

Pediatric Multiple Sclerosis

Ji Y. Lee, MD, PhD¹ Tanuja Chitnis, MD¹

¹Department of Pediatric Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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Address for correspondence Tanuja Chitnis, MD, Department of Pediatric Neurology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, ACC708, Boston, MA 02114 (e-mail: tchitnis@partners.org).

Abstract

Pediatric multiple sclerosis (MS) is a chronic inflammatory neurologic disease that is challenging to diagnose and treat. Although there are many clinical parallels between pediatric-onset MS and adult-onset MS, there is also accumulating evidence of distinguishing clinical features that may, in part, arise from development-specific, neuro-immune processes governing MS pathogenesis in children. Here the authors describe the clinical features, diagnosis, and treatment of pediatric MS, with a particular focus on describing clinical features and highlighting new developments that promise a better understanding of pediatric MS pathogenesis. An important task that lies ahead for pediatric neurologists is better understanding the early gene–environment interaction that precipitates the first demyelinating event in pediatric MS. This area is of particular importance for understanding the MS etiology and the natural history of pediatric MS. Such understanding should in turn inform new developments in diagnostic tools, long-term therapies, and much-needed biomarkers. Such biomarkers are not only valuable for defining the disease onset, but also for monitoring both the treatment response and a disease evolution that spans multiple decades in children with MS.

Keywords

- ▶ multiple sclerosis
- ▶ children
- ▶ demyelination
- ▶ diagnosis
- ▶ treatment

Clinical Features and Course of Pediatric MS

Pediatric multiple sclerosis (MS) is a chronic neurologic disease with an estimated overall incidence of 0.13 to 0.51 per 100,000 person-years.^{1,2} The etiology of MS is not fully understood, but it is thought that MS arises from the interplay between genetically susceptible individuals and environmental factors, which leads to chronic inflammation of the central nervous system (CNS) and immune dysregulation, and ultimately manifests as demyelinating lesions and progressive neurologic dysfunction. Although the youngest age of MS onset reported is 2 years,³ the majority of children are diagnosed in childhood and early adolescence. It is estimated that up to 10% of adults with MS have their first clinical event before the age of 18 years. Adult MS shows a female predominance with the sex ratio of 2 to 3:1. In contrast, the sex ratio of pediatric onset MS is 1:1 prior to the onset of puberty.² Although sex hormones have long been suspected to play a role in MS pathogenesis, the mechanisms underlying the role of sex hormones in MS pathogenesis are not well understood.

The initial clinical features of MS have been termed clinically isolated syndromes (CIS); these include transverse myelitis (TM), optic neuritis (ON), and brainstem/spinal syndromes either alone or in combination. Common presenting symptoms of pediatric MS may be similar to those seen in adult MS, in that they could present with visual, sensory, motor, and coordination deficits as well as bladder and bowel problems, depending on the lesion location along the CNS axis. Lhermitte's sign and Uhthoff's phenomenon commonly described in adult MS are not well described in pediatric MS. Although most children present with focal or multifocal neurologic syndromes similar to those seen in adult MS, ataxia and brainstem syndromes appear more prominent in children presenting under the age of 10 years.

Optic neuritis is a common presenting diagnosis in adolescent patients with MS. This typically presents with painful monocular vision loss over hours to days. Visual acuity typically improves over days to weeks, often with full clinical recovery either spontaneously or with the use of high-dose intravenous steroids. Other classical features that raise concern for MS include painless binocular diplopia, hemiparesis,

hemisensory deficit, symptoms of acute myelopathy with a spinal sensory level, varying degrees of motor deficits, rarely dystonia and bladder and/or bowel habit changes, or incontinence that generally lasts several days to weeks in duration. Children and adults who initially present with TM and then are subsequently diagnosed with MS share a propensity for cervical cord pathology.^{4,5} However, brain white matter lesions and longitudinally extensive TM occur in children with both monophasic TM as well as TM with an eventual diagnosis of MS, presenting a diagnostic challenge. Whether children with neuromyelitis optica and children with longitudinally extensive transverse myelitis of MS represent a continuum of common pathogenic mechanisms is currently unclear. Overall, multifocal presentation as well as encephalopathy and seizures are more common in pediatric MS. Clinical features such as encephalopathy and seizures in pediatric MS also highlight an overlap with common presenting symptoms of acute demyelinating encephalomyelitis (ADEM). About a third of children initially diagnosed with ADEM subsequently met the diagnostic criteria for MS within the first 3 years; however, subsequent studies have shown that when using strict definitions of ADEM, less than 5% of cases were subsequently diagnosed as MS.⁶ Whether ADEM and pediatric MS represent a distinct disease entity is an area of active investigation.

