Acute Transverse Myelitis and Acute Disseminated Encephalomyelitis

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Education Gap

Most pediatricians report lack of knowledge related to the understanding of the diagnosis and treatment of both acute disseminating encephalomyelitis and acute transvers myelitis. Pediatric providers should understand presenting symptoms, initial diagnostic testing, and acute treatment. Clinicians should know when to refer to a neurologist for evaluation of long-term treatment.

Objectives

After completing this article, readers should be able to:

1. Define and characterize acquired demyelinating syndromes.
2. Identify the prevalence, etiology, and clinical presentations of acute disseminating encephalomyelitis (ADEM) and acute transverse myelitis (ATM).
3. Initiate a diagnostic evaluation, including an evaluation for medical emergencies.
4. Make treatment decisions for acute management.
5. Counsel patients on long-term outcomes after ADEM and ATM.
6. Counsel patients on recurrence risks for multiphasic or chronic demyelinating diseases.

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ABBREVIATIONS

ADEM	acute disseminated encephalomyelitis
ADS	acquired demyelinating syndrome
AQP4	aquaporin-4
ATM	acute transverse myelitis
CNS	central nervous system
CSF	cerebrospinal fluid
IgG	immunoglobulin G
IVIg	intravenous immunoglobulin
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
OCB	oligoclonal band

INTRODUCTION

Acquired demyelinating syndromes (ADSs) encompass a group of immune-mediated disorders in which there is breakdown of the myelin sheath, the lipid-rich covering around the axon that increases conduction speed and metabolic efficiency of the neuron. ADSs are characterized by a sudden onset of new neurologic symptoms in concurrence with neuroimaging evidence of demyelination. Outcomes vary from full neurologic recovery to long-term severe disability. ADSs are characterized based on location and frequency of the demyelinating events. Location is either focal, limited to 1 specific location, or polyfocal, involving several areas of the central nervous system (CNS). Frequency is classified as monophasic or multiphasic, meaning either a single 1-time event or a recurrent,

potentially chronic, disease. It is important to keep at the forefront of your mind, however, that over time what seems to be a monophasic event may, in fact, turn out to be the initial or first attack of a multiphasic disorder. (1)(2) Multiple sclerosis (MS) is the most well-recognized example of a multiphasic acquired demyelinating disease. One must demonstrate that demyelinating lesions have occurred over more than 1 period of time and in more than 1 location in the CNS. These principles are referred to as dissemination in time and space. (3) Neuromyelitis optica spectrum disorder (NMOSD) is a second hallmark of multiphasic demyelinating disease that is associated with antibodies directed at aquaporin-4 (AQP4) in approximately 80% of patients. Clinically, this is characterized by recurrent episodes of transverse myelitis, optic neuritis, and inflammation of an area in the brain stem called the *area prostrema*. When involved, injury here leads to a characteristic syndrome of uncontrolled nausea and vomiting with or without hiccups. (4) During the past 5 years a pathogenic antibody against myelin oligodendrocyte glycoprotein (MOG) has been identified in both monophasic and multiphasic demyelinating diseases in childhood. (2)(4)

This article focuses on 2 specific ADSs: acute disseminated encephalomyelitis (ADEM) and acute transverse myelitis (ATM). Both ADEM and ATM can stand alone as individual clinical phenotypes with a monophasic course or may represent the initial attack of a chronic demyelinating syndrome with a multiphasic course, such as those mentioned previously herein. As advances are made in our understanding of pediatric acquired demyelinating diseases and as the options for long-term preventive treatments grow, it is more important to recognize these demyelinating events that may represent a first attack in a multiphasic disease so that one may monitor and intervene earlier to decrease risk of long-term disability.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Definition

ADEM is a polyfocal, typically monophasic, demyelinating event with encephalopathy. In 2013 the International Pediatric Multiple Sclerosis Study Group updated the diagnostic criteria so that all of the following are required (3):

