Pediatric Central Nervous System Demyelinating Diseases

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: This article provides an up-to-date summary of the categories, diagnosis, and management of pediatric demyelinating disorders.

RECENT FINDINGS: Understanding of the diverse spectrum of pediatric demyelinating disorders, including monophasic and multiphasic forms, has improved. Pediatric multiple sclerosis (MS) is the most common demyelinating disorder in children, and recent genetic and environmental risk research has clarified that pediatric MS is on the same continuum of disease as adult MS. Recent advances in the treatment of pediatric MS include clinical trials leading to regulatory agency–approved treatments. The identification of myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies in children has been a major advance, allowing for appropriate treatment and management of these syndromes.

SUMMARY: Antibody testing is now helping to define subtypes of pediatric demyelinating disorders, including myelin oligodendrocyte glycoprotein–seropositive and aquaporin-4–seropositive cases that are distinct from pediatric MS. Treatments for pediatric MS are being evaluated in clinical trials.

INTRODUCTION

Significant progress has been made in the field of pediatric central nervous system (CNS) demyelinating disorders over the past 5 years. These disorders include acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and clinically isolated syndromes. Major advances in the past 5 years include improved diagnostic criteria, antibody-based biomarkers, predictors of a multiphasic course, and treatment advances for these disorders, which are summarized in this article. Recent work on the genetic and environmental risk factors for pediatric MS points to similarities with adult disease. Immunobiological studies for MS suggest a continuum of disease with adult disease; however, both clinical and immunobiological features point to a more inflammatory profile in children.[1,2] Characterizations of the pediatric phenotypes associated with aquaporin-4 (AQP4) antibody–seropositive NMO and myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Chitnis discusses the unlabeled/investigational use of glatiramer acetate, interferon beta, natalizumab, and rituximab for pediatric multiple sclerosis and mycophenolate mofetil for myelin oligodendrocyte glycoprotein antibody–associated disorders and neuromyelitis optica spectrum disorder in children.

KEY POINTS

- Major advances in pediatric demyelinating disease in the past 5 years include improved diagnostic criteria, antibody-based biomarkers, predictors of a multiphasic course, and treatment advances for these disorders. Recent work on the genetic and environmental risk factors for pediatric multiple sclerosis points to similarities with adult disease.
- An important advance in pediatric demyelinating disorders is the recognition that an acute demyelinating syndrome can represent the first attack of not only multiple sclerosis but also neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein (MOG) antibody–associated demyelinating disease, and other multiphasic disorders in children.

have demonstrated diverse phenotypes that differ from adult presentations, which has relevance for both diagnostic and treatment considerations. Recent clinical trials and therapeutic cohort studies in pediatric MS have shed considerable light on the treatment response in this highly inflammatory disease and established new paradigms for clinical trial design and conduct in children with neuroinflammatory disorders.

CLASSIFICATION OF PEDIATRIC CNS DEMYELINATING DISEASES

Pediatric CNS demyelinating diseases are generally classified as either monophasic or multiphasic disorders. However, it is entirely possible that what appears to be a monophasic episode can represent the first attack of a multiphasic disorder. Initial attacks have been termed *acute demyelinating syndromes* or *clinically isolated syndromes* and include optic neuritis, transverse myelitis, and other initial attack demyelinating syndromes. ADEM is another acute demyelinating syndrome; it appears to have a pathophysiology that is distinct from clinically isolated syndromes. In contrast to clinically isolated syndromes, ADEM rarely represents a first attack of MS in children. An important advance is the recognition that an acute demyelinating syndrome can represent the first attack of not only MS but also NMOSD, MOG antibody–associated disease, and other multiphasic disorders in children.[3]

We now have a better understanding of predictors for a multiphasic disease course that can be seen at initial presentation. Identifying the location and symptomatology of the presenting syndrome, as well as the presence of brain lesions, is an important key step both for managing the current attack and for prognostication. Focal lesions in the optic nerve(s) may be unilateral or bilateral and may involve the optic chiasm. Myelitis may be focal or diffuse. The absence of brain lesions in the setting of optic neuritis or myelitis tends to favor a monophasic course. A diffuse or longitudinally extensive transverse myelitis may be seen in monophasic disorders (such as ADEM) and in MS and NMO in children (R. Ameli, MD, and the US Network of Pediatric MS Centers, unpublished data, 2019). The presence of encephalopathy is the hallmark of ADEM. Common presentations of pediatric demyelinating disorders, symptoms, and diagnostic considerations are presented in TABLE 11-1.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

The incidence of ADEM was estimated to be 0.3 to 0.6 per 100,000 per year in two population-based studies.[4,5] The neurologic symptoms of ADEM generally accrue rapidly over a period of a few days.[6] Symptoms include motor or sensory symptoms, ataxia, weakness, optic neuritis or other cranial nerve involvement, seizures, spinal cord syndrome, and impairment of speech. Encephalopathy is a critical component of the ADEM diagnosis.[7] Acute evaluation of ADEM should include a neurologic examination; gadolinium-enhanced MRI of the brain, spinal cord, and orbits; evaluation for urinary retention; and CSF examination to rule out infection, including cell count, protein, lactate, IgG index, and oligoclonal bands (in CSF and serum) in addition to screening for infectious agents, especially herpes simplex virus, Enterovirus, Epstein-Barr virus (EBV), and *Mycoplasma*. Blood work should include white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and AQP4 and MOG antibodies.

The author's practice is to start an infectious workup immediately; once initial tests, including polymerase chain reaction (PCR) for herpes simplex virus,

return as negative, treatment with a 5-day course of IV steroids is started and immediate transition to IV immunoglobulin (IVIg) or plasma exchange is considered in refractory cases. A prednisone taper is generally instituted for 4 weeks, starting at 1 mg/kg/d and halving the dose every 5 days. Typically, neurologic improvement occurs within days following initiation of steroid treatment, and recovery to baseline is generally reached within a few weeks.[8] Longer-term cognitive deficits have been observed involving executive function,

Common Presentations and Diagnostic Considerations of Pediatric Demyelinating Disorders TABLE 11-1

