

Review Article

Childhood multiple sclerosis

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Abstract. Childhood multiple sclerosis (MS) is a rare demyelinating autoimmune disease with different risk factors and clinical features than adult onset MS. Onset of MS is extremely uncommon in early childhood, particularly in those less than 10 years of age. The overall prevalence of MS varies significantly from 1–10 in 100,000 people in Japan to 248 in 100,000 in Canada. At least 5% of all MS patients have their first attack before 16 years of age with a female to male ratio of 1.4:1. Overall, childhood MS is being increasingly recognized. In this paper, an updated overview of childhood MS will be presented in the context of the available literature and our experience. Research into the earliest events in MS pathogenesis is needed to enhance our information of this disease. As well, understanding the triggers and initial immunologic targets involved may lead to the development of new therapies. Prospective longitudinal studies are required to evaluate the physical, cognitive, and psychosocial impact of childhood MS and the long term benefit of various therapeutic modalities.

Keywords: Multiple sclerosis, child, review, update

1. Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease that has been increasingly recognized in our region [1–5]. Childhood MS is rare and has different risk factors and clinical features than adult onset MS [6]. Exposure to extrinsic environmental factors during early childhood in genetically predisposed individuals is believed to trigger MS [7]. Onset of MS is extremely uncommon in early childhood, particularly in those less than 10 years of age [8]. However, childhood MS is being increasingly recognized. The increased awareness may be the result of early recognition or genuine increase in the proportion of MS patients presenting during childhood. Despite this, there are several barriers to early diagnosis as many physi-

cians still view MS as an exclusively adult disease and therefore, may not consider the diagnosis in children. As well, both clinical and radiological diagnostic criteria have not been validated in children. In this paper, an updated overview of childhood MS will be presented in the context of the available literature and our experience.

1.1. Epidemiology

MS is rare in children; however, the exact prevalence is unknown. At least 5% of all MS patients have their first attack before 16 years of age [9]. The overall prevalence of adult MS varies significantly from 1–10/100,000 people in Japan to 248/100,000 in Canada [10,11]. Regions further from the equator (Canada and north Europe) are high risk regions; however, MS does occur in all studied populations. The point prevalence of MS in a regional population of Saudi Arabia has been estimated at 0.04 [1]. Epidemiological studies have shown that individuals who migrate

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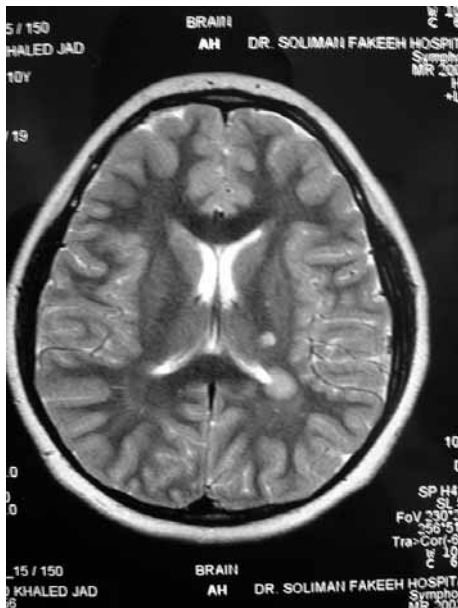


Fig. 1. Brain MRI showing multiple well-defined asymmetrical hyperintense T2 lesions in the periventricular and subcortical white matter.

during childhood to high risk areas adopt the MS risk of their new country rather than maintaining the MS risk of their original country [12]. Although environmental exposures may play a role, genetic influences are also contributory. Specific human leukocyte antigens (HLA) have been associated with increased MS risk in certain populations [13–15]. MS patients are more likely to carry HLA DRB1, DQA1, and DQB1 loci [16, 17]. As well, patients with HLA-DR15 had an earlier onset of their disease [18]. MS susceptibility in these people interacts with many other factors including immunologic, environmental, and myelin-related genes. Familial cases of MS has been well documented [15, 19]. The risk of MS in first degree relatives is about 5% compared to the 0.2% risk in the general population with a 30% concordance in identical twins [19,20]. Individual risk of MS increases with the number of affected relatives and with their earlier age of onset [21]. The female to male ratio of adult MS is 2.5:1. In contrast, the female to male ratio in children is 1.4:1 [22]. The lower female predominance in children suggests a hormonal factor in pathophysiology.

