g., lupus) with antinuclear antibodies, anti-double stranded antibodies, extractable nuclear antigen antibodies, and antiphospholipid antibodies should be considered.

Enteroviruses are rarely detected in the CSF of patients with AFM, and unlike poliomyelitis, EV-D68 does not shed in the stool [24, 29]. Respiratory samples have the highest yield for EV-D68, but the virus may not be detectable beyond the first 5–7 days of infection [29]. As neurologic symptoms present days after the onset of what is otherwise a mild respiratory infection, obtaining positive

testing in cases of AFM remains a particular challenge [29, 30].

MRI of the brain and spinal cord offers important clues to the underlying diagnosis in a child presenting with myelitis. In ATM, lesions typically involve the white matter of the spinal cord or both gray and white matter, whereas in AFM, lesions tend to be more restricted to the gray matter, particularly the anterior horn. However, this predilection for gray matter can be seen in other causes and has particularly been reported in MOG antibody-associated disorders [31••, 32•, 33]. Similarly, nerve root enhancement may be present in MOG antibody-associated myelitis or in AFM, with enhancement of the ventral nerve roots alone suggesting AFM [18••, 32•, 34]. Longitudinally extensive transverse myelitis (LETM), while classically associated with NMOSD, can be seen in MOG antibody-associated demyelination or in AFM. Spinal cord lesions in MS tend to be focal, favor the cervical spinal cord, and are partial in cross-sectional extent, though LETM is not an uncommon finding in pediatric MS [35]. While NMOSD lesions have a predilection for the cervicothoracic spine, anti-MOG-associated myelitis and AFM lesions are distributed throughout the spinal cord [32•]. T1-hypointensities on MRI may suggest a chronic relapsing demyelinating condition, such as MS or NMOSD. The presence of spinal cord cavitation is more suggestive of NMOSD [32•]. Dorsal subpial and central canal enhancement are classically associated with spinal cord sarcoidosis [36]. In AFM, brainstem lesions (particularly in the dorsal region) and cranial nerve enhancement can be seen, but supratentorial white matter lesions are not present [18••, 34]. The presence of supratentorial lesions on MRI is most commonly noted in pediatric MS and ADEM. ADEM is associated with diffuse, large T2-hyperintensities with indistinct borders that predominately involve the cerebral white matter, in contrast with the more circumscribed, ovoid lesions noted in MS [37]. Several radiographic examples of ATM and AFM cases from our center are presented for review in Fig. 1.

Treatment

Acute management of acute transverse myelitis

Medications

While there are no current FDA-approved therapies specifically for ATM, the acute inflammatory attack of ATM is typically managed first-line with high-dose intravenous (IV) corticosteroids [38•]. Pediatric dosing is 20 to 30 mg/kg/day (up to 1 g/day) of IV methylprednisolone (IVMP) for 3 to 5 days. An oral prednisone taper, starting at 1 to 2 mg/kg/day and tapered over 2–4 weeks, is a consideration for patients who are improved but have achieved an incomplete recovery following high-dose IVMP administration. Placebo-controlled trials assessing the efficacy of corticosteroids in ATM do not exist; however, retrospectively acquired data suggests that early treatment with corticosteroids improves neurologic outcomes and increases the likelihood of achieving a full recovery [39].

Intravenous immunoglobulin (IVIg) is sometimes used as an adjunctive treatment to corticosteroids or as a second-line option. IVIg is dosed at 2 g/kg,