- A first polyfocal clinical CNS event with a presumed inflammatory demyelinating cause
- Encephalopathy (alteration in consciousness or behavior unexplained by fever, systemic illness, or postictal symptoms)
- Brain magnetic resonance imaging (MRI) abnormalities consistent with demyelination during the acute (3 months) phase
- No new symptoms, signs, or MRI findings 3 months after the incident ADEM
- MRI typically shows diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter; T1 hypointense white matter lesions are rare; deep gray matter lesions (eg, thalamus or basal ganglia) can be present

There are 3 key points in this definition that are worth discussing in more detail. First, encephalopathy is a key distinguishing clinical characteristic that differentiates ADEM from other polyfocal demyelinating diseases. In the absence of encephalopathy, the same findings would be described as a polyfocal clinically isolated syndrome.

A second key feature often overlooked or misinterpreted is that demyelinating lesions may evolve and/or change over the first 3 months from onset. This means that some lesions will improve while others progress, and/or new lesions may develop. Any fluctuation during this first 3-month period does not represent new or multiphasic disease, which is particularly important to share with families during counseling for anticipatory guidance.

Third, it stands to reason that multiphasic ADEM (the term *recurrent ADEM* was eliminated in 2013) is defined as 2 episodes consistent with ADEM separated by 3 months but not followed by any further events. Beyond this, any further demyelinating disease that occurs after a second encephalopathic event or in the absence of encephalopathy is no longer consistent with multiphasic ADEM but indicates a chronic relapsing disorder, most often leading to the diagnosis of MS, NMOSD, or MOG antibody–associated disease. (1)(2)(3)(4)(5)

Epidemiology

Population-wide and nationwide studies estimate the incidence of ADEM to be 0.2 to 0.6 per 100,000 children per year. (6)(7)(8)(9)(10)(11) A nationwide UK study showed that ADEM made up 32% of all childhood ADSs. (10) ADEM is predominately a disorder of children younger than 10 years, with a mean age of 6 years (7)(9)(11)(12)(13)(14) and a slight male predominance of 3:2 (6)(7)(9)(11)(15) compared with other demyelinating syndromes that occur in older children. (7)(8)(10)(12)

Etiology

No single etiology has been identified, although the role of immunizations is a common question and concern for physicians and parents alike. Although there are many case reports of ADEM after vaccinations, the evidence for a causal association is lacking. (9)(16)(17)(18)(19)(20) Far more frequently patients experience a prodromal illness with flulike

symptoms of fever, cough, rhinorrhea, vomiting, and/or diarrhea. (9)(11)(12)(13)(15)(18) In a study conducted in southern California, only 5% of patients had received a vaccination within the 21 days before ADEM presentation, but 93% of patients reported 1 or more signs or symptoms of infection. (9)

Clinical Presentation

Most patients experience a combination of neurologic symptoms that vary based on the localization of the inflammatory lesions that often progresses rapidly, with a mean time to maximal deficits of 4.5 days. (11)(21) The degree of encephalopathy can vary from lethargy to coma. Common presenting signs include pyramidal signs, ataxia, hemiparesis, cranial nerve involvement, vision loss from optic neuritis, spinal cord involvement, impairment in speech, and seizures. (9)(10)(11)(12)(13)(21)(22) Seizures were found more frequently in children 5 years or younger and were most often focal motor seizures. (11) Severe presentation resulting in admission to an ICU has been reported in 15% to 43% of patients, (11)(12)(15)(23) with respiratory failure due to severely impaired consciousness and/or brainstem involvement in 16%. (11)

Diagnostic Evaluation

In addition to a detailed neurologic examination and clinical history, it is crucial that first steps in the diagnostic evaluation include an MRI of the brain and spine, with and without contrast, and a lumbar puncture. Contrast is given when evaluating for all demyelinating lesions. When contrast enhancement is seen, this is the hallmark sign of an active lesion, representing the presence of inflammatory infiltrates through leakage of the blood-brain barrier. This imaging should be performed acutely to evaluate for treatable causes of CNS viral or bacterial infections. The differential diagnosis for ADSs should also include, but is not limited to, leukodystrophies, mitochondrial disorders (ie, DNA polymerase subunit gamma [*POLG*] gene disorders), primary and secondary CNS vasculitis, tumor, abscess, posterior reversible encephalopathy, hemophagocytic lymphohistiocytosis, and lymphoma. (2)(5)