1.2. Clinical manifestations

Overall, childhood MS most commonly present in adolescence [23]. Ghezzi et al. [24] found that of 149 children younger than 16 years presenting with MS,

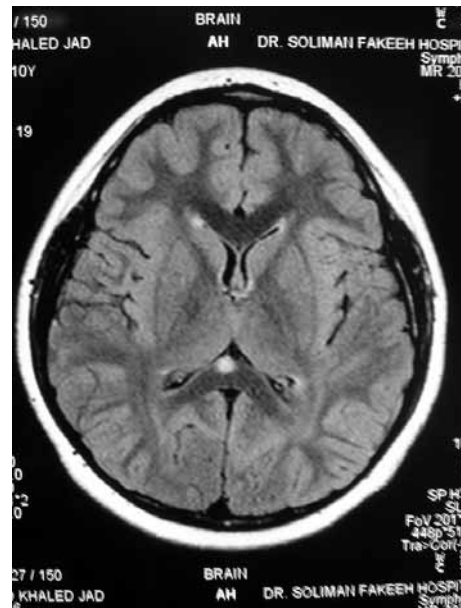


Fig. 2. MS lesions involving the splenium of the corpus callosum.

73% presented with an initial attack after 13 years of age. MS is characterized by multiple episodes of neurologic dysfunction secondary to inflammatory central nervous system (CNS) demyelination. The most characteristic presentation includes sensory, motor, and brainstem signs and symptoms. In a study by Daif et al. [4], involvement of the pyramidal system was the most common mode of presentation in young Saudi patients [4]. Episodes must be due to different CNS involvements (optic nerve, brain, spinal cord) and separated by more than 30 days interval [25]. Approximately 90% of children with MS present with this relapsing-remitting pattern, which is similar to adult MS. Relapses occur in the first 2 years in the majority of cases; however, up to 14% of children with MS had the second attack more than 10 years after the initial presentation. Primary progressive MS, characterized by worsening neurological disability over time in the absence of clear attacks, is extremely uncommon in children [26]. The clinical features of MS reflect the site of active CNS demyelination. Optic neuritis is a common initial manifestation that is characterized by progressive visual loss with decreased color perception and associated pain on eye movements. When compared to adults, optic neuritis in children is often bilateral. At initial presentation, optic neuritis is associated with an increased risk of subsequent MS [27]. Lucchinetti et al. [28] found in a long term follow up study that 26% were ultimately diagnosed with MS,

sometimes many years after the initial episode of optic neuritis [28]. Younger children (less than 6 years) commonly present with ataxia or seizures. A rare MS variant is Devic's syndrome (neuromyelitis optica), which is characterized by acute transverse myelitis and bilateral optic neuritis [29]. The clinical outcome of Devic's syndrome is generally poor.

1.3. Investigations

No single laboratory finding is necessary or sufficient for diagnosing MS. Cerebrospinal fluid (CSF) analysis often shows pleocytosis (66%), increased oligoclonal bands and intrathecal immunoglobulin G synthesis [30]. Increased oligoclonal bands are used in conjunction with serial magnetic resonance imaging (MRI) findings to confirm the diagnosis of MS [31]. Oligoclonal bands in the CSF were present in 75% of children with clinically definite MS. The percentage increases to 81% with the advance of the disease [20,32]. However, negative oligoclonal bands do not preclude the diagnosis of MS, especially in children. Recently, isoelectric focusing was found to be superior to the traditional agarose gel electrophoresis in detecting oligoclonal bands in the CSF with a sensitivity of 91% and a specificity of 96% in adult MS patients [33–35]. CSF examination is also useful to exclude CNS infection or malignancy. MRI features typically include multiple lesions in the periventricular, subcortical, infratentorial, and spinal cord white matter (Figs 1–3). Cortical gray matter lesions are either not present or rare, however, the author use of higher resolution MRI with thin cuts have identified cortical involvement. Serial MRI revealing new gadolinium-enhancing lesions, or new lesions on T2-weighted images, can be used to document progressive disease activity even in the absence of new clinical symptoms and signs [36]. Pediatric MS patients are less likely to meet the diagnostic MRI criteria when compared to adults, however, childhood MS remain a clinical diagnosis [31]. Occasionally, neuroimaging reveals atypical large or nodular demyelinating lesions that can be mistaken for tumors [3,37]. It is important to consider MS in these children in order to avoid unnecessary neurosurgical interventions. MS activity can be evaluated by using evoked potentials. Prolonged or absent visual and somatosensory evoked potentials can provide evidence of additional lesions in the optic pathway or spinal cord [38].