Presentation	Key Symptoms	Diagnostic Testing Considerations	Differential Diagnosis Beyond Demyelinating Syndromes
Optic neuritis	Blurred vision, loss of vision, pain on eye movement, change in color vision	Ophthalmoscopic examination, MRI orbits and brain and cervical-thoracic spine with gadolinium, visual evoked potentials, MOG and aquaporin-4 (AQP4) antibody testing; consider CSF evaluation especially if brain lesions; optical coherence tomography provides measures of retinal damage	Sarcoidosis, Leber hereditary optic neuropathy, vitamin B_{12} deficiency
Transverse myelitis	Subacute-onset arm or leg weakness, sensory changes, sensory level, bowel/bladder retention or incontinence, pain	CSF evaluation; MRI cervical-thoracic spinal cord, urodynamic studies, MOG and AQP4 antibody testing	Spinal cord infarction, arteriovenous malformation, acute flaccid myelitis, human lymphotropic virus type I (HTLV-I) myelopathy, systemic lupus erythematosus, Sjögren syndrome, vitamin B_{12} deficiency
Brainstem syndromes	Cranial nerve involvement, ophthalmoplegia, ataxia, nausea/vomiting	CSF evaluation; MRI brain, cervical-thoracic spine, and orbits; serum and CSF antibody testing for autoimmune encephalitis, including NMDA receptor antibody; serum and CSF AQP4 antibody; serum MOG antibody; GQ1b serum antibody	Systemic lupus erythematosus, antiphospholipid antibody syndrome, brainstem glioma, CLIPPERS, Miller Fisher syndrome
Acute disseminated encephalomyelitis (ADEM)	Encephalopathy, polyfocal neurologic symptoms, diffuse central nervous system lesions	CSF evaluation; MRI brain, cervical-thoracic spine, and orbits; serum and CSF antibody testing for autoimmune encephalitis, including NMDA receptor antibody; serum and CSF AQP4 antibody; serum MOG antibody; magnetic resonance spectroscopy	Herpes simplex virus encephalitis, regional encephalitis/meningitis, central nervous system vasculitis, autoimmune encephalitis, leukodystrophies, lymphoma, glioma, mitochondrial disorders

CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF = cerebrospinal fluid; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging; NMDA = *N*-methyl-D-aspartate.

attention, verbal processing, lowered IQ scores, and behavioral changes, especially in children younger than 5 years of age.[9,10] Rarely, some children will go on to have multiphasic disease, such as MS, NMOSD, or MOG antibody–associated disease; prognostic factors are listed in TABLE 11-2.[11–14]

CLINICALLY ISOLATED SYNDROMES

Clinically isolated syndrome is a general term used for isolated demyelinating syndromes. Clinically isolated syndrome events are heterogeneous; however, several dominant clinical phenotypes exist.

Optic Neuritis

Optic neuritis is one of the most common presentations of acquired demyelinating syndromes in childhood, with an estimated incidence of 0.2 per 100,000 (95% CI, 0.16–0.3) in Canada.[15] In optic neuritis, inflammation of one or both optic nerves leads to visual dysfunction. Unilateral presentation at onset may be followed rapidly by bilateral involvement within a few weeks, or bilateral involvement may occur at onset.[16] Approximately two-thirds of children with optic neuritis who are younger than 10 years of age present with bilateral optic neuritis, whereas most children older than 10 years of age present with unilateral optic neuritis.[11] Pain with eye movement is reported in approximately 50% of pediatric cases and thus does not consistently differentiate inflammatory

TABLE 11-2 Predictors of Multiphasic Demyelinating Disease in Children

Initial Presentation	Predictors of Multiple Sclerosis	Predictors of Neuromyelitis Optica Spectrum Disorder	Predictors of Multiphasic Myelin Oligodendrocyte Glycoprotein–Seropositive Disease
Optic neuritis	Oligoclonal bands in CSF,[4] presence of MRI brain ovoid lesions,[4,11] age >10[11]	Aquaporin-4 (AQP4) antibody in serum or CSF	Persistent serum MOG antibody Persistently elevated titers of MOG antibody
Transverse myelitis	Female gender,[5] presence of MRI brain ovoid lesions,[5] acute partial transverse myelitis[12]	AQP4 antibody in serum or CSF	Persistent serum MOG antibody
Clinically isolated syndrome (all clinical phenotypes)	Female gender,[13] age >10 years,[6] postpubertal status in females,[14] Epstein-Barr virus seropositivity,[6] low vitamin D levels,[6] multifocal/polyfocal symptoms at onset,[13] fulfillment of 2010 McDonald MRI criteria, presence of brain lesions	AQP4 antibody in serum or CSF	Persistent serum MOG antibody
Acute disseminated encephalomyelitis (ADEM)	Fulfillment of 2010 McDonald criteria, Epstein-Barr virus seropositivity, low vitamin D levels, age >11 years, postpubertal status	AQP4 antibody in serum or CSF	Persistent serum MOG antibody

CSF = cerebrospinal fluid; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging.

from noninflammatory optic neuropathies in children. Other symptoms include loss of or decreased visual acuity, decreased color vision, and visual field deficits. Evaluation should include an ophthalmologic examination and an MRI of the orbits and brain. Spine MRI should be included if the patient has any myelopathic symptoms. Visual evoked potential testing and optical coherence tomography may provide additional quantitative measures of optic nerve and retinal damage, respectively. Testing should include serum MOG and AQP4 antibodies.

Acute management includes a course of IV steroids and, in refractory cases, IVIg or plasma exchange. Ophthalmologic monitoring and institution of visual aids are important in the management of children with optic neuritis. Recovery, as measured by visual acuity, is generally good in children with optic neuritis.[17] Optic neuritis may occur in isolation or as an attack (or first attack) of MS, NMOSD, ADEM, or MOG antibody–associated disease. Up to one-third of children with optic neuritis will have a second attack, signifying the onset of MS or NMOSD. Some children will have a relapsing MOG antibody–associated disease. Prognostic factors for multiphasic disease are listed in **TABLE 11-2**.

Transverse Myelitis

The incidence of acute transverse myelitis in children younger than 16 years of age is 2 per 10^6 children per year, and acute transverse myelitis accounts for one-fifth of children experiencing a first demyelinating attack.[15,18] Pediatric transverse myelitis accounts for 20% of all cases of demyelinating disease in children and has a bimodal age distribution, with toddlers and adolescents most affected.[19] Although a slight predominance of males exists with acute transverse myelitis, a female preponderance is seen in adolescents and is associated with relapsing diseases, including MS and NMOSD. Symptoms can include weakness, numbness, urinary incontinence or retention, and myelopathic pain. Occasionally, respiratory symptoms and autonomic dysfunction may occur. Myelopathic symptoms are a neurologic emergency, and prompt diagnosis and treatment may lessen the severity of neurologic sequelae. Emergent spinal imaging with contrast-enhanced pan-spine MRI rapidly discerns alternative etiologies requiring surgical intervention. Testing should include serum MOG and AQP4 antibodies. CSF evaluation will aid in excluding infectious etiologies. CSF protein and white blood cell counts may be normal in up to 50% of children with transverse myelitis.

