Clinical features of children and adolescents with multiple sclerosis

J.M. Ness, MD, PhD; D. Chabas, MD, PhD; A.D. Sadovnick, PhD; D. Pohl, MD; B. Banwell, MD; and B. Weinstock-Guttman, MD; for the International Pediatric MS Study Group*

Abstract—There is increasing appreciation that multiple sclerosis (MS) can begin in childhood or adolescence, but pediatric MS continues to be a rare entity, with an estimated 2 to 5% of patients with MS experiencing their first clinical symptoms before age 16. A prompt diagnosis of pediatric MS is important to optimize overall management of both the physical and social impact of the disease. The widespread use of disease-modifying therapies (DMT) for MS in adults, as early as following an initial isolated episode, has led to the use of DMT in children and adolescents with MS. However, it is imperative to distinguish pediatric MS from other childhood CNS inflammatory demyelinating disorders such as acute disseminated encephalomyelitis. Although increasing evidence suggests a slower disease course in children with MS compared to adults, significant disability can still accumulate by early adulthood. Furthermore, associated neurocognitive deficits can impair both academic and psychosocial function at a critical juncture in a young person's life. This article reviews the clinical characteristics, neuroimaging, paraclinical findings, disease course, epidemiology, genetics, and pathophysiology of pediatric MS vis-à-vis adult MS. Further research of pediatric MS may advance our understanding of MS pathophysiology in general, as well as improve the long-term health care outcomes of children and adolescents diagnosed with MS.

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Multiple sclerosis (MS) is uncommon in adolescents and even rarer in pre-pubescent children, but there has been increased recognition of pediatric-onset MS over the past two decades. This is, in part, due to the advent of MRI, which has enabled sensitive detection of white matter abnormalities. A variety of terms are used to describe MS in children and teens, including early onset MS (EOMS), pediatric-onset MS, childhood MS, or pediatric MS. There is even controversy defining the pediatric cohort; depending on the study, the upper age limit ranges from 15 to 21 years of age. In this review, the term pediatric MS is used to mean that the first clinical presentation of a demyelinating episode occurred before a person's 18th birthday.

An estimated 2 to 5% of all people with MS have onset before age 16.[1,2] However, in several studies, the data were collected retrospectively from individuals diagnosed as adults (age 18 or older) who later recalled symptoms believed to represent the initial onset of MS. This retrospective group may in fact be very different from persons diagnosed with MS before the age of 18 years.

Inflammatory demyelinating diseases of the CNS have a variety of presentations in childhood. Acute disseminated encephalomyelitis (ADEM) is a polysymptomatic demyelinating disorder associated with encephalopathy. Other demyelinating conditions can affect a discrete region within the CNS without any mental status changes (hence, a clinically isolated syndrome, CIS) such as the brainstem or spinal cord (transverse myelitis, TM) or optic nerves (optic neuritis, ON). While these demyelinating syndromes are typically monophasic in childhood, recurrences can occur, raising the possibility of a diagnosis of MS. There are limited data about the risk of progression to MS after an initial demyelinating event in childhood. In addition, it remains uncertain whether criteria used to diagnose MS after an initial demyelinating episode in adults[3,4] are equally applicable in the pediatric population.[5]

Identifying MS in childhood is important for the overall management of both physical and quality of life issues. There appears to be benefit in the early initiation of disease-modifying therapies (DMT) in adults, which might also be the case in children with MS.[6] Thus, it may be more critical than ever to accurately diagnose MS as early as possible. Treatment issues are described elsewhere in this conference report by Pohl et al.[6b]

Clinical presentation. Over 20 centers worldwide have published descriptions of pediatric MS cohorts, encompassing over 1,000 patients. Articles published

*Members of the International Pediatric MS Study Group are listed in the Appendix.

From the Department of Pediatrics (J.M.N.), University of Alabama at Birmingham and Children's Hospital; Multiple Sclerosis Center at UCSF (D.C.), University of California, San Francisco; Department of Medical Genetics and Faculty of Medicine (A.D.S.), Division of Neurology, University of British Columbia, Vancouver, Canada; Department of Pediatrics and Pediatric Neurology (D.P.), Georg-August-University Goettingen, Germany; Department of Pediatrics (Neurology) (B.B.), The Hospital for Sick Children, Toronto, Canada; and Baird MS Center (B.W.-G.), Jacobs Neurological Institute, Buffalo, NY.

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Address correspondence and reprint requests to Dr. Jayne Ness, Children's Hospital of Alabama, 1600 7th Avenue South, CHB 314, Birmingham, AL 35233-1711; e-mail: jness@peds.uab.edu

in English, describing pediatric MS cohorts with more than 10 patients, are summarized in the table. Most of these studies were retrospective in nature, although some included limited prospective longitudinal data. Despite methodologic differences between studies (e.g., case definitions, subject recruitment, duration of follow-up) some common demographic findings are observed. Most pediatric MS cohorts described are disproportionately female, with gender ratios ranging between 1.3 and 3.0, with average age at onset between 8 and 14 years.

Reported frequencies of visual, sensory, motor, brainstem, or cerebellar deficits in pediatric MS varied widely. ON (both bilateral and unilateral) was identified in 0 to 50% of pediatric MS patients in the cohorts described and most of these studies reported at least 10% of patients presenting with visual changes (table). In a retrospective analysis of 85 patients with MS who had a disease onset at less than 16 years of age, abnormal visual evoked potentials (VEP) were detected in 56% of the children prior to the second attack.[7] Only 40% of these patients had prior visual disturbances. Thus, ON could be an underreported clinical manifestation of pediatric MS. A possible explanation for this phenomenon is a less precise recognition of visual acuity loss, especially in younger children who have not yet started to read and in children who may have difficulties in verbalizing this symptom. The functional impact of ON, particularly unilateral, is generally low and not easily recognized by parents.

Although some authors have suggested that pediatric MS more frequently presents with sensory deficits,[1,8,9] over half of the articles (table) list motor findings more frequently than sensory problems. These differences may be due, in part, to easier identification and recall of motor dysfunction in the young child. Polysymptomatic presentation was found in 10 to 67% of the patients.[2,9-23] Altered mental status was an initial symptom in 5 to 39% of patients, suggesting that some of these pediatric MS cases may have presented with ADEM, although most series lacked sufficient detail to allow us to make that determination.