Fig. 3. MS lesions involving the cerebellum and brainstem.

1.4. Differential diagnosis

Because MS is rare in children, several other causes of acquired demyelination should be considered. The most important differential diagnosis at initial presentation is acute disseminated encephalomyelitis (ADEM). The clinical presentation of ADEM may be the first presentation of MS. Some helpful differentiating clinical, laboratory, and radiological features of ADEM and MS at initial presentation are summarized Table 1 [23,39, 40]. However, the distinction in practice can be difficult and long term follow up is needed. As well, multiphasic ADEM has been described with recurrent symptoms 3–6 years after initial presentation [41]. Other differential diagnoses include infectious causes (Lyme disease, syphilis, HIV, brucellosis), CNS vasculitis such as systemic lupus erythematosus (SLE), CNS lymphoma, and neurosarcoidosis. Leukodystrophies and mitochondrial encephalopathy can be easily differentiated based on the clinical and radiological data. Several investigations can help in excluding other etiologies including brain MRI, serum and CSF viral studies, Lyme disease serology, serum lactate, serum markers for SLE (antinuclear antibody, double-stranded DNA). Further detailed tests are not indicated routinely and should be individualized and based on the clinical and radiological findings.

Table 1
Differentiating clinical, laboratory and MRI features of ADEM and MS at initial presentation [23,39,40]

Features	ADEM	MS
History of recent infection or vaccination	common	rare
Systemic symptoms	common	rare
Fever	43%	6%
Headache	57%	24%
Fatigue	71%	29%
Vomiting	57%	0%
Encephalopathy	71%	6%
Seizures	common	rare
Isolated optic neuritis	less common (23%)	common
Severity of illness	usually severe	less severe
CSF oligoclonal bands	29%	75%
MRI changes		
Periventricular distribution	50%	91%
Involvement of the corpus callosum	17%	64%
Recurrence	rare	common

MRI: magnetic resonance imaging; ADEM: Acute disseminated encephalomyelitis; MS: Multiple sclerosis; CSF: Cerebrospinal fluid.

1.5. Management

Once the diagnosis of MS is established, communicating such news to the parents is often both difficult and emotionally unwelcomes [42]. As well, most physicians do not feel comfortable dealing with rare and difficult neurological disorders such as MS [43]. At the same time, it is important that the transfer of such information is done well as the manner in which neurological bad news is conveyed to parents can significantly influence their emotions, beliefs, and attitudes towards the child, the medical staff, and the future [42]. Most families find the attitude of the news giver, combined with the clarity of the message and the news giver's knowledge to answer questions as the most important aspects of giving the news. The psychological impact of MS on the child and adolescent may also be profound. Psychological advice and support is needed for many of these children and their families.

Studies in adults suggest that early treatment may prevent or delay the occurrence of clinically definite MS and that disease modifying drugs can reduce the burden of the disease [31]. Intravenous (IV) methylprednisolone speeds recovery from an acute MS relapse. In optic neuritis, IV steroids resulted in rapid recovery of vision and delay in the subsequent diagnosis of MS [44]. Acute MS exacerbations in our pediatric MS patients are treated with 15 mg/kg/day of IV methylprednisolone in four divided doses for 3 days followed by 1 mg/kg/day oral prednisone as single morning dose for 2 weeks. This dose is then tapered slowly over 3–4 weeks. Other institutions may use higher doses reaching 30 mg/kg once daily with or

without maintenance doses depending on the clinical response. Some children do not respond to steroids or develop recurrent symptoms during the prednisone taper. These children are treated with 1 g/kg/day IV immunoglobulin (IVIG) for two days [45]. Monthly IVIG is required for 3–6 months in some children to improve clinical symptoms or to allow withdrawal of steroid therapy [46].

Several other immunomodulatory (disease-modifying) therapies have been used in MS. Interferon- β (Rebif) and interferon- β 1a (Avonex) have been shown to reduce the frequency of clinical relapses by 30% in patients with relapsing remitting MS [47]. Interferon therapy has been also shown to reduce the progression of disability and inflammatory activity as assessed by gadolinium enhancement on MRI [47,48]. This favorable response has been also documented in an open label study from Saudi Arabia [2]. There is increasing evidence supporting the impact of early therapy on long-term physical and cognitive outcome of adult MS [49,50]. However, there are limited reports on the use of interferons in children [51–53]. Liver function tests and complete blood count studies should be monitored carefully. Transaminase elevation may occur early and necessitates reduction in the dose. Flu-like side effects have been noted in 20% of children on interferons, which is usually managed easily with analgesics. Although interferons were well tolerated, prospective randomized studies are needed to determine if there is long term benefit in the pediatric population. Finally, cyclophosphamide has been used in MS with variable success. Careful review of the literature suggests that cyclophosphamide may be helpful in

children with frequent relapses or very aggressive MS that failed other treatments [54]. Potential risks of this therapy include immunosuppression, malignancy, and infertility.

