Published in final edited form as:

Lancet Neurol. 2014 September ; 13(9): 936–948. doi:10.1016/S1474-4422(14)70093-6.

Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research

Amy Waldman, MD, Prof Angelo Ghezzi, MD, Amit Bar-Or, MD, Yann Mikaeloff, MD, Prof Marc Tardieu, PhD, and Prof Brenda Banwell, MD

Division of Neurology, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA (A Waldman MD, Prof B Banwell MD); Ospedale di Gallarate, Centro Studi Sclerosi Multipla, Gallarate, Italy (Prof A Ghezzi MD); Montreal Neurological Institute, McGill University, Montreal, QC, Canada (A Bar-Or MD); and Unité de Rééducation Neurologique Infantile (Y Mikaeloff MD) and Service de Neurologie Pédiatrique (Prof Marc Tardieu PhD), Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Paris, France

Abstract

The clinical features, diagnostic challenges, neuroimaging appearance, therapeutic options, and pathobiological research progress in childhood—and adolescent—onset multiple sclerosis have been informed by many new insights in the past 7 years. National programmes in several countries, collaborative research efforts, and an established international paediatric multiple sclerosis study group have contributed to revised clinical diagnostic definitions, identified clinical features of multiple sclerosis that differ by age of onset, and made recommendations regarding the treatment of paediatric multiple sclerosis. The relative risks conveyed by genetic and environmental factors to paediatric multiple sclerosis have been the subject of several large cohort studies. MRI features have been characterised in terms of qualitative descriptions of lesion distribution and applicability of MRI aspects to multiple sclerosis diagnostic criteria, and quantitative studies have assessed total lesion burden and the effect of the disease on global and regional brain volume. Humoral-based and cell-based assays have identified antibodies against myelin, potassium-channel proteins, and T-cell profiles that support an adult-like T-cell repertoire and cellular reactivity against myelin in paediatric patients with multiple sclerosis. Finally, the safety and efficacy of standard first-line therapies in paediatric multiple sclerosis populations are now appreciated in more detail, and consensus views on the future conduct and feasibility of phase 3 trials for new drugs have been proposed.

Correspondence to Prof Brenda Banwell, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA 19104, USA, banwellb@email.chop.edu.

Contributors

AW and BB designed and wrote the core content of the manuscript and reviewed all referenced articles. MT, AG, AB-O and YM contributed content and edited the final manuscript.

Declaration of interests

BB serves as an adviser to Biogen-Idec, Serono, and Novartis. AG has received honoraria for consultancy from Biogen-Idec and Merck-Serono and travel grants or grants as a speaker from Teva Neuroscience, Sanofi-Genzyme, Novartis, and Merck-Serono. AB-O has served as an adviser for Biogen-Idec, EMD Serono, GSK, Medimmune, Mitsubishi, Novartis, Receptos, Roche, and Sanofi-Genzyme. MT serves as an adviser for Novartis, Sanofi, Biogen-Idec, and Teva; and has received a grant for a teaching session organised by Teva. AW and YM declare no competing interests.

Introduction

Since our previous Review¹ of the clinical, MRI, and pathobiological features of multiple sclerosis in children and adolescents (defined as 13 years to 17 years 11 months), the discipline has been informed by an increasing number of studies detailing paediatric multiple sclerosis cohorts from several countries. Advances in neuroimaging can now fully characterise the effect of multiple sclerosis on CNS integrity. Genetic and immunological assays support the notion of shared biological features of multiple sclerosis across the age spectrum.² Immunological studies identify patients with antibodies against CNS tissue, such as myelin oligodendroglial (MOG) protein, who might ultimately have distinct pathobiological diseases or specific multiple sclerosis subtypes.

In this Review, we summarise findings relating genetic and environmental risk factors to paediatric multiple sclerosis outcomes; describe MRI analyses of lesion characteristics and global measures of the effects of multiple sclerosis, visualised by advanced MRI techniques; and discuss therapeutic considerations, particularly in view of the upcoming results from the first clinical trials of therapies for paediatric multiple sclerosis.

Acute demyelination of the CNS

A first clinical attack can be termed as an acquired demyelinating syndrome. The classification of acquired demyelinating syndromes was defined by an international panel of experts in 2007,³ and has been updated in 2013⁴ and is summarised in the panel.

The overall incidence of acquired demyelinating syndromes in children and adolescents ranges from 0.6 to 1.66 per 100 000 children per year.^{8–10} The presentation of acquired demyelinating syndromes varies across studies,^{2,8–11} with 22–36% of patients manifesting with optic neuritis, 19–24% with acute disseminated encephalomyelitis, 3–22% with transverse myelitis, 9–16% with a monofocal acquired demyelinating syndrome, and 2–4% with neuromyelitis optica.

The proportion of children and adolescents with acquired demyelinating syndromes who will be diagnosed with multiple sclerosis within 5 years varies across studies: 13 (15%) of 88 in Australia,¹² 63 (21%) of 302 in Canada,² 52 (45%) of 116 in France,¹³ and 13 (46%) of 28 in the UK.¹⁴ The high variability will be due, in part, to the differences in inclusion criteria and the referral biases of centres participating in national studies. About 2–10% of all patients with multiple sclerosis have clinical onset before the age of 18 years.^{15–19} In a national multiple sclerosis registry from Wales, 111 (5.4%) of 2068 of patients had multiple sclerosis onset before the age of 18 years, and only 0.3% had onset before the age of 10 years.²⁰ The incidence of paediatric multiple sclerosis per 100 000 children per year has been estimated to be 0.13 in France,¹⁸ 0.18 in Canada,²¹ 0.66 in the Netherlands,⁸ 0.3 in Germany,²² and 0.51 per 100 000 person-years in the USA.¹⁰ The incidence of multiple sclerosis was 0.6 per 100 000 children in a German study, but the incidence increased to 2.64 when considering only paediatric multiple sclerosis onset between 14–15 years of age.

The likelihood that an incident attack represents the first episode of multiple sclerosis differs according to several parameters (table 1), including clinical presentation; age at onset of the

acquired demyelinating syndrome; sex; MRI features (some of which directly contribute to diagnostic criteria); evidence of intrathecal synthesis of oligoclonal bands (OCBs); and the presence of environmental and genetic risk factors.

Female sex and onset after the age of 11 years are associated with a high likelihood of multiple sclerosis as an outcome. A normal brain MRI, as might be seen in children with optic neuritis or transverse myelitis, portends a very low likelihood of multiple sclerosis as an outcome,² at least within 5 years of onset. Children with acute disseminated encephalomyelitis and those with polyfocal clinical features typically have several brain (and potentially spinal) lesions. Several studies have compared key MRI features of children with acute disseminated encephalomyelitis with those of children with a first multiple sclerosis attack (table 2)⁴⁰ or have assessed the MRI features predictive of multiple sclerosis as the outcome in children with acquired demyelinating syndromes.²⁹

Several diagnostic challenges remain—not all children with relapsing demyelination meet the criteria for multiple sclerosis. In addition to defining the monophasic syndromes, the panel summarises current criteria for relapsing disease in children such as neuromyelitis optica, chronic relapsing inflammatory optic neuropathy,^{6,7} and the features of patients with acute disseminated encephalomyelitis who experience subsequent episodes of optic neuritis.⁵ A full discussion of other disorders to consider in the differential diagnosis of multiple sclerosis in children^{28,41} is beyond the scope of this Review.

Multiple sclerosis in children

Criteria for multiple sclerosis diagnosis

The diagnosis of multiple sclerosis in both children and adults rests on evidence of inflammatory disease activity in several CNS regions and dissemination in time.^{4,42,43} Although previous diagnostic criteria have included multiple sclerosis onset after the age of 10 years,⁴² the present 2010 McDonald criteria formally address the diagnosis of multiple sclerosis in children and provide specific commentary on the application of MRI in paediatric multiple sclerosis. The ability to confirm a diagnosis of multiple sclerosis at the time of an incident attack is unique to the 2010 McDonald criteria, provided that the clinical features are typical of a multiple sclerosis attack and that the MRI shows two T2 lesions in two of four locations commonly affected in patients with multiple sclerosis (periventricular, juxtacortical, brainstem, or spinal cord), with at least one clinically silent enhancing lesion and a non-enhancing lesion.⁴³ The panel summarises the criteria for multiple sclerosis diagnosis in children.

The sensitivity and specificity of the 2010 McDonald criteria, particularly when applied solely to baseline scans, have now been assessed in paediatric populations.^{44–47} Findings from all studies showed increased sensitivity of the 2010 criteria and indicated that use of the 2010 criteria led to an early diagnosis of multiple sclerosis. In a study of 212 paediatric patients with an acquired demyelinating syndrome,⁴⁷ followed prospectively for longer than 2 years with serial clinical and MRI assessments, the sensitivity of the 2010 criteria applied at baseline was 100%, the specificity 86%, the positive predictive value 59%, and the negative predictive value 100% for a subsequent diagnosis of multiple sclerosis. When

children who presented with an acquired demyelinating syndrome were excluded, and when the criteria were applied in patients older than 11 years, the positive predictive value rose to 76%, which is similar to what is seen in adult first-attack populations.⁴⁷ The 2010 McDonald criteria include spinal lesions as one of the four sites that contribute to dissemination in space. However, spinal cord imaging is not routinely obtained in children with demyelination,⁴⁸ unless clinical features localise to the spine. When performed, however, T2 hyperintense lesions in the cord were often clinically silent, and were longitudinally extensive in ten (27%) of 36 children studied.⁴⁹ Spinal cord imaging increased the diagnostic yield of the 2010 criteria by 10% in a study of children imaged at onset of the acquired demyelinating syndrome.⁴⁵

Comparison of paediatric patients with multiple sclerosis who met the 2010 criteria at baseline with patients whose MRI does not conform to the criteria at onset (and who thus need further relapses or new lesions on serial imaging to confirm multiple sclerosis) showed a similar relapse frequency in both groups of patients in the first few years of disease, with no difference between Expanded Disability Status Scale (EDSS) scores, which suggests that the 2010 criteria do not select for paediatric patients with more clinically severe multiple sclerosis.⁵⁰

Clinical features and outcome

A relapsing-remitting disease course occurs in more than 97% of patients with multiple sclerosis onset before the age of 18 years.⁹ Primary progressive multiple sclerosis is very rare in children and adolescents, and should always prompt extensive assessment for alternative diagnoses.