There have been attempts to identify clinical presentations that predict the likelihood of a future diagnosis of MS. Visual symptoms are among the most common manifestations of demyelinating disease in adults. Approximately 15 to 30% of adult patients with MS have ON as their initial symptom. The Optic Neuritis Study Group reported that the 10-year risk for a diagnosis of MS following a single episode of ON in adults was 38%; the risk of MS increased to 56% if one or more demyelinating lesions were detected in the baseline brain MRI.[24] Some reports suggest this risk is lower (25% or less) in children,[25-29] whereas others have not found this to differ from adult data.[30,31] Bilateral pediatric ON was associated with a higher risk of MS in one report[27] while other groups found children with bilateral ON were less likely to progress to MS.[28,32,33]

In a recent study of 36 children with ON followed prospectively, 36% were diagnosed with MS within 2 years of ON.[34] In this study, bilateral ON was associated with a greater likelihood of MS diagnosis. Evidence of neurologic deficits or MRI evidence of white matter lesions extrinsic to the optic pathways were highly predictive of MS outcome. None of the children with a normal brain MRI were diagnosed with MS to date.

The largest prospective series of pediatric demyelinating disease to date, the KIDMUS pediatric MS cohort,[22] derived from the European Database for Multiple Sclerosis (EDMUS[35]), tracked 296 patients after an initial demyelinating episode. In this study, 168 patients (57%) experienced two or more episodes of demyelination and were diagnosed with MS. Forty percent of the 296 patients initially presented with ADEM, defined by KIDMUS investigators as altered mental status with polysymptomatic presentation and MRI "suggestive of ADEM" with poorly limited lesions and involvement of the thalamus or basal ganglia. Of the 119 children with an initial diagnosis of ADEM, 29% experienced recurrent demyelination and were thus re-classified as MS. Unfortunately, details about the subsequent demyelinating episodes are limited, so it is impossible to determine which of these cases may have actually represented recurrent or multiphasic ADEM.

Predictors for a second attack in the KIDMUS study included optic neuritis, age greater than 10 years, or an MRI "suggestive of MS" with multiple well-defined periventricular or subcortical lesions. A decreased risk of MS was found in patients who presented with myelitis or altered mental status. These findings are similar to that reported in a comparison of 28 patients with ADEM vs 13 patients with MS.[17] All these studies are limited by relatively short follow-up (3 to 6 years). More population-based, longitudinal studies are essential to determine which pediatric patients are at highest risk for MS after an initial demyelinating event so that we can identify those who may benefit from early initiation of DMT.

Variants. Variants of MS such as Marburg variant, Schilder myelinoclastic diffuse sclerosis, or Balo concentric sclerosis often have encephalopathy and large tumefactive lesions similar to those observed in some fulminant cases of ADEM. As many of these patients have destructive brain loss or even death, it has been difficult to differentiate between an explosive onset of MS vs a severe form of ADEM.[36] Acute MS (Marburg variant) is characterized by rapidly progressive demyelination. Pathologic examinations report hypercellular lesions infiltrated by macrophages.[37] This explosive form of MS can lead to clinical deterioration over days to weeks and often death.

In Schilder's myelinoclastic diffuse sclerosis, there are often bilateral regions of cerebral white matter demyelination that may mimic the appearance of adrenoleukodystrophy. Therefore, this diagnosis re-

Table *Summary of clinical features reported in pediatric multiple sclerosis (MS) series published in English with >10 patients*

First author, publication year	Study design, country	n	Mean age (range)	Sex ratio F:M	Clinical presentation with initial demyelinating episode—% of patients (n)								% patients with positive MS Profile (↑ IgG Index or +OCB)
					Optic neuritis	Sensory	Motor	Cerebellar	Brain stem	Spine or bladder/ bowel	Altered mental status or SZ	Poly-symptomatic	
Gall,[10] 1958	Retrospective, USA	40	11.7 ± 0.3 (7-14)	1.9	23% (9)	23% (9)	55% (22) with "disturbance in function of limb"		33% (13)	3% (1)	10% (4)	65% (26)	NA
Duquette,[1] 1987	Retrospective, Canada	125	13 (5-16)	3.0	14% (18)	26% (33)	11% (14)	5% (6)	11% (14)	4% (5)	NS	8% (10)	82% (32 of 39)
Boutin,[11] 1988	Retrospective, France	19	11.0 ± 0.9 (2-16)	2.1	21% (4)	37% (7)	32% (6)	16% (3)	11% (2)	21% (4)	NS	47% (9)	78% (10 of 13)
Hanefeld,[12] 1991	Prospective, Germany	15	8.9 (3-15)	2.8	27% (4)	40% (6)	47% (7)	60% (9)	60% (9)	7% (1)	33% (5)	73% (11)	73% (11)
Sindern,[81] 1992	Retrospective, Germany	31	13.5 ± 0.3 (9-15)	2.4	52% (16)	16% (5)	6% (2)	6% (1)	6% (1)	13% (4)	NS	NS	87%
Cole,[8]1995	Retrospective, Scotland	28	11.5 ± 0.7 (1-15)	1.5	18% (5)	32% (9)	45% (13)	11% (3)	7% (2)	11% (3)	39% (11)	11% Listed as "several"	NS
Guilhoto,[13] 1995	Retrospective, Brazil	14	8.6 ± 1.2 (2-15)	1.3	29% (4)	21% (3)	64% (9)	7% (1)	29% (4)	29% (4)	7% (1)	64% (9)	21% (3)
Selcen,[14] 1996	Retrospective, Turkey	16	11.4 ± 2.7 (6-17)	1.0	19% (3)	13% (2)	25% (4)	38% (6)	25% (4)	19% (3)	NS	38	75
Ghezzi,[2] 1997	Retrospective, Italy	149	12.6 ± 2.5 (6-15)	2.2	17% (25)	18% (26)	18% (27)	9% (13)	25% (37)	NS	NS	37% (55)	NS
Pinhas-Hamiel[16], 1998	Retrospective, Israel	72	18.5 (12-21)	1.4	28% (20)	17% (12)	53% (38)	32% (23)	25% (18)	NS	NS	51% (37)	NS
Dale,[17] 2000	Retrospective longitudinal, England	13	9.4 ± 1.1 (4-15)	0.9	31% (4)	15% (2)	23% (3)	23% (3)	23% (3)	31% (4)	15% (4)	38% (5)	82% (9 of 11)
Belopitova,[18] 2001	Prospective, Bulgaria	10	11.1 ± 0.5 (6-14)	2.6	0%	40% (4)	90% (9)	80% (8)	60% (6)	NS	NS	100% (10)	80% (8)
Boiko,[9] 2002	Retrospective longitudinal, Canada	116	12.7 (3-15)	2.9	22% (25)	26% (30)	10% (12)	7% (8)	13% (15)	1% (1)	NS	12% (14)	NS
Ghezzi,[15] 2002	Prospective, Italy	54	12.1 ± 2.1 (7-15)	2.0	13	19% (10)	26% (14)	43% (23)	20% (11)	3% (3)	NS	43% (23)	87% (41 of 47)
Gusev,[19] 2002	Retrospective, Russia	67	11.7 ± 0.3 (4-15)	1.3	32% (22)	21% (14)	14% (4)	5% (3)	25% (17)	4% (2)	5% (3)	10% (5)	NS
Simone,[20] 2002	Retrospective, Italy	83	14.3 (1-15)	1.9	23% (19)	18% (15)	36% (30)	41% with brainstem or cerebellar sxs		8% (7)	7% (6)	33% (26)	NS
Brass,[114] 2003	Retrospective, Canada	17	12.4 ± 4.5 (1-17)	0.7	35% (6)	59% (10)	65% (11)	35% (6)	24% (4)	NS	6% (1)	NS	67% (8 of 12)
Ozakbas,[21] 2003	Retrospective, Turkey	32	12.9 (8-16)	2.1	17% (5)	28% (9)	17% (5)	52% (16)	7% (2)	3% (1)	7% (2)	44% (14)	90% (29)
Mikaeloff,[22] 2004	Retrospective longitudinal, France	168*	12.0 ± 3.4 (2-16)	2.0	35% (58)	69% (116) with long tract signs; sensory vs motor not specified		NS	36% (61)	8% (13)	13% (21)	67% (113)	40% (68)
Shiraishi,[23] 2005	Retrospective longitudinal, Japan	27	11.7 ± 0.6 (2-15)	2.4	44% (12)	30% (8)	22% (6)	4% (1)	15% (4)	7% (2)	15% (4)	30% (8)	NS

* MS in this study includes all patients with second episode of demyelination; no distinction made between MS and recurrent forms of acute disseminated encephalomyelitis.

NS = not stated; NA = not available; SZ = seizure; MS = multiple sclerosis; OCB = oligoclonal bands; SXS = symptoms.

quires documentation of normal very long chain fatty acids and absence of peripheral nerve involvement.[38] Pathologic examination shows axonal-sparing demyelination and gliosis with or without edema. Gray matter involvement may be seen, but is less common than observed in ADEM, as reviewed in this supplement by Tenembaum et al. Smaller, sharply demarcated white matter lesions more typical of MS may be scattered elsewhere. These multifocal lesions may remit over time in conjunction with clinical recovery but can later evolve into accrual of smaller, circumscribed lesions of MS. Schilder disease is believed to

be more common in children than adults[39]; however, in monophasic disease, it may be indistinguishable from ADEM. In the absence of histologic confirmation, these patients would not be recognized as having MS until at least two additional episodes of demyelination are documented or progressive demyelination is observed.

The histopathologic hallmark of Balo's concentric sclerosis consists of alternating circular bands of demyelination and preserved myelin.[37] This distinctive lamellar pattern of myelin preservation and destruction is also appreciated on MRI.[40,41] There is no clear explanation for this concentric configuration. Serial proton magnetic resonance spectroscopy of four patients with Balo's concentric sclerosis identified decreases in the *N*-acetylaspartate/creatine ratio with concomitant increases in choline-containing compounds suggesting loss of axonal integrity.[42] A recent study identified increased hypoxia-inducible factor 1α and heat shock protein 70 in the regions of preserved myelin, raising the possibility that adjacent areas of inflammatory demyelination may promote protective preconditioning in adjacent tissue.[43] Infectious agents, such as human herpesvirus 6, have has also been associated with Balo's concentric sclerosis.[44] Balo's concentric sclerosis may follow a progressive, remitting, or relapsing-remitting course.[45-47]

While Marburg, Schilder, and Balo are generally recognized as variants of MS, neuromyelitis optica (NMO) or Devic disease is likely distinct from MS. Bilateral ON is much more common in NMO than MS, and the spinal cord lesions of NMO are more extensive with full thickness involvement of the cord extending over three or more segments.[48] Pathologic examination of spinal cord or optic nerves in NMO often reveals highly destructive necrotic lesions with macrophage, eosinophilic and neutrophilic infiltrates, vascular proliferation, and complement activation.[37,49]

Diagnostic criteria for NMO have included the requirement for optic nerve and spinal cord involvement along with evidence of inflammation.[48] NMO is more common in Asians, and particularly in women, but NMO is reported in all ethnic groups and has even been reported in preschool children.[50] The understanding of these clinical features of NMO in children is limited; however, available case reports show features similar to those in adults.[48,51-53] The clinical course is usually relapsing-remitting, but NMO carries a poor prognosis. The overall mortality is up to 20% during the acute stages and can reach 35 to 50% within the first 5 years, underscoring the severity of the underlying pathologic process.[48] Immunosuppression is the mainstay of therapy; however, in contrast to MS, interferon-beta treatment is considered ineffective.[54]

An NMO-specific antibody (NMO-IgG) has recently been developed[55] which has been found to be selective for the CNS water channel, aquaporin-4.[56] These findings support the concept that NMO is a B-cell mediated autoimmune channelopathy with pathophysiology distinct from MS. In a recently proposed revision of NMO diagnostic criteria the best combination (99% sensitive and 90% specific) required the history of myelitis and ON plus the presence of at least two of three elements, including longitudinally extensive cord lesion, initial brain MRI being nondiagnostic for MS, or NMO-IgG seropositivity.[57] Based on these findings, the authors suggested that the NMO phenotype be broadened to allow isolated brain involvement. However, further characterization of this antibody in NMO and related demyelinating syndromes is required in both adults and children of varied ethnic backgrounds before NMO-IgG is routinely included as part of NMO diagnosis.

MR imaging. A discussion of neuroimaging findings in pediatric MS is covered in detail in another article in this supplement. In adults, a specific constellation and chronology of white matter lesions on MRI are now considered to be an adequate surrogate for clinical dissemination in time, enabling diagnosis of MS after an initial demyelinating event.[3] However, application of these criteria is problematic in children, particularly those under age 10.[5] Only 53% of children with clinically definite MS by Poser criteria[38] had a positive MRI as required in the 2001 McDonald criteria, which these authors suggest may be due to a shorter period of time for accumulation of lesions.

Serial MRIs 3 to 6 months after an initial demyelinating event in childhood has been advocated.[58-60] However, optimal timing of repeat neuroimaging has not been studied and may be influenced by the clinical presentation and initial neuroimaging findings. In ADEM, there should be improvement in the T2-hyperintensities, if not complete normalization. In contrast, the hallmark of MS is accumulation of demyelinating lesions, many of which are clinically silent. Studies using MRI changes as a surrogate for a clinical event in children have not been published. In the KIDMUS study, corpus callosum long axis perpendicular lesions or sole presence of well-defined lesions were most predictive of repetitive demyelination,[61] but these findings await confirmation in a larger cohort.

Paraclinical criteria. Between 40 and 90% of pediatric MS patients are reported to have increased intrathecal IgG synthesis, or production of myelin basic protein, or oligoclonal bands (OCB) in CSF (table). A retrospective analysis of 136 patients with MS with disease onset <16 years showed that 92% had either an increased IgG index or OCB, with a sensitivity similar to that observed in adults.[62] Unfortunately, up to 30% of patients with ADEM also have OCB,[17,59,60] thus limiting the utility of CSF indices for predicting which pediatric patients are at risk for recurrent demyelination.

Furthermore, the specific technique used to identify OCB may influence the sensitivity and specific-

ity of these parameters in pediatric demyelinating disease, as has been well demonstrated in the adult MS population. A recently published consensus statement recommends a standardized CSF analysis that should consist of a qualitative assessment of paired CSF and serum samples for the detection of oligoclonal IgG bands that are present in the CSF, but not in the serum, by use of isoelectric focusing and some form of immunodetection (immunoblotting or immuno-fixation).[63] These criteria need to be tested in pediatric MS.

Other CSF indices such as detection of myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG) or antibodies to these proteins have been implicated as markers of increased relapse risk after a CIS,[64] but have not been systematically studied in the pediatric population. Polymorphisms in the MOG promoter region were analyzed in 75 German children with MS and compared to healthy matched controls with no distinct variation.[65]

Other paraclinical criteria include neurophysiologic testing such as visual evoked potentials (VEP), somatosensory evoked potentials (SSEP), or brainstem auditory evoked potentials (BAEP). These tests have been used primarily to identify asymptomatic areas of demyelination, although their use as outcome measures for monitoring the disease progression is being studied in adult MS.[66-69] The combination of BAEP and SEP testing identified clinically silent lesions in 12% of pediatric MS patients.[7] Although this is not a high percentage, these tests are useful for revealing lesions in the brainstem and spinal cord, areas with limited MRI sensitivity. The BAEP and SEP are particularly helpful in the evaluation of younger children since movement artifacts often impede MRI interpretation.

VEP is more sensitive than other EP tests and can be diagnostically helpful if delay or change in amplitude and morphology of the P100 wave is observed, suggesting injured areas (i.e., demyelination with or without axonal damage) along the course of the anterior visual pathways. However, negative testing or negative clinical history does not rule out prior demyelination of the optic nerve. In a retrospective analysis of 85 pediatric MS patients with a disease onset <16 years, 29 patients had pathologic VEP despite the absence of a clinical history of ON.[7] Unexpectedly, 25 of these 29 patients showed normal visual acuity using standard measures at the time of VEP testing. Use of more sensitive assessments such as the low-contrast letter acuity (L-CLA) may have identified subtle visual deficits, similar to what has been demonstrated in the adult MS population,[70] but validation of L-CLA is first needed in a pediatric population.

Disease course and outcome.

Disease course. The disease course is well over 90% relapsing-remitting (RRMS) in pediatric MS, rates that are somewhat higher than for adults.[9,15,20,71-73] A primary progressive course (PPMS), with or without relapses, is much rarer (2.3 to 7%) in pediatric MS than the 20 to 33% reported for the adult population.[9,15,20,71]

Overall, pediatric MS appears to follow a less progressive course than adult MS.[9,20,74] However, a subgroup of pediatric MS patients, usually very young children, manifest a more aggressive disease with irreversible severe psychomotor defects.[75] The first acute event is monosymptomatic and commonly followed by complete clinical recovery, at least in the initial stages.[1,21,76] Sixty percent of children relapse during the first year.[8] A shorter interval between the first and second relapse was seen in patients less than 16 years old compared to adults (1.6 ± 1.6 years vs 2.0 ± 1.8 years).[77] The relapse rate in pediatric MS is in some studies reported to be higher than in adult onset MS.[14,72,77,78] However, in children and adolescents, most symptoms are transitory and remit more quickly than in adult MS (mean time of relapse related symptoms: 4.3 weeks in pediatric MS vs 6 to 8 weeks in adult MS).[74]

Disease progression and predictors of clinical disability in pediatric MS. Kurtzke's Expanded Disability Status Scale (EDSS) from 0 to 10, with higher scores reflecting increased disability, is still considered the gold standard in MS research despite its recognized limitations (i.e., EDSS is an ordinal scale, heavily influenced in its higher end by ambulation; it also has large inter- and intrarater variability). A consistent finding in most pediatric MS retrospective studies is lower disability scores in pediatric MS compared to adult MS, even when disease duration is taken into account. Median time to reach an EDSS of 4 (defined as visible, often irreversible neurologic deficits in a patient able to walk at least 500 meters without assistance) was approximately 20 years for pediatric MS vs 10 years for adult MS.[20] Another longitudinal retrospective study (MS-COSTAR from British Columbia[79]) on 116 patients, all of whom reported a pediatric onset and were followed for a mean duration of 20 years, showed that the time necessary to reach an EDSS of 3 (considered as a moderate irreversible neurologic disability) was 15 years in pediatric MS patients vs 7 years in adult MS, while the time to reach EDSS of 6 (patient able to walk 100 meters but requiring one side assist) was 19 years in pediatric onset MS vs nearly 15 years in adult cases.[9] Time to conversion to a secondary progressive MS (SPMS) course was also longer in pediatric MS: 16 years vs approximately 7 years for adult MS. The probability to convert to SPMS was also lower in pediatric MS (14% vs 24% in adult MS).[20] However, SPMS patients' median age was lower in pediatric MS (30 years) vs adult MS (37 years), emphasizing that pediatric MS is not a benign disease as these young patients with MS can become disabled at an earlier age. The influence of the aging process itself is also important in that patients over 40 have been shown to have a mean EDSS > 4 in both pediatric and adult onset MS, and 50% already had SPMS.[80]

Prognostic factors. A short interval (less than 1 year) between the first two demyelinating episodes, incomplete recovery after the first attack, as well as a secondary progressive disease course are unfavorable prognostic factors associated with a greater risk of developing a higher level of clinical disability over time.[20,22] Increased number of attacks during the first 2 to 5 years is also associated with a higher risk of converting to secondary progressive disease.[9,20,22] However, there is no consistent correlation between gender, age of MS onset, or a polysymptomatic vs monosymptomatic onset, in disease course prognosis.[9,71] Although a significant association was found between a polysymptomatic onset and an increased disability in the French/KIDMUS group of pediatric MS,[22] this association could not be established in the Israeli Juvenile MS Group (72 patients, age < 21), where 51.4% of patients presented with polysymptomatic onset.[71]

The prognostic implications of pre-pubertal vs post-pubertal age at onset is unclear, with younger children found to have better,[74,81-83] worse,[84] or no difference in[85] outcome. However, rare cases with onset prior to 5 years of age consistently appear to carry a more unfavorable prognosis.[8,12] A recent study suggests that later onset of menses is associated with later age at disease onset although it is unknown whether menses occurred earlier in patients with pediatric-onset MS.[86] Most of the pediatric MS case series listed in the table have a mean age of 11 years or older, suggesting that puberty may be a pivotal age for susceptibility to MS. However, prospective studies of children and adolescents experiencing first time demyelinating events are necessary to determine whether being in or past puberty increases the risk of developing MS.

Among a large French MS cohort of 1,844 patients including a group of 207 patients 1 to 19 years of age, the median time from onset of MS to the assignment of an EDSS score of 4, 6, and 7 was significantly influenced by degree of recovery from the first demyelinating episode, time to a second neurologic episode, the number of relapses in the first 5 years of the disease, gender, and age.[73] However, after reaching the score of 4, the median time to attain a score of 6 was 5.7 years, with no further additional impact of any clinical disease variables. Similarly, another pediatric MS series[9] demonstrated that the mean time necessary to convert from the irreversible EDSS score of 3 to a score of 6 was 5 years in RRMS as well as in SPMS, which is comparable to data on adult MS.[73] These data suggest that although the time to reach the threshold associated with irreversible neurologic damage may be longer in early onset MS, once this point is reached, the period of time associated with progressive decline is similar between pediatric and adult MS with no significant influence of other clinical variables.

In addition to the well recognized motor and sensory defects associated with MS, cognitive and emotional sequelae have been documented for over a century as important MS disease parameters. However, the more subtle neuropsychological impairments are often underappreciated. The devastating effect of MS on cognitive performance has a direct impact on an individual's academic, social, and economic status. Cognitive deficits have been identified as the most frequent cause of unemployment in the MS population.[87] There is ongoing research to refine and develop sensitive methods of measuring and monitoring these deficits in both the adult and pediatric MS population.[88-90] The late teen and early adult years form a critical juncture in a young person's life with respect to schooling, development of self-esteem, socialization, vocational training, and childbearing, all of which impact one's quality of life. Thus, the cumulative effect of pediatric MS can significantly impact many areas other than neurologic outcomes. Long-term prospective studies are critical for determining appropriate interventions in the pediatric MS population. The psychosocial impact of neurocognitive deficits from pediatric demyelinating conditions is discussed further in this conference report.

Environment. MS has long been believed to be a disease of Caucasians of northern European ancestry with disease rates rising with increased distance from the equator in both northern and southern hemispheres.[91] It is yet to be determined whether pediatric cases of MS follow the same pattern. Preliminary data suggest that non-Caucasian ancestry may play a role in pediatric MS. At least two referral centers (United States and Canada) have a higher than expected number of MS patients under age 18 who are first generation North Americans with parents born in either Latin or Caribbean countries, where MS is usually less common.[92,93] Migration studies have been interpreted to imply that puberty is a critical stage for altering the risk of developing MS,[94] but more recent work from Australia suggests that even migration in adulthood could have an effect.[95] Environmental factors appear to affect populations rather than being reflected in the familial microenvironment.[96-98] The exact nature of these factors has yet to be determined in adults and may or may not be the same for children and adolescents with MS. One interesting factor appears to involve sunlight and vitamin D,[99,100] and there has even been speculation that this observation could lead to preventive measures in at risk individuals.[101,102]

Recent studies have also examined the role of prior infectious exposure in pediatric MS. A case control study in Toronto showed that 83% of 30 pediatric MS patients had serologic evidence for remote Epstein-Barr virus (EBV) infection, compared with 42% of 90 controls, suggesting a potential increased risk of pediatric MS being associated with EBV infection.[103] These findings have been replicated in a German[103b] and in a multinational cohort.[104] In contrast, a recent revised report showed an age-dependent relationship between EBV infection and

MS, but only for individuals aged 25 years and older.[105] *Chlamydia pneumoniae* and antibodies have been detected in CSF of adult[106] and pediatric MS patients[107] but the significance of these observations is unclear.[108]

Genetics. Evidence that MS is a complex trait has been reviewed recently.[109-111] There seems little doubt that MS risk is determined by genes and environment with the likely possibility that there is interaction between and among these in as yet unspecified ways.