Acute treatment includes IV steroids urgently and plasma exchange or IVIg in refractory cases. Bladder ultrasound and catheterization should be considered for urinary retention. Children with acute transverse myelitis have a better outcome than adults, with 50% making a complete recovery by two years.[19,20] Mortality is associated with respiratory failure and high cervical cord lesions.[19,21] Sensory issues and bladder dysfunction (15% to 50%) are the most common sequelae. Approximately one-third of patients require walking aids, and 10% to 20% of children lose mobility or bladder function.[22]

Other Clinically Isolated Syndromes

Clinically isolated syndromes may affect any one area or multiple areas of the CNS. A multifocal or polyfocal onset generally is more predictive for MS.

Brainstem syndromes may occur as monophasic disorders or part of multiphasic syndromes.

Predictors of a Multiphasic Disease Course

Several studies have identified risk factors for MS in children presenting with a clinically isolated syndrome, including CSF profiles with pleocytosis, EBV-positive serostatus, obesity, low vitamin D levels, and the presence of T2 lesions on brain MRI. Age older than 11 and postpubertal status at the time of a clinically isolated syndrome also increase the risk for MS. At present, investigations into NMOSD and MOG-seropositive disease beyond antibody presence are limited. The presence of AQP4 antibodies predicts multiphasic NMOSD regardless of clinical presentation, and patients with AQP4 seropositivity should be treated with preventive immunotherapy because of the significant disability associated with attacks. The presence of MOG antibodies at initial attack does not necessarily predict multiphasic disease. Several studies have suggested that persistent MOG antibodies at follow-up time points are associated with multiphasic disease, but definitive studies to determine the specific timeline and retesting parameters are needed.[23,24]

MULTIPLE SCLEROSIS

Multiple sclerosis is an immune-mediated demyelinating disorder of the CNS with typical onset in young adulthood. Over the past 15 years, there has been a growing recognition that MS occurs in children and adolescents.

Epidemiology and Demographics

Pediatric MS is defined as MS with an onset before age 18. The cutoff age varies, with some studies using age 16; however, for practical purposes, most studies (including treatment trials) use age 18 as the cutoff.[25] Case reports of MS in children as young as 2.5 to 3 years of age exist, but the vast majority of patients are age 11 or older, with a mean age at onset of 15 at first symptom in the US Network of Pediatric MS Centers.[25]

Studies in large MS cohorts have consistently found that approximately 3% to 5% of all patients with MS are pediatric at the time of first symptoms.[26] Pediatric MS cases are increasingly being diagnosed in many world regions, particularly in countries distal to the equator. A study from California estimated the incidence of pediatric MS as approximately 0.51 per 100,000 insured persons younger than 18 years of age,[5] while a German study estimated the incidence as 0.64 per 100,000 between 2009 and 2011.[15,18] Children with MS have a more diverse ethnic background than adult patients with MS,[26] and one study in a large US cohort found that 40% of patients were first-generation Americans.[25]

Risk Factors

The risk factors for pediatric MS are largely similar to the risk factors for adult MS and include the environmental risk factors of low vitamin D status,[13] exposure to cigarette smoking,[17] obesity,[6,27] and remote EBV infection. Puberty is an important transition period for the clinical onset of pediatric MS, with 80% to 85% of children being peripubertal or postpubertal at the time of first symptoms in a large US cohort.[27]

The genetic susceptibility factors largely replicate those observed in adult MS, with the major histocompatibility complex locus HLA-DRB1*1501

being the major contributor, as demonstrated in several studies of pediatric MS.[2,16,28]

Pathophysiology

MS is an autoimmune disease that is mediated by a variety of immune cells, likely in response to a CNS antigen.[29] T lymphocytes and B lymphocytes play a key role in MS immunopathogenesis, recruiting macrophages and dendritic cells in the peripheral immune system to participate in antigen presentation and amplification of a proinflammatory milieu. CNS immune cells, including microglia and astrocytes, are activated early and increasingly in the progressive stages of disease.[30] Pediatric MS likely represents MS disease in its earliest stages. Two studies have demonstrated increased activation of CD4+ T memory cells in pediatric patients with MS.[1,28] Increased CD4+ T-cell responses to myelin peptides and increased proportions of T_H17 central memory T cells were found in untreated pediatric patients with MS compared to healthy children and adults with MS.[1] Another group found increased proportions of memory cells and fewer recent immature T cells or thymic emigrants in children with MS in comparison to healthy children.[28] This study also found that the suppressive function of FOXP3 regulatory cells was impaired in pediatric patients with MS. Increased levels of proinflammatory B cells and fewer regulatory B cells are found in pediatric MS.[2]

The pathology of MS in adults demonstrates activated T cells and macrophages/microglia. Few studies of the pathology of pediatric MS have been conducted. A systematic analysis of 19 pediatric patients with MS showed a 50% increase in acute axonal damage in pediatric patients compared to adult patients with MS. This study found an inverse relationship of age at biopsy and acute axonal damage as well as an increase in activated macrophages and microglia in pediatric patients with MS.[31]

Clinical Presentation

Pediatric-onset MS has clinical features similar to adult MS overall; however, the pediatric disease is characterized by a more inflammatory disease course as well as important age-associated symptoms.

ACUTE ATTACKS. More than 95% of pediatric patients with MS present with the relapsing-remitting form of MS. In general, children with MS experience 2 to 3 times as many relapses as adult patients with MS,[32,33] reflecting a continuum in the inverse relationship of age and relapse rate.[32] Types of relapses or attacks in pediatric MS include optic neuritis, myelitis, brainstem attacks, and cerebral attacks. These can affect vision, cognition, motor function, sensation, and bladder/bowel function and cause pain and spasticity.[34] The clinical course and attack types vary from patient to patient.[34] In general, children tend to recover better from attacks than adults[17]; however, given the higher attack rate, pediatric patients with MS can still accrue significant disability in later life. Children with MS may also experience subacute or chronic symptoms of fatigue, depression,[35] and anxiety, which may appear or worsen with attacks or appear independently. Cognitive deficits may occur in the context of attacks or chronically.