MRI findings are strikingly abnormal, with multiple, typically large, bilateral but asymmetrical and poorly marginated hyperintense lesions on T2 and fluid-attenuated inversion recovery sequences. Typical occurrence involves the subcortical and central white matter as well as the cortical gray-white matter junction, cerebellum, and brain stem. The gray matter of the thalami and basal ganglia are frequently involved as well. (11)(12)(13)(24)(25) Spinal cord involvement has been described in up to one-third of patients and contrast enhancement in up to 30%. (11)(13)

Cerebrospinal fluid (CSF) studies should be chosen based on clinical judgment, with specific recommendations for cell count, protein, glucose, bacterial culture, herpes simplex virus polymerase chain reaction, lactate, AQP4 antibodies, and oligoclonal bands (OCBs) (must be obtained in serum at the same time). One would expect to see mild CSF lymphocytosis, possible elevation in protein, and negative OCBs. (10)(11)(12)(13)(21)(25) Serum studies should also include an evaluation for infectious causes and antibody testing for MOG antibodies and AQP4 antibodies for NMOSD, which has been shown to be more sensitive in serum. (26) Serum antibodies to MOG have been reported in approximately one-third of children with a first presentation of an ADS and more than half of patients presenting with ADEM. (1)(27) Positive findings for either of these antibodies will have a large effect on diagnosis, prognosis, and long-term treatment. (2)(28)

Treatment

As soon as a clinical diagnosis has been determined, treatment should be initiated. There are no clinical trials to guide treatment, but the consensus is for high-dose corticosteroids with intravenous methylprednisone at 30 mg/kg per day (maximum of 1,000 mg daily) for 3 to 5 days. Some may choose to continue an oral corticosteroid taper of 1 to 2 mg/kg per day of prednisolone for 4 to 6 weeks. (2)(5)(7)(9)(10)(11)(12)(13)

Intravenous immunoglobulin (IVIg) has been described in case reports and small case series as combination therapy with corticosteroids or as second-line therapy when there has been a poor response to corticosteroids. However, there are no studies directly comparing IVIg to corticosteroids. Dosing is typically 2 g/kg divided over 2 to 5 days. (2)(5)(12)(13)(28)(29) Plasma exchange has been reported to help in primarily severe cases that did not improve after high-dose corticosteroids alone or combined with IVIg. (21)(28)(29)

Outcomes

Most patients with ADEM have good outcomes with treatment. Studies reporting full neurologic recovery represent 57% to -92% of patients. (9)(11)(12)(13)(14)(21) In children who improve, signs and symptoms begin to get better by the end of the first week after presentation, with full recovery within 1 month. (21) Persistent focal motor deficits are the most common sequela reported, with problems ranging from mild ataxia to hemiparesis. A large cohort of 102 children followed in southern India for up to 10 years (mean, 4.8 years) after presentation showed motor sequelae in 17%. This was significantly associated with a poor

modified Rankin Scale score (disability scale) at the time of discharge and the presence of thalamic lesions on MRI. (30) Other deficits reported include headache, epilepsy, paresthesia, and vision impairment. (12)(21)(28) Most patients will also show complete or near complete resolution of MRI lesions. (11)(12)(31)