In a study of clinical presentation as a function of age of onset,⁵¹ children younger than 11 years were more likely to manifest with polyfocal features (23 [49%] of 47 children, compared with 9 [37%] of 41 patients aged 14–16 years), have attacks affecting the brainstem or have motor deficits, and tended to have more severe acute deficits than older patients. Whether young children are able to articulate mild sensory deficits or alert parents to symptoms of mild visual loss, for example, is a consideration.

A high frequency of relapses in the first few years after disease onset has been reported in 21 paediatric patients with multiple sclerosis compared with 110 adult-onset patients (annualised relapse rate 1.13 vs 0.4; adjusted rate ratio 2.81, 95% CI, 2.07–3.81).⁵² In a retrospective analysis of 88 paediatric patients with multiple sclerosis in Germany,⁵¹ the mean number of relapses per year was highest in the first year following incident attack (2.2, range 1–6 in children presenting at age <11 years; 1.8, range 1–5 in adolescents presenting between ages 14 and 16 years). The annualised relapse rate in the fifth year of the disease was reduced in both groups (0.79, range 0–4 in children who initially presented at age <11 years; 0.42, range 0–2, in the adolescent onset group). The effect of treatment could not be fully assessed in the German study, but more than 80% of the children received immunomodulatory therapy.

Paediatric-onset multiple sclerosis is associated with a longer period between first attack and physical disability (EDSS score) compared with adult-onset multiple sclerosis, although the

biological age of disability onset is about 10 years earlier in patients with paediatric-onset.¹⁷ The median EDSS scores in the 88 children from Germany previously mentioned were less than 1 at 2 years, 1.2 at 10 years, and 2.5 at 15 years (although only ten patients reached 15 years of observation).⁵¹

Paediatric multiple sclerosis occurs during the key formative years of education and during the period of active brain maturation. Findings from three studies^{53–55} that collectively assessed almost 300 paediatric patients with multiple sclerosis (many of whom were receiving disease-modifying therapy at the time of cognitive assessment) showed cognitive impairment in about 30% of patients, with the domains of executive function, processing speed, visuomotor integration, and attention being the most commonly affected. Younger age at onset and low scores on measures of intellectual function predict greater impairment across cognitive domains.⁵⁴ Academic metrics are also impaired, with 26% of patients in one study⁵⁶ showing poor mathematics performance. Findings from two longitudinal studies have showed cognitive decline in 7 (25%) of 28 patients after 1 year,⁵⁷ and in 42 (75%) of 56 patients after 2 years.⁵⁸ Correlation of cognitive performance and MRI features is discussed later. Cognitive rehabilitation is an area of active discussion, but meaningful interventions that enhance cognitive reserve and improve function have yet to be reported.

MRI in paediatric multiple sclerosis

MRI analysis of disease activity

Lesion burden at the time of first attack has been hypothesised to be lower in paediatric-onset than in adult-onset multiple sclerosis because of the young age of many paediatric multiple sclerosis patients and the age-related inherent limitation in time for accrual of subclinical lesions on MRI. However, quantitative analysis of T2 lesion volumes in patients with paediatric-onset or adult-onset multiple sclerosis, who were imaged early in the disease and matched for disease duration, showed very similar T2 lesion volumes.^{30,59} T1 lesion volumes were greater in adult-onset patients, but when assessed regionally, paediatric-onset patients had a higher T1 lesion volume in infratentorial brain regions.⁶⁰ These MRI findings are consistent with the high frequency of brainstem symptoms reported in patients with paediatric-onset multiple sclerosis.⁵¹

Collaborative research will be needed to further assess lesion burden and the acquisition of lesions in large cohorts. A standardised MRI scoring method has been proposed for assessment of paediatric multiple sclerosis scans acquired in clinical practice.⁶¹ The importance of standardised MRI acquisition protocols was emphasised in an analysis of imaging data from the US paediatric multiple sclerosis network.³¹

MRI analyses of focal and global brain integrity

MRI studies using non-conventional sequences, such as diffusion tensor or magnetisation transfer imaging, have provided novel insights into the structural integrity of tissue.⁶² Diffusion tensor imaging (DTI) in paediatric multiple sclerosis cohorts has shown reduced fractional anisotropy (FA) in normal-appearing white matter, both globally in lobar regions and within the corpus callosum, relative to healthy age-matched children.^{53,63} Differences in FA are consistently noted, while measures of diffusivity have been less consistent in

distinguishing children with multiple sclerosis from healthy children.^{63,64} A correlation between reduced FA and impaired performance in mathematics⁵⁶ and with impaired processing speed⁶⁵ has been reported in 34 young patients with paediatric-onset multiple sclerosis. Findings from two studies of tract-based analyses have showed reduced FA in normal-appearing white matter in 14 paediatric patients⁶⁶ and ten paediatric patients⁶⁷ compared with age-matched and sex-matched healthy controls. Taken together, findings from these studies suggest that myelin architecture might be disrupted early in multiple sclerosis, but large serial studies and tract-based analyses are needed to further assess the effect of multiple sclerosis on myelinated pathways over time.

Magnetisation transfer ratio (MTR) imaging has been proposed as a means to assess the integrity of myelin. MTR imaging capitalises on the capacity of hydrogen ions bound to macromolecules, which when excited by a magnetisation pulse, transfer excitation differently from free (non-bound) hydrogen ions.⁶⁸ MTR is decreased in demyelinated lesions compared with normal white matter but increases with remyelination.⁶⁹ Abnormal MTR was also reported in normal-appearing brain tissue in a study of 11 adolescents and 11 adults with multiple sclerosis compared with 22 healthy controls.⁷⁰ Further studies of large cohorts followed for long periods of time are needed to fully appreciate MTR analyses in paediatric multiple sclerosis cohorts.

The effect of multiple sclerosis on brain volume and, of particular relevance in the paediatric context, the effect of multiple sclerosis on age-expected maturational brain growth has been explored.^{30,71,72} In a cross-sectional analysis of 38 patients with paediatric-onset multiple sclerosis⁷² imaged at a mean age of 15.2 (SD 2.4) years (mean disease duration 3.1 years, range 0.3–13), global brain volume in patients with multiple sclerosis was more than 1 SD lower than age-expected values. Thalamic volume, even when corrected for brain volume, was more affected in paediatric patients, which suggests a particular vulnerability of the thalamus early in multiple sclerosis.⁷¹ In patients with paediatric-onset multiple sclerosis, reduced thalamic volume and reduced corpus callosal area could distinguish patients with cognitive impairment from those with intact cognitive performance.⁵³

Functional MRI

The potential of functional imaging to inform on neural network activity, both at resting state and in terms of specific neural connections, is an emerging area of interest in multiple sclerosis research.⁷³ Application of functional MRI in 17 patients with paediatric-onset multiple sclerosis has showed preservation of normal coefficients of connectivity, compared with adults who show an increase in connectivity for a given task.⁷⁴ When analysed for a specific sensorimotor task, patients with paediatric-onset multiple sclerosis again showed preserved functional reserve.⁷⁵ The authors hypothesised that the preserved connectivity might contribute to the low level of disability in patients with paediatric-onset multiple sclerosis in the early stages of the disease. Functional MRI studies in paediatric multiple sclerosis cohorts are limited by age-normative changes in developing networks, individual resilience provided by heightened network capacity in different people, and the possibility that multiple sclerosis-related changes might include initial compensatory expansion of connectivity followed by a subsequent loss of connectivity with advanced disease. Methods

to distinguish these different patterns will be required, and increased sample sizes will certainly be needed.

Pathobiological insights

Genetic and environmental risk factors

The greatest contribution to genetic risk in both paediatric-onset and adult-onset multiple sclerosis is conferred by specific haplotypes in the *HLA-DR* allele of the major histocompatibility complex (MHC), with a lesser contribution of several single nucleotide polymorphisms in genes that mostly affect immune-related function. In a study assessing *HLA-DRB15* allele frequency in 64 children with multiple sclerosis,²⁵ 206 children with monophasic acquired demyelinating syndromes, and 196 controls, children with at least one *DRB1*15* allele were more likely to be diagnosed with multiple sclerosis (odds ratio 2.7, $p<0.001$). An association between paediatric multiple sclerosis, viral infections, and *HLA-DR15*01* was also reported in a US cohort⁷⁶ (table 1).

In a study of 188 children with acquired demyelinating syndromes (53 of whom were diagnosed with multiple sclerosis) compared with 466 patients with adult-onset multiple sclerosis and 2046 adult controls,⁷⁷ 57 single nucleotide polymorphisms (SNPs) were identified through genome-wide association studies (GWAS); the frequency of these was preferentially detected in paediatric patients with multiple sclerosis compared with children with monophasic acquired demyelinating syndromes and was similar to the detection of these SNPs in the adult-onset multiple sclerosis cohort. Genetic studies in paediatric multiple sclerosis populations are challenged by the small sample sizes. Although the very large GWAS done in adult multiple sclerosis cohorts will not be replicated in the paediatric population, candidate gene regions implicated in adult studies can be assessed in children.

Several cohort studies have implicated vitamin D deficiency as a contributory factor to risk of multiple sclerosis in children^{2,78} and have shown a relationship between vitamin D concentrations and relapse rate.²⁷ Increased risk of multiple sclerosis has also been associated with adolescent obesity,²³ an association that might be confounded by the fact that obesity is also associated with low vitamin D in serum. However, in a multinational adult study in 1830 patients and 2015 controls,⁷⁹ low vitamin D concentrations were associated with an increased risk of multiple sclerosis in people with a history of adolescent obesity (defined as a body-mass index [BMI] of ≥ 27 kg/m² at the age of 20 years).