Greater than 95% of pediatric MS shows a relapsing-remitting (RRMS) course. A prospective study showed a two- to threefold higher rate of relapse frequency in pediatric MS (age of onset before 18 years) compared with adult MS, up to 6 years after onset.^{7,8} Approximately 40% of children experienced a second event within 1 year of initial presentation, 60% by 2 years, and 66% by 3 years.⁹ In contrast, approximately 45% of adults diagnosed with CIS will be diagnosed with MS within 2 years, and 50% in 3 years. The mean recovery time, on the other hand, was shorter in pediatric MS (4.3 weeks) compared with adult MS (6–8 weeks).¹⁰ Children with ON recover better in terms of visual acuity than adults, despite similar measures of disability at the time of their acute attacks.¹¹ Children with MS experience a longer period between first attack and physical disability (Expanded Disability Status Scale [EDSS] score) compared with adults with MS.¹² However, the disability onset by chronological age is approximately a decade earlier in pediatric-onset MS compared with adult-onset MS.¹²

In recent years, there has been a growing appreciation of cognitive deficits in children with MS. Cognitive impairments have been described in the domains of executive function, processing speed, visuomotor integration, and attention.^{13–16} Younger age of MS onset and low scores on measures of intellectual function appear to predict greater impairment, underscoring the importance of regular neuropsychological testing and evaluation of school performance as critical parts of longitudinal clinical management in pediatric MS. There are also recent studies that report smaller brain volumes in children with MS compared with age- and sex-matched control children. Whether such differences are applicable to all developmental ages across pediatric MS requires more data. Given MS strikes within a child's developmental win-

dow, there is a critical need to understand how the disease affects cognitive development in children with MS. Furthermore, we currently lack detailed understanding of the long-term effect of disease-modifying therapies (DMTs) on cognitive development in pediatric MS. The data regarding which factors confer risk or provide protection from cognitive impairment in children with MS should help in developing future interventions that target cognitive health in pediatric MS. In addition, the emerging data should help further refine age-appropriate screening tools and metrics for studying MS-related cognitive impairments. Ultimately, studies regarding cognitive outcome in pediatric MS should help define the critical developmental window that may be particularly vulnerable for adverse cognitive outcomes, and to implement preventive interventions for the best cognitive outcome possible. Although fatigue, cognitive deficits, and pain are not disease-defining features of MS, these are nonetheless common complaints in children with MS. How best to study and incorporate these clinical features in the framework of MS pathogenesis remain a challenge.

Unlike RRMS, primary-progressive MS in children and adolescents is very rare. Ongoing and future efforts toward detailed clinical phenotyping of children with MS continue to be vitally important for better understanding of the clinical features of pediatric MS, and the natural history of pediatric MS.

Diagnosis of Pediatric MS

The diagnosis of both pediatric and adult MS requires evidence of inflammatory disease activity in the central nervous system (CNS) that is disseminated in space and time, and classic clinical symptoms typical of an MS attack. The diagnostic approach for a child with suspected MS is similar to other neurologic diseases, in that the history and exam should help narrow the wide differential diagnoses under consideration. The neurologic exam may reveal suggestive features of MS described above, including signs of optic neuropathy (decreased visual acuity, central scotoma, relative afferent pupillary defect, and red desaturation), internuclear ophthalmoplegia, a spinal sensory level, signs of myelopathy, paraparesis, dysmetria, and gait ataxia. However, a normal exam does not exclude the diagnosis of MS. In general, diagnosis of MS typically involves serologic, cerebrospinal fluid (CSF) analyses and imaging studies of the brain and/or spine. The specifics of laboratory and magnetic resonance imaging (MRI) investigations are guided by careful history, exam, demographics, and risk factors. The overall goal is to confirm the diagnosis of MS, and to rule out MS mimics from varying etiologies such as infectious disease (viral, Lyme, West Nile Virus), acute disseminated encephalomyelitis (ADEM), vasculopathies, inflammatory disorders, mitochondrial disorders, nutritional disorders, and neoplasms (– **Table 1**).

