

Multiple Sclerosis in Israeli Children: Incidence, and Clinical, Cerebrospinal Fluid and Magnetic Resonance Imaging Findings

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ABSTRACT: **Background:** Multiple sclerosis (MS) occurs in young adults and infrequently appears in childhood.

Objectives: To determine the incidence of MS and describe the clinical, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings at onset of MS in children in Israel.

Methods: Incidence and case-specific data were obtained through the MS Center Database and Israeli Health Statistics Census Data over 15 years, from 1995 to 2009, and compared between patients with childhood (< 12 years), juvenile (≥ 12 years, ≤ 18 years) and adult (> 18 years) MS onset.

Results: Of 1129 eligible MS patients, we identified 10 (0.89%) with childhood-onset MS, 74 (6.55%) with juvenile-onset MS, and 1045 (92.56%) with adult-onset MS. There were 0 to 3 incident childhood cases/year, leading to an annual incidence of 0.1/100,000 among Israeli children; the incidence of juvenile and adult MS was 2.6 and 5.4/100,000, respectively. Neurological presentation among children with MS was optic neuritis, motor weakness or brainstem involvement. CSF oligoclonal immunoglobulin (IgG) were positive in 62.5%. The most frequent MRI finding was the occurrence of ≥ 3 periventricular white matter lesions followed by corpus callosum lesions, with 71% co-occurrence. Cervical and thoracic lesions occurred in 33% and 43%, respectively. Time to second neurological event ranged from 0.3 to 4.2 years and none of the patients with childhood MS reached EDSS = 6.0 within a mean follow-up period of 8.4 years.

Conclusions: Childhood-onset MS is rare, with an incidence of 0.1/100,000 Israeli children. Childhood MS does not differ significantly from juvenile and adult-onset MS in terms of clinical, laboratory and imaging findings.

IMAJ 2012; 14: 234–239

KEY WORDS: multiple sclerosis (MS), childhood, incidence, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), acquired demyelinating syndrome (ADS)

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Multiple sclerosis is a common cause of neurological disability among young adults and usually appears between 20 and 40 years of age with a peak incidence at 25 years [1]. Recently, the World Health Organization Multiple Sclerosis International Federation reported that the interquartile range for symptom onset is between 25.3 and 31.8 years, and the average age of onset is 29.2 years [2]. The onset of MS in childhood is infrequent. Furthermore, many studies define the period of childhood differently, and patients are thus diagnosed with childhood MS in a range between a few months to 18 years [3–13] [Table 1].

MS diagnosis requires evidence of dissemination of inflammatory demyelination within the brain and/or spinal cord over time. The first presentation of acute demyelination, defined as acquired demyelinating syndrome, could be either a transient illness or the first attack of MS [14]. Accordingly, ADS is subdivided clinically into acute disseminated encephalomyelitis, clinically isolated syndromes including optic neuritis, transverse myelitis and brainstem, cerebellar and/or hemispheric dysfunction [15]. Prospective studies of children with ADS have shown that 16%–25% are ultimately diagnosed with MS before age 18 years [16,17].

In the current retrospective long-term study we identified patients who presented with ADS and at follow-up proved to suffer from childhood MS. We defined childhood MS as patients who presented with the first neurological demyelinating event during the prepubertal or early pubertal years (Tanner stage 1 or 2), up to the age of 12 years, and during follow-up demonstrated further disease activity with dissemination in space either clinically or by the appearance of new brain magnetic resonance imaging demyelinating lesions. We aimed to define the incidence, demographic features, and clinical, laboratory and imaging findings at onset of childhood MS in Israel. Furthermore, we assessed the time to the second attack and to irreversible progression in these patients.