Although there is no evidence for a specific infectious cause of multiple sclerosis, exposure to specific viral and parasitic infections has been linked to both increased⁸⁰ and decreased multiple sclerosis risk.⁸¹ Serological evidence for remote infection with Epstein-Barr virus (EBV) is present in 85–88% of paediatric-onset patients with multiple sclerosis compared with 44–77% of regional healthy controls.^{16,26,82,83} Findings from one study⁸⁴ showed serum anti-EBNA1 titres to be higher in paediatric-onset multiple sclerosis patients compared with EBV-exposed healthy controls. In a 1-year study exploring immune control of latent EBV behaviour, the frequency of EBV DNA detection in monthly mouth swabs was 66% in paediatric EBV-positive patients with multiple sclerosis, compared with the expected frequency of 20% detected in age-matched and regional-matched healthy

controls.⁸⁵ Exposure to cytomegalovirus (CMV) has a negative predictive association with the risk of multiple sclerosis in paediatric onset²⁶ and adult onset.⁸⁶ Although herpes simplex virus (HSV) exposure did not affect risk alone, risk of multiple sclerosis was increased in patients with HSV exposure and one or more *HLA-DRB15* allele.²⁶

One study analysed genetic factors, viral exposures, and vitamin D status concurrently in children followed prospectively from incident acquired demyelinating syndromes.² The presence of all three of *HLA-DRB15* (one or two alleles), seropositivity for remote EBV infection, and low vitamin D concentrations were associated with multiple sclerosis outcome in 16 (57%) of 28 patients with an acquired demyelinating syndrome, whereas the remaining 12 (43%) with all three risk factors remained monophasic. Of 20 children with acquired demyelinating syndromes who had none of the three risk factors, only one (5%) has been diagnosed with multiple sclerosis to date, suggesting that the absence of all three risk factors might be protective.

CSF analyses

In a study⁸⁷ assessing the CSF features of 107 patients with paediatric-onset multiple sclerosis, the 40 children with onset <11 years had higher CSF white blood cells counts than the 67 adolescent-onset patients (ages 11–18 years). The younger children (<11 years) were also more likely to have neutrophils in the CSF compared with those aged 11–18 years. Intrathecal synthesis of immunoglobulins (OCBs) restricted to the CSF (ie, not present in serum) is a hallmark of multiple sclerosis. In the same study, CSF OCBs were detected in 21 (43%) of the younger patients, compared with 49 (63%) of the 11–18 year old patients with multiple sclerosis. In a study² of children with acquired demyelinating syndromes, OCBs were detected in 44 of 170 patients (26%, all aged <16 years), which increased to 60% (24 of 40) when children subsequently diagnosed with multiple sclerosis were considered alone. In a study of 88 paediatric patients with multiple sclerosis in Germany,⁵¹ 28 (60%) of 47 children younger than 11 years had OCBs detected at onset as compared with 30 (73%) of 41 of those older than 11 years. Repeat CSF analysis, done during subsequent attacks, showed OCBs in 43 (91%) of 47 younger children and 35 (85%) of 41 of the older group. Analysis of CSF IgM was also assessed by the German group, and showed the presence of intrathecal IgM synthesis in 44 (62%) of 70 children.⁸⁸ The absence of CSF IgM was associated with an increased relapse rate, particularly in the first 2 years of disease, and especially in girls. These findings have not yet been replicated in subsequent cohorts and seem to differ from findings regarding CSF IgM in adults.

A proteomic analysis was done on CSF obtained at onset from 19 children with acquired demyelinating syndromes, nine of whom were subsequently confirmed to have multiple sclerosis after a median period of observation of 4.88 years. Compact myelin antigens (traditionally viewed as potential disease targets in multiple sclerosis) were not detected in the CSF of the children who subsequently went on to develop multiple sclerosis compared with those with a monophasic acquired demyelinating syndrome. Of all CSF proteins, the concentrations of those that were known at the time to localise to the axoglial apparatus (the region of contact between the myelinating cell and the underlying axon),⁸⁹ were 41 times higher than those in children with monophasic acquired demyelinating syndromes. When

CSF was compared between the monophasic patients and those who developed multiple sclerosis, several axoglial apparatus proteins (OMGP, gliomedin, ADAM22, TENASCIN-R, and CASPR4) were differentially expressed in children with multiple sclerosis relative to children with monophasic acquired demyelinating syndromes. Replication of these findings and correlation with serum antibodies against axoglial proteins such as contactin-2 protein,⁹⁰ neurofascin-155, and neurofascin-186 (detected in adult patients with multiple sclerosis)⁹¹ will be of interest. Analysis of serum from 65 children with an acquired demyelinating syndrome did not identify antibodies to contactin-2 or contactin-associated protein 2 (CASPR2).⁹² CSF analysis in 25 patients with paediatric-onset multiple sclerosis and 67 paediatric and adult controls did not detect group differences in protein concentrations of the non-myelin proteins tau, phosphor-tau, or S-100B; the concentrations of these proteins can be increased in the context of CNS injury.⁹³ CSF tau concentrations were raised in the nine paediatric patients with multiple sclerosis from whom CSF was obtained during acute relapse, suggesting either a transient increase during acute insult, or perhaps that these patients with active disease have a greater CNS insult.

Serum antibodies

Serum antibodies directed against myelin proteins are detected in 25–50% of children with acute CNS demyelination.^{94–99} In a study of children with multiple sclerosis (25 of whom had paired serum and CSF samples) and 106 age-matched controls,⁹⁹ immunoblot analysis identified antibodies directed against both mature and immature myelin basic protein (MBP) in 22 (24%) of 91 patients with paediatric multiple sclerosis with a similar frequency (20%) in the controls. In the same study, some of the children with serum MBP antibodies also had anti-MBP antibodies in their CSF. The serum anti-myelin antibodies detected in these children were of high affinity, based on results of soluble-phase as well as plasmon-resonance (Biacore Life Sciences, Sweden) assays.

Several studies have explored antibody responses to MOG, a myelin protein expressed on the outermost myelin lamellae, and thus a potentially accessible antigenic target. Methods for myelin-antibody identification vary between studies, even when using cell-based assays.¹⁰⁰ With use of a cell-based assay in which MOG is expressed in its native conformation, high titre IgG antibody responses were detected in nine of 19 children with acute disseminated encephalomyelitis, nine of 25 children with clinically isolated syndrome (four diagnosed with multiple sclerosis), and in none of the healthy or those with other neurological disease controls.⁹⁸ Additionally, using a different cell-based assay, Rostasy and colleagues⁹⁵ identified anti-MOG antibodies in two of ten children with monophasic optic neuritis (with normal brain MRI), 12 of 15 children with recurrent optic neuritis (isolated relapses to the optic nerves and MRI not meeting criteria for multiple sclerosis), and in three of 12 children with optic neuritis as a first episode of multiple sclerosis. In a second study by the same authors,¹⁰¹ describing eight children with neuromyelitis optica spectrum disorders, three were positive for MOG, two were positive for antibodies against aquaporin-4, and three were seronegative for both MOG and aquaporin-4. Analysis of anti-MOG antibodies in 126 paediatric patients with acquired demyelinating syndromes with a cell-based assay showed that 31 patients had anti-MOG antibodies.⁹⁴ Findings from serial serum analyses showed persistent anti-MOG antibodies in six of eight children with acquired demyelinating

syndromes subsequently confirmed to have multiple sclerosis, but in none of the 16 patients with acute disseminated encephalomyelitis who had detectable anti-MOG antibodies at the time of their acute illness.⁹⁷ Finally, the presence of anti-MOG antibodies appeared to differentiate children with CNS demyelination from children with encephalitis.¹⁰²

Components of compact myelin might not be the only target of the immune response in children with CNS demyelination. Using an ELISA-based assay, serum antibodies directed against the potassium-rectifier channel KIR4.1 were detected in 27 (57%) of 47 children with acquired demyelinating syndromes and in none of 62 control individuals (44 with other diseases, 18 healthy children).¹⁰³ Serum from the KIR4.1-positive patients stained human brain tissue sections in a pattern similar to that reported in KIR4.1 antibody-positive adult patients with multiple sclerosis.¹⁰⁴ Serum MOG antibodies were not detected in the KIR4.1 patients, suggesting a distinct humoral profile. However, a more recent study did not detect KIR4.1 antibodies in serum and CSF of adult multiple sclerosis patients nor did it detect the loss of KIR4.1 expression in glia from multiple sclerosis lesions.¹⁰⁵

Cellular responses

Several studies have explored T-cell profiles and functional responses in paediatric multiple sclerosis cohorts. In a study focusing on regulatory T-cell subsets,¹⁰⁶ the proportion of circulating naive and regulatory T cells and recent thymic emigrants was compared between 30 paediatric patients with multiple sclerosis, 67 age-matched paediatric controls, and 26 adults. The T-cell profile of the paediatric patients with multiple sclerosis differed from the age-expected profile (characterised by a high proportion of naive T cells relative to regulatory T cells, and by a relative paucity of recent thymic emigrants) and seemed more similar to the profile expected in adults, suggesting that paediatric patients with multiple sclerosis have premature ageing of their immune profile. Furthermore, regulatory T cells in the paediatric patients with multiple sclerosis had reduced suppressive capacity compared with age-matched controls, indicating a functional defect in immune control. In a study focusing on effector immune responses,¹⁰⁷ T-cell reactivities to myelin were assessed in ten untreated paediatric-onset patients with multiple sclerosis, ten adult-onset patients with multiple sclerosis, and 20 age-matched controls. Although T-cell reactivities against myelin could be shown in all cohorts, they were greatest in the paediatric patients with multiple sclerosis. T cells from the paediatric patients with multiple sclerosis also had a higher expression of interleukin 17 compared with control individuals, suggesting a heightened Th17 central memory response in paediatric multiple sclerosis.