According to the 2010 McDonald criteria, the ability to confirm the diagnosis of MS on the first attack rests on establishing the presence of typical clinical symptoms of an MS attack, and the brain or spine MRI showing T2 lesions in at least two of four typical white matter locations commonly affected in patients with MS (periventricular, juxtacortical, infratentorial, and spinal cord), with at least one clinically

Table 1 Differential diagnoses of pediatric demyelinating diseases

Primary demyelinating	ADEM, ON, TM, MS, NMOSD
Autoimmune/paraneoplastic/connective tissue disorders	SLE, RA, Sjögren's syndrome, antiphospholipid antibody syndrome, Behçet's disease, hemophagocytic lymphohistiocytosis, Wegener's granulomatosis, lymphomatoid granulomatosis, sarcoidosis, OMS, paraneoplastic autoimmune encephalitis (including anti-NMDAR encephalitis)
Vasculitides	CNS and systemic vasculitides
Infectious	Lyme, HIV, PML, SSPE, tropical spastic paraparesis/HTLV-1 associated myelopathy, neurosyphilis, CMV, HSV, cat scratch disease
Vascular and hypoxic-ischemic	HIE, delayed hypoxic cerebral demyelination, stroke, sickle cell disease, PRES, CADASIL, migraine, Susac's syndrome
Metabolic	Subacute combined degeneration, CPM
Mitochondrial disease	MELAS, Leigh's syndrome, NARP syndrome
Secondary demyelinating	X-linked adrenoleukodystrophy, metachromatic leukodystrophy, adrenomyeloneuropathy, Alexander's disease, Canavan's disease, Krabbe's disease, Aicardi-Goutieres syndrome
Hypomyelinating	Pelizaeus-Merzbacher disease, Cockayne's disease, 18q syndrome, Pol III-related leukodystrophies/4H
Neoplasm	Glioma, CNS lymphoma

Abbreviations: ADEM, acute disseminated encephalomyelitis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system, CMV, cytomegalovirus; CPM, central pontine myelinolysis; HIE, hypoxic-ischemic encephalopathy; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MS, multiple sclerosis; NARP, neuropathy, ataxia, and retinitis pigmentosa; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; OMS, opsoclonus myoclonus syndrome; ON, optic neuritis; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSPE, subacute sclerosing panencephalitis; TM, transverse myelitis.

silent enhancing lesion, and a nonenhancing lesion.¹⁷ These criteria have been applied and have been found to be sensitive and specific in detecting MS in adolescents older than 11 years of age,¹⁸ and have been incorporated into the revised International Pediatric MS Study Group (IPMSSG) 2012 Updated Criteria for Pediatric Multiple Sclerosis.^{19,20}

Application of the 2010 criteria for children younger than 11 years requires careful consideration. The current data suggest that approximately 40% of children younger than 11 years of age initially meet the 2010 criteria yet fail to demonstrate further attacks of new MRI lesions over the ensuing 5 years. Therefore, in the absence of specific biomarkers that predict MS after a first demyelinating event, the longitudinal clinical follow-up is essential. In addition, imaging is of particular importance, not only for distinguishing MS from other pediatric demyelinating diseases, but also for assessing the overall course of MS. For example, the diagnosis of MS in a child with ADEM requires at least one non-ADEM attack with further MRI evidence of new lesion accrual over time or two clinical non-ADEM attacks. In some situations, children and adolescents may present with radiologically isolated syndrome (RIS), which is characterized by lesions that are highly typical of MS in an otherwise asymptomatic child. We have known for some time now that patients with RIS are at an approximately 30% risk of a future attack over 5 years, again underscoring the importance of long-term follow-up and interval imaging. In the absence of predictive biomarkers of MS, interval imaging is an essential tool for assessing for demyelinating lesions that may be under the threshold of clinical expression. In conjunction with