DISABILITY ACCRUAL. In general, with equal disease durations, disability accrual as measured by the Expanded Disability Status Scale (EDSS), which focuses on

KEY POINTS

- Several studies have identified risk factors for multiple sclerosis in children, including CSF profiles with pleocytosis, Epstein-Barr virus–positive serostatus, obesity, low vitamin D levels, and the presence of T2 lesions on brain MRI. Age older than 11 and postpubertal status at the time of a clinically isolated syndrome also increase the risk for multiple sclerosis.
- Puberty is an important transition period for the clinical onset of pediatric multiple sclerosis, with 80% to 85% of children being peripubertal or postpubertal at the time of first symptoms in a large US cohort.
- In general, children with multiple sclerosis experience 2 to 3 times as many relapses as adult patients with multiple sclerosis, reflecting a continuum in the inverse relationship of age and relapse rate.
- Types of relapses or attacks in pediatric multiple sclerosis include optic neuritis, transverse myelitis, brainstem attacks, and cerebral attacks.

locomotor disability, is slower in a child or adolescent with MS compared to an adult patient with MS.[36,37] Poor prognostic features in pediatric MS include a short interval (less than 1 year) between the first two demyelinating episodes, incomplete recovery after the first attack, and a progressive disease course.[37]

COGNITIVE DEFICITS. Between one-third and two-thirds of pediatric patients with MS may have significant cognitive deficits, including issues with information processing and processing speed, memory deficits, executive dysfunction, and lowered IQs, as well as deficits in social cognition.[38,39] Evaluation and monitoring by a neuropsychologist shortly after diagnosis is important to evaluate for the presence of cognitive dysfunction. A 504 plan or individualized education program (IEP) should be instituted to address cognitive deficits and ensure appropriate programming at school.

Diagnostic Criteria

The current diagnostic criteria for pediatric MS from the 2012 International Pediatric MS Study Group[7] are based on the 2010 McDonald criteria for adult MS and were validated in children older than 11 years of age. However, these diagnostic criteria may be nonspecific, and further work is required to differentiate pediatric MS from the emerging entities NMOSD and MOG antibody–associated disease.

Treatment and Management

The management of pediatric MS is subcategorized into acute attack management, attack prevention, symptomatic therapy, and rehabilitation.

GENERAL APPROACH. Immunotherapy is generally used for acute attacks to mitigate attack severity and duration. Disease-modifying therapies are

TABLE 11-3 Options for Disease-Modifying Treatments in Pediatric Multiple Sclerosis

Disease-Modifying Treatment	Level of Evidence	Potential Side Effects
Fingolimod (oral)	US Food and Drug Administration (FDA) approved for pediatric multiple sclerosis (2018) based on phase 2 randomized controlled trial[40]	Bradycardia, macular edema, lymphopenia, infections, seizures (rare)
Interferon beta-1a and interferon beta-1b (IM or subcutaneous injections)	European Medicines Agency approval for children >12 years of age; prospective and retrospective observational studies[44,45]	Injection site reactions, flulike symptoms, depression
Glatiramer acetate (subcutaneous injections)	Retrospective observational studies[8]	Injection site reactions, postinjection tachycardia
Natalizumab (IV infusion)	Prospective observational studies[9,10]	Progressive multifocal leukoencephalopathy, infusion reactions
Rituximab (IV infusion)	Retrospective observational studies[46–48]	Infusion reactions, infections, hypogammaglobulinemia

IM = intramuscular; IV = intravenous.

strongly recommended once a diagnosis of pediatric MS has been established. The primary effect of disease-modifying therapies is to reduce relapse frequency.

ACUTE ATTACKS. Treatment of an acute attack with immunotherapy reduces the degree and impact of inflammation on the CNS. Methylprednisolone, IVIg, and plasma exchange have been used for acute attacks in pediatric MS. IV methylprednisolone is generally used as first-line relapse treatment at a dose of 30 mg/kg/d, with a maximum of 1000 mg daily for 5 to 7 days. If response to IV methylprednisolone is minimal or if the patient has severe symptoms upon presentation, IVIg administered at 2 g/kg divided over 2 to 5 days or plasma exchange is appropriate. Upon completion of IV methylprednisolone in a first attack, the author uses an oral steroid taper starting at 1 mg/kg/d up to 60 mg/d maximum dosing. The author then tapers the prednisone by reducing the dose by half every 5 days for a total of 4 weeks starting on the first day after completion of IV steroids. The author generally does not use prednisone tapers for subsequent attacks in pediatric patients with MS to reduce the exposure to long-term steroids.

DISEASE-MODIFYING THERAPIES. Over the past 20 years, significant advances have been made in MS therapeutics, with regulatory approval by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for more than 15 therapies for adult MS. In 2018, fingolimod was approved by the FDA for use as first-line treatment in children with MS aged 10 to 17; it has received preliminary approval by the EMA as second-line treatment based on the results of the PARADIGMS (Safety and Efficacy of Fingolimod in Pediatric Patients With Multiple Sclerosis) clinical trial.[40] Interferon beta and glatiramer acetate have received limited approval from the EMA for use in children 12 years of age or older based on open-label or retrospective studies.[41] Safety data for interferon beta-1a subcutaneously 3 times a week for children older than 2 years of age are included in the European label. Other treatments studied in open-label or retrospective studies in pediatric MS include natalizumab and rituximab. Prospective clinical trials of dimethyl fumarate, teriflunomide, and alemtuzumab for pediatric MS are ongoing, with results anticipated in 2019–2020.[42,43] A summary of studies of disease-modifying therapies used in pediatric MS and their potential side effects is found in TABLE 11-3.[44–48]

FINGOLIMOD. Fingolimod is an oral sphingosine-1-phosphate immunomodulator that primarily inhibits the egress of central memory T cells from lymph nodes. It is approved by the FDA and EMA for use in adult MS and received FDA approval for pediatric MS in 2018 based on the result of the PARADIGMS clinical trial.[40] This study demonstrated an 82% reduction in annualized relapse rate in patients treated with fingolimod compared to those treated with interferon beta-1a. Fingolimod is dosed at 0.5 mg orally daily in pediatric patients with MS who weigh more than 40 kg (88 lb) and at 0.25 mg in patients who weigh 40 kg (88 lb) or less. First-dose observation for 6 hours is required to monitor for bradycardia. Monitoring and pretesting for macular edema, varicella titers, hepatic enzymes, and lymphocyte counts are recommended.

KEY POINTS

- Between one-third and two-thirds of pediatric patients with multiple sclerosis may have significant cognitive deficits, including issues with information processing and processing speed, memory deficits, executive dysfunction, and lowered IQs, as well as deficits in social cognition.
- In 2018, fingolimod was approved by the US Food and Drug Administration for use as first-line treatment in children with multiple sclerosis aged 10 to 17; it has received preliminary approval by the European Medicines Agency as second-line treatment based on the results of the PARADIGMS clinical trial.

INTERFERON BETA. Interferon beta is a type I interferon with diverse effects on lymphocytes and innate immune cells approved for use in adult MS, with several different forms and dosing schedules. Interferon beta use in pediatric MS was compared with a control group in two randomized unblinded studies.[49,50] Both studies demonstrated a reduction of relapses and new MRI T2 lesions and delayed disability accumulation in comparison to the untreated group.[49,50] The retrospective REPLAY (Retrospective Cohort Study of Rebif Use in Pediatric Multiple Sclerosis Subjects) phase 4 study is the largest cohort study to be conducted in pediatric MS; it evaluated the safety profile of interferon beta-1a in 307 pediatric patients with MS treated with 22 mcg or 44 mcg interferon beta-1a.[44] This study reported adverse events (less than 2%) including allergic reactions (1.6%), epilepsy and convulsive disorders (1.6%), thyroid dysfunction (1.0%), autoimmune disorders (0.7%), osteogenic disorders (0.7%), and serious infections (0.7%).