Treatment

Care of children and adolescents with multiple sclerosis needs input from a multidisciplinary team. Medical, psychological, and cognitive assessments, psychiatric care when required, and social work support to enable access to therapies, resources, and to educate the school system regarding multiple sclerosis are essential.¹⁰⁸

The safety and tolerability of first-line immuno-modulatory therapies in children show an overall high-safety profile.^{109–113} Transient increase of liver transaminases is the most notable side-effect of interferon- β therapy, although this seems to be less commonly noted

when treatment is initiated at a quarter of the targeted full dose and titrated gradually. Transaminase increase might resolve with reduction in dose, and such patients might subsequently tolerate escalation to full dose after a period of time. In a study¹¹¹ including more than 300 patients, the safety profile of interferon beta-1a was similar to that observed in adults, even in children younger than 12 years. No major adverse events have been reported in children treated with glatiramer acetate, although hepatotoxicity was reported in one patient.¹¹⁴

The rationale for prompt initiation of first-line therapies in children and adolescents was reviewed by the International Paediatric Multiple Sclerosis Study Group (IPMSSG)¹¹⁵ and by a European consensus group.¹¹⁶ The consensus statement advocates offering therapy to all patients diagnosed with multiple sclerosis, because there are no reliable means to identify patients destined to have few relapses.

Several new drugs have been approved (not all drugs are approved in all countries) for adult patients with multiple sclerosis, and include oral and infusion-based therapies. None to date have been studied in paediatric multiple sclerosis, although future trials are expected. Key considerations for the use of several of these drugs in the paediatric multiple sclerosis population have been the subject of recent reviews^{117,118} and have been discussed by the IPMSSG.^{115,119}

Advocacy for new treatments is based on three factors: the inability of around 30% of paediatric patients with multiple sclerosis to tolerate first-line injectable therapies;¹¹⁸ a general preference among paediatric patients for oral as opposed to injectable treatments; and novel mechanisms of action that might render a new therapy effective in patients with inadequate treatment response to interferon-beta or glatiramer acetate. Criteria to define patients with poor response to first-line treatments are not standardised. The IPMSSG has proposed guidelines for assessment of first-line treatment efficacy, which require that patients first receive a minimum of compliant exposure to full-dose therapy for 6 months. After this initial treatment phase, an inadequate response is defined by three factors: an increase or no reduction in relapse rate over the next 12 months compared with that in the pre-treatment period; new T2 or contrast enhancing lesions on MRI from pre-treatment period; or two or more confirmed clinical relapses within a 12-month period.¹¹⁵

The decision to initiate second-line therapies needs careful assessment of the risk-to-benefit profile. At present, the most promising treatment is natalizumab because of its clear capacity to reduce relapse rate and substantially reduce MRI activity,^{120–125} although no paediatric trials have been done with this drug. The major risk of natalizumab is active cerebral infection with JC virus, leading to the development of progressive multifocal leukoencephalopathy. The risk of progressive multifocal leukoencephalopathy is negligible in patients who are naive to the JC virus and remain unexposed throughout treatment with natalizumab. Since primary JC virus infection is thought to occur in late adolescence or early adulthood, a portion of patients with paediatric multiple sclerosis might have a low risk of exposure. Tests for anti-JC virus antibodies in high-quality laboratories are essential for estimation of risk and for ongoing monitoring of treated patients. In patients exposed to the JC virus, the risk of progressive multifocal leuko-encephalopathy can be estimated as a

function of duration of treatment with natalizumab, and is highest in patients treated with other immunosuppressant therapies (such as cyclophosphamide, mitoxantrone, azathioprine) before initiation of natalizumab. Owing to acute toxic effects and long-term cancer risk, use of cyclophosphamide and mitoxantrone in paediatric multiple sclerosis is infrequent in countries with access to natalizumab.

Conclusions and future directions

To date, the clinical features and outcomes of children with acquired demyelinating syndromes have largely been derived from studies in regions of high multiple sclerosis prevalence. Whether the clinical features and outcome of acquired demyelinating syndromes differ in world regions where multiple sclerosis is very rare, such as in Africa and equatorial countries, will be interesting to investigate.

Application of standardised MRI acquisition protocols and scoring methods for both clinical and research quality images are essential for multicentre collaboration. Use of advanced imaging technology provides a window into the effect of multiple sclerosis on regional tissue injury and failure of age-expected brain growth, the extent of which correlates with cognition. Finally, functional MRI studies will provide insight into compensatory and dysfunctional activation of neural networks, with a novel potential to inform on the consequences of multiple sclerosis in networks not yet mature at the time of disease onset.

The past several years have supported the notion of a shared risk profile for paediatric-onset and adult-onset multiple sclerosis. Serum and CSF antibody profiles suggest heightened immunological responses against MOG that seem most prominent in young children with demyelination, might be transient in acute disseminated encephalomyelitis, and might be particularly prevalent in children with relapsing optic neuritis. Findings from studies of immune cell subsets have shown a relative reduction in naive immune cells, reduced numbers of recent thymic emigrants, and a derangement in the regulatory immune cell pool, observations that raise the intriguing possibility of premature senescence of particular immune cell substrates in patients with paediatric-onset multiple sclerosis.

Care of patients with paediatric multiple sclerosis will be improved by high-quality data of treatment safety and efficacy, and before the use of therapies in children we must ensure that both of these metrics in paediatric multiple sclerosis patients are indeed similar to those in adults. Regulatory authorities in North America and Europe require paediatric investigation plans to be proposed for all emerging treatments approved for adult multiple sclerosis. Clinical trials in paediatric multiple sclerosis need multicentre, international enrolment to achieve sufficient patient numbers for analysis, one of several challenges articulated in the proceedings of an international meeting on this topic.¹¹⁹ Pivotal phase 3 trials are typically powered for clinical endpoints (relapse rate, time to first relapse, time to confirmed clinical disability, EDSS score, or proportion of patients with confirmed disability progression). In paediatric multiple sclerosis, although relapse rates early in the disease might exceed those of adult cohorts,⁵² the number of patients needed to show treatment efficacy, with relapses as a primary outcome, is prohibitively high. MRI detection of new lesions occurs in adult patients with multiple sclerosis at a far greater frequency than clinically appreciated relapses

do, and thus new or enlarging T2 lesions have served as key outcome metrics in phase 2 adult multiple sclerosis trials.¹²⁶ An analysis¹²⁷ of lesion accrual in paediatric patients followed-up prospectively from first attack estimates the number of patients needed to show differences in treatment effect in a paediatric multiple sclerosis clinical trial. Secondary MRI metrics, such as brain volume, can also be measured, although the restricted extent of change in measurable brain volume in short duration trials and the potential confounders of acute relapse treatment and the corticosteroid-associated transient flux in brain volume must be considered. Paediatric multiple sclerosis is a rare disease and thus the potential to enrol sufficient patients to power meaningful trials of many drugs concurrently, even with international collaboration, will be severely restricted. Wise stewardship of clinical trials for children and adolescents with multiple sclerosis must occur, and is a major area of focus of the IPMSSG and its members.

Increased recognition of paediatric multiple sclerosis has led to an improved understanding of the clinical features, especially those that characterise multiple sclerosis in very young children. Genetic, serum, CSF, and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease and, when studied in children at the time of first attack, provide particular insight into the biological signature of disease.

The detection of cognitive impairment in paediatric patients with multiple sclerosis and MRI evidence of global and focal loss of age-expected brain volume suggest that the neurodegenerative aspect of multiple sclerosis is not a late sequela of long-standing disease, and that this degeneration is not mitigated by the resiliency of youth, emphasising the need for discovery of neuroprotective strategies for all patients with multiple sclerosis.

Although evidence to date suggests that multiple sclerosis is one disease manifesting across the age span, the age of multiple sclerosis onset plays a pivotal part in the effect of the disease. Just as children are not small teenagers, adolescents are not small adults. At a biological level, primary myelination continues into early adulthood, which might affect regional lesion formation and myelin repair capacity. Maturation of neural networks through childhood and adolescence substantially affects regional expression of excitatory and inhibitory synapses, and thus connectivity and compensatory network formation in paediatric patients with multiple sclerosis might be fundamentally different from the connectivity enabled in the mature CNS of an adult patient with multiple sclerosis. Functional MRI studies and analyses directed at myelin integrity are exciting avenues of ongoing research. Finally, as the number of therapies for multiple sclerosis increases, clinicians must assume a depth of knowledge regarding the mechanism of action of each therapy, immunological effect and monitoring requirements, infection and other risks, and rationale for treatment selection and for escalation or change of therapeutics. Most paediatric neurology training programmes do not currently provide such education, necessitating ongoing medical education of clinicians and partnerships with other specialties that are familiar with immunosuppressive therapies.

Acknowledgments

We thank the Canadian Multiple Sclerosis Society and the Canadian Multiple Sclerosis Scientific Research Foundation, the Children's Hospital of Philadelphia Foundation, the Italian centres involved in the Italian

prospective study of early onset multiple sclerosis, the ITEMS study group, and the Société Française de Neurologie Pédiatrique. AW is supported by a K23 award, US National Institutes of Health. BB is supported by the Multiple Sclerosis Scientific Research Foundation of Canada, and the Children's Hospital of Philadelphia. MT is supported by Institut National de la Recherche Médicale, Université Paris Sud 11, Assistance Publique-Hôpitaux de Paris. AB-O is supported by the Multiple Sclerosis Scientific Research Foundation of Canada and the Canadian Institutes of Health Research.