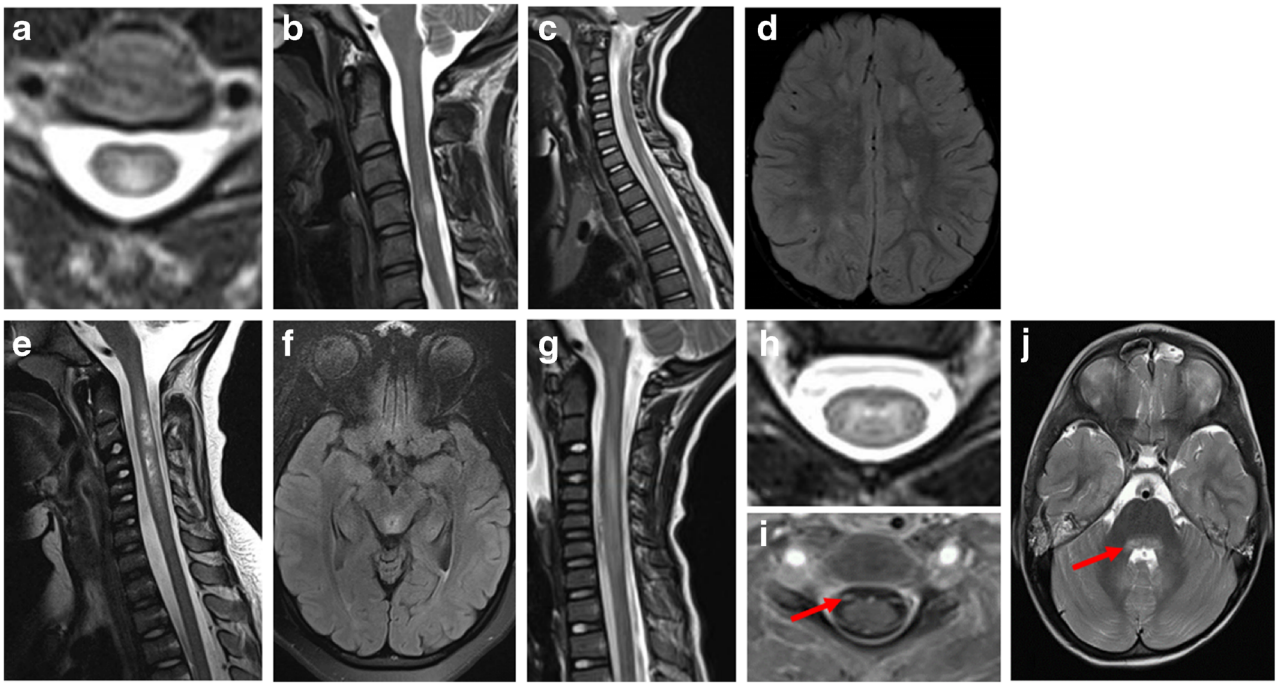

Fig. 1. **a**, **b** Idiopathic transverse myelitis in a 15-year-old girl presenting with a sensory deficit with a normal brain MRI, and a single, well-defined hyperintense lesion within the central dorsal cord at C4 as shown in both the axial T2-weighted image (**a**) and sagittal T2-weighted image of the cervical cord (**b**). **c**, **d** A 2-year-old girl with multifocal neurologic deficits, including leg weakness who was diagnosed with MOG antibody-associated ADEM. MRI of the cervical spine demonstrates a longitudinally extensive hyperintensity from C7 to T4 on T2-weighted MRI of the spine (**c**). Additionally, axial FLAIR imaging of the brain demonstrates multiple large, fluffy, hyperintensities throughout the white matter (**d**), consistent with ADEM. **e**, **f** An 8-year-old boy with weakness was found to have longitudinally extensive hyperintensities from C2 to C5 with cavitation on T2-weighted imaging of the spine (**e**) and was found to be AQP4 antibody positive. MRI FLAIR imaging of the brain on axial demonstrates hyperintense signal within the periaqueductal gray (**f**). **g**-**j** Selected MRIs from panel of patients presenting with acute flaccid myelitis. Findings include longitudinally extensive T2 hyperintensities of the central gray matter from C2 to C7 on sagittal (**g**) and axial (**h**), nerve root enhancement of the cervical spine on post-contrast T1-weighted imaging (**i**), and dorsal brainstem hyperintensities on axial T2-weighted imaging (**j**).

administered over 2 to 5 days. The data for IVIg use in acquired demyelinating syndromes is currently limited to case series and case reports [40]. To better define the role of IVIg in the treatment of ATM, the STRIVE trial was launched. This was a multicenter randomized controlled trial of IVMP alone versus IVMP plus IVIg in children and adults with ATM and/or NMOSD [41]. Unfortunately, the study was unable to achieve full recruitment, only randomizing 2 subjects [42]; however, this trial identified important barriers to studying the acute management of ATM. The importance of the research question posed in this trial remains highly relevant to the field.