Neurocognitive outcomes of varying degrees have been reported, with deficits in attention, executive functions, and behavior being the most common. (12)(31)(32)(33)(34) Deficits in processing speed and visuospatial skills have also been reported. (31)(32) Earlier age at disease onset may incur a greater vulnerability to impairments, such as poorer sustained attention and psychosocial problems. (32) In addition, significantly lower IQ and educational achievement, as well as more behavioral and emotional problems, have been reported in children who were younger than 5 years at the time of disease onset. (33) Although this did not correlate with MRI lesion burden, (33) longer follow-up may affect these neurocognitive findings positively. (33)(34) In a single study comparing outcomes in patients with follow-up of 2 to 6 years vs 7 to 15 years, attention scores were worse in those with shorter follow-up, suggesting that more improvement is possible over time. Interestingly, this study also incorporated quality of life measures using the Pediatric Quality of Life Inventory and found that, overall, most patients reported a good quality of life with only a few showing lower scores in emotional and behavioral functioning. However, unlike the cognitive problems, this effect did not improve over time and did not correlate with cognitive impairments. It was also more likely to be associated with failure to improve on MRI. (34) Larger study numbers and more long-term follow-up of both neuropsychological and quality of life measures are clearly needed to better understand these findings.

Recurrence Risks

Several studies have looked into rates of recurrence and risk factors with a specific focus on risk of future events leading to the diagnosis of MS. To meet the 2013 International Pediatric Multiple Sclerosis Study Group consensus definition of MS after ADEM, the second event must be nonencephalopathic, occur 3 months or more after the initial episode, and be associated with new MRI findings that are consistent with dissemination in space. (3) The rate of second demyelinating attacks in patients with ADEM has been reported to range from 10% to 30%, (11)(12)(13)(14)(35) with 80% occurring within 2 years of the initial episode. (3) Of these, the French KIDSEP cohort is among one of the largest studies to examine the recurrence rates of demyelinating events in pediatrics after ADEM over a mean of 5.4 years. An increased risk of relapse was associated with optic neuritis during initial presentation, familial history of CNS inflammatory demyelination, Barkhof MS criteria on MRI, and no neurologic sequelae after the first attack. (35)

Other studies have focused specifically on MRI findings and determined that MS should be strongly considered if MRI shows T1 black holes, 2 or more periventricular lesions, and/or the absence of a diffuse bilateral lesion pattern. The presence of 2 of these 3 findings has sensitivity of 81% and specificity of 94% in identifying a child with MS than one with ADEM. (24) No specific guidelines exist on when to repeat imaging in patients after their initial presentation. However, with exceptions based on clinical judgment, it is generally recommended to do a follow-up MRI screening at 3 months to establish a new baseline and then again 9 to 12 months after clinical onset to rule out ongoing disease activity. (5)(28) Positive OCBs in the CSF are also more frequently seen in MS. (7)(10)(11)(12)(13)(21)(25) Future studies will focus more and more on the presence and role of MOG antibodies and how to predict or prevent relapses associated with these antibodies. (2)(27)

ACUTE TRANSVERSE MYELITIS

Definition

ATM is a focal demyelinating event not associated with encephalopathy, with inflammation localized to the spinal cord. ATM is typically a monophasic demyelinating disease and often idiopathic. It can also present as part of other multifocal ADSs, such as ADEM, or as an initial event in MS, MOG antibody–associated disease, or NMOSD. The diagnostic criteria for idiopathic ATM were established in 2002 by the Transverse Myelitis Consortium Working Group. (36) The criteria require the following:

- Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord
- Bilateral signs and/or symptoms (although not necessarily symmetrical)
- Clearly defined sensory level
- Exclusion of extra-axial compressive etiology by neuroimaging
- Inflammation in the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement
- Progression to nadir between 4 hours and 21 days after the onset of symptoms

The criteria also include a list of exclusions that focus on ruling out other vascular, metabolic, and systemic causes of spinal cord injury, as well as other chronic demyelinating syndromes. (36) It must be kept in mind that the criteria

were established with primarily adult data. Although they can be applied to pediatrics, an exception must be made when assessing for a clearly defined sensory level because this is typically not reliably reported in younger children. (37)