References

1. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *Lancet Neurol.* 2007; 6:887–902. [PubMed: 17884679]
2. 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; 10:436–45. [PubMed: 21459044]
3. Krupp LB, Banwell B, Tenenbaum S. International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology.* 2007; 68(suppl 2):S7–12. [PubMed: 17438241]
4. Krupp LB, Tardieu M, Amato MP, et al. the 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; 19:1261–67. [PubMed: 23572237]
5. Huppke P, Rostasy K, Karenfort M, et al. Acute disseminated encephalomyelitis followed by recurrent or monophasic optic neuritis in pediatric patients. *Mult Scler.* 2013; 19:941–46. [PubMed: 23128668]
6. Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy: a systematic review of 122 cases reported. *J Neurol.* 2014; 261:17–26. [PubMed: 23700317]
7. Kidd D, Burton B, Plant GT, Graham EM. Chronic relapsing inflammatory optic neuropathy (CRION). *Brain.* 2003; 126:276–84. [PubMed: 12538397]
8. Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. *J Neurol.* 2012; 259:1929–35. [PubMed: 22349866]
9. Reinhardt K, Weiss S, Rosenbauer J, Gärtner J, von Kries R. Multiple sclerosis in children and adolescents: incidence and clinical picture—new insights from the nationwide German surveillance (2009–2011). *Eur J Neurol.* 2014; 21:654–59. [PubMed: 24471864]
10. Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. *Neurology.* 2011; 77:1143–48. [PubMed: 21865580]
11. Absoud M, Lim MJ, Chong WK, et al. the UK and Ireland Childhood CNS Inflammatory Demyelination Working Group. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. *Mult Scler.* 2013; 19:76–86. [PubMed: 22516794]
12. Tantsis EM, Prelog K, Brilot F, Dale RC. Risk of multiple sclerosis after a first demyelinating syndrome in an Australian Paediatric cohort: clinical, radiological features and application of the McDonald 2010 MRI criteria. *Mult Scler.* 2013; 19:1749–59. [PubMed: 23579092]
13. Mikaeloff Y, Adamsbaum C, Husson B, et al. the KIDMUS Study Group on Radiology. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain.* 2004; 127:1942–47. [PubMed: 15289266]
14. Dale RC, Pillai SC. Early relapse risk after a first CNS inflammatory demyelination episode: examining international consensus definitions. *Dev Med Child Neurol.* 2007; 49:887–93. [PubMed: 18039234]
15. Simone IL, Carrara D, Tortorella C, Ceccarelli A, Livrea P. Early onset multiple sclerosis. *Neurol Sci.* 2000; 21 (suppl 2):S861–63. [PubMed: 11205364]
16. 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; 6:773–81. [PubMed: 17689148]

17. Renoux C, Vukusic S, Mikaeloff Y, et al. the Adult Neurology Departments KIDMUS Study Group. Natural history of multiple sclerosis with childhood onset. *N Engl J Med.* 2007; 356:2603–13. [PubMed: 17582070]
18. Fromont A, Binquet C, Sauleau EA, et al. Geographic variations of multiple sclerosis in France. *Brain.* 2010; 133:1889–99. [PubMed: 20551111]
19. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler.* 2009; 15:627–31. [PubMed: 19299440]
20. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry.* 2013; 84:141–47. [PubMed: 23154123]
21. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology.* 2009; 72:232–39. [PubMed: 19153370]
22. 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; 166:405–12. [PubMed: 17219129]
23. Langer-Gould A, Brara SM, Beaver BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. *Neurology.* 2013; 80:548–52. [PubMed: 23365063]
24. Mikaeloff Y, Caridade G, Tardieu M, Suissa S. the KIDSEP study group. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. *Brain.* 2007; 130:2589–95. [PubMed: 17827175]
25. Disanto G, Magalhaes S, Handel AE, et al. the Canadian Pediatric Demyelinating Disease Network. HLA-DRB1 confers increased risk of pediatric-onset MS in children with acquired demyelination. *Neurology.* 2011; 76:781–86. [PubMed: 21288988]
26. Waubant E, Mowry EM, Krupp L, et al. the US Pediatric MS Network. Common viruses associated with lower pediatric multiple sclerosis risk. *Neurology.* 2011; 76:1989–95. [PubMed: 21646624]
27. Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol.* 2010; 67:618–24. [PubMed: 20437559]
28. O'Mahony J, Shroff M, Banwell B. Mimics and rare presentations of pediatric demyelination. *Neuroimaging Clin N Am.* 2013; 23:321–36. [PubMed: 23608693]
29. Verhey LH, Branson HM, Shroff MM, et al. the Canadian Pediatric Demyelinating Disease Network. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol.* 2011; 10:1065–73. [PubMed: 22067635]
30. Yeh EA, Weinstock-Guttman B, Ramanathan M, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. *Brain.* 2009; 132:3392–400. [PubMed: 19892770]
31. Chitnis T, Guttman CR, Zaitsev A, et al. Quantitative MRI analysis in children with multiple sclerosis: a multicenter feasibility pilot study. *BMC Neurol.* 2013; 13:173. [PubMed: 24225378]
32. Verhey LH, Shroff M, Banwell B. Pediatric multiple sclerosis: pathobiological, clinical, and magnetic resonance imaging features. *Neuroimaging Clin N Am.* 2013; 23:227–43. [PubMed: 23608687]
33. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006; 66:1485–89. [PubMed: 16717206]
34. Trebst C, Jarius S, Berthele A, et al. the Neuromyelitis Optica Study Group (NEMOS). Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol.* 2014; 261:1–16. [PubMed: 24272588]
35. Cheng C, Jiang Y, Chen X, et al. Clinical, radiographic characteristics and immunomodulating changes in neuromyelitis optica with extensive brain lesions. *BMC Neurol.* 2013; 13:72. [PubMed: 23819854]
36. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. *Neurology.* 2008; 71:93–100. [PubMed: 18509092]

37. Mayer MC, Breithaupt C, Reindl M, et al. Distinction and temporal stability of conformational epitopes on myelin oligodendrocyte glycoprotein recognized by patients with different inflammatory central nervous system diseases. *J Immunol.* 2013; 191:3594–604. [PubMed: 24014878]
38. Benseler S, Schneider R. Central nervous system vasculitis in children. *Curr Opin Rheumatol.* 2004; 16:43–50. [PubMed: 14673388]
39. Benseler SM, Silverman E, Aviv RI, et al. Primary central nervous system vasculitis in children. *Arthritis Rheum.* 2006; 54:1291–97. [PubMed: 16575852]
40. Callen DJ, Shroff MM, Branson HM, et al. Role of MRI in the differentiation of ADEM from MS in children. *Neurology.* 2009; 72:968–73. [PubMed: 19038851]
41. Hahn JS, Pohl D, Rensel M, Rao S. the International Pediatric MS Study Group. Differential diagnosis and evaluation in pediatric multiple sclerosis. *Neurology.* 2007; 68(suppl 2):S13–22. [PubMed: 17438234]
42. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983; 13:227–31. [PubMed: 6847134]
43. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011; 69:292–302. [PubMed: 21387374]
44. Sedani S, Lim MJ, Hemingway C, Wassmer E, Absoud M. Paediatric multiple sclerosis: examining utility of the McDonald 2010 criteria. *Mult Scler.* 2012; 18:679–82. [PubMed: 22013145]
45. Hummel HM, Brück W, Dreha-Kulaczewski S, Gärtner J, Wuerfel J. Pediatric onset multiple sclerosis: McDonald criteria 2010 and the contribution of spinal cord MRI. *Mult Scler.* 2013; 19:1330–35. [PubMed: 23828866]
46. Kornek B, Schmitl B, Vass K, et al. Evaluation of the 2010 McDonald multiple sclerosis criteria in children with a clinically isolated syndrome. *Mult Scler.* 2012; 18:1768–74. [PubMed: 22526931]
47. Sadaka Y, Verhey LH, Shroff MM, et al. the Canadian Pediatric Demyelinating Disease Network. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. *Ann Neurol.* 2012; 72:211–23. [PubMed: 22926854]
48. Waldman AT, Gorman MP, Rensel MR, Austin TE, Hertz DP, Kuntz NL. the Network of Pediatric Multiple Sclerosis Centers of Excellence of National Multiple Sclerosis Society. . Management of pediatric central nervous system demyelinating disorders: consensus of United States neurologists. *J Child Neurol.* 2011; 26:675–82. [PubMed: 21518802]
49. Verhey LH, Branson HM, Makhija M, Shroff M, Banwell B. Magnetic resonance imaging features of the spinal cord in pediatric multiple sclerosis: a preliminary study. *Neuroradiology.* 2010; 52:1153–62. [PubMed: 20721543]
50. Bigi S, Marrie RA, Verhey L, Yeh EA, Banwell B. 2010 McDonald criteria in a pediatric cohort: is positivity at onset associated with a more aggressive multiple sclerosis course? *Mult Scler.* 2013; 19:1359–62. [PubMed: 23620544]
51. Huppke B, Ellenberger D, Rosewich H, Friede T, Gärtner J, Huppke P. Clinical presentation of pediatric multiple sclerosis before puberty. *Eur J Neurol.* 2014; 21:441–46. [PubMed: 24330201]
52. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol.* 2009; 66:54–59. [PubMed: 19139299]
53. Till C, Ghassemi R, Aubert-Broche B, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. *Neuropsychology.* 2011; 25:319–32. [PubMed: 21534686]
54. Amato MP, Goretti B, Ghezzi A, et al. the Multiple Sclerosis Study Group of the Italian Neurological Society. . Cognitive and psychosocial features of childhood and juvenile MS. *Neurology.* 2008; 70:1891–97. [PubMed: 18474844]
55. Julian L, Serafin D, Charvet L, et al. the 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; 28:102–07. [PubMed: 23155206]
56. Till C, Deotto A, Tipu V, et al. White matter integrity and math performance in pediatric multiple sclerosis: a diffusion tensor imaging study. *Neuroreport.* 2011; 22:1005–09. [PubMed: 22045260]