Plasma exchange (PLEX) is typically used when (a) steroids are contraindicated, (b) patients are not responsive to corticosteroid treatment, or (c) the patient presents with life-threatening deficits (e.g., severe respiratory compromise). While invasive, several retrospective studies provide evidence to support the safety, tolerability, and clinical benefits of PLEX [43–46] in the setting of pediatric ATM. Typically, PLEX consists of 5 to 7 exchanges, run every other day over the course of 10 to 14 days.

Of note, in patients with ATM and coexisting rheumatologic disease, particularly systemic lupus erythematosus, early treatment with combined IVMP and IV cyclophosphamide may prove effective [3, 47]; however, the evidence basis for this is limited. The acute treatment options for management of ATM are summarized in Table 1.

Acute management of acute flaccid myelitis

Medications

There are no high-quality clinical trials to guide acute treatment in the clinical management of AFM. The CDC task force, formed to investigate AFM and provide recommendations, ultimately concluded that there is insufficient current evidence to endorse or discourage specific treatments [50]. Patients with AFM have been primarily treated with various combinations of IVIg, intravenous steroids, and/or PLEX, though no clear correlation of specific treatments with improved outcome has been reported to date [19, 51•, 52].

IVIg is the empiric treatment of choice and is dosed with the same regimen specified above [53]. IVIg has been used in the treatment of enteroviral infection in neonates and in children with agammaglobulinemia [50, 54]. In the polio era, IVIg demonstrated some efficacy in the prevention of poliomyelitis when administered before poliovirus infection in children at the onset of an epidemic; however, it did not prevent progression to paralysis in patients who were already infected [19, 50, 55]. In a mouse model of EV-D68 infectious myelitis, administration of IVIg (confirmed to contain neutralizing antibodies to EV-D68) prevented the occurrence of motor impairment when started on day 1 post-infection and resulted in less severe motor impairment when the treatment was initiated on days 3 to 6 post-infection, suggesting that implementation of appropriate treatment may be time-sensitive [56••]. Mice treated with IVIg also had lower mortality and lower viral titers in the spinal cord when compared to controls [56••]. Clinical experience has not demonstrated any clear evidence of improvement with IVIg, despite the fact that testing of commercially available IVIg products confirmed the presence of neutralizing antibodies against EV-D68. The difficulty in achieving treatment initiation within 3 to 6 days of infection may be a limiting factor in clinical practice. As contemporary EV-D68 strains become more prevalent, levels of neutralizing antibodies in IVIg products may continue to increase, improving the potential for efficacy [54••, 56••].

High-dose IV corticosteroids have been used sequentially or in combination with IVIg, particularly when the etiology remains uncertain. Cord edema is common in AFM, and ongoing inflammation could potentially exacerbate spinal cord injury, making steroids a rational therapeutic intervention. However, steroid treatment in the setting of Enterovirus-A71, a non-polio enterovirus that can have neurologic complications (including AFM), may worsen outcomes and increase mortality [29]. In a mouse model of EV-A71 CNS infection, treatment with dexamethasone in the first few days of infection increased mortality and disease severity. In the same model, later treatment with dexamethasone showed no obvious benefit [57]. Based on these findings, the WHO concluded that steroids should be avoided in the management of EV-A71-associated neuro-invasive disease [50]. Experiments in the EV-D68 mouse

Table 1. Acute therapeutic options for the management of acute transverse myelitis and acute flaccid myelitis