No pharmacodynamic/pharmacokinetic studies of interferon beta and glatiramer acetate have been conducted in pediatric MS. In general, it is recommended to initiate interferon beta therapy at 25% to 50% of the adult dose and then titrate up to the full adult dose as tolerated, especially for children older than 12 years of age with a body weight greater than 30 kg (66 lb).

GLATIRAMER ACETATE. Glatiramer acetate is a copolymer of peptides administered by subcutaneous injection and is approved for use in adult MS. Glatiramer acetate was evaluated in a retrospective cohort of seven pediatric patients with MS with favorable clinical outcomes and safety profile.[8] A case of acute hepatotoxicity in an adolescent treated with glatiramer acetate was reported in 2013.[51] The author generally initiates and uses full adult dosing in pediatric patients with MS.

NATALIZUMAB. Natalizumab is a humanized monoclonal antibody that targets the α4 subunit of α4β1 integrin and is approved for the treatment of adult MS. Several prospective observational studies have described the effect of natalizumab in pediatric MS.[9,10] The largest study to date is the Italian study cohort of 101 patients (69 females) with a mean age of MS onset of 12.9 ± 2.7 years and mean age at natalizumab initiation of 14.7 ± 2.4 years.[10] Mean treatment duration was 34.2 ± 18.3 months. The annualized relapse rate decreased from 2.3 ± 1.0 in the year prior to 0.1 ± 0.3 (P=.001) after natalizumab initiation. Disability scores stabilized or improved, and MRI lesion accrual was reduced. No relevant adverse events were reported in this study.[10] The frequency of JC virus antibodies was reported in these studies as 38% to 39%,[10,52] which is lower than that reported in adults (57%) but higher than the rate in non-MS pediatric populations. Mild to moderate side effects can include infections and hypersensitivity. The author generally doses at 6 mg/kg IV infusions monthly to a maximum adult dose of 300 mg per dose. JC virus antibodies should be monitored every 6 months at minimum, and, if seroconversion to a positive test, then consider switching to an alternate therapy. Extensive studies in adult patients have demonstrated an increased risk of progressive multifocal leukoencephalopathy (PML) in patients who are JC virus positive compared to patients who are JC virus negative. Risk factors of prolonged duration on natalizumab as well as prior immunosuppression are associated with increased risk of PML in the setting of seropositive JC virus

testing. For more information on risk factors for PML, refer to the article "Monitoring, Switching, and Stopping Disease-Modifying Therapies" by Robert H. Gross, MD, and John R. Corboy, MD, FAAN,[53] in this issue of *Continuum*.

RITUXIMAB. Rituximab is a monoclonal antibody that targets CD20+ B lymphocytes and reduces clinical and magnetic resonance activity in adult patients with MS[54] and in patients with NMO. A small retrospective case series of 11 patients, including three pediatric patients with MS, reported stabilization of disease.[55] A detailed discussion of rituximab dosing is included in the NMO treatment section later in this article.

CHEMOTHERAPEUTICS. Other treatments historically used in pediatric MS include the chemotherapeutic agents cyclophosphamide and mitoxantrone. However, because of their significant toxicity, these agents are now rarely used. A retrospective study of cyclophosphamide use in 17 pediatric patients with MS found a decreased relapse rate and stabilization of disability scores.[56] However, side effects included nausea and vomiting in 15 of 17 patients, alopecia in 10 of 17 patients, menstrual irregularities in five patients, anemia in 10 patients, and thrombocytopenia in five patients. A case series of four pediatric patients with MS who received mitoxantrone for highly active relapsing-remitting MS followed for 3.8 to 18 years reported laboratory abnormalities in all patients.[57]

MANAGEMENT CONSIDERATIONS. The author monitors disease-modifying therapy response clinically and with annual MRIs.[58] Annual MRIs may be conducted with gadolinium if a new relapse is suspected. Noncontrast MRIs may be conducted for routine monitoring to reduce the long-term exposure to gadolinium, especially since linear forms of gadolinium have been noted to accumulate in brain regions, although the clinical effects of this accumulation are unclear.[59] Adherence to medications may be challenging, particularly in adolescents, in the setting of miseducation about the expectations for disease-modifying therapies, unaddressed side effects, busy family schedules, and travel/college.[60]

If evidence of intractable nonadherence, intolerance, or treatment failure is present, switching treatments should be considered.[61] Treatment failure may be defined as one to two new lesions or attacks occurring within a 12-month period. The tolerance for new lesions or attacks versus switching and the risks and benefits of both should be discussed between the neurologist and family.

Contraceptives should be considered in sexually active teenagers. This is an important conversation to have before treatment initiation, since many disease-modifying therapies may have adverse effects on a pregnancy and some are teratogens. For more information on the use of disease-modifying therapies in pregnancy, refer to the article "Pregnancy and Family Planning in Multiple Sclerosis" by Annette M. Langer-Gould, MD, PhD,[62] in this issue of *Continuum*. Symptomatic treatments should be considered as needed and may include antidepressants, fatigue medications, and bladder management medications.[63]

KEY POINT

- **Adherence to disease-modifying therapy may be challenging, particularly in adolescents, in the setting of miseducation about the expectations for disease-modifying therapies, unaddressed side effects, busy family schedules, and travel/college.**

NEUROMYELITIS OPTICA SPECTRUM DISORDER

NMOSDs are distinct from MS and are characterized by predominant optic neuritis and transverse myelitis attacks. The majority of patients with NMOSDs have AQP4 antibodies.[64,65]

Epidemiology and Demographics

Up to 3% to 5% of cases of NMOSD have pediatric onset.[66] The overall incidence of NMOSD in children and adults ranges from 0.05 to 4 per 100,000 per year, and prevalence ranges from 0.52 to 4.4 per 100,000.[67] In Japan, the incidence of pediatric NMOSD was reported as 0.06 per 100,000 children.[68] Patients as young as 16 months of age have been reported; however, the typical age of onset is 10 to 12 years.[3] Females are more likely to be affected than males at a ratio of 3:1 in the pediatric population but up to 9:1 in adults.[69]