conventional MRI techniques, imaging-based analytic measures are being developed to better determine the evolution of whole brain versus region-specific atrophy in pediatric MS. The studies that assessed the total T2 and T1 lesion volumes suggest that children with MS have comparable lesion volumes to those measured in adult MS when matched for disease duration. Furthermore, recent studies also report decreased skull size as well as brain volumes in children with MS compared with age- and sex-matched controls.²¹ Together, these studies signal a need for quantitative and sensitive imaging assays to better understand the evolution of focal CNS MS pathology and its impact on CNS development and longitudinal cognitive function in pediatric MS. Although pathogenic mechanisms underlying reduced brain volume and skull size are unclear, the data suggest that the effect of MS on CNS development may predate a child's first observable clinical attack. More advanced MRI techniques combined with detailed clinical phenotyping, including longitudinal neuropsychological testing in children with MS, should help provide more data regarding the effect of MS on cognitive outcome in pediatric MS. Several key questions to address regarding the relationship between pediatric MS and cognitive deficits are (1) how best to monitor cognitive deficits in pediatric MS (i.e., which screening modalities and analytic tools provide the best screening tools for detecting cognitive deficits), (2) which clinical features confer risk or provide protection from cognitive deficits, and (3) is there a defined developmental window during which a child's cognitive development is particularly vulnerable to the pathogenic mechanisms of MS?

Cerebrospinal fluid assessment is important in the evaluation of MS. It allows assessment of an autoimmune and/or inflammatory CNS process at the time of an acute demyelinating event. Specifically, identification of elevations in CSF oligoclonal bands and immunoglobulin G (IgG) index are considered characteristic, although not diagnostic, of multiple sclerosis. Importantly, CSF analyses often help distinguish MS from other etiologies. For example, CSF abnormalities such as substantial elevations in white blood cell count might indicate an infectious or an alternative chronic inflammatory cause, and marked elevations in protein may occur in compressive myelopathies with CSF block or other infectious or inflammatory diseases. Investigation of autoantibodies such as anti-aquaporin 4 should also help distinguish patients whose clinical presentations may overlap with neuromyelitis optica spectrum disorder (→Table 2).

Given the emerging clinical trials in pediatric MS, there is an urgent need to consolidate our best algorithm for diagnosis of pediatric MS, and to develop best screening modalities and analytic tools that accurately assess for disease progression, treatment response, and associated clinical outcomes of interest.

Treatment of Pediatric MS

Acute Management

Intravenous glucocorticoid treatment is the mainstay of acute symptomatic management of a demyelinating event and relapses in both children and adults with MS. For children

whose weight is < 40 kg, the typical regimen is methylprednisolone administered at 20 to 30 mg/kg daily for 3 to 5 days. For those weighing > 40 kg, the dose is similar to that of an adult at 1 g/kg daily for 3 to 5 days. Intravenous immunoglobulin (IVIg) or plasmapheresis can be considered for refractory cases. A typical regimen used at our center is IVIg, dosed at 0.4 mg/kg/d for 5 days, or plasma exchange for 5 to 7 exchanges. The side-effect profile of methylprednisolone is well established; hyperglycemia and hypertension require close monitoring. Increased appetite, poor sleep, and irritability are also common in children, but often subside without major interventions following the termination of acute treatment.

Disease-Modifying Therapies in Pediatric MS

Several medications have been approved for adults with RRMS: interferon-β (IFN-β; Rebif, Merck Serono; Avonex, Biogen; Betaseron, Bayer HealthCare Pharmaceuticals), glatiramer acetate (GA; Copaxone, Teva Pharmaceuticals), mitoxantrone (MTX; Novantrone, EMD Serono), dimethylfumarate, fingolimod, natalizumab (Tysabri, Biogen), and teriflunomide. None of these DMTs are currently approved for the treatment of pediatric MS; therefore, their use remains off label. First-line immunomodulatory therapies used to treat pediatric MS include intramuscular (IM) and subcutaneous (SC) IFN-β1a, SC IFN-β1b, and GA.²² Currently, most treatment decisions for the use of these DMTs in children are