1.6. Prognosis

In large studies, childhood MS appears to be less severe than the adult form. However, this is not a universal finding and severe disability can occur with childhood MS, particularly in younger children. The presence of seizures seems to carry a poor prognosis in terms of death or primary progressive course [31]. Children with this chronic disease are at increased risk of experiencing chronic fatigue, emotional, cognitive, and school difficulties. Adolescents with MS frequently report difficulty with higher cortical functions and multiple task organization. Cognitive deficits may occur early in as many as 65% of patients [55]. Children are at higher risk because of the impact on ongoing development and maturation. In addition to cognitive decline, motor and visual disabilities are the most commonly encountered. Over time, approximately 70% of relapsing remitting MS patients may experience progressive motor disability in the absence of a definable attack (secondary progressive MS) [56]. The time from initial presentation to this advanced stage ranged between 10–15 years in 50% of MS patients [26]. However, the disease progression and disability scores were generally less severe in childhood MS, with 76% of patients still ambulating 15 years after initial diagnosis.

In conclusion, MS is rare in children and the etiology remains unknown. Research into the earliest events in MS pathogenesis is needed to enhance our information of this disease. As well, understanding the triggers and initial immunologic targets involved may lead to the development of new therapies. Both clinical research and patient management will be enhanced by clinical and MRI criteria validated in the pediatric MS population and by increased knowledge of the safety and efficacy of immunomodulatory therapies. Prospective longitudinal studies are required to evaluate the physical, cognitive, and psychosocial impact of childhood MS and the long term benefit of various therapeutic modalities.

References

- [1] S. Al-Rajeh, O. Bademosi, H. Ismail et al., A community survey of neurological disorders in Saudi Arabia: the Thughbah study, *Neuroepidemiology* **12** (1993), 164–178.
- [2] H. Kargwell, B.A. Yaqub and S.M. Al-Deeb, Response to beta interferon 1b among Saudi patients with multiple sclerosis, *Saudi Med J* **24** (2003), 44–48.
- [3] M.A. Al-Bunyan, Tumor-like presentation of multiple sclerosis, *Saudi Med J* **21** (2000), 393–395.
- [4] A.K. Daif, S. Al-Rajeh, A. Awada et al., Pattern of presentation of multiple sclerosis in Saudi Arabia: analysis based on clinical and paraclinical features, *Eur Neurol* **39** (1998), 182–186.
- [5] B.A. Yaqub and A.K. Daif, Multiple sclerosis in Saudi Arabia, *Neurology* **38** (1988), 621–633.
- [6] B.L. Banwell, Pediatric multiple sclerosis, *Curr Neurol Neurosci Rep* **4** (2004), 245–252.
- [7] J.H. Noseworthy, C. Lucchinetti, M. Rodriguez and B.G. Weinshenker, Multiple sclerosis, *N Engl J Med* **343** (2000), 938–952.
- [8] M. Tardieu and Y. Mikaeloff, Multiple sclerosis in children, *Int MS J* **11** (2004), 36–42.
- [9] P. Duquette, T.J. Murray, J. Pleines et al., Multiple sclerosis in childhood: clinical profile in 125 patients, *J Pediatr* **111** (1987), 359–363.
- [10] T. Itoh, H. Aizawa, K. Hashimoto et al., Prevalence of multiple sclerosis in Asahikawa, a city in northern Japan, *J Neurol Sci* **214** (2003), 7–9.
- [11] M. Pugliatti, S. Sotgiu and G. Rosati, The worldwide prevalence of multiple sclerosis, *Clin Neurol Neurosurg* **104** (2002), 182–191.
- [12] A.D. Sadovnick and G.C. Ebers, Epidemiology of multiple sclerosis: a critical overview, *Can J Neurol Sci* **20** (1993), 17–29.
- [13] L.F. Barcellos, J.R. Oksenberg, A.B. Begovich et al., HLA-DR2 dose effect on susceptibility to multiple sclerosis and influence on disease course, *Am J Hum Genet* **72** (2003), 710–716.
- [14] A. Ligers, D.A. Dymnt, C.J. Willer et al., Evidence of linkage with HLA-DR in DRB1*15-negative families with multiple sclerosis, *Am J Hum Genet* **69** (2001), 900–903.
- [15] D.A. Dymnt, A.D. Sadovnick and G.C. Ebers, Genetics of multiple sclerosis, *Hum Mol Genet* **6** (1997), 1693–1698.
- [16] S.L. Hauser, E. Fleischnick, H.L. Weiner et al., Extended major histocompatibility complex haplotypes in patients with multiple sclerosis, *Neurology* **39**(2 Pt 1) (1989), 275–277.
- [17] M. Allen, M. Sandberg-Wollheim, K. Sjogren, H.A. Erlich, U. Petterson and U. Gyllensten, Association of susceptibility to multiple sclerosis in Sweden with HLA class II DRB1 and DQB1 alleles, *Hum Immunol* **39** (1994), 41–48.
- [18] T. Masterman, A. Ligers, T. Olsson, M. Andersson, O. Olerup and J. Hillert, HLA-DR15 is associated with lower age at onset in multiple sclerosis, *Ann Neurol* **48** (2000), 211–219.
- [19] A.D. Sadovnick, A. Dircks and G.C. Ebers, Genetic counselling in multiple sclerosis: risks to sibs and children of affected individuals, *Clin Genet* **56** (1999), 118–122.
- [20] A.D. Sadovnick, H. Armstrong, G.P. Rice et al., A population-based study of multiple sclerosis in twins: update, *Ann Neurol* **33** (1993), 281–285.
- [21] A.D. Sadovnick, I.M. Yee and G.C. Ebers, Factors influencing sib risks for multiple sclerosis, *Clin Genet* **58** (2000), 431–435.
- [22] M. Ruggieri, A. Polizzi, L. Pavone and L.M. Grimaldi, Multiple sclerosis in children under 6 years of age, *Neurology* **53** (1999), 478–484.
- [23] C.T. Jones, Childhood autoimmune neurologic diseases of the central nervous system, *Neurol Clin* **21** (2003), 745–764.