Treatment	Indication	Dosing	Mechanism of action	Side effects
Intravenous methylprednisolone	- Considered first-line for ATM - Animal models suggest that steroids may worsen neurologic outcomes in AFM	20 to 30 mg/kg/day (max dose of 1 g/day) for 3–5 days	- Modifies cytokine responses - Reduces T cell activation - Reduces blood-brain barrier permeability - Facilitates apoptosis of activated immune cells [48]	- Hyperglycemia - Hypertension - Insomnia - Irritability/anxiety - Gastritis - Weight gain
Oral prednisone	- May have benefit for ATM immediately following high-dose IVMP if an improved, but incomplete neurologic recovery is achieved - Animal models suggest that steroids may worsen neurologic outcomes in AFM	Start at 1 to 2 mg/kg/day and taper over 2–4 weeks	As above	As above
Intravenous immunoglobulin	- Used as adjunctive or first-line when corticosteroids are contraindicated or as a second-line treatment for ATM - First-line for AFM, with animal data suggesting greater benefits if given early in disease course	2 g/kg divided over 2–5 days	- Binds circulating pathologic antibodies/antigens - Affects cytokine production and T-cell proliferation [49]	- Headache - Myalgias - Fever - Aseptic meningitis - Anaphylaxis (in IgA deficiency)
Plasma exchange	- First-line in ATM when steroids are contraindicated or in severe, life-threatening cases. Second-line in ATM when case is steroid-refractory - Currently not recommended in AFM given the theoretical risk of removing native neutralizing antibodies	5 to 7 exchanges provided every other day over 10–14 days	- Removes circulating pathologic antibodies and immune complexes from the blood	- Procedural complications - Infection - Alteration of electrolyte profiles - Depletion of coagulation factors - Hypotension

Table 1. (Continued)

Treatment	Indication	Dosing	Mechanism of action	Side effects
Cyclophosphamide	- Considered in combination with IVMP in ATM of known rheumatologic disease (e.g., systemic lupus erythematosus)	Provided monthly (with or without induction) with dose titration per lymphocyte counts	- Immune suppressant alkylating agent that interferes with DNA transcription of rapidly dividing cells - Affects cytokine expression and T cell/B cell function	- Nausea/vomiting/anorexia - Hemorrhagic cystitis - Alopecia - Amenorrhea, infertility - Increased risk of infections and secondary malignancies

model of AFM similarly illustrated that treatment with dexamethasone worsened motor impairment, increased viral titers in the spinal cord, and resulted in higher mortality compared to controls [56••]. These observations from animal models speculate a potentially detrimental effect of steroids in AFM, particularly when used early in the course of infection.

PLEX has been used in cases of AFM without definitive evidence of benefit [15, 52]. The appropriateness of this treatment is in question given that AFM is not an antibody-mediated disease. Furthermore, there is a distinct possibility that PLEX may be counterproductive in AFM, with the potential to remove important neutralizing antibodies formed in the setting of acute infection [50].

Fluoxetine decreases in vitro growth of EV-D68 by inhibiting the enteroviral 2C protein; however, in vivo studies of mice treated with fluoxetine did not demonstrate improvement in motor outcomes or viral titers [56••, 58•]. A multicenter, retrospective trial in AFM patients treated with fluoxetine (compared to untreated AFM controls) showed no improvement in neurologic outcomes [58•]. Of note, the median time to initiation of treatment in this study was 5 days after the onset of neurologic symptoms, and a subgroup analysis of those patients confirmed to have EV-D68 did demonstrate a trend toward improved outcomes with earlier initiation of fluoxetine treatment, though this did not reach statistical significance [58•].

Other antiviral agents have also been tested in vitro, with limited positive results to date. The CDC reported negative results in tests of the agents pleconaril, pocapavir, and vapendavir for antiviral activity against EV-D68 [50]. Telaprevir, an FDA-approved drug for treatment of hepatitis C infection, may have antiviral activity against EV-D68 by targeting the 2A protease enzyme in cell culture [59]. Picornavirus protease inhibitors (rupintrivir and V-7404) and a sialidase (DAS181) have shown in vitro antiviral activities against EV-D68, but the in vivo efficacy of these agents remains to be evaluated [60].