Table 2 Diagnostic evaluation for acute disseminated encephalomyelitis and transverse myelitis

Acute demyelinating encephalomyelitis	<p>Labs: Serologic studies: ESR, CRP, and NMO-IgG. Consider further infectious testing based on clinical context, immune status (see below). Screening laboratories such as ANA, TSH, and ACE as clinically indicated. CSF studies: Rule out viral and bacterial meningitis/infectious encephalitides. Measure the opening pressure. Send CSF for glucose, protein, cell count, bacterial culture, gram stain, IgG index, oligoclonal bands. Consider further infectious testing based on history, clinical context, and immune status (e.g., EBV, HSV, CMV, enterovirus, VZV, WNV, mycoplasma).</p> <p>Imaging: Brain MRI ± cervical and thoracic spine MRI with gadolinium as clinically indicated</p> <p>Additional workup: EEG and VEPs as clinically indicated</p>
Transverse myelitis	<p>Labs: Serologic studies: ESR, CRP, NMO-IgG (anti-aquaporin 4 Ab), and vitamin D level. Consider further infectious testing based on clinical context, immune status (see below). Screening laboratories such as ANA, TSH, anti-Ro, anti-La AAbs, and ACE as clinically indicated. CSF studies: Measure the opening pressure. Send CSF for glucose, protein, cell count, bacterial culture, gram stain, IgG index, oligoclonal bands, NMO-IgG. Consider further infectious testing based on history, clinical context, and immune status (e.g., EBV, HSV, CMV, enterovirus, VZV, WNV, mycoplasma).</p> <p>Imaging: Brain MRI ± cervical, thoracic, and lumbar spine MRI with gadolinium as clinically indicated</p> <p>Additional workup: Urodynamic testing as clinically indicated</p>

Abbreviations: ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CRP, C-reactive protein; CSF, cerebrospinal fluid; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; La AAbs, autoantibodies; MRI, magnetic resonance imaging; NMO-IgG, neuromyelitis optica-immunoglobulin G; TSH, thyroid-stimulating hormone; VEPs, visual evoked potentials; VZV, varicella zoster virus; WNV, West Nile virus.

largely based on studies performed in adults. However, recently launched randomized clinical trials in pediatric MS should begin to provide long-awaited data regarding safety and efficacy of DMTs in pediatric MS. If proven safe and effective, new oral medications would be available for children with MS. Although IM and SC injection forms of DMTs are relatively well tolerated, oral medications with their ease of administration would result in a child's better adherence to a treatment regimen.

To date, several case reports and case series studies suggest that IFN- β 1a is relatively well tolerated in children with MS. Nine children receiving a 30- μ g IM weekly dose of IFN- β 1a (Avonex) generally tolerated the medication. Side effects included flu-like symptoms, including myalgias and headache. In 51 children and adolescents with MS treated with IFN- β 1a (Rebif) 22 to 44 μ g 3 times weekly via SC injection, the treatment was well tolerated. Similar to the IFN- β 1a side-effect profile, flu-like symptoms were common in children treated with IFN- β 1a (65%). Other notable side effects were elevation of serum transaminases (35%) and mild leukopenia (27%). Of note, there were two notable serious side effects in this single-center study: systemic reaction and depressed mood. Data on adequate treatment response are currently lacking; however, a reduction in relapse rate during the first 2 years of disease from 1.0 to less than 0.6 would be comparable to the 30% to 40% relapse rate reductions observed in adults. Several open-label studies show that IM and SC IFN- β treatment reduced the annualized relapse rate in pediatric MS.^{23,24} Despite extensive investigation, therapeutic mechanisms of IFN- β in MS remain unclear. Broadly speaking, most DMTs are thought to act on the immune-mediated inflammatory component of the disease. The proposed mechanisms include inhibition of T-cell activation and proliferation, apoptosis of autoreactive T cells, induction of regulatory T cells, inhibition of leukocyte migration across the BBB, and immunomodulation via cytokine production. In general, the side effect profile appears similar to that of adult MS; injection site reactions were common, affecting more than 60% of children. Abscesses and injection site necrosis occurred in approximately 6%. Other side effects include flu-like symptoms (35–65%), leukopenia (8–27%), thrombocytopenia (16%), anemia (12%), and transient elevation in transaminases (21–33%).