Epidemiology

Population studies in the United Kingdom and Canada have reported incidence rates of 0.17 to 0.2 per 100,0000 per year, with ATM making up one-third of all monophasic demyelinating syndromes not including ADEM. (8)(10)(38) Children are slightly older than the ADEM population, with a mean age at onset of 9 to 12.6 years. (8)(10)(38)(39)(40)(41)(42) A bimodal age distribution of children younger than 5 years and teenagers has also been described. (38)(40) Although there are trends toward male predominance in the younger age group and a slight female predominance in the older age group likely after puberty, no statistically significant differences were found. (8)(10)(39)(40)

Etiology

In most patients there is a presumed postinfectious etiology, with patients reporting a prodromal event and/or fever in the preceding 4 weeks, although it is rare to identify a specific infectious agent. (38)(39)(40) Some data support a majority of presentations in colder months; however, no predilection for season has been clearly established. (39)

Clinical Presentation

The mean time to the peak of symptoms is typically 2 to 4 days and no more than 7 days. The most prominent presenting clinical features in all patients are sensory symptoms (numbness, paresthesia, hyperesthesia), weakness, pain, and bowel and bladder dysfunction. Urinary retention and need for catheterization is extremely common. (38)(39)(40) Up to 89% have been reported to be nonambulatory or required ventilator support in the acute phase. (40)

Diagnostic Evaluation

In addition to detailed neurologic examination and clinical history, it is crucial that first steps in the diagnostic evaluation also include MRI of the brain and spine, with and without contrast, and a lumbar puncture. Evaluation should include immediate exclusion of other neurologic emergencies, such as acute cord compression, spinal cord infarct, Guillain-Barre syndrome, acute flaccid myelitis, and treatable viral or bacterial myelitis. Other disorders in the differential diagnosis may include systemic diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren disease, as well as idiopathic myelopathy. (37)(42)(43)

The MRI typically shows hyperintense lesions on T2 and fluid-attenuated inversion recovery sequences that are often centrally located with surrounding edema but can vary in size and location. (39)(42) Most lesions reported are cervical or cervicothoracic. (40)(41)(42) When there is involvement of 3 or more contiguous segments this is referred to as a *longitudinally extensive lesion*. Longitudinally extensive lesions are classically thought of as primarily being associated with neuromyelitis optica (NMO); however, multiple studies in pediatrics support the finding that longitudinally extensive lesions are more common in kids than in adults and are not indicative of NMO. Contrast enhancement is variable and has been reported in 19% to 74% of patients. (39)(40)(42) In idiopathic ATM, normal findings on MRI of the brain would be expected. However clinically silent lesions in the brain have been found in up to 40% of patients. (41)

CSF analysis should include cell count, protein, OCBs or immunoglobulin G (IgG) index, NMO AQP4 antibodies, as well as specific testing for bacterial or viral antigens as indicated clinically. CSF pleocytosis and/or an elevation in the CSF protein level are seen in approximately half of reported cases. (40)(41) Positive OCBs or elevated IgG index are less common and may be a sign of relapsing disease such as MS. (39–41) A positive correlation between absolute CSF WBC count and longitudinal length of the lesions has also been reported in one study. (39) Serum evaluations should always include testing for NMO aquaporin 4 antibodies and MOG antibodies, as positive results will drive treatment and long term management. Keep in mind that serum NMO testing is more sensitive than CSF testing. (26) Clinical judgement should be used to guide any further serum studies focused on evaluation for systemic inflammation, infectious causes, and nutritional or metabolic causes of myelopathy. (43)

Treatment

Once again, there are no clinical controlled trials or specific guidelines to drive therapy. However, high dose IV corticosteroids, usually 30mg/kg/day of methylprednisolone to a maximum of 1g for 3-5 days, either alone or in combination with IVIg is widely accepted as a first-line treatment. Plasma exchange is sometimes utilized, but only when there is little to no response to the first-line therapy. (38–41) Symptomatic treatment of pain, urodynamic evaluation and early involvement of rehabilitation medicine is also extremely important in long-term management.