57. Till C, Racine N, Araujo D, et al. Changes in cognitive performance over a 1-year period in children and adolescents with multiple sclerosis. *Neuropsychology*. 2013; 27:210–19. [PubMed: 23527649]
58. Amato MP, Goretti B, Ghezzi A, et al. the Multiple Sclerosis Study Group of the Italian Neurological Society. . Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. *Neurology*. 2010; 75:1134–40. [PubMed: 20876467]
59. Ghassemi R, Antel SB, Narayanan S, et al. the Canadian Pediatric Demyelinating Disease Study Group. . Lesion distribution in children with clinically isolated syndromes. *Ann Neurol*. 2008; 63:401–05. [PubMed: 18306242]
60. Ghassemi R, Narayanan S, Banwell B, Sled JG, Shroff M, Arnold DL. the Canadian Pediatric Demyelinating Disease Network. . Quantitative determination of regional lesion volume and distribution in children and adults with relapsing-remitting multiple sclerosis. *PLoS One*. 2014; 9:e85741. [PubMed: 24586244]
61. Verhey LH, Branson HM, Laughlin S, et al. Development of a standardized MRI scoring tool for CNS demyelination in children. *AJNR Am J Neuroradiol*. 2013; 34:1271–77. [PubMed: 23348761]
62. Filippi M, Absinta M, Rocca MA. Future MRI tools in multiple sclerosis. *J Neurol Sci*. 2013; 331:14–18. [PubMed: 23706475]
63. Tillema JM, Leach J, Pirko I. Non-lesional white matter changes in pediatric multiple sclerosis and monophasic demyelinating disorders. *Mult Scler*. 2012; 18:1754–59. [PubMed: 22641299]
64. Mezzapesa DM, Rocca MA, Falini A, et al. A preliminary diffusion tensor and magnetization transfer magnetic resonance imaging study of early-onset multiple sclerosis. *Arch Neurol*. 2004; 61:366–68. [PubMed: 15023813]
65. Bethune A, Tipu V, Sled JG, et al. Diffusion tensor imaging and cognitive speed in children with multiple sclerosis. *J Neurol Sci*. 2011; 309:68–74. [PubMed: 21821263]
66. Blaschek A, Keeser D, Müller S, et al. Early white matter changes in childhood multiple sclerosis: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2013; 34:2015–20. [PubMed: 23681354]
67. Vishwas MS, Chitnis T, Pienaar R, Healy BC, Grant PE. Tract-based analysis of callosal, projection, and association pathways in pediatric patients with multiple sclerosis: a preliminary study. *AJNR Am J Neuroradiol*. 2010; 31:121–28. [PubMed: 19850763]
68. Arnold DL. Evidence for neuroprotection and remyelination using imaging techniques. *Neurology*. 2007; 68 (suppl 3):S83–90. discussion S91–96. [PubMed: 17548574]
69. Brown RA, Narayanan S, Arnold DL. Segmentation of magnetization transfer ratio lesions for longitudinal analysis of demyelination and remyelination in multiple sclerosis. *Neuroimage*. 2012; 66C:103–09. [PubMed: 23110887]
70. Oguz KK, Kurne A, Aksu AO, Taskiran A, Karabulut E, Karabudak R. A comparative assessment of cerebral white matter by magnetization transfer imaging in early- and adult-onset multiple sclerosis patients matched for disease duration. *J Neurol*. 2010; 257:1309–15. [PubMed: 20221767]
71. Aubert-Broche B, Fonov V, Ghassemi R, et al. Regional brain atrophy in children with multiple sclerosis. *Neuroimage*. 2011; 58:409–15. [PubMed: 21414412]
72. 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; 78:194–201. [PubMed: 22218275]
73. Sacco, R.; Bonavita, S.; Esposito, F.; Tedeschi, G.; Gallo, A. The contribution of resting state networks to the study of cortical reorganization in MS. *Mult Scler Int*. 2013. published online Oct 31. <http://dx.doi.org/10.1155/2013/857807>
74. Rocca MA, Absinta M, Moiola L, et al. Functional and structural connectivity of the motor network in pediatric and adult-onset relapsing-remitting multiple sclerosis. *Radiology*. 2010; 254:541–50. [PubMed: 20093525]
75. Rocca MA, Absinta M, Ghezzi A, Moiola L, Comi G, Filippi M. Is a preserved functional reserve a mechanism limiting clinical impairment in pediatric MS patients? *Hum Brain Mapp*. 2009; 30:2844–51. [PubMed: 19107755]

76. Waubant E, Mowry EM, Krupp L, et al. Antibody response to common viruses and human leukocyte antigen-DRB1 in pediatric multiple sclerosis. *Mult Scler*. 2013; 19:891–95. [PubMed: 23232601]
77. van Pelt ED, Mescheriakova JY, Makhani N, et al. Risk genes associated with pediatric-onset MS but not with monophasic acquired CNS demyelination. *Neurology*. 2013; 81:1996–2001. [PubMed: 24198294]
78. Mowry EM, James JA, Krupp LB, Waubant E. Vitamin D status and antibody levels to common viruses in pediatric-onset multiple sclerosis. *Mult Scler*. 2011; 17:666–71. [PubMed: 21212086]
79. Hedström AK, Lima Bomfim I, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. *Neurology*. 2014; 82:865–72. [PubMed: 24500647]
80. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. *Lancet Neurol*. 2010; 9:727–39. [PubMed: 20610348]
81. Correale J, Farez M, Razzitte G. Helminth infections associated with multiple sclerosis induce regulatory B cells. *Ann Neurol*. 2008; 64:187–99. [PubMed: 18655096]
82. Alotaibi S, Kennedy J, Tellier R, Stephens D, Banwell B. Epstein-Barr virus in pediatric multiple sclerosis. *JAMA*. 2004; 291:1875–79. [PubMed: 15100207]
83. Pohl D, Krone B, Rostasy K, et al. High seroprevalence of Epstein-Barr virus in children with multiple sclerosis. *Neurology*. 2006; 67:2063–65. [PubMed: 17159123]
84. Lünemann JD, Huppke P, Roberts S, Brück W, Gärtner J, Münz C. Broadened and elevated humoral immune response to EBNA1 in pediatric multiple sclerosis. *Neurology*. 2008; 71:1033–35. [PubMed: 18809840]
85. Yea C, Tellier R, Chong P, et al. the Canadian Pediatric Demyelinating Disease Network. . Epstein-Barr virus in oral shedding of children with multiple sclerosis. *Neurology*. 2013; 81:1392–99. [PubMed: 24014504]
86. Sundqvist E, Bergström T, Daialhosein H, et al. Cytomegalovirus seropositivity is negatively associated with multiple sclerosis. *Mult Scler*. 2014; 20:165–73. [PubMed: 23999606]
87. Chabas D, Ness J, Belman A, et al. the US Network of Pediatric MS Centers of Excellence. Younger children with MS have a distinct CSF inflammatory profile at disease onset. *Neurology*. 2010; 74:399–405. [PubMed: 20124205]
88. Stauch C, Reiber H, Rauchenzauner M, et al. Intrathecal IgM synthesis in pediatric MS is not a negative prognostic marker of disease progression: quantitative versus qualitative IgM analysis. *Mult Scler*. 2011; 17:327–34. [PubMed: 21123302]
89. Dhaunchak AS, Becker C, Schulman H, et al. the Canadian Pediatric Demyelinating Disease Group. Implication of perturbed axoglial apparatus in early pediatric multiple sclerosis. *Ann Neurol*. 2012; 71:601–13. [PubMed: 22473675]
90. Boronat A, Sepúlveda M, Llufríu S, et al. Analysis of antibodies to surface epitopes of contactin-2 in multiple sclerosis. *J Neuroimmunol*. 2012; 244:103–06. [PubMed: 22245283]
91. Mathey EK, Derfuss T, Storch MK, et al. Neurofascin as a novel target for autoantibody-mediated axonal injury. *J Exp Med*. 2007; 204:2363–72. [PubMed: 17846150]
92. Hachohen Y, Absoud M, Woodhall M, et al. the UK & Ireland Childhood CNS Inflammatory Demyelination Working Group. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. *J Neurol Neurosurg Psychiatry*. 2014; 85:456–61. [PubMed: 24133290]
93. Rostasy K, Withut E, Pohl D, et al. Tau, phospho-tau, and S-100B in the cerebrospinal fluid of children with multiple sclerosis. *J Child Neurol*. 2005; 20:822–25. [PubMed: 16417878]
94. McLaughlin KA, Chitnis T, Newcombe J, et al. Age-dependent B cell autoimmunity to a myelin surface antigen in pediatric multiple sclerosis. *J Immunol*. 2009; 183:4067–76. [PubMed: 19687098]
95. Rostasy K, Mader S, Schanda K, et al. Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis. *Arch Neurol*. 2012; 69:752–56. [PubMed: 22371853]
96. Van Haren K, Tomooka BH, Kidd BA, et al. Serum autoantibodies to myelin peptides distinguish acute disseminated encephalomyelitis from relapsing-remitting multiple sclerosis. *Mult Scler*. 2013; 19:1726–33. [PubMed: 23612879]

97. Pröbstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. *Neurology*. 2011; 77:580–88. [PubMed: 21795651]
98. Selter RC, Brilot F, Grummel V, et al. Antibody responses to EBV and native MOG in pediatric inflammatory demyelinating CNS diseases. *Neurology*. 2010; 74:1711–15. [PubMed: 20410464]
99. O'Connor KC, Lopez-Amaya C, Gagne D, et al. Anti-myelin antibodies modulate clinical expression of childhood multiple sclerosis. *J Neuroimmunol*. 2010; 223:92–99. [PubMed: 20381173]
100. Reindl M, Di Pauli F, Rostásy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. *Nat Rev Neurol*. 2013; 9:455–61. [PubMed: 23797245]
101. Rostásy K, Mader S, Hennes EM, et al. Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica. *Mult Scler*. 2013; 19:1052–59. [PubMed: 23257621]
102. Lalive PH, Häusler MG, Maurey H, et al. Highly reactive anti-myelin oligodendrocyte glycoprotein antibodies differentiate demyelinating diseases from viral encephalitis in children. *Mult Scler*. 2011; 17:297–302. [PubMed: 21177754]
103. Kraus V, Srivastava R, Kalluri SR, et al. Potassium channel KIR4.1-specific antibodies in children with acquired demyelinating CNS disease. *Neurology*. 2014; 82:470–73. [PubMed: 24415573]
104. Srivastava R, Aslam M, Kalluri SR, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. *N Engl J Med*. 2012; 367:115–23. [PubMed: 22784115]
105. Brickshawana A, Hinson SR, Romero MF, et al. Investigation of the KIR4.1 potassium channel as a putative antigen in patients with multiple sclerosis: a comparative study. *Lancet Neurol*. 2014; 13:765–806.
106. Balint B, Haas J, Schwarz A, et al. T-cell homeostasis in pediatric multiple sclerosis: old cells in young patients. *Neurology*. 2013; 81:784–92. [PubMed: 23911752]
107. Vargas-Lowy D, Kivisäkk P, Gandhi R, et al. Increased Th17 response to myelin peptides in pediatric MS. *Clin Immunol*. 2013; 146:176–84. [PubMed: 23352968]
108. Yeh EA. Management of children with multiple sclerosis. *Paediatr Drugs*. 2012; 14:165–77. [PubMed: 22497553]
109. Ghezzi A. the Immunomodulatory Treatment of Early Onset MS (ITEMS) Group. Immunomodulatory treatment of early onset multiple sclerosis: results of an Italian Co-operative Study. *Neurol Sci*. 2005; 26(suppl 4):S183–86. [PubMed: 16388355]
110. Tenenbaum SN, Segura MJ. Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. *Neurology*. 2006; 67:511–13. [PubMed: 16775230]
111. Tenenbaum SN, Banwell B, Pohl D, et al. the REPLAY Study Group. Subcutaneous interferon Beta-1a in pediatric multiple sclerosis: a retrospective study. *J Child Neurol*. 2013; 28:849–56. [PubMed: 23666046]
112. Kornek B, Bernert G, Balassy C, Geldner J, Prayer D, Feucht M. Glatiramer acetate treatment in patients with childhood and juvenile onset multiple sclerosis. *Neuropediatrics*. 2003; 34:120–26. [PubMed: 12910434]
113. Banwell B, Reder AT, Krupp L, et al. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. *Neurology*. 2006; 66:472–76. [PubMed: 16505297]
114. Makhani N, Ngan BY, Kamath BM, Yeh EA. Glatiramer acetate-induced acute hepatotoxicity in an adolescent with MS. *Neurology*. 2013; 81:850–52. [PubMed: 23884038]
115. Chitnis T, Tenenbaum S, Banwell B, et al. the International Pediatric Multiple Sclerosis Study Group. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult Scler*. 2012; 18:116–27. [PubMed: 22146610]
116. Ghezzi A, Banwell B, Boyko A, et al. The management of multiple sclerosis in children: a European view. *Mult Scler*. 2010; 16:1258–67. [PubMed: 20685764]
117. Banwell B, Bar-Or A, Giovannoni G, Dale RC, Tardieu M. Therapies for multiple sclerosis: considerations in the pediatric patient. *Nat Rev Neurol*. 2011; 7:109–22. [PubMed: 21224883]
118. Yeh EA, Waubant E, Krupp LB, et al. the National Network of Pediatric MS Centers of Excellence. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. *Arch Neurol*. 2011; 68:437–44. [PubMed: 21149803]

119. Chitnis T, Tardieu M, Amato MP, et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. *Neurology*. 2013; 80:1161–68. [PubMed: 23509048]
120. Ghezzi A, Pozzilli C, Grimaldi LM, et al. Safety and efficacy of natalizumab in children with multiple sclerosis. *Neurology*. 2010; 75:912–17. [PubMed: 20820002]
121. Ghezzi A, Pozzilli C, Grimaldi LM, et al. the Italian MS Study Group. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. *Mult Scler*. 2013; 19:1106–12. [PubMed: 23401129]
122. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. *JAMA Neurol*. 2013; 70:469–75. [PubMed: 23420110]
123. Arnal-Garcia C, García-Montero MR, Málaga I, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. *Eur J Paediatr Neurol*. 2013; 17:50–54. [PubMed: 23021975]
124. Yeh EA, Weinstock-Guttman B. Natalizumab in pediatric multiple sclerosis patients. *Ther Adv Neurol Disord*. 2010; 3:293–99. [PubMed: 21179619]
125. Huppke P, Stark W, Zürcher C, Huppke B, Brück W, Gärtner J. Natalizumab use in pediatric multiple sclerosis. *Arch Neurol*. 2008; 65:1655–58. [PubMed: 19064754]
126. Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol*. 2009; 65:268–75. [PubMed: 19334061]
127. Verhey LH, Signori A, Arnold DL, et al. Clinical and MRI activity as determinants of sample size for pediatric multiple sclerosis trials. *Neurology*. 2013; 81:1215–21. [PubMed: 23966255]

Panel: Current clinical definitions**Paediatric monophasic acute disseminated encephalomyelitis¹**

1. A first polyfocal clinical event affecting the central nervous system.
2. Encephalopathy defined as alteration in consciousness that is not due to fever, systemic illness, or a postictal phase.
3. Abnormal brain MRI within the first 3 months of clinical symptoms, typically demonstrates:
 - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly affecting the white matter.
 - Lesions in the thalamus, basal ganglia, deep grey matter, or spinal cord (typically longitudinally extensive) are also common.
4. After the first 3 months from symptom onset, no new clinical symptoms or MRI abnormalities are found.

Multiphasic acute disseminated encephalomyelitis¹

1. Two clinical events meeting criteria for acute disseminated encephalomyelitis, separated in time by greater than 3 months.
2. No evidence for clinically-silent new lesion formation on MRI between acute disseminated encephalomyelitis episodes.

Paediatric clinically isolated syndrome (all are required)¹

1. A first monofocal or polyfocal clinical event affecting the central nervous system.
2. Encephalopathy is not present (unless transient and caused by fever).
3. For patients between 12–18 years, the 2010 McDonald MRI criteria for dissemination in space and time as applied to the baseline MRI are not met.

Paediatric multiple sclerosis^{1,2}

1. Two clinical events (without encephalopathy) both consistent with attacks typical of MS, separated by more than 30 days, and affecting more than one area of the brain, optic nerves, or spinal cord.
2. A first clinical event consistent with multiple sclerosis in a patient between 12–18 years who fulfills the 2010 McDonald MRI dissemination in space (≥ 1 T2 lesion in two of the four following locations: periventricular, juxtacortical, infratentorial, or spinal cord), and dissemination in time (clinically-silent enhancing or non-enhancing on T1-weighted images) criteria on baseline MRI.
3. One clinical event (without encephalopathy) typical of multiple sclerosis and MRI demonstrating at least one new T2 lesion on a scan more than 30 days after the incident attack.

4. An event that fulfills criteria initially for acute disseminated encephalomyelitis, followed by a second non-acute disseminated encephalomyelitis event (>3 months from symptom onset) associated with new MRI lesions demonstrating 2010 McDonald dissemination in space criteria.

Neuromyelitis optica (all are required)³

1. Optic neuritis.
2. Myelitis.
3. At least 2 of the following:
 - Longitudinally extensive spinal cord lesion over three vertebral segments
 - Brain MRI does not meet criteria for multiple sclerosis.
 - Anti-aquaporin-4 IgG seropositivity.

Acute disseminated encephalomyelitis followed by recurrent optic neuritis⁵

1. Initial presentation fulfills criteria for acute disseminated encephalomyelitis.
2. Optic neuritis diagnosed after acute disseminated encephalomyelitis with objective evidence of loss of visual function.
3. The optic neuritis occurs after a symptom-free interval of four weeks and not as part of the acute disseminated encephalomyelitis or recurrent acute disseminated encephalomyelitis.
4. Supportive criteria:
 - Oligoclonal bands are not detected in the CSF (a pleocytosis may be present).
 - Anti-aquaporin-4 IgG seronegativity.
 - Initial MRI reveals typical brain or spinal cord T2 lesions consistent with acute disseminated encephalomyelitis; however, subsequent imaging shows resolution or near-complete resolution of lesions and new brain or spinal cord lesions do not appear during the optic neuritis attacks.

Chronic relapsing inflammatory optic neuropathy^{6,7}

1. Optic neuritis and at least one relapse of optic neuritis;
2. Objective evidence for loss of visual function;
3. Anti-aquaporin-4 IgG seronegativity;
4. MRI of the orbits reveals contrast enhancement of the acutely inflamed optic nerves;
5. Response to immunosuppressive treatment and relapse on withdrawal or dose reduction of immunosuppressive treatment.

Search strategy and selection criteria

Publications in English were identified by Medline searches (Jan 1, 1975 to April 30, 2014) and review of their respective bibliographies. Search terms used were “multiple sclerosis”, “acute disseminated encephalomyelitis”, “optic neuritis”, “transverse myelitis”, “neuromyelitis optica”, or “demyelinating diseases” and combined with “child” or “pediatrics” or “adolescent.” Single case reports, data only published in abstract form, and articles where a few children were included as part of a larger adult series were excluded. Review articles are referenced if recent and believed to be important for readers. All references were checked for completeness. We only included articles published in English.