Glatiramer acetate is a synthetic amino acid polymer that was originally developed to resemble myelin basic protein. However, the exact therapeutic mechanism of GA in MS is unknown. Several small pediatric studies that evaluated the use of GA in pediatric MS reported no major adverse events and a trend toward favorable clinical outcomes. Larger studies are required to assess safety and efficacy of GA in pediatric MS.

Vitamin D is a commonly available supplement, and lowered vitamin D (25-OH) levels are frequent²⁵ and have been found to correlate with relapse rate in children with MS.²⁶ Therefore, we recommend supplementation of vitamin D to levels at least > 30 ng/mL, or ideally between 40 to 60 ng/mL.

Emerging Treatments in Pediatrics MS

Approximately 40% of children will require switching from a first- to second-line therapy largely due to treatment failure, and secondary reasons include intolerance or poor adherence.^{27,28}

Natalizumab has been used as a second-line treatment in children with MS in several case and cohort reports.^{29,30} Overall safety and efficacy profiles have been favorable; however, a large proportion of children with MS (~50%) are positive for the John Cunningham virus antibody, therefore prohibiting its long-term use. Rituximab has been used in some children with MS, although knowledge about safety and efficacy profiles is limited.^{31,32} Other treatments less commonly used presently because of toxicity concerns are cyclophosphamide³³ and mitoxantrone.³⁴

Recently launched clinical trials are evaluating the clinical outcome of pediatric MS patients treated with fingolimod, dimethylfumarate, and teriflunomide. If proven safe and effective, new oral medications will expand therapeutic options for children with MS.³⁵

Summary

Pediatric MS is a chronic inflammatory neurologic disease that strikes a susceptible child during his or her childhood or adolescence, affecting various aspects of development including cognition. Our collective clinical experience in diagnosing and treating children with MS has grown considerably in recent years. There are now several well-established clinical features that help distinguish pediatric onset MS from adult-onset MS. Our understanding of early disease activity in pediatric MS and clinical management expertise are also growing. Treating children with DMTs has thus far largely relied on studies conducted on adult MS. Success of these DMTs in treating children with MS underscores the importance of common immunomediated pathogenic mechanisms shared between pediatric and adult MS. With the recent launch of clinical trials evaluating safety and efficacy of DMTs in pediatric MS, we may soon begin to construct a rational treatment algorithm specifically tailored to children with MS. Given the long duration of the disease in pediatric MS, there is an urgent need for early detection, accurate diagnosis, and better therapeutic interventions that can reduce relapses and ultimately halt disease progression.

References

- Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology* 2009; 72(3):232–239
- Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. *Eur J Pediatr* 2007;166(5):405–412
- Ness JM, Chabas D, Sadovnick AD, Pohl D, Banwell B, Weinstock-Guttman B; International Pediatric MS Study Group. Clinical features of children and adolescents with multiple sclerosis. *Neurology* 2007;68(16, Suppl 2):S37–S45
- Deiva K, Absoud M, Hemingway C, et al; United Kingdom Childhood Inflammatory Demyelination (UK-CID) Study and French