Outcomes

Most patients have good recovery and show improvement in gait within the first 2 weeks of symptom onset. (38)(39) Poor outcomes, characterized by continued problems with mobility (including wheelchair dependence) and ongoing bladder dysfunction, are reported in 17-30% of patients. (38)(39)(41) Abnormal sensory symptoms may also persist; with numbness being the most common sensory complaint in up to 75% of patients followed by dysesthesias. (40)

Several studies have looked for predictors of outcome, the largest of which is a multicenter French–UK collaborative cohort study with a median follow-up of 1.4 years. They found that a severe American Spinal Injury Association (ASIA) impairment score at onset, absence of cervical or cervicothoracic lesions, absent pleocytosis, female sex and contrast enhancement were more prevalent in children with a poor outcome. (41) This is in contrast to a separate, single center study with fewer patients but a mean follow-up of 3.2 years that showed that the absence of pleocytosis and fewer cervical lesions was predictive of better functional outcomes. It was also reported that fewer involved segments were associated with better outcomes for activities of daily living and mobility but not urinary symptoms. (40) Lastly, younger age of onset has been associated with poorer outcome, specifically with more bladder dysfunction reported. (39)(40) The differences in predictive factors noted above is likely due to the different outcome measures used between studies. This highlights the need for more uniform outcome measurements that include both physical and functional components.

Recurrence Risk

In the above-mentioned multicenter French–UK collaborative cohort study, 17% of patients had relapsing disease: 14% with MS and 3% with NMOSD. Of these, female sex and presence of one or more brain lesions at the onset were seen more frequently in children with relapsing courses than in idiopathic ATM. No spinal MRI characteristics were significantly associated with relapse. (41) The presence of oligoclonal bands in the CSF is also more commonly seen in the children who were subsequently diagnosed with MS. (39) No specific guidelines exist on when to reimage patients after their initial presentation. Clinical judgement based on risk factors and presentation should be used to determine need for neuroimaging surveillance.

Summary

- ADEM is a polyfocal, typically monophasic demyelinating event with encephalopathy.
- ATM is a focal, typically monophasic demyelinating event without encephalopathy.
- Consensus recommends follow-up neuroimaging 3 months after initial presentation of ADEM to establish a new baseline and then again between 9–12 months after clinical onset to rule out ongoing disease activity.
- Recurrent events after the first 3 months may represent multiphasic ADEM if encephalopathy is present. In the absence of encephalopathy, one must evaluate for a relapsing demyelinating syndrome.
- Based on some research evidence as well as consensus, workup in all patients with suspected ADEM or ATM should include MRI of the brain and spine with and without contrast and a lumbar puncture. Patients should also all be tested for NMO aquaporin 4 antibodies and MOG abs in the serum.
- Based primarily on consensus due to lack of relevant clinical studies, treatment recommendations for both ADEM and ATM are for high dose IV steroids alone or in combination with IVIg. Plasma exchange can be used in refractory or severe cases.
- Based on some research evidence as well as consensus, supportive care with urodynamic studies, pain management and rehabilitation services should be initiated early in the treatment of ATM.
- Neuropsychology follow-up should be highly considered in long-term treatment of ADEM.

References for this article are at http://pedsinreview.aappublications.org/content/41/7/313.