To date, genetic studies specifically focused on pediatric MS have been relatively few and findings have been neither definitive nor replicated in large, independent samples. The major histocompatibility complex (MHC) is unambiguously associated with MS susceptibility in adults.[102] Similar overall findings have been reported for pediatric MS in two studies from Russia.[112,113] Similar frequencies of DRB1 alleles and genotypes were identified, regardless of whether the onset of MS was younger than 16 years of age (n = 56) or 16 and older (n = 234).[112] The other study of a Russian cohort suggested an association between DR15 (DRB1*150) alleles and susceptibility in children to ON and MS.[113]

Conclusion. In the initial stages, pediatric MS is associated with a more favorable outcome compared to adult MS; however, over the long term, pediatric MS patients can become disabled at a younger age, underscoring that MS in pediatric population does not have a benign prognosis and early initiation of DMT should be considered. MS was described for the first time more than 100 years ago, but today its origin remains enigmatic: both the initiating event in MS (autoimmune, degenerative, or infectious) and the chronological timing (when does MS begin?) are unknown. Studying the epidemiology and pathobiology of pediatric MS might lead to new hypotheses and promote better understanding and treatment of both children and adults with MS.

Appendix

The International Pediatric MS Study Group: Lauren Krupp, MD (chair), Brenda L. Banwell, MD, Anita Belman, MD, Dorothee Chabas, MD, PhD, Tanuja Chitnis, MD, Peter Dunne, MD, Andrew Goodman, MD, Jin S. Hahn, MD, Deborah P. Hertz, MPH, Nancy J. Holland, EdD, RN, MSCN, Douglas Jeffery, MD, PhD, William MacAllister, PhD, Raul Mandler, MD, Maria Milazzo, RN, MS, CPNP, Jayne Ness, MD, PhD, Jorge Oksenberg, PhD, Trena L. Pelham, MD, Daniela Pohl, MD, PhD, Kottil Rammohan, MD, Mary R. Rensel, MD, Christel Renoux, MD, Dessa Sadovnick, PhD, Steven Robert Schwid, MD, Silvia Tenembaum, MD, Cristina Toporas, Emmanuelle Waubant, MD, PhD, Bianca Weinstock-Guttman, MD.

References

1. Duquette P, Murray TJ, Pleines J, et al. Multiple sclerosis in childhood: clinical profile in 125 patients. J Pediatr 1987;111:359–363.
2. Ghezzi A, Deplano V, Faroni J, et al. Multiple sclerosis in childhood: clinical features of 149 cases. Mult Scler 1997;3:43–46.
3. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127.
4. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840–846.
5. Hahn CD, Shroff MM, Blaser SI, et al. MRI criteria for multiple sclerosis: evaluation in a pediatric cohort. Neurology 2004;62:806–808.
6. Rieckmann P, Toyka KV, Bassetti C, et al. Escalating immunotherapy of multiple sclerosis—new aspects and practical application. J Neurol 2004;251:1329–1339.

6b. Pohl D, Waubant E, Banwell B, et al., for the International Pediatric MS Study Group. Treatment of pediatric multiple sclerosis and variants. Neurology 2007;68(suppl 2):S54–S65.

7. Pohl D, Rostasy K, Treiber-Held S et al. Pediatric multiple sclerosis: detection of clinically silent lesions by multimodal evoked potentials. J Pediatr 2006;149:125–127.
8. Cole GF, Stuart CA. A long perspective on childhood multiple sclerosis. Dev Med Child Neurol 1995;37:661–666.
9. Boiko A, Vorobeychik G, Paty D, et al. Early onset multiple sclerosis: a longitudinal study. Neurology 2002;59:1006–1010.
10. Gall JC, HAYLES AB, Seikert RG, et al. Multiple sclerosis in children; a clinical study of 40 cases with onset in childhood. Pediatrics 1958;21: 703–709.
11. Boutin B, Esquivel E, Mayer M, et al. Multiple sclerosis in children: report of clinical and paraclinical features of 19 cases. Neuropediatrics 1988;19:118–123.
12. Hanefeld F, Bauer HJ, Christen HJ, et al. Multiple sclerosis in childhood: report of 15 cases. Brain Dev 1991;13:410–416.
13. Guilhoto LM, Osorio CA, Machado LR, et al. Pediatric multiple sclerosis report of 14 cases. Brain Dev 1995;17:9–12.
14. Selcen D, Anlar B, Renda Y. Multiple sclerosis in childhood: report of 16 cases. Eur Neurol 1996;36:79–84.
15. Ghezzi A, Pozzilli C, Liguori M, et al. Prospective study of multiple sclerosis with early onset. Mult Scler 2002;8:115–118.
16. Pinhas-Hamiel O, Barak Y, Siev-Ner I, et al. Juvenile multiple sclerosis: clinical features and prognostic characteristics. J Pediatr 1998; 132:735–737.
17. Dale RC, de SC, Chong WK, et al. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000;123 Pt 2:2407–2422.
18. Belopitova L, Guergueltcheva PV, Bojinova V. Definite and suspected multiple sclerosis in children: long-term follow-up and magnetic resonance imaging findings. J Child Neurol 2001;16:317–324.
19. Gusev E, Boiko A, Bikova O, et al. The natural history of early onset multiple sclerosis: comparison of data from Moscow and Vancouver. Clin Neurol Neurosurg 2002;104:203–207.
20. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology 2002; 59:1922–1928.
21. Ozakbas S, Idiman E, Baklan B, et al. Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. Brain Dev 2003; 25:233–236.
22. Mikaeloff Y, Suissa S, Vallee L, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr 2004;144:246–252.
23. Shiraishi K, Higuchi Y, Ozawa K, et al. Clinical course and prognosis of 27 patients with childhood onset multiple sclerosis in Japan. Brain Dev 2005;27:224–227.
24. Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Arch Ophthalmol 2003;121:944–949.
25. Kriss A, Francis DA, Cuendet F, et al. Recovery after optic neuritis in childhood. J Neurol Neurosurg Psychiatry 1988;51:1253–1258.
26. Visudhiphan P, Chiemchanya S, Santadusit S. Optic neuritis in children: recurrence and subsequent development of multiple sclerosis. Pediatr Neurol 1995;13:293–295.
27. Lucchinetti CF, Kiers L, O'Duffy A, et al. Risk factors for developing multiple sclerosis after childhood optic neuritis. Neurology 1997;49: 1413–1418.
28. Morales DS, Siatkowski RM, Howard CW, et al. Optic neuritis in children. J Pediatr Ophthalmol Strabismus 2000;37:254–259.
29. Lana-Peixoto MA, Andrade GC. The clinical profile of childhood optic neuritis. Arq Neuropsiquiatr 2001;59:311–317.
30. Riikonen R, Donner M, Erkkila H. Optic neuritis in children and its relationship to multiple sclerosis: a clinical study of 21 children. Dev Med Child Neurol 1988;30:349–359.
31. Mizota A, Niimura M, chi-Usami E. Clinical characteristics of Japanese children with optic neuritis. Pediatr Neurol 2004;31:42–45.
32. Parkin PJ, Hierons R, McDonald WI. Bilateral optic neuritis. A long-term follow-up. Brain 1984;107 (Pt 3):951–964.
33. Hwang JM, Lee YJ, Kim MK. Optic neuritis in Asian children. J Pediatr Ophthalmol Strabismus 2002;39:26–32.
34. Wilejto M, Shroff MM, Buncic JR, et al. The clinical features, MRI findings and outcome of optic neuritis in children. Neurology 2006;67: 258–262.
35. Confavreux C, Compston DA, Hommes OR, et al. EDMUS, a European database for multiple sclerosis. J Neurol Neurosurg Psychiatry 1992; 55:671–676.
36. Brinar VV. Non-MS recurrent demyelinating diseases. Clin Neurol Neurosurg 2004;106:197–210.