Table 1

Risk factors for paediatric multiple sclerosis susceptibility or disease activity

Risk factor	Study population			Results	
	Paediatric MS	Comparator group	Methods (location)	Ratio, adjusted (95% CI)	Covariates
Banwell et al ²	Sex (female)	Children with MS onset <16 years followed for a mean of 3.51 years (IQR 2.51–4.53) (n=63, of whom 41 were female)	Children with monophasic ADS (<16 years of age) followed for 3.06 years (mean) (IQR 1.48–4.53) (n=231, of whom 112 were female)	Prospective national study of incident demyelination (Canada)	HR=1.87 (1.11–3.14) None
Langer-Gould et al ²³	BMI	Children with MS onset <18 years* (n=75)	Healthy patients age <18 years (n=913 172)	Cases and healthy controls identified through the Kaiser Permanente Health System (Southern California, CA, USA)	OR 1.58 (0.71–3.50) overweight vs normal weight (85 percentile or >25 kg/m ²); OR 1.78 (0.70–4.49) moderately obese (95 percentile or >30 kg/m ²); OR 3.76 (1.54–9.16) extremely obese (95 percentile or >35 kg/m ²) Age, sex, and neighbourhood education
Mikaeloff et al ²⁴	Exposure to second-hand smoke	Children with MS onset between 10 and <16 years [†] (n=90, of whom 62 were exposed)	Age, sex, and geographically matched controls (n=708, of whom 337 were exposed)	Prospective national study of incident MS (KIDSEP cohort) and controls recruited from the general population by population-based methods (France)	RR 2.49 (1.53–4.08) Familial history of MS, family history of other autoimmune conditions, socio-economic status of the head of the family
Disanto et al ²⁵	1HLA-DRB3 alleles	Children with MS onset <16 years followed for a mean of 3.5 years (range 0.7–5.8) (n=64 [‡])	Children (n=231 [‡]) with monophasic ADS (<16 years of age) followed for a mean of 3.1 (range 0.3–5.8) years	Prospective national study of incident demyelination (Canada)	OR 3.2 (1.7–6.1) Age, sex
Banwell et al ²	Remote EBV infection	Children with MS onset <16 years followed for a mean of 3.5 years (IQR 2.51–4.53) (n=49, of whom 37 had remote infection)	Children with monophasic ADS (<16 years of age) followed for a mean of 3.06 years (IQR 1.48–4.53) (n=185, of whom 82 had remote infection)	Prospective national study of incident demyelination (Canada)	HR 2.58 (1.33–5.02) Age
Waubant et al ²⁶	Remote EBV infection	Children with MS [§] onset <18 years (n=189, of whom 164 had remote infection [¶])	Healthy controls (n=28) and other neurological diseases// (n=38) (total n=66, of whom 34 had remote infection)	Cases and healthy controls recruited from six US regional paediatric MS centres (University of California, San Francisco, CA; State University	OR 3.72 (1.48–8.85)** Age at blood draw, sex, race, ethnicity, and DRB3* 1501/1503-positivity

* Among children with MS onset between 12 and 18 years, there was a trend of increased risk of MS with increased BMI ($p=0.03$); however, this trend was not seen in younger children with MS onset (ages 2–11 years, $p=0.92$), although only one child with MS younger than 12 years had extreme obesity as defined.

Risk factor		Study population		Results		
		Paediatric MS	Comparator group	Methods (location)	Ratio, adjusted (95% CI)	Covariates
Waubant et al ²⁶	CMV sero-positivity	Children with MS ^S <18 years at onset (n=189, of whom 53 had remote infection)	Healthy controls (n=28) and other neurological diseases// (n=38) (n=66, of whom 23 had remote infection)	Cases and healthy controls recruited from six regional paediatric MS centres (University of California, San Francisco, CA; State University of New York at Stony Brook, Stony Brook, NY; University at Buffalo, Buffalo, NY; University of Alabama, Birmingham, AL; Harvard University, Cambridge, MA; Mayo Clinic, Rochester, MN), with additional healthy controls from other sites (Oklahoma, New York City, and Southern California, USA)	OR 0.27 (0.11–0.67)	Age at blood draw, sex, race, ethnicity, and <i>DRB3*1501/1503</i> -positivity, and anti-EBNA-1 positivity
		Children with MS onset <16 years followed for a mean of 3.51 years (IQR 2.51–4.53) (n=63, of whom 41 were female)	Children with monophasic ADS onset <16 years followed for a mean of 3.06 years (IQR 1.48–4.53 years) (n=231, of whom 112 were female)	Prospective national study of incident demyelination (Canada)	HR 0.9 (0.8–1.0)	Age at onset
Banwell et al ²	Vitamin D (10 nmol/L ^{††} increase in serum level)	Children with MS or CIS onset less than or equal to 18 years followed for a mean of 1.7 years (IQR 0.2–4.0) (n=110)	Within cohort analysis of relapse rate ^{††}	Prospective longitudinal cohort study (University of California, San Francisco, CA, USA; and State University of New York at Stony Brook, Stony Brook, NY, USA)	IRR 0.66 (0.46–0.95)	Season, race, and ethnicity
Mowry et al ²⁷	Vitamin D (10 ng/mL ^{††} increase in serum level)					

[†] Smoke exposure was not significant among children <10 years (18 of 39 cases exposed vs 131 of 330 matched controls, adjusted RR 1.47, 95% CI 0.73–2.96).

[‡] The number of children in each group with one or more *HLA-DRB3* alleles was not reported.

[§] Includes children with CIS or MS at enrolment; however, all children ultimately met criteria for MS.

[¶] Remote infection was defined as anti-EBV VCA-positivity.

// Other neurological diseases include neuromyelitis optica (n=4), acute disseminated encephalomyelitis (n=9), bladder cyst (n=1), sarcoidosis (n=1), vasculitis (n=1), headaches (n=1), anxiety disorder (n=1), scleroderma en coup de sabre (n=2), mitochondrial or metabolic disorder (n=2), paraneoplastic syndrome (n=2), low-grade tumour (n=1), peripheral neuropathy (n=3), non-specific white matter changes on MRI (n=1), recurrent optic neuritis with normal CSF and normal MRI (n=2), transverse myelitis (n=1), and unknown neurological disorders (n=6).

^{**} Similar results were reported for anti-EBNA-1 positivity, OR 3.78 (95% CI 1.52–9.38, adjusted for age at blood draw, sex, race, ethnicity, and *DRB3***I501/I503* positivity).

^{††} 10 nmol/L=4 ng/mL and 10 ng/mL=24.96 nmol/L.

^{‡‡} IRR was calculated based on time to relapse.

Table 2

MRI features of paediatric multiple sclerosis and its mimics

	Frequent MRI findings	Common MRI features	Features that suggest alternative diagnoses ²⁸
MS [*]	<ul style="list-style-type: none"> • >1 periventricular T2 lesion(s) • Periventricular lesions oriented perpendicular to corpus callosum • >1 T1 hypointense lesion • Gadolinium-positive and gadolinium-negative lesions • Low thalamic volume 	<ul style="list-style-type: none"> • Juxtacortical lesions • Brainstem or cerebellar lesions • Low global brain volume 	<ul style="list-style-type: none"> • Absence of T2 lesions at baseline • Failure to document T2 lesion accrual • Meningeal gadolinium-positive • Visible cortical lesions on T2 at 1.5 or 3T • Focal cortical volume loss
ADEM	<ul style="list-style-type: none"> • <2 periventricular lesions • Absence of non-enhancing T1 hypointense lesions 	<ul style="list-style-type: none"> • Diffuse ill-defined multifocal bilateral lesions • LETM (when cord involvement is present) 	<ul style="list-style-type: none"> • Enhancement of all lesions
NMO [†]	<ul style="list-style-type: none"> • LETM • Long optic nerve lesions • Diencephalic lesions • Periaqueductal lesions 	<ul style="list-style-type: none"> • Diffuse ill-defined brain lesions • Tumefactive lesions • Chiasmal lesions 	<ul style="list-style-type: none"> • Absence of optic nerve or spinal cord involvement over time • Sole presence of well defined lesions • Focal spinal cord lesions
CRION [‡]	<ul style="list-style-type: none"> • Absence of brain or spine involvement • Unilateral or bilateral optic nerve involvement 	<ul style="list-style-type: none"> • Gadolinium-positive optic nerve lesions • Chiasmal lesions 	<ul style="list-style-type: none"> • Expansive lesions of the optic nerve • MRS lactate
CNS vasculitis [§]	<ul style="list-style-type: none"> • Meningeal gadolinium-positive • Focal cortical T2 lesions • MRA lesions • Angiographic evidence of vascular beading 	<ul style="list-style-type: none"> • Multifocal T2 lesions • Optic neuritis and cord lesions • Normal or near-normal brain MRI 	<ul style="list-style-type: none"> • Absence of cortical lesions

MS=multiple sclerosis. T=Tesla. ADEM=acute disseminated encephalomyelitis. LETM=longitudinally extensive transverse myelitis. NMO=neuromyelitis optica. CRION=chronic relapsing inflammatory optic neuropathy. MRS=magnetic resonance spectroscopy. MRA=magnetic resonance angiography.

^{*} Specific MRI features of paediatric MS have been characterised through prospective studies;^{13,29} detailed descriptions of MRI findings commonly seen in paediatric MS cohorts have also been provided.^{30–32}

[†] Although conventional clinical and MRI criteria for NMO focused on optic nerve and spinal cord involvement,³³ later work has emphasised longitudinally extensive involvement of the optic nerve and spine;³⁴ extensive brain lesions similar to those seen in ADEM and tumefactive lesions have also been reported;³⁵ NMO is characterised by attacks involving the optic nerve and the spinal cord (with LETM), as well as by brainstem and diencephalic syndromes such as persistent hiccups and hypersomnolence, and in some patients by an ADEM-like polyfocal presentation;³⁴ the formal diagnosis, according to current criteria (which are soon to be revised), requires two of the following: optic neuritis, LETM, or the presence of anti-aquaporin (NMO-IgG) antibodies;³³ published reports of NMO in children reveal a female predominance, an increased representation of non-white patients, and coexistent autoimmune disease in 42% of children.³⁶

[‡]Although the rarity of CRION has led to limited descriptions of MRI features, absence of brain or spinal cord involvement is a consistent feature. A systematic review of the clinical features and outcome of 122 patients with CRION has been recently published.⁶ A subset of paediatric CRION patients have been found to harbour antibodies against myelin oligodendroglial protein (MOG),³⁷ although the presence of such antibodies is not specific and can be detected in MS, transverse myelitis or ADEM.

[§]CNS vasculitis of the small-medium vessels may be detectable using MRA or conventional angiography, vascular imaging is normal in isolated small vessel vasculitis.^{38,39} Meningeal enhancement and cortical lesions are the most commonly reported features, although it is important to note that a normal brain MRI does not exclude vasculitis and brain biopsy may be required for diagnosis.³⁸

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript