

Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions



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The onset of multiple sclerosis (MS) in childhood poses diagnostic and therapeutic challenges, particularly if the symptoms of the first demyelinating event resemble acute disseminated encephalomyelitis (ADEM). MRI is an invaluable diagnostic tool but it lacks the specificity to distinguish ADEM from the first attack of MS. Advanced MRI techniques might have the required specificity to reveal whether the loss of integrity in non-lesional tissue occurs as a fundamental feature of MS. Although the onset of MS in childhood typically predicts a favourable short-term prognosis, some children are severely disabled, either physically or cognitively, and more than 50% are predicted to enter the secondary-progressive phase of the disease by the age of 30 years. Immunomodulatory therapies for MS and their safe application in children can improve long-term prognosis. Genetic and environmental factors, such as viral infection, might be uniquely amenable to study in paediatric patients with MS. Understanding the immunological consequences of these putative exposures will shed light on the early pathological changes in MS.

Introduction

Multiple sclerosis (MS) in children and adolescents is increasingly recognised worldwide. The disorder presents almost exclusively as a relapsing-remitting disease in children, and most recover from the initial attacks. The accumulation of disabilities and the development of secondary-progressive MS most commonly occur more than 15 years after the first attack. MRI has contributed substantially to the increasing recognition of and certainty in the diagnosis of MS in children. The potential for advanced MRI techniques to visualise fundamental features of myelin integrity and repair provides exciting opportunities for future research. Treatment is currently based on strategies optimised for adult-onset MS and seems to be safe and well tolerated, although prospective therapeutic trials in paediatric MS have not been done.

We describe the clinical, radiographic, and biological characteristics of MS and the other disorders considered in the differential diagnosis in children. We also describe current therapeutic practice and discuss avenues of future research.

Acute demyelination of the CNS

The first acute demyelinating event, termed a clinically isolated syndrome, can manifest with signs and symptoms caused by a single lesion (monofocal clinically isolated syndrome) or with polyfocal features, implicating multiple lesions. There are published clinical definitions for these various clinical demyelinating presentations (figure 1).^{1–23}

In a prospective study of 296 children with acute demyelination, 81 presented with focal involvement, 119 with acute disseminated encephalomyelitis (ADEM), and 96 with symptoms that suggest already established MS (defined as MRI features of well-defined lesions or lesions perpendicular to the corpus callosum combined with appropriate clinical features). Long-tract (motor, sensory, or sphincter) dysfunction was the commonest finding in 226 children (76%), followed by symptoms localised to the brainstem in 121 children (41%), optic neuritis in 67 children

(22%), and transverse myelitis in 42 children (14%).²⁴ Monofocal presentation was more common in adolescents. Recovery from acute demyelination is variable: 85% of children with optic neuritis recover full visual acuity.^{25–27} In published reports of 250 children with transverse myelitis, 80% were paraplegic or tetraplegic and had incontinence or severe urinary symptoms at onset, and 5% died.^{28–40} More than 30% of survivors remain wheelchair dependent, and 70% have residual bladder control problems.²⁹

Published reports of neuromyelitis optica in children are scarce.^{41–43} In one study of nine children, none had relapsing neuromyelitis optica, and visual and motor recovery was excellent⁴³ compared with adults with relapsing neuromyelitis optica, of whom 50% developed paraplegia, 60% developed severe visual loss, and 32% died.⁵

Recovery from ADEM can take several months,^{18,19,22} and residual physical deficits, although mild, were noted in 11–43% of children.^{18,22} Furthermore, mild cognitive sequelae can be detected in children with full physical recovery.⁴⁴

Risk of subsequent attacks after a demyelinating event

A prospective study of 296 children with acute demyelination led to the diagnosis of MS in 168, after a mean observation of 2.9±3 years (mean±SD), in 38 (47%) of 81 patients with initial focal involvement, and in 34 (29%) of 119 patients with an initial diagnosis of ADEM.²⁴ Several features were highly predictive of MS outcome: being older than 10 years at the first demyelinating event; the absence of mental-state change at onset; and a family history of optic neuritis or MS. None of these predictors was absolute, as shown by the fact that of the 168 children diagnosed with MS, some were as young as 2 years old, 34 had encephalopathy and were initially diagnosed with ADEM, and there was a family history of MS in only 7%.²⁴ Of the children with relapsing disease, being younger than 10 years old predicted a longer time from first to second attack (median 6 years), compared with that in older children (median 1 year).

Lancet Neurol 2007; 6: 887–902

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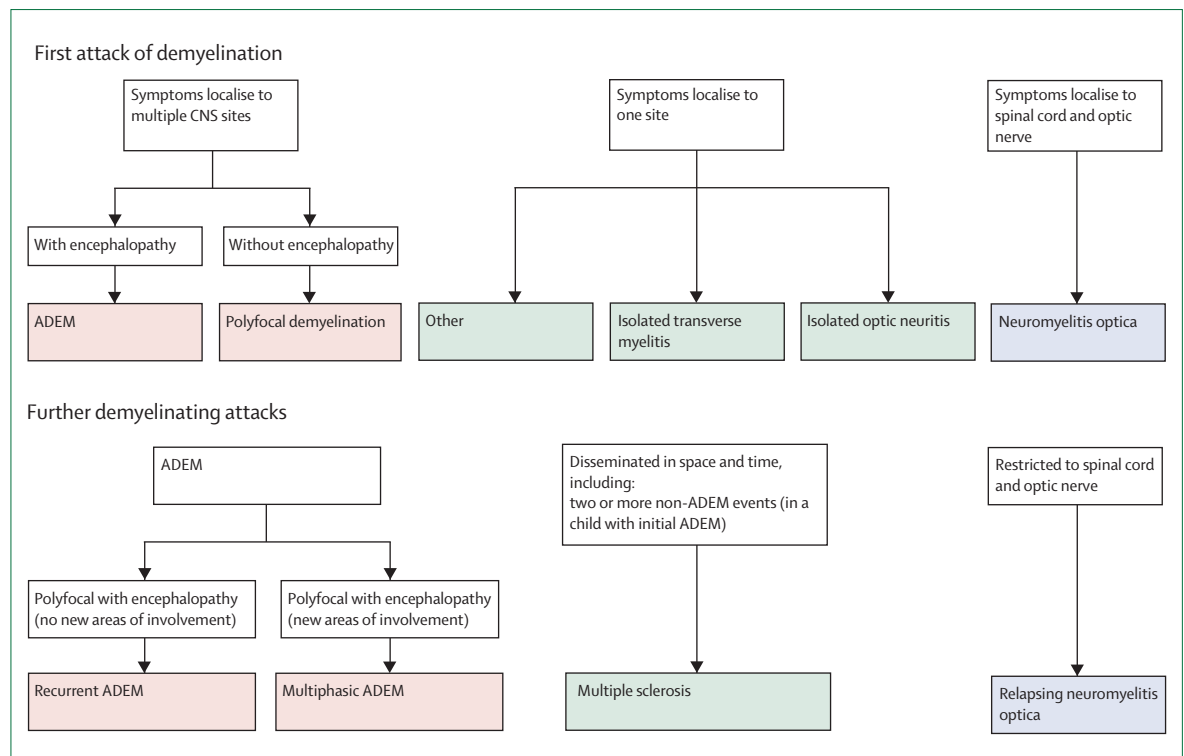


Figure 1: Classification of acquired inflammatory CNS demyelination in children

When the diagnosis of acute inflammatory demyelination of the CNS is made, the description of the clinical presentation is delineated on the basis of clinical features and whether the patient has a single or relapsing disease course. Optic neuritis is defined by acute or sub-acute visual loss, relative afferent pupillary defect, restricted visual fields, and pain with ocular movement.³ Diagnostic criteria for transverse myelitis have been developed.¹⁰ The currently proposed definition for ADEM requires polyfocal deficits accompanied by encephalopathy.¹ Neuromyelitis optica, or Devic's disease, is characterised by optic neuritis and transverse myelitis that occur simultaneously or in close succession.^{11–13} Spinal MRI typically has lesions that extend over more than three vertebral segments (longitudinally extensive transverse myelitis). Brain MRI is typically healthy, or shows cerebral lesions in regions of the brainstem and hypothalamic structures, in a pattern atypical for MS.¹³ ADEM is characterised by polyfocal clinical deficits, alterations in consciousness (irritability, somnolence, encephalopathy, or coma), can follow recent infection, and is commonly associated with fever, seizures, or meningism.^{14–23} MRI typically shows ill-defined, bilateral lesions in the deep grey nuclei and cortical grey matter, and diffuse supratentorial and infratentorial white matter involvement.^{4,18,22} Further demyelinating events can occur as a recurrence of the same features, as seen in the initial event of ADEM (recurrent ADEM), or rarely can occur as a second, distinct episode of ADEM (new neurological deficits with encephalopathy, termed multiphasic ADEM).¹ Relapsing symptoms in new areas of involvement in the CNS, separated by more than 1 month, are the hallmark of relapsing-remitting MS.^{6,7} Patients with neuromyelitis optica can continue to have recurrent attacks in the optic nerves or spinal cord, leading to a diagnosis of relapsing neuromyelitis optica.^{5,8} Primary-progressive MS is exceptionally rare in children; thus it is not shown.

In a prospective study of 36 children with optic neuritis, 13 children were diagnosed with MS after a mean observation of 2.4 years (range 0.3–8.3 years).²⁵ The risk of developing MS after childhood optic neuritis, reported in retrospective series, varied from 15% to 42%.^{26,45} A second attack that would confirm MS might occur many years after childhood optic neuritis, as shown in a longitudinal study in which MS was diagnosed in 15 patients (19%) during the period of observation. Kaplan-Meier analysis showed a probability of a diagnosis of MS of 13% at 10 years and 22% at 23 years after optic neuritis.⁹ Bilateral optic neuritis is associated with a greater likelihood of MS outcome.^{25,27} Recurrent optic neuritis, and optic neuritis in the context of opticospinal MS or neuromyelitis optica, might be more common in Asian children.^{27,46} MRI evidence of at least one demyelinating lesion separate from the optic nerves at onset of optic neuritis is strongly associated with a diagnosis of MS

within 2 years.²⁵ Ocular coherence tomography, a non-invasive technique that uses near-infrared light to measure retinal nerve fibre layer thickness, provides a quantitative measure of axonal loss.⁴⁷ This is a promising technique with potential implications for visual prognosis and estimation of the risk of MS in adults.⁴⁸ There are no published studies of ocular coherence tomography in paediatric optic neuritis.

In contrast to optic neuritis, MS is rarely diagnosed after acute isolated transverse myelitis in children.³⁵ Of 168 children diagnosed with MS in a prospective study, only 13 (8%) had isolated transverse myelitis as the first occurrence of MS.²⁴

In children with ADEM, the risk of recurrent or multiphasic forms of the disorder is less than 10%.^{18,49} Recurrent and multiphasic ADEM are thought of as restricted illnesses not associated with chronic relapsing demyelination. At least 20% of children initially diagnosed

with ADEM have further demyelinating events that are atypical for ADEM, which leads to a diagnosis of MS.^{20,24,49}

Commentary

In the proposed diagnostic criteria for paediatric MS,¹ the consensus was that the diagnosis of MS in a child with an initial diagnosis of ADEM should be made only after two subsequent non-ADEM events (demyelinating events that do not include encephalopathy), a criterion that is deliberately conservative, and future multinational collaborations will establish whether such a restriction ensures or delays an appropriate diagnosis of MS.

Confirmation of the diagnosis

Differential diagnosis

A cornerstone of the diagnosis of MS in adults and children rests on showing lesion dissemination in space and time and the exclusion of other disorders.⁷ One approach to discount disorders in the differential diagnosis of acute CNS demyelination was set out in a recent consensus article (figure 2 and webfigure).⁵⁰ CNS infection and intracerebral malignancy must always be considered. Although CNS lymphoma is rare in children, intracallosal involvement can be similar to the white-matter lesions seen in MS.⁵¹

Primary small-vessel vasculitis of the CNS is one of the most difficult disorders to distinguish from acquired demyelination. Vasculitis of the CNS in children can occur as systemic vasculitis, such as systemic lupus erythematosus, or as a CNS-restricted angiitis.^{52–54} Serum vasculitic markers and features of systemic disease are completely absent in isolated CNS angiitis. The results of CNS angiography can show vascular disease in children with moderate-vessel to large-vessel involvement but can seem healthy in patients with small-vessel inflammation.⁵⁵ Multifocal areas of increased signal of the CNS white matter, deep grey nuclei, optic nerves, and spinal cord appear in a pattern that is difficult to distinguish from inflammatory demyelination. Persistent headache and malaise, and recurrence of symptoms with corticosteroid taper, should prompt the consideration of CNS vasculitis; however, brain biopsy is essential for diagnosis.⁵⁴

The symptoms of macrophage-activation syndrome can initially resemble ADEM or MS.^{56–58} Although macrophage-activation syndrome is typically a multisystem illness—with hepatomegaly, splenomegaly, adenopathy, fever, and signs of intravascular coagulation—neurological symptoms might be the only features at onset. Treatment with corticosteroids will alleviate the symptoms, but the malaise, headache, and polyfocal neurological deficits will recur when patients are weaned off the corticosteroid therapy. Clues to the diagnosis of macrophage-activation syndrome include the young age of the patient (usually less than 2 years but cases in adolescents have been reported), parental consanguinity or death of a sibling, the presence of acute necrotic lesions seen on MRI, and

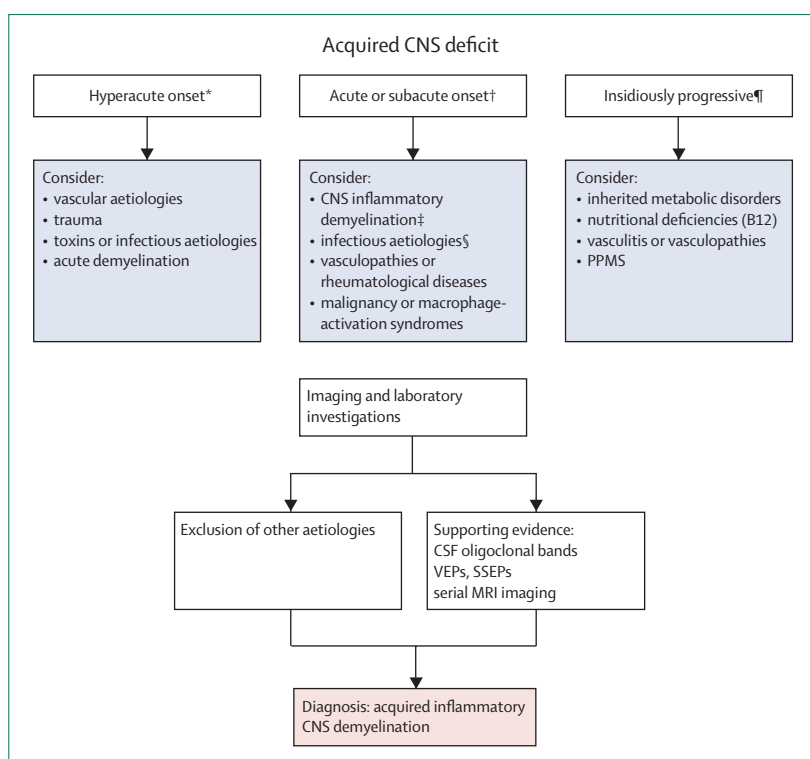


Figure 2: Approach to the diagnosis of acute demyelination in children

Diseases in the differential of inflammatory demyelination. The figure is not meant to be exhaustive but instead provides an overview of common disorders included in the differential and rare disorders that should not be missed. *Maximal neurological deficit reached within hours of onset. †Neurological deficits that fluctuate or reach maximum intensity over a period of several days to about 3 months. ‡Clinical examination localised the neurological signs and symptoms within the CNS. §Causes of infections include viruses such as herpes, HIV, *Mycoplasma pneumoniae*, and other viruses relevant to specific geographical regions. ¶Accrual of deficits over the course of 6 months or more. PPMS=primary-progressive multiple sclerosis. VEPs=visual evoked potentials. SSEPs=somatosensory evoked potentials. A fuller version of this figure is available (webfigure).

the development of multisystemic involvement.^{59,60} The diagnosis is confirmed by haemophagocytosis of cells in cerebrospinal fluid or in bone marrow aspirates, elevated concentrations of serum ferritin and triglycerides, low concentrations of serum fibrin, indirect signs of lymphocyte activation (including high expression of DR antigen), lack of perforin expression in lymphocytes, and evidence of lymphocyte cytotoxicity. Mutations in the genes encoding perforin 1, Munc 13-4, and syntaxin 11 result in haemophagocytic lymphohistiocytosis;⁶¹ mutations in *LYST* cause Chediak–Higashi syndrome; mutations in *RAB27A* cause Griscelli syndrome; and mutations in *SH2D1A* result in the X-linked proliferative syndrome.⁵⁹ Prompt diagnosis is essential to enable early bone marrow transplantation, which is the only effective long-term treatment for all the familial haematophagocytosis syndromes.^{61,62}

The clinical and radiographic delineation of inherited white-matter leukodystrophies are described in detail.⁶³ Children with metachromatic leukodystrophy present with progressive psychomotor slowing, ataxia, spasticity, peripheral neuropathy, and MRI evidence of bilateral,

See Online for webfigure

symmetric, increased signal in white matter;⁶⁴ arylsulfatase A deficiency is a diagnostic finding. Episodic neurological deficits occur in Fabry's disease, which is diagnosed by the presence of dermal angiokeratomata, corneal dystrophy, MRI evidence of a vascular distribution of the disease, and laboratory evidence of leucocyte α -galactosidase deficiency.⁶⁵ X-linked adrenoleukodystrophy manifests with progressive behavioural and cognitive decline in late childhood, followed by progressive spasticity. MRI shows bilateral, anterior-predominant increased signal in white matter with gadolinium enhancement in the border between visibly healthy and abnormal white matter.^{66,67} Occasionally, patients present with relapsing-remitting symptoms, which precede the inevitable progressive deterioration;⁶⁴ thus, X-linked adrenoleukodystrophy should be considered in male adolescents, particularly if the features seen on MRI are atypical for MS. High serum concentrations of very-long-chain fatty acids are diagnostic for adrenoleukodystrophy. In general, the insidiously progressive nature of inherited leukodystrophies enables them to be distinguished readily from MS, particularly because primary-progressive MS is exceptionally rare in children.⁶⁸

Laboratory investigations

CSF analysis has a key role in the exclusion of acute infection and malignancy from the diagnosis of MS. The CSF white-cell count in children presenting with the first attack of MS typically ranges from 0–30 leucocytes/mm³, although cell counts of up to 60 leucocytes/mm³ are seen in about 8% of children;⁶⁹ higher CSF cell counts are more characteristic of infection, vasculitis, or neuromyelitis optica.^{53,70} Oligoclonal bands in spinal fluid analysed with isoelectric focusing are reported in about 90% of children with MS;^{69,71–73} however, CSF oligoclonal bands develop over the course of the disease, and not all children have positive results at first.^{69,71} Although the results of previous studies suggested that CSF oligoclonal bands were rare in young patients with MS,⁷⁴ a recent study detected CSF oligoclonal bands in 24 of 25 children under the age of 10 years with MS.⁶⁹ CSF oligoclonal bands were absent in a study of 84 children with ADEM.¹⁸ Similarly, CSF oligoclonal bands are rarely detected in patients with neuromyelitis optica and, if detected, they tend to be transient.⁷⁰ Serum antibodies against aquaporin 4 (NMO-IgG) distinguish adults with neuromyelitis optica from those with relapsing-remitting MS, with 73% sensitivity and 91% specificity.⁷⁵ Aquaporin 4 is an active astrocytic water channel implicated in cellular electrolyte influx, particularly at the blood–brain barrier.⁷⁶ Serum NMO-IgG was seen in a case report of a child with clinical neuromyelitis optica.⁷⁷ The prognostic role of NMO-IgG in children with demyelination is an area for further study.

Multimodal evoked potential testing can confirm the involvement of or detect clinically silent deficits in the

visual evoked potential, brainstem auditory evoked potential, or somatosensory evoked potential pathways.^{78,79} In a study of 156 children with MS, 85 children had visual evoked potentials tested at the time of the first attack. Visual evoked potentials were abnormal in 48 children (56%), 29 of whom had no clinical evidence of optic nerve disease.⁸⁰ However, investigation of brainstem auditory evoked potentials and somatosensory evoked potentials rarely detected abnormalities not apparent on clinical examination, which is consistent with other reports.^{79,80} Visual evoked potentials were abnormal in 26 of 27 participants in a study of children with optic neuritis,²⁵ confirming the usefulness of visual evoked potential testing in the assessment of demyelination of the optic pathways.

MRI features

MRI has a pivotal role in confirming the presence of CNS lesions consistent with inflammatory demyelination and in the exclusion of other CNS disorders (figure 3).⁸¹ Ill-defined lesions that include the deep grey nuclei in MS are more commonly seen in young children.²⁴ Ill-defined lesion borders, large lesions, and lesions in the central grey-matter regions are also characteristic of ADEM.^{16,19} Several studies of both children and adults have shown that MRI is not sufficient to distinguish between ADEM and MS.^{82–84} MRI of children with ADEM should not show the accrual of clinically silent lesions, in contrast to MS.¹⁸ Spinal cord imaging of patients with MS typically shows lesions in only a portion of the diameter and only a short longitudinal expanse of the spinal cord.⁸⁵ However, some children with MS have longitudinally extensive transverse myelitis.⁸⁶ Demyelination in children with MS might be associated with a greater degree of oedema or with a greater propensity for widespread white-matter involvement during acute relapses than is typically seen in adults with the disorder.

The diagnostic criteria for MS in adults include MRI evidence of dissemination of the disease both in space (within the CNS) and over time.^{6,87} These criteria have a sensitivity of only 52–54% when applied to images obtained in children at the time of the first MS attack,^{82,88} and a sensitivity of 67% at the time of the second MS-defining event.⁸⁸ Low sensitivity (37%) was particularly notable when the MRI criteria were applied to images from children who were less than 10 years old when they had the first attack of MS.⁸²

Mikaeloff and co-workers⁸² used standardised methods to identify MRI features predictive of MS outcome in a group of 116 children imaged at an initial acute demyelinating event. After a mean observation period of 4.9±3 years (mean±SD), 45% of the children had a second demyelinating event and were diagnosed with MS. MRI features predictive of such an outcome included lesions located perpendicular to the long axis of the corpus callosum and the sole presence of well-defined

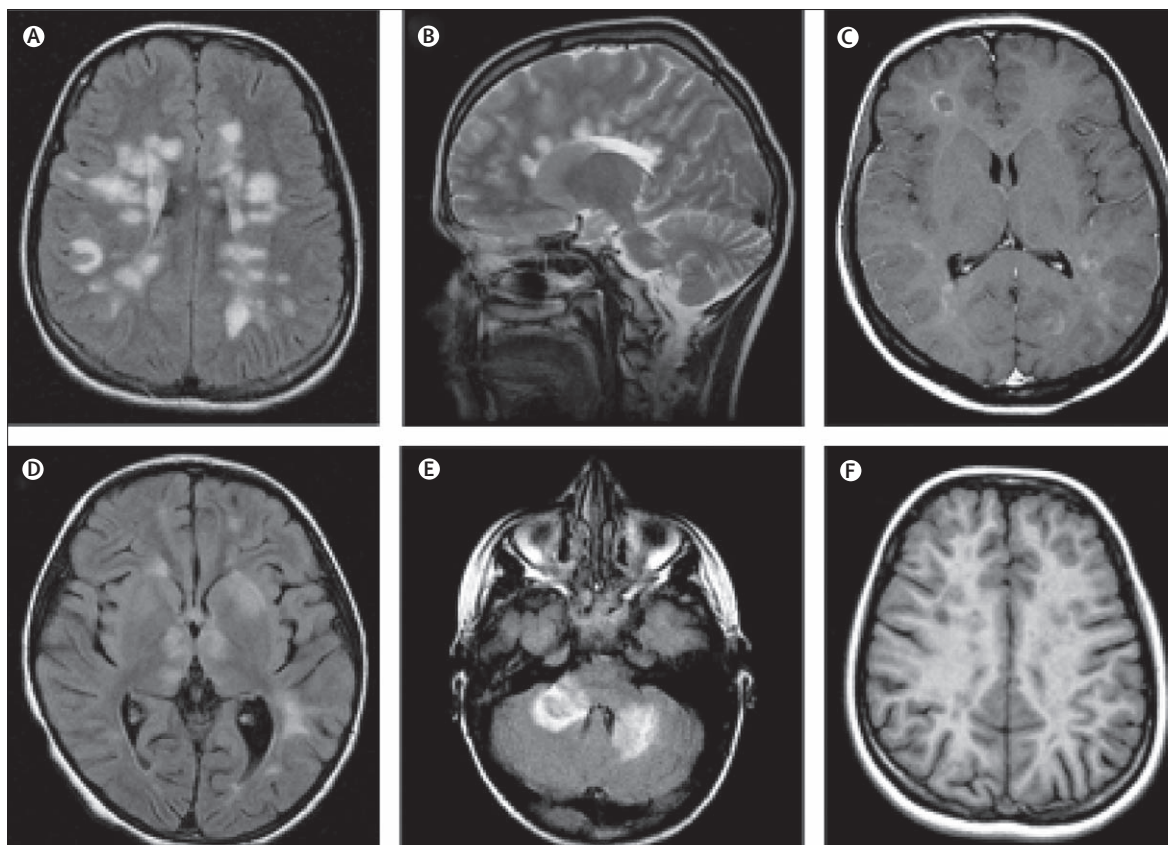


Figure 3: MRI of MS in children

A: Axial FLAIR image of a 12-year-old boy with MS with multiple lesions. B: Sagittal T2-weighted image of a 14-year-old girl with MS; numerous lesions emanating from the corpus callosum (Dawson's fingers) are highlighted. C: Axial T1-weighted image with gadolinium that shows several enhancing lesions in a 15-year-old boy with MS. D: Axial FLAIR image of a 7-year-old girl with a first demyelinating event, who was subsequently diagnosed with MS on the basis of numerous further attacks. As can be seen in younger children with MS, the involvement of the deep grey-nuclei is prominent. E: Axial FLAIR image of an 8-year-old boy with MS that shows the prominent involvement of the posterior fossa white matter. F: Axial T1-weighted image of a 14-year-old boy with severe MS with multiple black holes.

lesions in the brain. The presence of both these features was 100% specific for MS outcome, although the sensitivity was only 21%.⁸² The presence of only one of these criteria (55% of patients) increased the sensitivity to 79%, whereas specificity decreased to only 63%.

MRI-based techniques can also be used to investigate tissue integrity (magnetisation transfer imaging or diffusion tensor imaging) and tissue biochemistry (magnetic resonance spectroscopy). The mean diffusivity—an index of the loss of tissue integrity and thus an increased capacity for protons to move—of brain tissue that looks otherwise healthy was only slightly higher in 13 children with MS than in healthy children,⁸⁹ suggestive of limited damage early in the disease. The results of another study of 23 children with MS also showed no difference between children with MS and healthy children on magnetisation transfer imaging and diffusion measures in the grey matter.⁹⁰ MRI in eight children with MS revealed decreased N-acetylaspartate and creatine concentrations and increased concentrations of choline and lipids within lesions and the adjacent cortical grey matter.⁹¹ Magnetic

resonance spectroscopy spectra in healthy-looking tissue did not differ from those in healthy controls, which suggests that the widespread abnormalities in tissue that looks healthy in adults with MS might not be detectable in children with the disorder. A single study of magnetisation transfer imaging in 15 children with ADEM identified a citrulline peak in the healthy-looking white matter in seven patients and in one control.⁹² Post-translational citrullination of myelin is an age-dependent process, with a high degree of citrullination seen only in immature myelin (<2 years).⁹³ Myelin in adults with MS might be developmentally immature⁹³ and thus might be more prone to degradation, in turn leading to increased myelin debris, which might then incite an immunological reaction. Detailed magnetic resonance spectroscopy studies specifically looking for citrulline spectra in children with relapsing-remitting MS would be of interest.

Commentary

Diligent exclusion of other diseases by use of a standardised approach and the application of the

	Details	N†	Mean observation (years)‡	PPMS (N)	SPMS (%)
Belopitova and co-workers ⁹⁸	Bulgaria, single centre*	10 (P)	NR	0	10
Boiko and co-workers ⁹⁴	Canada, single centre	116 (A)	19.8	3	53
Boutin and co-workers ⁹⁹	France, single centre	19 (P)	Variable	3	NR
Bye and co-workers ¹⁰⁰	UK, single centre	5 (P)	6.8	0	NR
Chiemchanya and Visudhiphan ⁴⁶	Thailand	17 (P)	6.5	0	NR
Cole and Stuart ¹⁰¹	Scotland, single centre	28 (A)	3–47	4	10
Dale and co-workers ⁷²	UK, single centre	13 (P)	5.6	0	0
Deryck and co-workers ¹⁰²	Belgium, single centre	49 (A)	20.8	1	43
Duquette and co-workers ⁹⁵	Canada, multicentre	125 (A)	15	28	22
Gall and co-workers ¹⁰³	USA, single centre	40 (P)	NR	0	NR
Ghezzi and co-workers ⁹⁷	Italy, national programme*	149 (A)	14.2	7	29
Ghezzi and co-workers ⁷³	Italy, national programme*	54 (A)	10.9	0	28
Glasier and co-workers ⁸⁶	USA, single centre	7 (P)	5	0	NR
Guilloto and co-workers ¹⁰⁴	Brazil, single centre	14 (P)	NR	0	0
Gusev and co-workers ¹⁰⁵	Russia and Canada, two-centre comparison	67 (A/P)	4.9	0	11
Hanefeld and co-workers ¹⁰⁶	Germany, single centre*	15 (P)	NR	4	NR
Haslam ¹⁰⁷	Canada, single centre	29 (P)	Variable	NR	NR
Iannetti and co-workers ¹⁰⁸	Italy, single centre	5 (P)	3	0	0
Mattyus and Veres ¹⁰⁹	Hungary, single centre	16 (P)	9	2	NR
Mikaeloff and co-workers ⁹²	France, national programme*	116 (P)	4.9	0	
Mikaeloff and co-workers ⁷⁴	France, national programme*	168 (P)	2.9	1	5
Mikaeloff and co-workers ⁶⁸	France, national programme*	197 (P)	5.5	0	5
Millner and co-workers ¹¹⁰	Austria, single centre	6 (P)	NR	0	NR
Ozakbas and co-workers ⁷²	Turkey, single centre	32 (A)	7.4	0	31
Perniola and co-workers ¹¹¹	Italy, single centre	14 (A)	5.0	1	14
Pinhas-Hamiel and co-workers ¹¹²	Israel, single centre	13 (A)	NR	NR	NR
Ruggieri and co-workers ¹¹³	Italy, preliminary results of a national programme	31 (P)	NR	0	NR
Selcen and co-workers ¹¹⁴	Turkey, single centre	16 (P)	NR	0	6
Shiraishi and co-workers ¹¹⁵	Japan, single centre	27 (P)	13.5	0	7
Simone and co-workers ⁹⁶	Italy, national programme	83 (A)	5.3	0	15
Sindern and co-workers ⁷¹	Germany, single centre	31 (A)	11.4	3	61
Trojano and co-workers ¹¹⁶	Italy, national programme*	90 (A)	NR	0	1
Weng and co-workers ¹¹⁷	Taiwan, single centre	21 (P)	6.8	0	14
Zelnik and co-workers ¹¹⁸	USA, single centre	6 (P)	1–7	0	NR

*Prospective studies. †Each article was carefully reviewed, and only patients with confirmed multiple sclerosis and age less than 18 years were included. ‡Mean follow-up was either provided directly by the authors in the text, or was calculated from the clinical information on patients described in tables or text format. A=adult centre. NR=not recorded. P=paediatric centre. PPMS=primary-progressive MS. SPMS=secondary-progressive MS.

Table 1: Studies of the clinical features of multiple sclerosis in children

proposed criteria for paediatric MS¹ will enable an accurate diagnosis in most affected children. Furthermore, investigation of oligoclonal bands with advanced techniques is almost as sensitive in children with MS as it is in adults. MRI evidence of the accrual of clinically silent lesions is particularly important in the assessment of children with an initial ADEM-like event, and MRI of young patients with initial lesions that are atypical for adult-onset MS might change over time into a pattern similar to that seen in adults.

Characteristics of child-onset MS

An estimated 3–10% of all patients with MS have onset before the age of 18 years.^{71,94–97} The true frequency of

paediatric MS will be determined only from prospective studies from both paediatric and adult clinical centres.

Demographic features

MS in childhood has been reported in numerous countries (table 1).^{94–118} The ethnic diversity of children with MS in a Canadian study closely mirrored the diverse cultures of recent immigrants to that region, even when the parental countries of origin had low prevalence of MS.¹¹⁹ The results of migration studies of adult-onset MS show that people who emigrate during childhood to areas of high risk have the risk of MS associated with their adopted home.¹²⁰

Gender ratios in paediatric MS differ with age at onset (figure 4). Whether the substantial increase in female

preponderance in adolescence is indicative of a hormonal influence on risk of MS, a gender-specific genetic influence on immunological reactivity, or some other age-related factor is unknown.

A family history of MS is reported by 6–8% of children and adolescents with MS,^{24,72,96,121} although retrospective studies with longer observation periods report a familial prevalence of about 20%.^{95,102} The difference is probably due to sufficient time having elapsed for a diagnosis of MS in parents, relatives, or siblings who, at the time of diagnosis in a pediatric relative, might not have manifested the disorder.

Clinical features

Of 1540 children (table 1), 96% were diagnosed initially with relapsing-remitting MS, and only 57 (3.7%) were diagnosed with primary-progressive MS.

Variable descriptions in the literature and inconsistent use of the term polysymptomatic (which might imply multiple lesions or multiple symptoms from a single lesion) versus polyfocal (which implies multiple lesions) hampers recognition of the frequencies of different presenting features of the first attack of MS. Overall, about 50–70% of children will have a polyfocal or polysymptomatic presentation,^{24,72,96} whereas 30–50% of children will have a monofocal presentation: of the latter presentation, 10–22% of children present with optic neuritis, 30% have motor dysfunction, 15–30% have sensory symptoms, 5–15% present with ataxia, and 25% have brainstem symptoms.^{72,73,96,105} Optic neuritis as the first presentation of MS is more commonly reported in studies from Asia,^{27,115} which is consistent with the higher representation of optic neuritis in adults with MS from these regions. Isolated transverse myelitis as the presenting symptom of MS occurs in less than 10% of children.^{24,71,95} Symptoms consistent with ADEM were noted in prospective studies at presentation in 20–28% of children.^{24,49}

Fatigue that is severe enough to limit scholastic or recreational activities is reported by 40% of children with MS. Seizures occur in about 5% of children with MS^{105,107} but are much more common in children under the age of 10 years.⁷⁴

The onset of MS in childhood occurs during the key formative academic years, which might restrict school attendance and has the potential to affect negatively the developing neural connections implicated in learning and higher-order information processing. Deficits in general cognition, visuomotor integration, and memory have been documented in at least 30% of children with MS.^{122–124} The most common impairments were in complex attention (eg, shifting attention from one idea to another), visuomotor integration, confrontation naming, receptive language, and executive function, whereas verbal fluency was intact in all patients.^{122,124} Academic test scores were relatively spared and, when combined with preserved verbal fluency, might serve to mask the depth of cognitive deficits present in these children. Furthermore, the

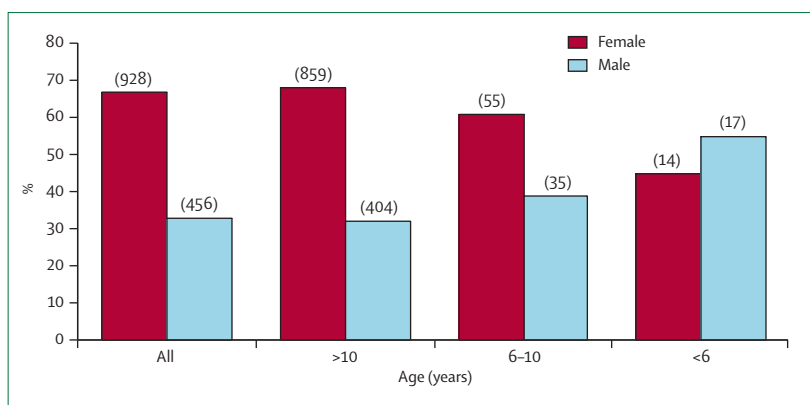


Figure 4: Age and gender relationships in paediatric MS

Data on gender from demographic information on the 1384 children with MS listed in table 1 and table 2, which is summarised as a proportion of children of each sex as a function of the total number of children (first bars) and subdivided into age at first attack.

deficits in attention, executive functions, and memory are likely to have greater importance as children enter secondary and postsecondary education, when these skills are paramount. The severity of cognitive impairment also increases with longer disease duration and is of greater severity in patients who are young at disease onset.^{122,125} Larger studies are clearly needed to document more fully the morbidity of MS on cognitive functioning and to understand better the consequences of impaired cognitive processing on academic and future vocational success.

MS in young children

Of 1540 participants (table 1), 263 (17%) were under the age of 10 years at the time of their first attack. Clinical information is available on 87 of these children (table 2).^{74,86,98,98–100,104,106,108,109,111,114,115,117,118,126–128}

Ataxia is particularly common (53%) as a presenting feature in this age group, whereas brainstem features were not always clearly described. Fever was reported in 26% of patients, which is a rare feature of relapses in older patients or adults. Cognitive functioning was specifically mentioned for 30 patients, and was impaired in 20 (66%), which supports concerns regarding the cognitive morbidity of MS in young children.

Relapses

The time from the initial acute attack to the second, MS-defining event is highly variable. Younger children tend to have a longer interval from first to second attack (median 6 years), in contrast to most adolescent patients with MS, who have their second attack within 12 months.²⁴ The relapse rate reported in retrospective studies with long observation periods ranges from 0.38 a year¹⁰² to 1.0 a year.¹⁰⁵

Commentary

The clinical features of MS in children vary as a function of age at first attack. Younger children are

more likely to present with widespread demyelination seen on MRI, polyfocal clinical features, and encephalopathy. Whether these cataclysmic manifestations of acute demyelination are the response of an immature brain to immunological insult, the heightened inflammatory capacity of an immature or developing immune system, age-related immunogenicity of myelin proteins, or another age-related factor is unknown. Future immunological studies and the application of advanced MRI analyses might provide further insights.

Outcome

Disability and outcome

Kurtzke's expanded disability status scale (EDSS) is the most common measure of physical neurological sequelae in adults and children with MS (table 3),^{68,73,94,96,105} although the measure has several key limitations (non-linear ordinals, wide intraobserver and interobserver variability, and, essentially, exclusive weighting of motor dysfunction at the higher range of the scale).

	Number
N*	87
F:M	1:23
Patients <6 years of age	37
Mean (median) age at first attack	6.1 (6.3) years
Features of first attack	
Polysymptomatic†	76
Monosymptomatic	24
Encephalopathy	31
Ataxia	49
Optic neuritis	23
Motor	39
Sensory	11
Transverse myelitis	17
Fever	22
Mean (median) age at second attack	7.2 (7.1) years
Initial multiple sclerosis course	87 relapsing-remitting multiple sclerosis
Multiple sclerosis outcome	
Seizures	23
Cognitive impairment‡	20
Died	1

*Data from all articles in which specific clinical information was provided on children presenting with their first attack of MS under the age of 10 years, including 21 patients from the paediatric MS programme in Toronto.^{74,86,98-100,104,106,108,109,111,114,115,117,118,126-128} †Polysymptomatic and monosymptomatic are used, rather than polyfocal or monofocal, because the case descriptions were not sufficiently detailed to determine whether a single lesion or multiple lesions would best describe the clinical presentation. ‡Cognitive impairment was specifically mentioned in the case histories of 20 of the 30 children, for whom cognition was specifically discussed. In the histories of the remaining 57 patients, cognitive ability was not mentioned. PPMS=primary-progressive MS SPMS=secondary-progressive MS.

Table 2: Clinical features and outcome of MS with onset under the age of 10 years

In a prospective study of 54 children or adolescents with MS disease duration of 8 years or longer, 36 had an EDSS of less than 4, five had scores between 4 and 6, and 13 had significant physical disability, with scores greater than 6.⁷³ After 10 years of follow-up, the mean EDSS score was 3.8. The proportion of children with substantial disability increases with disease duration, as shown by a mean EDSS score of 5.8 in a group of 28 patients with disease duration of 29 years.¹⁰² The mean time to reach an EDSS score of 4 was 10.8 years (range 2–24 years), and it took a mean time of 18.2 years (range 5–48 years) to reach a score of 6. Of 197 children followed from first attack in a prospective study, an EDSS score of 4 was reached by 15% of the children after a mean observation of 7.8 years.⁶⁸ Survival analysis in a retrospective group of 83 patients with paediatric-onset MS showed that the median time to an EDSS score of 4 was 14 years, and such an outcome occurred in 25%.⁹⁶ Overall, 15–25% of these patients will accrue fixed disabilities 10 years or more after disease onset.⁹⁶

In a detailed database analysis of clinical outcome in 394 patients with paediatric-onset MS, the median times from onset to EDSS scores of 4, 6, and 7 were 20 years, 29 years, and 37 years, respectively.¹²⁹ When compared with 1775 patients with adult-onset MS enrolled in the same database cohort, patients with paediatric-onset MS took 10 years longer to accrue disability but were about 10 years younger than patients with adult-onset MS with comparable impairment.

Secondary-progressive MS

Four studies describe in detail the long-term risk of secondary-progressive MS in 441 patients with paediatric-onset, relapsing-remitting MS.^{68,94,96,102} Secondary-progressive disease was seen in 60 of 113,⁹⁴ 21 of 49,¹⁰² 12 of 83,⁹⁶ and 9 of 197⁶⁸ patients after mean disease durations of 17.7 years, 12.9 years, 10.0 years, and 4.8 years, respectively, which suggests that a key determinant of entry into secondary-progressive MS is disease duration. Furthermore, although the mean disease duration associated with a 50% risk of secondary-progressive MS is 23 years in patients with paediatric-onset, relapsing-remitting MS, compared with 10 years in patients with adult-onset, relapsing-remitting MS,⁹⁴ the actual age at which disability progression occurs is much younger in patients with paediatric-onset disease.⁹⁴ The risk of secondary-progressive MS was also associated with a high frequency of relapse and shorter intervals between attacks in the first few years of disease.^{94,96}

Predictors of clinical disease severity

Prognostic factors for early disease severity were assessed in a prospective study of 197 children from onset of the first MS attack.⁶⁸ Severe disease outcome was defined by the occurrence of a third attack or by an EDSS score greater than 4 (persisting for more than 12 months). At a mean observation of 5.5 years, severe disease outcome

was recorded in 144 children (73%), of whom 139 had a third attack and 30 had sustained EDSS scores greater than 4. Predictors of severity included being a girl, the absence of encephalopathy at onset, well-defined lesions or lesions perpendicular to the corpus callosum seen on MRI, less than 1 year between the first and second attacks, and secondary-progressive disease (noted in nine children). The accrual of disability within 1 year of disease onset or a high frequency of relapse in the first 2 years of the disease have also been associated with higher EDSS scores at 8 years.⁷³

Commentary

The published work has focused on disability-related outcomes; little is known about the long-term cognitive outcomes, vocational success, or measures of societal independence. Whether outcomes can be predicted by detailed MRI measures or whether demographic characteristics influence disease severity is unknown. These issues are of paramount importance if the true morbidity of MS onset in childhood is to be fully appreciated.

Management

The care of children with MS needs a multidisciplinary team comprising paediatric and adult neurologists, nurses, physiotherapists, occupational therapists, social workers, psychologists, and psychiatrists.¹³⁰ The diagnosis of chronic illness has substantial emotional effects on children with MS and their families. Compliance with medication, particularly in adolescents, rests on a strong relationship between medical teams, patients, and parents.

Acute demyelination

Acute demyelination in children is managed with corticosteroid therapy. Although there are no specific studies of the dose or effectiveness of corticosteroids, most regimens for severe demyelination use 10–30 mg/kg/dose (to a maximum of 1000 mg/dose) of methylprednisolone by intravenous infusion for 3–5 days. The decision to offer oral prednisone, the starting dose (typically 1–2 mg/kg/day), and the tapering schedule are empirical. If substantial resolution of symptoms is achieved within 3–5 days of intravenous therapy, oral prednisone might be therapeutically unnecessary, and the risk of adrenal suppression is short lived.¹³¹ Mild attacks that do not limit activities or school attendance do not require corticosteroid therapy.

Children with acute relapses who do not respond to the first course of corticosteroids might respond to a further 3–5 days of intravenous therapy (doses as above). For children in whom corticosteroid therapy is contraindicated or ineffective, treatment with intravenous immunoglobulin (IVIg) might be of value (class IV evidence).^{132,133} Published case series advocate doses of 2 g/kg over 2–5 days.

	Endpoint	Positive correlation	No correlation
Boiko and co-workers ⁹⁴	Shift to SPMS course	Relapse rate >0.6* Brainstem involvement at onset	
	Disability	High number of relapses in the first year and in the first 5 years	Gender Age at onset
Ghezzi and co-workers ⁷³	Disability	EDSS after the first year† Number of relapses in the first 2 years SPMS evolution	Gender Symptoms Age at onset
Gusev and co-workers ¹⁰⁵	Disability	Relapse rate Short interval between first and second attacks	Gender Age at onset
Mikaeloff and co-workers ⁶⁸	Severity score	Being female Interattack interval <1 year Progressive course No mental change MRI criteria‡	Age at onset
Simone and co-workers ⁹⁶	Disability	Short interval between first and second attacks Involvement of sphincter at onset SPMS course	Age at onset Gender Cognitive impairment at onset
	Shift to SPMS course	Interattack interval <1 year First relapse in the first 2 years	Age at onset Gender Symptoms at onset Cognitive impairment at onset

*Annualised relapse rate calculated for all patients in the study, over the entire study period. †EDSS 0=healthy neurological examination; EDSS 10=death due to MS; EDSS <4=abnormal neurological signs in one or more functional systems, with no restriction on physical independence; EDSS between 4 and 6 indicates some limitations in daily motor function; and EDSS >6 indicates marked limitations in gait that require assistance. ‡MRI criteria: lesions perpendicular to the corpus callosum or only well-defined lesions. EDSS=Kurtzke's expanded disability status score. SPMS=secondary-progressive MS.

Table 3: Studies of predictors of clinical outcome in paediatric MS

Life-threatening acute demyelination

Acute demyelination in children can be life threatening because of profound encephalopathy, respiratory depression (commonly associated with extensive white-matter oedema of the brainstem and upper cervical spine), and tetraplegia. There is class I evidence for the benefit of plasma exchange for life-threatening demyelination in adults who do not respond to corticosteroids;¹³⁴ five to eight exchanges are typically needed. Optimisation of therapeutic strategies for children with this devastating disorder is urgently needed.

Immunomodulatory therapies

Class I level evidence for a reduction in the relapse frequency in adults with MS^{135–139} has led to the use of interferon beta (30 µg interferon beta-1a by intramuscular injection once a week, 22–44 µg interferon beta-1a by subcutaneous injection three times a week, or 8 mIU interferon beta-1b by subcutaneous injection every second day) and glatiramer acetate (20 mg by subcutaneous injection daily) in children. None of the immunomodulatory therapies has been formally assessed in large clinical trials of children. A single-centre study of 16 children randomly assigned to low-dose interferon beta-1a (15 µg/week) or placebo reported a favourable effect of therapy on relapse rate ($p=0.04$), disability

progression ($p=0.01$), and accrual of T2-visualised lesions ($p=0.006$).¹³⁹

Favourable safety and tolerability profiles of immunomodulatory therapies in children have been shown in the results of several recent open studies (table 4);^{140–148} a few patients developed depression,¹⁴⁷ generalised oedema,¹⁴⁶ and high titres of liver enzymes.¹⁴²

The rationale for starting immunomodulatory therapy in children with MS is based on data that show these therapies are effective in the early stages of the disease,^{139,149,150} that the risk of future disability might be reduced, and that early treatment might limit the rate of cerebral atrophy in adults.^{150–152}

Although safety and tolerability studies cannot formally address treatment efficacy, a reduction in relapse rate is seen in all studies of interferon therapy in children. The annual relapse rate decreased from 2.4 to 0.4 in children and adolescents treated with interferon beta-1a once a week, and from 3.2 to 0.85 in children and adolescents treated with interferon beta-1a three times a week or interferon beta-1b on alternate days.¹⁴⁶ Similar results were obtained in a larger group after an additional follow-up of 1 year.¹⁵³ Relapse rate decreased from 1.9 to 0.8 in 51 children and adolescents treated with interferon beta-1a three times a week.¹⁴⁷ Glatiramer acetate might also have a favourable effect on relapse rate,¹⁴⁵ although the small number of reported patients limits interpretation of these data. Interpretation of the efficacy of disease-modifying therapies must be viewed in light of the fact that relapse rate declines over time in untreated patients. EDSS scores in treated groups did not seem to change substantially but the effect of treatment on disability accrual needs longer observation.

Immunomodulatory therapies in young children

Several studies have investigated immunomodulatory therapy in patients of age less than 12 years.^{141,147} Young children treated with interferon beta-1a have a prominent reduction in relapse rate;¹⁴⁸ however, elevation of liver enzyme concentrations seems more probable in these patients.^{142,147}

Monitoring immunomodulation

White-blood-cell count and liver function should be monitored monthly for the first 6 months, and every 3 months thereafter. Thyroid function should be monitored annually. All sexually active adolescents with MS should receive contraceptive counselling because the potential teratogenicity of immunomodulatory therapies has yet to be studied fully. Paracetamol or ibuprofen help to reduce the severity of flu-like symptoms. 20% of children treated with glatiramer acetate have a transient flushing-like reaction associated with tachycardia.¹⁴⁴ Children and their parents must be made aware of this potential side-effect because this is a self-limited reaction that has not been associated with cardiac sequelae.

Escalation of therapy in severe MS

There are no published studies of safety, efficacy, or the selection of drugs for children with relapsing-remitting MS refractory to interferon or glatiramer acetate; however, anecdotal reports describe giving azathioprine, mitoxantrone, cyclophosphamide, or methotrexate. Few children have been offered treatment with natalizumab, which is not licensed for patients under the age of 18 years, and rigorous safety-monitoring protocols are required for its use in adults. The safety and efficacy of these powerful immunosuppressive drugs in children with MS requires collaborative study.

Commentary

Evidence from adults with MS suggests that frequent relapses, shorter intervals between attacks, and failure to recover from early relapses predict a greater probability of fixed disability—as measured with the EDSS—and a greater propensity to enter the secondary-progressive phase of MS, in which disability is irrevocable. The currently available immunomodulatory therapies are most effective in patients with active disease. The paediatric MS programmes in France, Italy, and Toronto, Canada, use a clinical-care model that offers immunomodulatory therapies to all children with confirmed relapsing-remitting MS. More than 90% of children in Toronto begin immunomodulatory therapy after their second demyelinating attack (ie, at the time of diagnosis), irrespective of the age of the patient. Interferon is started at 25% of the recommended adult dose and, if monthly laboratory tests of liver function tests are normal, the dose is increased monthly to the full dose. Immunomodulatory therapies are offered in France to children with a clinical score predictive of early severe disease.⁶⁸ Children with mild relapses or clinical or MRI findings that suggest mild disease are offered therapy if their disease activity increases. In Italy, treatment protocols vary with clinical centre but are typically started in patients with frequent relapses in the first few years of disease.¹⁴⁶ In all centres, selection of the type of interferon or glatiramer acetate was determined by discussion with the patient and family. Compliance is closely aligned with patient autonomy, in the authors' experience, and even young patients are capable of determining whether they are more likely to accept weekly intramuscular injections or more frequent subcutaneous injections.¹³⁰

Pathobiological insights

Genetic studies

HLA-DR2 was more common in 47 children¹⁵⁴ and adults¹⁵⁵ with MS from Russia than in the general population. Unlike in adults from the same region with MS, a high prevalence of the TNF α 7 allele was also found, and this was proposed as a potential biomarker for paediatric MS.¹⁵⁶ By contrast, a study of 24 children with MS in Turkey did not detect MS-specific TNF α

	Drug	N	Mean age at first attack (years)	Mean pretreatment duration (months)	Mean treatment duration (months)	Side-effects	Clinical results
Banwell and co-workers ¹⁴²	IFNB-1b	43	10.9	25.4	29.2	No serious or unexpected events Flu-like symptoms (15) Injection-site reaction (9) Abnormal liver enzymes (9) Discontinued (25)*	Reduction of relapse rate of 50%
Ghezzi and co-workers ¹⁴⁶	IFNB-1a†	38	12.1	20	23.3	Flu-like symptoms (19) Headache (10) Myalgia or arthralgia (6)	Decreased relapse rate (2.4 to 0.4) Final EDSS unchanged
	IFNB-1a‡ IFNB-1b§	16+2	12.0	19	34.4	Injection-site reaction (4) Fatigue (1) Nausea (?) Haematological abnormalities (< 10%) Discontinued (6) Chest pain (1)	Decreased relapse rate (3.2 to 0.85) Final EDSS unchanged
	GA¶	9	13.2	9.2	33.3	No haematological abnormalities (NA)	Decreased relapse rate (2.8 to 0.25) Final EDSS slightly improved
Kornek and co-workers ¹⁴⁵	GA	7	13.7	35	24	No laboratory abnormalities Transient systemic reaction (1)	28% relapse-free No change in mean EDSS
Mikaeloff and co-workers ¹⁴¹	IFNB-1a†	13	13.1	27	12	Flu-like symptoms (11) Injection-site reactions (3) Transient abnormal liver enzymes (1)	Treatment failure (25%) EDSS stable
	IFNB-1a‡	2					
	IFNB-1b¶	1					
Pakdaman and co-workers ¹³⁸	IFNB-1a	16			48	No significant side-effects No discontinuation of treatment	Significantly fewer relapses, less disability progression, and fewer new lesions in treated group
Pohl and co-workers ¹⁴⁷	IFNB-1a‡	51	13.4	24	21.6	Injection-site reaction (36) Flu-like symptoms (33) Gastrointestinal symptoms (5) Abnormal liver enzymes (18) Abnormal blood counts (20) Discontinued (9)	Decreased relapse rate (1.9 to 0.8) EDSS score stable (48)
Tenenbaum and Segura ¹⁴⁸	IFNB-1a‡	24	9.3	40.3	44.4	Two serious adverse events (chronic arthritis and attempted suicide) Flu-like symptoms (14) Myalgia or arthralgia (4) Injection-site reaction (18) Abnormal liver enzymes (8)	Significant reduction of relapse rate Decreased EDSS (in patients ≤ 10 years)
Waubant and co-workers ¹⁴³	IFNB-1a†	9	11	36	17	Flu-like symptoms (4) Injection-site reaction (1)	No effect on relapse rate

*Injection pain (1), perceived lack of efficacy (5), lack of adherence (4), funding (4), lost to follow-up (5), other diagnosis (3), unknown (3). †Once a week. ‡Three times a week. §Alternate days. ¶Once a day. ||Randomised design: 8 patients treated with 15 µg IFNB-1a by weekly intramuscular injection; 8 patients untreated. GA= glatiramer acetate. IFNB-1a=interferon beta 1a. IFNB-1b=interferon beta 1b. EDSS=Kurtzke's expanded disability status scale. NA=not available.

Table 4: Treatment studies in paediatric MS

mutations.¹⁵⁷ Genetic studies of *MOG*, the gene encoding myelin oligodendrocyte glycoprotein, located in close proximity to the HLA region on chromosome 6, did not show any disease-specific associations in a study of 75 German children with MS.¹⁵⁸

Environmental triggers

Epidemiological evidence suggests that the risk of MS is strongly influenced by place of residence during childhood,¹⁵⁹ and that childhood viral exposures might have a role in the MS disease process.^{159–161} Serological evidence of remote infection with Epstein Barr virus has been documented in over 85% of children with MS, which differs significantly from the seroprevalence of 40–60% in age-matched, healthy children.^{162–164} Adults

with MS are also more likely to be seropositive for Epstein Barr virus, to have high Epstein Barr virus nuclear antigen titres relative to healthy adults, and to have high Epstein Barr virus titres before the onset of their MS.¹⁶⁵ Infection with Epstein Barr virus is biologically plausible in the pathogenesis of MS because of its innate ability to transform and chronically activate B cells¹⁶⁶ and the potential for molecular mimicry between Epstein Barr virus proteins and specific epitopes of myelin basic protein,¹⁶⁷ which is one of the putative target myelin antigens in MS. The same myelin basic protein epitopes have been used to induce experimental allergic encephalomyelitis, a commonly used animal model of demyelination.¹⁶⁸ In contrast to Epstein Barr virus, exposure to several common childhood infectious agents,

such as varicella, parvovirus B19, and cytomegalovirus, does not differ between children with MS and age-matched controls,^{162,163} nor do children with MS differ from controls in serological responses to vaccine-related agents (measles, mumps, rubella, or pertussis).¹⁶⁹ However, not all children with MS are Epstein Barr virus positive; thus, if infection triggers MS pathogenesis, then other infections must be implicated. Although seven of 25 children with MS had intrathecal antibodies against *Chlamydia pneumoniae*, this was thought to be part of a polyspecific immune response, rather than a disease-related association.¹⁷⁰

Although vaccinations have been frequently deemed as potential triggers of the MS disease process, recent studies did not show an association between hepatitis B vaccine and recurrent demyelination in children or adults with the disease.^{171,172}

Immunological studies

An early study of three children with relapsing demyelination (two diagnosed with MS, one with neuromyelitis optica) showed, through T-cell subset analyses, acute and chronic reduction of circulating T cells and relapse-specific depletion of the T-suppressor and T-cytotoxic subsets.¹⁷³ Myelin basic protein, myelin basic protein exon 2, and myelin oligodendroglial-specific T-cell lines were obtained from 18 patients who had MS onset in childhood.¹⁷⁴ T-cell proliferative responses against specific immunodominant myelin basic protein and myelin oligodendroglial epitopes, and the amount of interferon γ produced by these T-cell lines were similar to those from adults with MS, and there was no obvious difference in these T-cell responses between children and adults with MS. Future studies are needed to determine whether, and how, T-cell responses in children with MS differ from those in matched control groups.

The results of a tetramer radioimmunoassay show that myelin-oligodendroglial-specific autoantibodies seem to be a more important target antigen in ADEM than in MS.¹⁷⁵ Further studies are needed to investigate the humoral responses to other CNS targets, including antigens such as myelin basic protein, that can be extracted directly from CNS tissue, which undergoes important biochemical changes during early childhood.

Studies of cellular injury and cellular stress responses

Axonal injury and glial cell activation are important features of neurodegeneration in MS. The results of a study of CSF from 25 children with MS and 67 controls showed nine children sampled at the time of MS relapse had high concentrations of tau protein, suggestive of axonal injury.¹⁷⁶ Cellular responses to injury or stress are, in part, mediated by mitochondria. So far, sequencing of mitochondrial DNA, and specifically the loci implicated in Leber's hereditary optic neuropathy, from children with MS has not identified mutations specific for MS.¹⁷⁷⁻¹⁷⁹ Although these preliminary analyses do not identify a

Search strategy and selection criteria

Publications in English were identified by MEDLINE searches (1975 to March, 2007), and the respective bibliographies. Search terms included "multiple sclerosis", "acute disseminated encephalomyelitis", "encephalomyelitis", "transverse myelitis", "optic neuritis", "neuromyelitis optica", "Devic's disease", and the more general term "demyelination", combined with either "child(ren)(hood)", "pediatric(s)", "adolescen(t)ce", "early onset", or "very early onset". Single case reports or case series of fewer than five children were included only if the manuscript covered specific clinical issues (such as MS onset under the age of 10 years) or issues of historical relevance. Published review articles were not selected but their references were reviewed. Data published only in abstract form were not included. Adolescent patients included in series that focused on adult MS might have been missed. For discussion of therapies, the standardised rating of therapeutic trials was applied: class I are prospective, randomised, controlled clinical trials, with clear outcome measures, defined populations of patients, adequate accounting for people who dropped out of studies, and relative consistency between treated patients and controls; class II are prospective matched group cohort trials with masked outcome evaluations, with at least three of four features defined for class I; class III are controlled trials in appropriate populations of patients, with outcome assessments that are independent of treatment; and class IV are uncontrolled studies, case series, case reports, or expert opinion.

mitochondrial contribution to MS, there are no functional assays of oxidative phosphorylation, mitochondrial calcium homeostasis, or the protein-folding responses in neurons or glial cells from children with MS. The potential contribution of intracellular stress responses to autoimmune disease is highlighted by recent evidence of impaired folding mechanisms for endoplasmic reticulum proteins in inflammatory bowel disease.¹⁸⁰

Commentary

There are many key questions in the pathobiology of MS: whether individuals have an inherent CNS or immunological predisposition to the disease; whether myelin is structurally or biochemically aberrant or abnormally immunogenic; whether immunological regulatory processes are fundamentally deficient in their capacity to distinguish self from non-self proteins and to limit sufficiently target-directed injury to a monophasic event; and whether certain environmental exposures lead to improperly regulated or misdirected immunological responses. Studies of children with MS provide opportunities to explore these questions in patients only recently exposed to the disease trigger. As such, research into paediatric MS might provide new directions for therapeutic strategies to stop the immunological components early in the disease process.

Conclusions

The diagnosis and care of children with MS will be helped by the recognition of the presenting features of the disease, the use of MRI, and the laboratory exclusion of the other disorders considered in the differential. Consensus criteria for the diagnosis of paediatric MS now exist, and the development of evidence-based radiographic criteria will promote even greater diagnostic certainty. Immunomodulatory therapies are well tolerated and efficacious, although prospective studies are required to appreciate fully the long-term effect of these therapies on MS outcome in children. The potential for physical and cognitive disability, even early in the disease, highlights the urgent need for therapeutic strategies for neurorehabilitation, neuroregeneration, and neurorepair. The opportunity to gain insights into such strategies might actually rest with the population of patients with MS most likely to benefit; identification of the early features of what turns on the MS disease process might, in turn, identify the mechanisms required to turn off the disease.

Contributors

BB designed the content of the manuscript, reviewed all referenced articles, contributed patient-related data, and was the primary author. MT, YM, and AG assisted in the design of the manuscript, contributed to, and edited the final manuscript. AB-O contributed to the text of the manuscript and edited the final manuscript.

Conflicts of interest

We have no conflicts of interest related to the present work. BB has received speakers' honoraria from Biogen-Idec, Serono, Teva Neurosciences, and Schering. AG has received honoraria for consultancy from Biogen-Idec, and travel grants or grants as a speaker from Teva Neuroscience, Aventis, Dompe, and Serono. AB-O has received honoraria for speaking at meetings supported by, or consulting for, Aventis, Bayhill Therapeutics, Berlex, Biogen-Idec, Genentech, Serono, Teva Neuroscience, BioMS, and the Immune Tolerance Network/NIH. YM and TD have nothing to declare.

Acknowledgments

The authors thank Julia Kennedy for her invaluable assistance, the Canadian Multiple Sclerosis Society and the Canadian Multiple Sclerosis Scientific Research Foundation, the Italian centres involved in the prospective study of early-onset multiple sclerosis, the ITEMs study group, and the Société Française de Neurologie Pédiatrique. BB, AB-O, and JK are supported by the Multiple Sclerosis Scientific Research Foundation of Canada. AB-O holds a Don Paty Career Development Award from the Multiple Sclerosis Society of Canada. YM and MT are supported by Institut National de la Recherche Médicale (INSERM U802), Université Paris Sud 11, Assistance Publique—Hôpitaux de Paris.

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