37. Prineas JW, McDonald WI, Franklin RJ. Demyelinating diseases. In: Graham DI, Lantos PL, eds. Greenfield's neuropathology. 7th ed. London: Arnold, 2002:471–550.
38. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13:227–231.
39. Gallucci M, Caulo M, Cerone G, et al. Acquired inflammatory white matter disease. Childs Nerv Syst 2001;17:202–210.
40. Gharagozloo AM, Poe LB, Collins GH. Antemortem diagnosis of Balo concentric sclerosis: correlative MR imaging and pathologic features. Radiology 1994;191:817–819.
41. Caracciolo JT, Murtagh RD, Rojiani AM, et al. Pathognomonic MR imaging findings in Balo concentric sclerosis. AJNR Am J Neuroradiol 2001;22:292–293.
42. Chen CJ. Serial proton magnetic resonance spectroscopy in lesions of Balo concentric sclerosis. J Comput Assist Tomogr 2001;25:713–718.
43. Stadelmann C, Ludwin S, Tabira T, et al. Tissue preconditioning may explain concentric lesions in Balo's type of multiple sclerosis. Brain 2005;128:979–987.
44. Pohl D, Rostasy K, Krone B, et al. Balo's concentric sclerosis associated with primary human herpesvirus 6 infection. J Neurol Neurosurg Psychiatry 2005;76:1723–1725.
45. Courville CB. Concentric sclerosis. In: Vinken PJ, Bruyn GW, eds. Handbook of clinical neurology, Vol. 9 Multiple sclerosis and other demyelinating diseases. Amsterdam, 1970:437–451.
46. Yiao ML. Clinical and pathological analysis of 10 cases of concentric sclerosis. Zhonghua Shen Jing Jing Shen Ke Za Zhi 1983;16:299–302.
47. Ordinario AT, Tabira T. Fifteen autopsied cases of concentric sclerosis (Balo) seen in the Philippines. Int Center Med Res Ann 1987;139–148.
48. Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53: 1107–1114.
49. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125:1450–1461.
50. Bencherif MZ, Karib H, Tachfouti S, et al. Devic's neuromyelitis optica. A childhood case and review of the literature. J Fr Ophtalmol 2000;23:488–490.
51. Ch'ien LT, Medeiros MO, Belluomini JJ, et al. Neuromyelitis optica (Devic's syndrome) in two sisters. Clin Electroencephalogr 1982;13:36–39.
52. DeLara F, Tartaglino L, Friedman D. Spinal cord multiple sclerosis and devic neuromyelitis optica in children. AJNR Am J Neuroradiol 1995;16:1557–1558.
53. Ghezzi A, Bergamaschi R, Martinelli V, et al. Clinical characteristics, course and prognosis of relapsing Devic's Neuromyelitis Optica. J Neurol 2004;251:47–52.
54. Weinshenker B. Western vs optic-spinal MS: two diseases, one treatment? Neurology 2005;64:594–595.
55. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106–2112.
56. Lennon VA, Kryzer TJ, Pittock SJ, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202:473–477.
57. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–1489.
58. Dale RC, Branson JA. Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis? Arch Dis Child 2005;90:636–639.
59. Hynson JL, Kornberg AJ, Coleman LT, et al. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. Neurology 2001;56:1308–1312.
60. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology 2002;59:1224–1231.
61. Mikaeloff Y, Adamsbaum C, Husson B, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 2004;127:1942–1947.
62. Pohl D, Rostasy K, Reiber H, et al. CSF characteristics in early-onset multiple sclerosis. Neurology 2004;63:1966–1967.
63. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. Arch Neurol 2005;62:865–870.
64. Berger T, Rubner P, Schautzer F, et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med 2003;349:139–145.
65. Ohlenbusch A, Pohl D, Hanefeld F. Myelin oligodendrocyte gene polymorphisms and childhood multiple sclerosis. Pediatr Res 2002;52:175–179.
66. Halliday AM, McDonald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. BMJ 1973;4:661–664.
67. Holder GE. Multiple sclerosis. In: Heckenlively JR, Arden GB, eds. Principles and practices of clinical electrophysiology of vision. St. Louis, MO: Mosby, 1991:797–805.
68. Frederiksen JL, Petrera J. Serial visual evoked potentials in 90 untreated patients with acute optic neuritis. Surv Ophthalmol 1999;44 suppl 1:S54–S62.
69. Weinstock-Guttman B, Baier M, Stockton R, et al. Pattern reversal visual evoked potentials as a measure of visual pathway pathology in multiple sclerosis. Mult Scler 2003;9:529–534.
70. Baier ML, Cutter GR, Rudick RA, et al. Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. Neurology 2005;64:992–995.
71. Pinhas-Hamiel O, Sarova-Pinhas I, Achiron A. Multiple sclerosis in childhood and adolescence: clinical features and management. Paediatr Drugs 2001;3:329–336.
72. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112(Pt 1):133–146.
73. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003;126:770–782.
74. Ruggieri M, Iannetti P, Polizzi A, et al. Multiple sclerosis in children under 10 years of age. Neurol Sci 2004;25 suppl 4:S326–S335.
75. Ruggieri M, Polizzi A, Pavone L, et al. Multiple sclerosis in children under 6 years of age. Neurology 1999;53:478–484.
76. Simone IL, Carrara D, Tortorella C, et al. Early onset multiple sclerosis. Neurol Sci 2000;21:S861–S863.
77. Trojano M, Liguori M, Bosco ZG, et al. Age-related disability in multiple sclerosis. Ann Neurol 2002;51:475–480.
78. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 1989;112 (Pt 6):1419–1428.
79. Paty D, Studney D, Redekop K, et al. MS COSTAR: a computerized patient record adapted for clinical research purposes. Ann Neurol 1994;36 suppl:S134–S135.
80. Trojano M, Paolicelli D, Bellacosa A, et al. Atypical forms of multiple sclerosis or different phases of a same disease? Neurol Sci 2004;25 suppl 4:S323–S325.
81. Sindern E, Haas J, Stark E, et al. Early onset MS under the age of 16: clinical and paraclinical features. Acta Neurol Scand 1992;86:280–284.
82. Leibowitz U, Halpern L, Alter M. Clinical studies of multiple sclerosis in Israel. I. A clinical analysis based on a country-wide survey. Arch Neurol 1964;10:502–512.
83. Muller R. Studies on disseminated sclerosis. Acta Med Scand 1949; 222:1–214.
84. Lazarte JA. Multiple sclerosis: prognosis for ambulatory and nonambulatory patients. Res Publ Assoc Res Nerv Ment Dis 1950;28:512–523.
85. Poser S, Raun NE, Poser W. Age at onset, initial symptomatology and the course of multiple sclerosis. Acta Neurol Scand 1982;66:355–362.
86. Sloka JS, Pryse-Phillips WE, Stefanelli M. The relation between menarche and the age of first symptoms in a multiple sclerosis cohort. Mult Scler 2006;12:333–339.
87. Rao SM, Leo GJ, Ellington L, et al. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991;41:692–696.
88. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. Neurology 2005;64:891–894.
89. MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology 2005; 64:1422–1425.
90. Hahn CD, Miles BS, MacGregor DL, et al. Neurocognitive outcome after acute disseminated encephalomyelitis. Pediatr Neurol 2003;29: 117–123.
91. Kurtzke JF, Beebe GW, Norman JE Jr. Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. Neurology 1979;29:1228–1235.
92. Krupp LB, MacAllister WS, Milazzo M, et al. Unexpected demographic profile in Pediatric MS. Ann Neurol 2004;56:S56.
93. Kennedy J, O'Connor P, Sadovnick AD, et al. Age at onset of multiple sclerosis may be influenced by place of residence during childhood rather than ancestry. Neuroepidemiology 2006;26:162–167.
94. Dean G. Annual incidence, prevalence, and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. BMJ 1967;2:724–730.
95. Hammond SR, English DR, McLeod JG. The age-range of risk of developing multiple sclerosis: evidence from a migrant population in Australia. Brain 2000;123:968–974.
96. Ebers GC, Sadovnick AD, Dyment DA, et al. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet 2004;363: 1773–1774.
97. Dyment D, Yee IM, Ebers GC, et al. Multiple sclerosis in stepsiblings: recurrence risk and ascertainment. J Neurol Neurosurg Psychiatry 2006;77:258–259.
98. Eyles D, Brown J, Mackay-Sim A, et al. Vitamin D3 and brain development. Neuroscience 2003;118:641–653.
99. van der Mei AIF, Ponsonby AL, Dwyer T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ 2003;327:316.