MS = multiple sclerosis

ADS = acquired demyelinating syndrome

Table 1. World-wide definitions of childhood MS

Country	Definition of childhood MS by age at onset (yrs)	No. of patients	Type of study (Duration)	Author, year [ref]
Germany	< 18	166	Case series, one center	Stark, 2008 [3]
Netherlands	< 16	37	Nationwide (1990–2007)	Neuteboom, 2010 [4]
France	< 16 ≤ 12	197 114 (58%)	Multicenter (1990–2003)	Mikaeloff, 2006 [5]
Turkey	< 16	36	One center (1985–2001)	Ozakbas, 2003 [6]
European MS database	< 16 ≤ 12	364 71 (18%)	13 French & Belgian centers (1976–2001)	Renoux, 2007 [7]
Iran	< 16 ≤ 10	82 7	Case series One center (1997–2003)	Etemadifar, 2007 [8]
Taiwan	< 18	21	One center (1983–2005)	Weng, 2006 [9]
Japan	< 15	8	Prevalence 1.3 per 100,000 persons (1998–2003)	Torisu, 2010 [10]
Japan	< 15	27	1 center 1979–2001	Shiraishi, 2005 [11]
China	< 12	25	Case series, one center (1993–2006)	Xiong, 2007 [12]
Canada (Montréal)	< 17	17	Two centers (1987–2001)	Brass, 2003 [13]

PATIENTS AND METHODS

The Sheba Multiple Sclerosis Computerized Database was reviewed for the period 1 January 1995 to 31 January 2009 (15 years) to identify patients by age of disease onset. This database is a prospective population-based register documenting demographic and clinical data of all MS patients followed at Sheba Medical Center, Tel Hashomer, Israel since 1 January 1995. It includes an electronic record-keeping software system that is used to archive patients’ demographic, clinical and imaging data which are prospectively updated by the Center’s neurologists at each clinic visit. Patients are followed consecutively and neurologically evaluated once every 3 months. Code numbers were assigned to each patient’s record to ensure confidentiality during statistical analyzes. The Sheba Institutional Review Board approved the study.

CASE ASCERTAINMENT

Standardized criteria were applied to ensure completeness of case ascertainment and the diagnosis of MS was performed according to McDonald’s criteria [18]. The population in the

Sheba Medical Center and Schneider Children’s Hospital catchment area were obtained from the Health Statistics Census Data annually, for the period 1 January 1995 to 31 December 2009.

STUDY ELIGIBILITY CRITERIA

Patients were included in the study if their age at the onset of the first acute demyelinating event was < 12 years, defined as childhood MS; 12–18 years, defined as juvenile MS; and above 18 years, defined as adult MS. A cutoff of up to 12 years to define childhood MS was chosen because this period is considered as the pre- or early pubertal period.

DIAGNOSTIC CRITERIA FOR CHILDHOOD MS

Specifically for the establishment of the diagnosis of childhood MS the following criteria were applied:

Inclusion criteria

- Onset of neurological symptomatology before the age of 12 years
- Patients at prepubertal or early pubertal years – Tanner stage 1 or 2 by either breast tissue development (B1/B2) or testicular volume (T1/T2) [19]
- No prior history of central nervous system demyelination
- Brain MRI positive for demyelination according to the new proposed diagnostic algorithm in patients with clinically isolated syndromes [20], or spinal cord MRI lesions where any number of cord lesions were included in the total lesion count.

Exclusion criteria

- Evidence for acute infection such as culture-proven bacterial meningitis, viral encephalitis, demyelination of the peripheral nervous system (i.e., Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy)
- Biochemical or radiological suspicion of inherited or genetically defined leukodystrophy, metabolic or mitochondrial disease, systemic and laboratory features suggestive of systemic lupus erythematosus or connective tissue disease, or radiation or chemotherapy-associated white matter damage
- Brain or spinal cord compression by extrinsic or intrinsic lesions.

Demographic, clinical and imaging data were collected for all patients with the diagnosis of childhood MS. Family history of autoimmune diseases, preceding events, and systemic symptoms were also recorded. Comparisons with respect to age of onset were performed between patients with childhood MS, juvenile MS and adult MS, across clinical presentations categorized by type of functional system involvement as follows:

- Visual involvement with the presentation of optic neuritis defined by acute or subacute visual loss, typically associated with a relative afferent pupillary defect, restricted visual fields, pain with ocular movement, and/or with optic nerve swelling

- Long-tract involvement with motor and/or sensory and/or urinary and/or gastrointestinal symptoms defined by limb weakness typically associated with a defined spinal sensory level, bladder or bowel dysfunction, and MRI evidence of spinal cord swelling, increased signal, or enhancement
- Brainstem and/or cerebellar symptoms.