Clinical Features

Pediatric NMO is a relapsing disease. A mean of 1.8 attacks per year during the first 2 years of disease was noted in a US study of 38 children with NMO.[3] As described in case series from the United States and United Kingdom, the most common presenting symptoms are unilateral or bilateral optic neuritis, transverse myelitis, and brainstem/cerebellar syndromes.[3,70] Vomiting and intractable hiccups are observed in area postrema syndrome and can be initial symptoms of NMOSD.[71] ADEM and seizures have also been described as presenting attacks of NMO.[72] As compared to MS or ADEM, pediatric patients with NMOSD have a higher EDSS score within 2 years of disease onset (2.25 versus 1.28 and 0.5, respectively).[3]

Laboratory Testing

Approximately 65% of pediatric patients with NMOSD are AQP4 antibody seropositive; however, seropositivity may not occur at the time of the initial attack but up to 4 years later. Therefore, serial testing is recommended for highly suspicious cases.[3] Although rare cases of AQP4 antibody in the CSF with negative serum testing have been reported in adults, this was not observed in a large pediatric NMOSD case series.[3]

TABLE 11-4

Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder From the 2015 International Panel for Neuromyelitis Optica Diagnosis[a]

Aquaporin-4 (AQP4) Antibody Positive

- **One core clinical characteristic, positive AQP4 antibodies, and exclusion of alternative diagnoses**
  - Core clinical characteristics include optic neuritis, acute myelitis, area postrema syndrome of hiccups or nausea, symptomatic narcolepsy or acute diencephalic clinical syndrome with MRI diencephalic lesions typical of neuromyelitis optica (NMO) spectrum disorder, acute brainstem syndrome, and symptomatic cerebral syndrome with NMO spectrum disorder–typical brain lesions

AQP4 Antibody Negative or Unknown AQP4 Status

- **Two core clinical characteristics that meet all the following requirements:**
  - One core clinical characteristic must include optic neuritis, acute myelitis with longitudinally extensive transverse myelitis, or area postrema syndrome
  - Dissemination in space of two or more core clinical characteristics
  - Fulfillment of additional MRI requirements

MRI = magnetic resonance imaging.
[a] Data from Wingerchuk, DM, et al, Neurology.[65]

Approximately 10% to 15% of cases of pediatric NMOSD are MOG antibody seropositive, which has implications for both prognosis and treatment, and they may be considered separately from AQP4 antibody–seropositive cases. Dual seropositivity has not been reported in children. Approximately 15% of pediatric NMOSD cases are both AQP4 and MOG antibody seronegative. Coexisting autoimmune diseases, including systemic lupus erythematosus, Sjögren syndrome, and autoimmune thyroid disease, are observed with NMOSD and were reported in 16% in a multicenter US study,[3] 9% of patients in a Brazilian study,[73] and 42% in a study from Mayo Clinic in children who were AQP4 seropositive.[72] Testing for these comorbid diseases should be considered on a case-by-case basis.

CSF testing in pediatric NMOSD typically shows pleocytosis with a lymphocyte predominance. CSF leukocyte counts vary between 100 cells/mm^3 and 200 cells/mm^3 and are typically higher than in pediatric MS or ADEM.[3] Among the CSF leukocytes, the lymphocyte percentage is approximately 75%, while pediatric MS typically has 90% lymphocytes. Elevated IgG index and positive oligoclonal band testing was observed in 30% of pediatric patients with NMO.[3]

KEY POINTS

- Up to 3% to 5% of cases of NMOSD have pediatric onset. The overall incidence of NMOSD in children and adults ranges from 0.05 to 4 per 100,000 per year, and prevalence ranges from 0.52 to 4.4 per 100,000. In Japan, the incidence of pediatric NMOSD was reported as 0.06 per 100,000 children.

- Approximately 65% of pediatric patients with NMOSD are aquaporin-4 antibody seropositive; however, seropositivity may not occur at the time of the initial attack but up to 4 years later. Therefore, serial testing is recommended for highly suspicious cases.

Pathophysiology

AQP4-seropositive patients with NMO have pathologic features that are distinct from those of MS. The immune attack is focused on the astrocytes, with secondary damage to myelin and axons; a variety of immune cells, including T cells, B cells, plasma cells, and neutrophils, are found in NMO lesions.[74,75] Complement and antibody deposition is also found in lesions.

Diagnostic Criteria

The most recent diagnostic criteria for NMOSD were published by the International Panel for NMO Diagnosis in 2015.[65] These diagnostic criteria classify patients as AQP4 antibody positive and AQP4 antibody negative (TABLE 11-4) and were found to detect pediatric NMO cases with a 97% sensitivity compared to earlier diagnostic criteria.[3]

Treatment Options

Management of NMOSD includes treatment of acute attacks, preventive therapy, and symptomatic management. Limited Class I evidence is available for treatments for both pediatric and adult NMOSD.

ACUTE ATTACKS. Treatment for an acute attack with immunotherapy reduces the degree and impact of inflammation on the CNS in patients with NMO. Aggressive management of relapses is recommended in pediatric NMO since these patients accrue disability with attacks and have higher disability rates than pediatric patients with MS.[3] The author's practice is to initiate IV methylprednisolone at a dose of 20 mg/kg to 30 mg/kg (up to 1 g/d) for 5 days. If no evidence of improvement is seen or symptoms worsen, then five cycles of plasma exchange should be started immediately.

PREVENTIVE THERAPY. Preventive or disease-modifying therapy is used to decrease the risk of relapses and associated disability. Disease-modifying treatment options used in adult and pediatric NMOSD include mycophenolate mofetil, rituximab, and azathioprine.

MYCOPHENOLATE MOFETIL. Mycophenolate mofetil has been shown to reduce relapse rate and stabilize disability scores in adults with NMOSD.[76–78] A retrospective study also demonstrated the efficacy of mycophenolate mofetil in children with NMOSD.[77] Mycophenolate mofetil is generally dosed based on body surface area at 600 mg/m^2 2 times a day to a maximum dose of 1000 mg 2 times a day (2000 mg maximum per day). To improve tolerability, an initial dose titration schedule should be followed: one-fourth of 600 mg/m^2 2 times a day for 1 week; then one-half of 600 mg/m^2 2 times a day for 1 week, then three-fourths of 600 mg/m^2 2 times a day for 1 week, then 600 mg/m^2 2 times a day. Side effects of this drug include gastrointestinal symptoms (nausea, diarrhea, abdominal pain), dizziness, rash, increased risk of infection, and fatigue.[76,79] Rarely, cases of PML have been associated with mycophenolate mofetil.[80]

RITUXIMAB. Rituximab is a chimeric monoclonal anti-CD20 antibody that depletes B cells. It has been used for both adults[81,82] and children with NMOSD[83] as well as for other autoimmune diseases. One retrospective study in 16 pediatric patients found a reduction in relapse rate with rituximab.[46] B-cell repopulation was associated with recurrence of relapse; however, a wide range of time to B-cell repopulation was noted, with a mean of 6.8 months.[46] Therefore, B-cell repopulation times should be initially monitored monthly starting at 3 months, and redosing times should be individualized to pediatric patients. The dosing protocol for children is 375 mg/m^2 every week (maximum total loading dose of 2 g) for 4 weeks and then 750 mg/m^2 (maximum total dose of 1 g) at approximately 6 months or earlier upon B-cell return.[48] Side effects of rituximab include nausea, vomiting, infusion reactions, and risk for infections, including hepatitis B virus reactivation.[84] PML has been rarely associated with rituximab in the treatment for lymphoma.[85]

AZATHIOPRINE. Azathioprine, a purine analogue, interferes with DNA synthesis in proliferating B cells and T cells. Azathioprine at a dose of 2 mg/kg/d to 3 mg/kg/d decreases relapse rates in adults and children with NMOSD.[86,87] However, tolerability issues were noted in children. Side effects include nausea, elevated liver function tests, diarrhea, severe leukopenia, rash, and hypersensitivity reactions. Lymphoma is a rare side effect.[86]

MEDICATIONS TO AVOID IN NEUROMYELITIS OPTICA SPECTRUM DISORDER. Some of the disease-modifying therapies used in MS are either ineffective for or exacerbate NMOSD, demonstrating the need for accurate diagnosis. Increased relapses have been associated with the use of interferon,[88,89] glatiramer acetate,[90] dimethyl fumarate,[91] alemtuzumab,[92] and natalizumab.[93–95]

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY–ASSOCIATED DEMYELINATING SYNDROMES

MOG antibody–associated demyelinating syndromes are a recently recognized group of syndromes that predominantly occur in children.

Epidemiology and Demographics

Since cell-based assays became available, anti-MOG antibodies have been reported in the serum of 18% to 35% of children with an acute demyelinating syndrome.[96,97]

More females are affected than males at a ratio of approximately 3:1. The disease occurs throughout the age spectrum but is more common in children.

Clinical Features

Children with MOG antibodies in the serum present with a variety of clinical syndromes that include, but are not limited to, ADEM, multiphasic ADEM, optic neuritis, ADEM followed by optic neuritis, recurrent optic neuritis, encephalitis or meningitis (often associated with seizures), transverse myelitis, and NMOSD.[96–98] The phenotype seems to follow an age-related spectrum, with ADEM and optic neuritis being the most common presentations in children, while NMO and transverse myelitis are the most common in adults (**CASE 11-1**). Rarely, cases of typical MS have been associated with MOG antibodies. Other features of MOG-seropositive disease are elevated CSF lymphocyte counts and elevated neutrophil counts.[97] Brain lesions from MOG-seropositive syndromes have been associated with acute inflammation with demyelination and relative preservation of astrocytes.[99] Occasionally MOG seropositivity has been observed in association with other CNS autoimmune syndromes, including *N*-methyl-D-aspartate (NMDA) receptor antibody–associated encephalitis.[100]

Approximately 50% of cases follow a relapsing course.[101] Of note, relapses may occur within a few weeks or more than 10 years after the initial attack. At present, data on which patients are at highest risk of relapse are limited. MOG-seropositive ADEM in children seems to follow a monophasic course in the majority of patients. Generally, demonstration of new MRI lesions or a new relapse indicates a relapsing course and warrants longer-term immunomodulatory treatment.

Laboratory Testing

MOG antibody testing has now been optimized with a cell-based assay expressing a short-length MOG intracellular chain, offering increased sensitivity and specificity compared to other methods.[102] The MOG antibody is most often detected in the serum and rarely in the CSF. The current consensus is that serum testing has the highest yield. The presence of antibody is usually detected at the time of acute inflammation and may decrease with time or with immunomodulatory therapy.[103] In some cases, the antibody is transient, while in other cases, the antibody persists. The transient detection of anti-MOG antibodies is more frequent in children at the onset of ADEM, optic neuritis, and relapsing optic neuritis, and anti-MOG positivity predicts a non-MS disease course.[23,104] The persistence of anti-MOG antibodies has been associated with a relapsing course, although fewer than 10% of pediatric patients with classic features of MS have detectable anti-MOG antibodies.[104]

Diagnostic Criteria

Diagnostic criteria for MOG antibody–associated demyelinating syndrome have been suggested by several groups but have not been fully validated.[104] Ultimately, MOG antibody–associated demyelinating syndrome needs to be reconciled with existing MS and NMOSD criteria, and efforts to comprehensively evaluate clinical presentations, MRI features, and treatment response of MOG antibody–associated demyelinating syndrome and the similarities to and differences from MS and NMOSD are under way.

KEY POINTS

- Since cell-based assays became available, anti–MOG antibodies have been reported in the serum of 18% to 35% of children with an acute demyelinating syndrome.
- MOG antibody testing has now been optimized, offering increased sensitivity and specificity compared to other methods. The MOG antibody is most often detected in the serum and rarely in the CSF. The current consensus is that serum testing has the highest yield.

Treatment Options

The management of MOG antibody–associated demyelinating syndrome can be divided into treatment of acute attacks and attack prevention.

ACUTE ATTACKS. Acute attacks generally respond to a 3- to 7-day course of methylprednisolone or other high-dose IV steroids. Rebound attacks or worsening symptoms have been described with prednisone tapers, and debate exists regarding the duration of prednisone taper. Rebound attacks in this setting may indicate a relapsing disease course, warranting longer-term treatment. The author has used periodic IVIg in the case of prednisone-dependent worsening, 1 g/kg for one to two doses (if two doses, then give 2 days apart) every 4 to 8 weeks if symptoms return. Plasma exchange has been used in some cases with severe attacks that do not respond to steroids or IVIg.

CASE 11-1

A 15-year-old girl presented to the emergency department with 1 week of worsening eye pain and, over the past 2 hours, complete loss of vision in her left eye. Her past medical history was notable for headaches with onset in the past 2 months.

Neurologic examination showed complete blindness in the left eye, left optic disc edema, a left afferent pupillary defect, and limited upgaze in both eyes. Vision in her right eye was 20/20. The neurologic examination was otherwise normal. MRI demonstrated left optic nerve enhancement but no brain lesions. Her CSF showed a leukocyte count of 84 cells/mm^3 with 80% lymphocytes and negative oligoclonal bands. She received 3 days of IV methylprednisolone (1 g/d) followed by 14 days of oral prednisone. She had immediate improvement of ocular pain and slow improvement of vision.

One week after her final dose of prednisone, she developed loss of vision in her right eye along with pain. She again presented to the emergency department, where she was able to count fingers in both eyes. Examination demonstrated right optic disc edema and left optic atrophy.