Chronic management of acute transverse myelitis

Monophasic idiopathic ATM represents the majority of pediatric cases (> 80%) [8•, 9, 11•, 13]. While close clinical vigilance is needed to ensure a monophasic course, this subset of patients does not necessitate treatment with chronic immunotherapy.

Less commonly, the first attack of ATM may represent the initial presentation of a relapsing demyelinating syndrome. Identified risk factors for relapsing disease include female sex and an abnormal brain MRI [8•]. In these particular cases, use of chronic immunotherapy should be considered. The chronic management of ATM secondary to an underlying relapsing demyelinating syndrome will vary depending on the underlying etiology and is beyond the scope of this review. In general, children with relapsing MOG antibody-associated demyelination may be treated with mycophenolate, azathioprine, rituximab, or recurrent IVIg [61•]. Children with AQP4+ NMOSD are most commonly treated with rituximab, azathioprine, and mycophenolate [23], though tocilizumab and eculizumab are viable considerations [62•]. Pediatric MS patients should be treated with MS disease modifying therapies, which include injectables (interferons, glatiramer acetate), oral therapies (fingolimod, teriflunomide, dimethyl fumarate), and infusions (natalizumab, rituximab, ocrelizumab) [63].

Chronic management of acute flaccid myelitis

Nerve transfer

Nerve transfer is an accepted intervention for the treatment of traumatic plexopathy and peripheral nerve injury in adults. Nerve transfer has been applied to the AFM population with some success in selected cases [64]. Limitations include difficulty identifying a suitable donor nerve due to the widespread muscle dysfunction commonly seen in AFM, as well as potential viral injury to the Schwann cells, resulting in decreased ability for reinnervation. To further confound the picture, there continues to be limited observational data regarding the course of spontaneous recovery from AFM to guide surgical intervention timelines. Prolonged observation greater than 12 months may decrease the viability of the receiving nerve and muscle [64].

Rehabilitation

Early and aggressive physical therapy is a key component for the treatment of both ATM and AFM [53]. The benefit of early intensive rehabilitation was widely reported in cases of poliomyelitis. Therapy is essential for maintaining flexibility and stamina, minimizing pain and deformity, and maximizing muscle strength and functional outcomes. Ongoing clinical surveillance for potential development of a post polio-like syndrome following AFM is important [65].

Prevention

Vaccination as a means to prevent AFM is an area of high interest. Following several large scale outbreaks of EV-A71 in Asia in the late 1990s, efforts were allocated toward vaccine development. As a result, two EV-A71 vaccines were approved and are commercially available in China—with efficacy toward preventing neuro-invasive disease [24, 66]. Research to develop targets for EV-D68 vaccines is currently underway; however, the feasibility of mass vaccination

remains unclear, particularly as multiple different enterovirus strains have been associated with AFM [67].

Conclusion

Careful consideration of the clinical history, neurologic examination, neuroimaging findings, and laboratory results in a child presenting with myelitis may reveal a pattern of findings suggestive of a specific diagnosis. In transverse myelitis, whether it ultimately proves to be monophasic or the initial presentation of a relapsing demyelinating syndrome, acute treatment with high-dose IV corticosteroids is considered first-line. The addition of IVIg and/or PLEX may be appropriate in refractory or severe cases, while cyclophosphamide may have a role in acute treatment of ATM in the setting of a rheumatologic etiology.

Spinal cord injury in AFM is largely driven by an infectious myelitis, and current evidence suggests that steroid treatment has the potential to worsen neurologic outcomes. Practitioners need to be aware of the distinguishing clinical and radiographic features of AFM and the need for early testing of respiratory samples to isolate a viral pathogen. These aspects are key to achieving a correct diagnosis and to provide the most optimal, evidence-based acute management for this emerging form of myelitis. Further research efforts are needed to better identify the most safe and effective treatment(s) for acute transverse myelitis and acute flaccid myelitis.

Compliance with Ethical Standards

Conflict of Interest
Liana M. Theroux declares no potential conflicts of interest.
J. Nicholas Brenton reports personal fees for consulting for Novartis.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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