STATISTICAL ANALYSES

Demographic and clinical data are presented by descriptive statistics. Comparisons across demographic and clinical parameters with regard to age of onset categorized as childhood MS (< 12 years), juvenile MS (≤ 12 years, ≥ 18 years) and adult MS (> 18 years) were performed using *t*-test for continuous variables and chi-square test for categorical variables. Annual MS incidence rates were calculated using Israeli Health Statistics Census Data for the period 1 January 1995 to 31 December 2009. All the tests applied were two-tailed, and a *P* value of $\leq 5\%$ was considered statistically significant. The data were analyzed using the SAS software (SAS Institute, Cary, NC, USA).

RESULTS

DEMOGRAPHIC AND CLINICAL DATA

Of 1129 eligible MS patients, with disease onset between 1 January 1995 and 31 December 2009, we identified 10 patients (0.89%) with childhood MS (onset < 12 years), 74 patients (6.55%) with juvenile MS (onset ≥ 12 years, ≤ 18 years), and 1045 patients (92.56%) with adult MS (onset > 18 years).

All patients were Caucasians and no significant statistical changes were found between the demographic and clinical variables of the three groups [Table 2]. The proportion of males was greater in the childhood MS group as compared to juvenile and adult MS groups. All patients with childhood MS presented with a tendency for higher neurological disability as evaluated by the Expanded Disability Status Scale score at onset and shorter interval until a second relapse as compared to juvenile and adult patients. None of the patients with childhood MS reached EDSS = 6.0, which signifies irreversible disability, within the mean follow-up period of 8.4 years, while 9.4% and 14.4% of patients with juvenile and adult MS reached EDSS = 6.0 within a mean follow-up period of 8.6 and 8.7 years, respectively.

INCIDENCE

The incidence of MS in Israeli children was calculated using national population data. The annual average incidence was 0.1/100,000 Israeli children with 95% confidence interval of 0.0 to 0.31/100,000 [Figure 1]. Specifically, for years 1, 4, 5, and 8 the annual incidence was 0.17/100,000 Israeli children; for years 2, 3, 7, 9 to 12, 14 and 15 the annual incidence was

Table 2. Demographic and clinical parameters

	Childhood MS (N=10)	Juvenile MS (N=74)	Adult MS (N=1045)
Age at onset (yrs)	9.3 \pm 0.70 (5.2–11.9)	16.3 \pm 0.18 (13–18)	34.5 \pm 0.31 (19–65)
Gender, Female:Male	1:1.5 (4:6)	1.7:1 (47:27)	2.2:1 (721:324)
Ethnicity (%)			
Ashkenazi	30	36	52
Sephardic	50	45	29
Mixed	20	19	19
EDSS at onset	3.8 \pm 0.57 (2–8.0)	2.7 \pm 0.15 (0–7.5)	2.4 \pm 0.03 (0–8.0)
Follow-up period (yrs)	8.4 \pm 1.31 (2.9–15.0)	8.6 \pm 0.50 (1.0–15.0)	8.7 \pm 0.12 (1.0–15.0)
Time to 2nd attack (yrs)	1.5 \pm 1.28 (0.3–4.2)	2.20.30 (0.1–12.2)	2.6 \pm 0.08 (0.3–12.4)
No. of patients (%)	9/10 (90%)	61/74 (82.4%)	829/1045 (79.3%)
Time to EDSS = 6.0 (yrs)	–	5.1 \pm 1.49 (0.3–12.5)	5.7 \pm 0.27 (0.1–13.7)
No. of patients (%)	–	7/74 (9.4%)	151/1045 (14.4%)

Values are mean \pm SE (range)

Ashkenazi = Jews with European ancestry, Sephardic = Jews of Middle East or North African ancestry

0/100,000, and for years 6 and 13 the annual incidence was 0.5/100,000. The incidence of juvenile and adult MS onset was 2.6 and 5.4 per 100,000 Israeli juveniles and adults, respectively, demonstrating an increased age-dependent incidence.

CLINICAL PRESENTATIONS

The family history, antecedent events and clinical features at presentation of patients with childhood MS are presented in Table 3. All subjects were in the prepuberty stage and no significant family history was noted. Antecedent events were non-specific and occurred in 4/10 children; systemic symptoms at onset occurred in 4/10 children, were not associated with antecedent events and included headache (3/10), vomiting (1/10), fever (2/10) and lethargy (1/10). Neurological symptoms at presentation included optic neuritis in 4 of 10 patients (40%), motor weakness with long tract dysfunction in 4 of 10 (40%), and brainstem involvement manifested by diplopia and nystagmus in 2 (20%). All children had a relapsing-remitting course. Time to the second neurological event ranged from 0.3 years to 4.2 years and only one patient did not experience a second attack.