- Kidbiosep Study. Acute idiopathic transverse myelitis in children: early predictors of relapse and disability. *Neurology* 2015;84(4):341–349
- 5 Meyer P, Leboucq N, Molinari N, et al. Partial acute transverse myelitis is a predictor of multiple sclerosis in children. *Mult Scler* 2014;20(11):1485–1493
 - 6 Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. *Lancet Neurol* 2011;10(5):436–445
 - 7 Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord* 2014;3(2):186–193
 - 8 Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol* 2009;66(1):54–59
 - 9 Mikaeloff Y, Suissa S, Vallée L, et al; KIDMUS Study Group. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. *J Pediatr* 2004;144(2):246–252
 - 10 Fay AJ, Mowry EM, Strober J, Waubant E. Relapse severity and recovery in early pediatric multiple sclerosis. *Mult Scler* 2012;18(7):1008–1012
 - 11 Malik MT, Healy BC, Benson LA, et al. Factors associated with recovery from acute optic neuritis in patients with multiple sclerosis. *Neurology* 2014;82(24):2173–2179
 - 12 Renoux C, Vukusic S, Mikaeloff Y, et al; Adult Neurology Departments KIDMUS Study Group. Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007;356(25):2603–2613
 - 13 Julian L, Serafin D, Charvet L, et al; Network of Pediatric MS Centers of Excellence. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. *J Child Neurol* 2013;28(1):102–107
 - 14 MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005;64(8):1422–1425
 - 15 Amato MP, Goretti B, Ghezzi A, et al; Multiple Sclerosis Study Group of the Italian Neurological Society. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology* 2010;75(13):1134–1140
 - 16 Charvet LE, O'Donnell EH, Belman AL, et al; US Network of Pediatric MS Centers. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US Pediatric Multiple Sclerosis Network. *Mult Scler* 2014;20(11):1502–1510
 - 17 Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69(2):292–302
 - 18 Sadaka Y, Verhey LH, Shroff MM, et al; Canadian Pediatric Demyelinating Disease Network. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. *Ann Neurol* 2012;72(2):211–223
 - 19 Krupp LB, Banwell B, Tenenbaum S; International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007;68(16, Suppl 2):S7–S12
 - 20 Krupp LB, Tardieu M, Amato MP, et al; International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013;19(10):1261–1267
 - 21 Kerbrat A, Aubert-Broche B, Fonov V, et al. Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS. *Neurology* 2012;78(3):194–201
 - 22 Chitnis T, Tenenbaum S, Banwell B, et al; International Pediatric Multiple Sclerosis Study Group. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult Scler* 2012;18(1):116–127
 - 23 Tenenbaum SN, Segura MJ. Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. *Neurology* 2006;67(3):511–513
 - 24 Ghezzi A, Amato MP, Capobianco M, et al; Immunomodulatory Treatment of Early-onset MS (ITEMS) Group. Treatment of early-onset multiple sclerosis with intramuscular interferon-beta-1a: long-term results. *Neurol Sci* 2007;28(3):127–132
 - 25 Banwell B, Krupp L, Kennedy J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. *Lancet Neurol* 2007;6(9):773–781
 - 26 Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol* 2010;67(5):618–624
 - 27 Yeh EA, Waubant E, Krupp LB, et al; National Network of Pediatric MS Centers of Excellence. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. *Arch Neurol* 2011;68(4):437–444
 - 28 Lulu S, Julian L, Shapiro E, Hudson K, Waubant E. Treatment adherence and transitioning youth in pediatric multiple sclerosis. *Mult Scler Relat Disord* 2014;3(6):689–695
 - 29 Ghezzi A, Moiola L, Pozzilli C, et al; MS Study Group-Italian Society of Neurology. Natalizumab in the pediatric MS population: results of the Italian registry. *BMC Neurol* 2015;15:174
 - 30 Huppke P, Stark W, Zürcher C, Huppke B, Brück W, Gärtner J. Natalizumab use in pediatric multiple sclerosis. *Arch Neurol* 2008;65(12):1655–1658
 - 31 Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014;83(2):142–150
 - 32 Chitnis T, Waubant E. B-cell depletion in children with neuro-immunologic conditions: the learning curve. *Neurology* 2014;83(2):111–112
 - 33 Makhani N, Gorman MP, Branson HM, Stazzone L, Banwell BL, Chitnis T. Cyclophosphamide therapy in pediatric multiple sclerosis. *Neurology* 2009;72(24):2076–2082
 - 34 Kornek B, Bernert G, Rostasy K, et al. Long-term follow-up of pediatric patients treated with mitoxantrone for multiple sclerosis. *Neuropediatrics* 2011;42(1):7–12
 - 35 Chitnis T, Tardieu M, Amato MP, et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. *Neurology* 2013;80(12):1161–1168