100. Willer CJ, Dyment DA, Sadovnick AD, et al. Timing of birth and risk of multiple sclerosis: population based study. BMJ 2005;330:120.
101. Chaudhuri A. Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis. Med Hypoth 2005;64:608–618.
102. Sotgiu S, Pugliatti M, Sanna A, et al. Multiple sclerosis complexity in selected populations: the challenge of Sardinia, insular Italy. Eur J Neurol 2002;9:329–341.
103. Alotaibi S, Kennedy J, Tellier R, et al. Epstein-Barr virus in pediatric multiple sclerosis. JAMA 2004;291:1875–1879.
103b. Pohl D, Krone B, Rostasy K, et al. High seroprevalence of Epstein-Barr virus in children with multiple sclerosis. Neurology 2006;67: 2063–2065.
104. Banwell BL, Tellier R, Krupp LB, et al. Viral exposures in pediatric multiple sclerosis: preliminary data from a multinational collaborative study. Neurology 2005;64:A319.
105. Levin LI, Munger KL, Rubertone MV, et al. Temporal relationship between elevation of Epstein-Barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA 2005;293:2496–2500.
106. Munger KL, Peeling RW, Hernan MA, et al. Infection with Chlamydia pneumoniae and risk of multiple sclerosis. Epidemiology 2003;14:141–147.
107. Rostasy K, Reiber H, Pohl D, et al. Chlamydia pneumoniae in children with MS: frequency and quantity of intrathecal antibodies. Neurology 2003;61:125–128.
108. Hammerschlag MR, Apfalter P, Boman J, et al. The Role of Chlamydia pneumoniae in multiple sclerosis: real or fictitious? J Infect Dis 2005; 192:1305–1307.
109. Dyment DA, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis. Lancet Neurol 2004;3:104–110.
110. Oksenberg JR, Barcellos LF. Multiple sclerosis genetics: leaving no stone unturned. Genes Immun 2005;6:375–387.
111. Kurtzke JF. Epidemiology and etiology of multiple sclerosis. Phys Med Rehabil Clin N Am 2005;16:327–349.
112. Boiko AN, Gusev EI, Sudomoina MA, et al. Association and linkage of juvenile MS with HLA-DR2(15) in Russians. Neurology 2002;58:658–660.
113. Guseva MR, Boiko SI, Sudomoina MA, et al. [Immunogenetics of optic neuritis in children with multiple sclerosis.] Vestn Oftalmol 2002;118: 15–19.
114. Brass SD, Caramanos Z, Santos C, et al. Multiple sclerosis vs acute disseminated encephalomyelitis in childhood. Pediatr Neurol 2003;29: 227–231.