MRI FINDINGS

The most frequent MRI finding at the onset of childhood MS was more than three periventricular white matter lesions (70%), followed by ≥ 1 corpus callosum lesion (60%), with 71% co-occurrence. Cervical cord lesions occurred in 33% and thoracic cord lesion in 43% of the children [Table 4].

EDSS = Expanded Disability Status Scale

Table 3. Family history, antecedent events and clinical features of patients presenting with childhood MS

	Age at onset (yrs)*	Gender	Family history	Antecedent event	Systemic symptoms	Neurological presentation	Time to 2nd relapse (yrs)
1	11.8/T2	M	Aortic aneurysm/M	Flu, 1 mon	–	Horizontal diplopia	0.6
2	9.1/B1	F	–	Minor trauma Rt mandible, 1 wk	–	Left ON	–
3	10.2/T1	M	–	–	Headache, vomiting	Diplopia & nystagmus	0.5
4	5.2/T1	M	Vitiligo/F	–	Fever 37.1°C	Quadripareisis	4.2
5	10.3/T1	M	Hypertension/F	LBP, 2 wk; abdominal pain, 1 wk	–	Left ON	1
6	10.4/T1	M	Epilepsy/B	–	–	Right ON	1.3
7	9.2/B1	F	Arthritis/M Hypothyroidism/S	Muscle pain, arthropathy, 2 mon	–	Paraparesis	2.8
8	8.2/B1	F	Cystic fibrosis/N	–	Fever 38.5°C, headache	Quadripareisis	0.25
9	11.9/B2	F	–	–	–	Left ON	2
10	7.2/T1	M	Syrinx/F	–	Headache, lethargy	Quadripareisis	0.9

* Tanner stage

M = mother, F = father, B = brother, S = sister, N = nephew, ON = optic neuritis, LBP = low back pain, wk = week, mon = month

Table 4. Imaging, CSF and electrodiagnostic findings at onset in patients with childhood MS

MRI features at onset No. of lesions	No. of patients (%)
≥ 9 T2	5/10 (50)
≥ 1 Gd-enhancing	1/10 (10)
≥ 3 PV	7/10 (70)
≥ 1 JC	2/10 (20)
≥ 1 PF	5/10 (50)
≥ 1 CC	6/10 (60)
≥ 1 cervical cord	3/9 (33)
≥ 1 thoracic cord	3/7 (43)
CSF chemistry	
Cell count > 10 cells/μl	7/8 (87.5)
Protein level > 5 g/dl	1/8 (12.5)
Positive oligoclonal IgG	5/8 (62.5)
Evoked potentials	
VEP > 110 msec	9/10 (90)
BERA III-V > 3 msec	5/10 (50)
SSEP	
N19 > 22 msec	5/9 (55)
N43 > 45 msec	4/9 (44)

Gd = gadolinium, PV = periventricular, JC = juxtacortical, PF = posterior fossa, CC = corpus callosum, VEP = visual evoked potentials, BERA = brainstem evoked potentials, SSEP = somatosensory evoked potentials

CSF FINDINGS

Mild pleocytosis (CSF cell count ≥ 10) occurred in 87.5% of patients while CSF chemistry was normal in the vast majority of patients. Oligoclonal immunoglobulin G bands were positive in 62.5% of subjects [Table 4].

CSF = cerebrospinal fluid

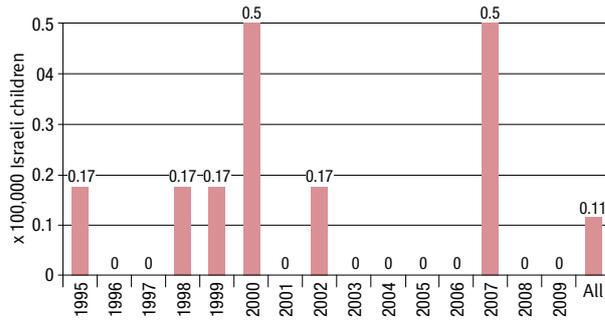
ELECTRODIAGNOSTIC FINDINGS

Visual evoked potentials demonstrated prolonged latencies in 90% of patients, brainstem evoked potentials were abnormal in 50% of patients, and upper and lower limbs somatosensory evoked potential were prolonged in 55% and 44% of patients, respectively [Table 4].