Repeat MRI 1 month later demonstrated diffuse enhancement of the optic nerves bilaterally (FIGURE 11-1A). Full-spine MRI showed no lesions. She received a 5-day course of IV methylprednisolone.

Six months later, she presented with an attack of right facial weakness, dysarthria, clumsiness and weakness of her right hand, gait ataxia, and bilateral pallor of the optic discs. MRI showed multiple new enhancing foci in both the white and gray matter of the brain (FIGURE 11-1B). Serologic testing demonstrated myelin oligodendrocyte glycoprotein (MOG) antibodies. Aquaporin-4 antibody testing was negative. She was treated with 5 days of IV steroids followed by a 4-week prednisone taper and was started on mycophenolate mofetil 750 mg 2 times a day. She had no further episodes over 1.5 years of follow-up.

PREVENTIVE THERAPY. For relapsing cases of MOG antibody–associated demyelinating syndrome, mycophenolate mofetil and rituximab are the most commonly used immunomodulatory treatments, with approximately 50% efficacy.[96,105] Azathioprine has also been used in MOG-seropositive patients who meet diagnostic criteria for NMOSD.[106]

CONCLUSION

Much progress has been made over the past 10 years in pediatric demyelinating diseases. The diverse spectrum of pediatric demyelinating disorders, including monophasic and multiphasic forms, is now better understood (FIGURE 11-2). The identification of MOG and AQP4 antibodies in children has been a major advance, which now allows for appropriate treatment and management of these disorders. In the past 5 years,

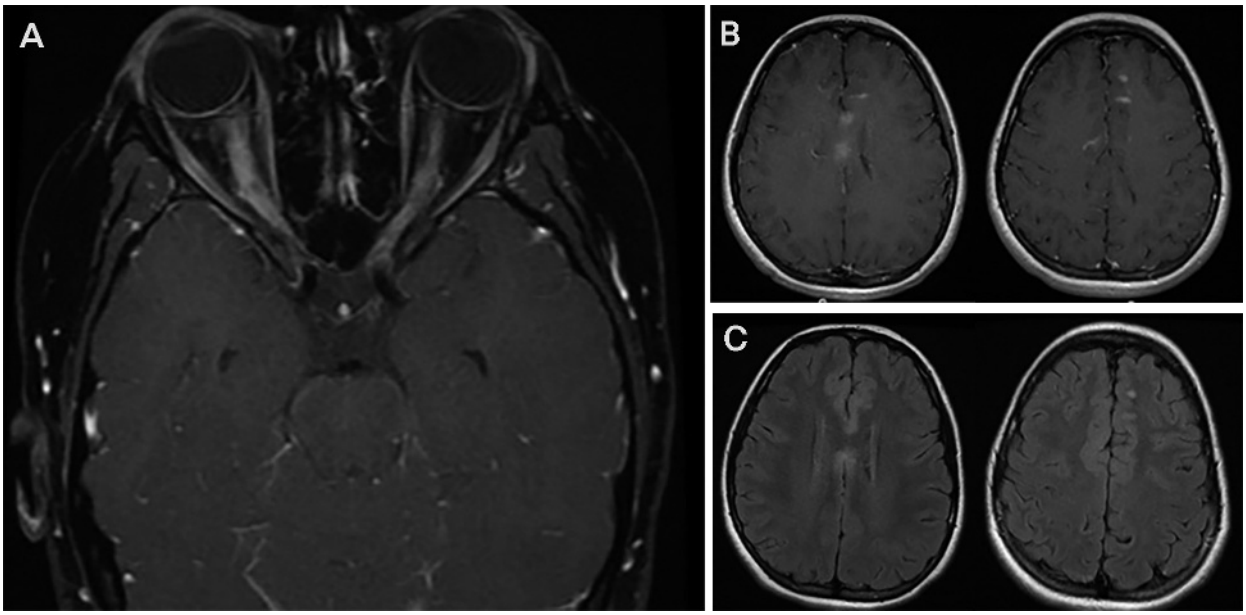

FIGURE 11-1

Imaging of the patient in CASE 11-1. *A*, Axial postcontrast T1-weighted MRI showing bilateral optic neuritis. *B*, Axial postcontrast T1-weighted MRIs showing multiple juxtacortical lesions demonstrating gadolinium enhancement. *C*, Axial fluid-attenuated inversion recovery (FLAIR) MRIs showing increased T2-signal lesions in the bilateral corpus callosum and juxtacortical white matter.

COMMENT

This case exemplifies a diagnosis of MOG antibody–associated disease, which has unique features on MRI and requires management strategies that differ from pediatric MS.

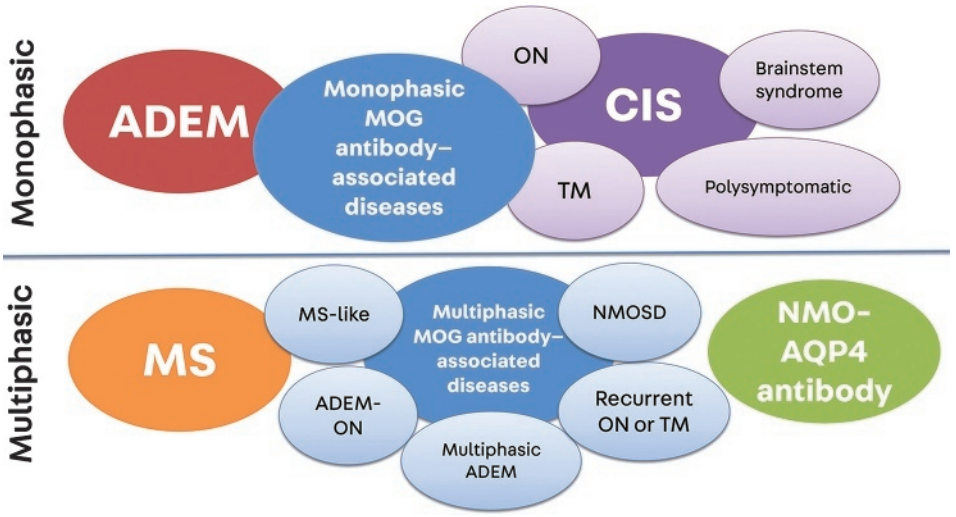

FIGURE 11-2

Spectrum of monophasic and multiphasic demyelinating disorders in children.

ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4; CIS = clinically isolated syndrome; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; ON = optic neuritis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; TM = transverse myelitis.

enormous strides have been made in the treatment of pediatric MS with the introduction of regulatory agency–approved treatments and new clinical trials. The establishment of refined diagnostic criteria for these disorders and the continued development and evaluation of treatments are important future directions. Biomarkers that aid in the prognostication of a relapsing course or relapse may further enhance patient management. Studies focused on long-term outcomes of all these pediatric-onset disorders are needed.

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