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1. A 7-year-old girl presents to the emergency department with 2 days of fatigue, vision loss in her right eye, poor balance, and tingling in both hands. She is admitted to the hospital. Over the next 3 days, she becomes lethargic and both arms become weak. Magnetic resonance imaging (MRI) of the brain and spinal cord with and without contrast shows bilateral, poorly demarcated, nonenhancing, T2 hyperintense lesions in the right and left cerebral white matter, thalamus, and cerebellum, and a T2 hyperintense lesion in the cervical spinal cord extending more than 3 segments. Cerebrospinal fluid (CSF) studies showed no evidence of infection or lymphoma, although clonal bands are negative. She is treated for an acquired demyelinating syndrome and discharged to the rehabilitation service and then eventually to home. At home, she continues to recover, and there are no new symptoms. Her follow-up brain MRI with and without contrast 3 months later shows new T2 lesions in the cerebral white matter. Which of the following is the most appropriate diagnosis?
   A. Acute disseminated encephalomyelitis.
   B. Acute transverse myelitis.
   C. Multiple sclerosis.
   D. Neuromyelitis optica.
   E. Polyfocal clinically isolated syndrome.
2. A 5-year-old boy presents with confusion and limping 1 week after a viral upper respiratory tract infection. His neurologic examination shows lethargy and flaccid right hemiparesis. A more detailed examination is not possible due to his altered mental status. His MRIs of the brain and spine with and without contrast show multiple bilateral, enhancing, poorly marginated, T2 hyperintensities in the subcortical white matter and basal ganglia; there are no lesions in the spinal cord. Laboratory evaluation of the CSF shows only oligoclonal bands. Serum laboratory results show no evidence of acute infection; aquaporin-4 antibodies and myelin oligodendrocyte glycoprotein antibodies are pending. Which of the following is the most appropriate next step in the management of this patient?
   A. Defer treatment until serum laboratory results are available.
   B. Start disease-modifying therapy for multiple sclerosis.
   C. Start intravenous corticosteroids.
   D. Start oral prednisone.
   E. Start plasma exchange.
3. A 6-year-old girl presents to the emergency department with new onset of lethargy and right arm and leg weakness. Her MRIs of the brain and spinal cord with and without contrast show multiple, bilateral, poorly demarcated, enhancing lesions in the subcortical white matter, cerebellum, and basal ganglia; there are no lesions in her spine. Serum and CSF testing show no signs of an acute infection. In the emergency department she becomes comatose. She is treated for an acute demyelinating syndrome and admitted to the hospital. Over the next several days her mental status improves and she regains movement in her right arm and leg. At discharge she has almost no disability. Once at home her mother noticed new inattentiveness. In discussing her prognosis, you explain to the family that in most cases, which of the following outcomes is most likely to be expected?
   A. Full recovery in 3 to 6 months.
   B. Persistent right hemiparesis at follow-up in 5 years.
   C. Resolution of MRI lesions on follow-up imaging in 3 months.
   D. Significant decrease in IQ on follow-up neuropsychological testing.
   E. Low likelihood of continued improvement in behavior over time.

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4. A 9-year-old boy presents to the emergency department with 1 day of progressive bilateral upper extremity weakness. He also reports numbness and tingling in his feet, neck pain, and urinary urgency but inability to void. There is no confusion or lethargy. His neurologic examination shows flaccid weakness and areflexia in his upper extremities, and decreased sensation in both arms. He is scheduled for MRI of the brain and spine with and without contrast in 2 hours. While waiting for the MRI, assessment of which of the following is the most important to be performed next in this patient?

    A. Ambulatory status.
    B. CSF studies.
    C. Respiratory status.
    D. Serum aquaporin-4 antibodies.
    E. Urodynamics.

5. An 8-year-old boy is brought to the emergency department with sudden onset of inability to use his left arm. There was no history of injury, and he does not have any symptoms of infection. His mother is known to have systemic lupus erythematosus. His neurologic examination shows normal mental status and flaccid left upper extremity weakness. His MRIs of the brain and spine with and without contrast show 3 nonenhancing, poorly demarcated, T2 hyperintensities in the bilateral subcortical white matter and a T2 hyperintensity in the cervical spinal cord extending over 4 segments. CSF and serum laboratory tests show no signs of infection. Serum aquaporin-4 and myelin oligodendrocyte glycoprotein antibody results are pending. Over the next 4 hours in the emergency department, his right arm and both legs become weak and he is found to have urinary retention. He is treated for an acute demyelinating syndrome. Which of the following factors is most likely to be associated with a relapsing course of the disease in this patient?

    A. Family history of autoimmune disease.
    B. Initial MRI brain results.
    C. Initial rapid progression of symptoms.
    D. Length of the cervical spinal cord lesion.
    E. Male sex.

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