DISCUSSION

In the current study we assessed the incidence of childhood MS in Israel and evaluated the demographic, clinical, imaging and laboratory findings at onset. To the best of our knowledge this is the first study to report MS incidence in children younger than 12 years. Over a 15 year period (1995–2009), the average incidence of MS among Israeli children was 0.1 per 100,000 children. This low incidence is not surprising as only “true” childhood-onset MS subjects presenting under the age of 12 years were included in our analysis. This group of patients accounted for 0.89% of all MS patients, while the percentage of juvenile MS was sevenfold higher. These low rates probably reflect variability in both ethnic background and geographic region. In the literature there are only sparse data regarding MS onset before puberty and these are case series. Similar to our results childhood-onset MS appears to be uncommon; onset before 10 years of age is unusual, and occurs in only 0.2%–0.7% of all MS patients [21].

In a nationwide survey in Germany, an incidence of 0.1/100,000 was reported for children under 10 years of age, while the incidence for children aged 10 to 16 years increased to 0.6/100,000 [22]. Although the small number of patients with childhood MS makes comparison difficult,

Figure 1. Annual incidence of childhood MS in Israel

the gender ratio at the young age group favored males and reversed to females in the juvenile and adult groups, suggesting a role of sex hormones [1]. Further comparison between childhood-onset MS with juvenile and adult-onset forms shows a difference also in disease progression. It has been largely known that children have enhanced capacity for learning and memory compared to adults, and that children also have a remarkable ability to recover from early brain injuries [23]. This enhanced brain plasticity during childhood may account for our finding that during a similar follow-up period none of the patients with childhood MS progressed to significant disability compared to 9.4% in the juvenile and 14.4% in the adult MS groups, despite the fact that the second attack occurred at a shorter time interval in the childhood MS group, implicating a more active inflammatory process.

Taken together, the clinical, CSF and MRI findings at presentation are similar to those reported in adults with MS. We documented low rates of antecedent events and systemic symptoms, similar to what has been reported in the pediatric MS population [3]. The most common neurological presentations in our study were motor weakness with long tract dysfunction and visual symptoms as previously reported [3,6,9,11,13].

In our study the MRI findings at presentation of childhood MS were characterized by more than three periventricular white matter lesions that occurred in 70% of the children and followed by corpus callosum lesions in 60%, with 71% co-occurrence. The presence of lesions perpendicular to the corpus callosum were reported to be suggestive of MS and as a prognostic finding for developing the disease [13,15,16]. Imaging of the spinal cord at onset showed cervical cord lesions in 33% and thoracic cord lesions in 43% of patients, demonstrating dissemination in space occurring already at the first clinical presentation. Interestingly, our data show a higher occurrence than previously reported in other geographic areas. In a cohort of 21 cases with childhood-onset MS in Taiwan 27.8% had spinal lesions [9], and among 8

patients with MS onset below 17 years in Canada 25% had spinal cord involvement [13]. Only 15% of 82-early onset MS patients from Iran had spinal cord lesions [8], whereas in 26 children with early-onset MS in Japan no spinal cord lesions were documented at onset [10].

The CSF findings in our cohort disclosed positive oligoclonal IgG bands in 62.5% of subjects compared with 55.3% in subjects with childhood-onset MS under age 12 in France [5], 35% in MS patients with onset before 11 years in the United States [24], 46% of children with MS onset before age 15 years of age in the U.S. [25], and in 44% of patients with MS onset before age 20 in France [7].

Regarding electrophysiological findings we documented VEP abnormalities among 90%, BERA in 50% and upper limbs SSEP in 55% and lower limbs SSPE in 44% of patients. These results are in agreement with other studies. Ozabakas et al. [6] reported that among 36 MS patients whose symptoms began before age 16, VEP abnormalities were found in 65.5%, BERA in 41.3% and SSEP in 58.6% [6]. Brass and co-authors [13] reported abnormal VEP in 77%, BERA in 43% and SSEP in 57% of subjects with MS onset before age 17.

In summary, our findings show that childhood MS in Israel is rare and does not differ significantly from adult-onset MS in terms of clinical, laboratory and imaging findings. At presentation, children with MS onset up to the age of 12 years demonstrated dissemination of the disease as manifested by spinal cord lesions and electrophysiological abnormalities. Nevertheless, these patients did not demonstrate poor prognosis and did not progress to irreversible disability, suggesting that the brain in children might be more resilient to the inflammatory disease process.

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References

1. Achiron A, Gurevich M. Gender effects in relapsing-remitting multiple sclerosis: correlation between clinical variables and gene expression molecular pathways. *J Neurol Sci* 2009; 286: 47-53.
2. http://www.msif.org/en/news/press_room/atlas_of_ms_launch/index.html. 1-9-2010.
3. Stark W, Huppke P, Gartner J. Paediatric multiple sclerosis: the experience of the German Centre for Multiple Sclerosis in Childhood and Adolescence. *J Neurol* 2008; 255 (Suppl 6): 119-22.
4. Neuteboom RF, Ketelslegers IA, Boon M, Catsman-Berrevoets CE, Hintzen RQ. Barkhof magnetic resonance imaging criteria predict early relapse in pediatric multiple sclerosis. *Pediatr Neurol* 2010; 42: 53-5.
5. Mikaeloff Y, Caridade G, Assi S, Suissa S, Tardieu M. Prognostic factors for

IgG = immunoglobulin G

VEP = visual evoked potential

BERA = brainstem evoked potentials

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- early severity in a childhood multiple sclerosis cohort. *Pediatrics* 2006; 118: 1133-9.
6. Ozakbas S, Idiman E, Baklan B, Yulug B. Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. *Brain Dev* 2003; 25: 233-6.
 7. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007; 356: 2603-13.
 8. Etemadifar M, Nasr-Esfahani AH, Khodabandehlou R, Maghzi AH. Childhood-onset multiple sclerosis: report of 82 patients from Isfahan, Iran. *Arch Iran Med* 2007; 10: 152-6.
 9. Weng WC, Yang CC, Yu TW, Shen YZ, Lee WT. Multiple sclerosis with childhood onset: report of 21 cases in Taiwan. *Pediatr Neurol* 2006; 35: 327-34.
 10. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. *Brain Dev* 2010; 32: 454-62.
 11. Shiraishi K, Higuchi Y, Ozawa K, Hao Q, Saida T. Clinical course and prognosis of 27 patients with childhood onset multiple sclerosis in Japan. *Brain Dev* 2005; 27: 224-7.
 12. Xiong H, Zhang YH, Zhou R, et al. Clinical features and management of multiple sclerosis in children. *Zhonghua Er Ke Za Zhi* 2007; 45: 568-73.
 13. Brass SD, Caramanos Z, Santos C, Dilenge ME, Lapierre Y, Rosenblatt B. Multiple sclerosis vs acute disseminated encephalomyelitis in childhood. *Pediatr Neurol* 2003; 29: 227-31.
 14. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology* 2009; 72: 232-9.
 15. Mikaeloff Y, Adamsbaum C, Husson B, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain* 2004; 127: 1942-7.
 16. 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: 246-52.
 17. Banwell BL. Pediatric multiple sclerosis. *Curr Neurol Neurosci Rep* 2004; 4: 245-52.
 18. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58: 840-6.
 19. Tanner JM. The measurement of maturity. *Trans Eur Orthod Soc* 1975: 45-60.
 20. Montalban X, Tintore M, Swanton J, et al. MRI criteria for MS in patients with clinically isolated syndromes. *Neurology* 2010; 74: 427-34.
 21. Ruggieri M, Polizzi A, Pavone L, Grimaldi LM. Multiple sclerosis in children under 6 years of age. *Neurology* 1999; 53: 478-84.
 22. Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. *Eur J Pediatr* 2007; 166: 405-12.
 23. Boatman D, Freeman J, Vining E, et al. Language recovery after left hemispherectomy in children with late-onset seizures. *Ann Neurol* 1999; 46: 579-86.
 24. Chabas D, Ness J, Belman A, et al. Younger children with MS have a distinct CSF inflammatory profile at disease onset. *Neurology* 2010; 74: 399-405.
 25. Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: comparison of presenting features. *Dev Med Child Neurol* 2009; 51: 480-6.