- [24] A. Ghezzi, V. Deplano, J. Faroni et al., Multiple sclerosis in childhood: clinical features of 149 cases, *Mult Scler* **3** (1997), 43–46.
- [25] C.M. Poser, D.W. Paty, L. Scheinberg et al., New diagnostic criteria for multiple sclerosis: guidelines for research protocols, *Ann Neurol* **13** (1983), 227–231.
- [26] A. Boiko, G. Vorobeychik, D. Paty, V. Devonshire and D. Sadovnick, Early onset multiple sclerosis: a longitudinal study, *Neurology* **59** (2002), 1006–1010.
- [27] D.S. Morales, R.M. Siatkowski, C.W. Howard and R. Warman, Optic neuritis in children, *J Pediatr Ophthalmol Strabismus* **37** (2000), 254–259.
- [28] C.F. Lucchinetti, L. Kiers, A. O'Duffy et al., Risk factors for developing multiple sclerosis after childhood optic neuritis, *Neurology* **49** (1997), 1413–1418.
- [29] D.M. Wingerchuk, W.F. Hogancamp, P.C. O'Brien and B.G. Weinshenker, The clinical course of neuromyelitis optica (Devic's syndrome), *Neurology* **53** (1999), 1107–1114.
- [30] D. Pohl, K. Rostasy, H. Reiber and F. Hanefeld, CSF characteristics in early-onset multiple sclerosis, *Neurology* **63** (2004), 1966–1967.
- [31] C.T. Jones, Childhood autoimmune neurologic diseases of the central nervous system, *Neurol Clin* **21** (2003), 745–764.
- [32] R.C. Dale, C. de Sousa, W.K. Chong, T.C. Cox, B. Harding and B.G. Neville, Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children, *Brain* **123**(Pt 12) (2000), 2407–2422.
- [33] I. Nakashima, K. Fujihara, S. Sato and Y. Itoyama, Oligoclonal IgG bands in Japanese patients with multiple sclerosis. A comparative study between isoelectric focusing with IgG immunofixation and high resolution agarose gel electrophoresis, *J Neuroimmunol* **159** (2005), 133–136.
- [34] C. Caudie, A.M. Birouk, J. Bancel et al., Cytoimmunological profile of multiple sclerosis, *Pathol Biol* **53** (2005), 68–74 (in French).
- [35] A. Bourahoui, J. De Seze, R. Gutierrez et al., CSF isoelectrofocusing in a large cohort of MS and other neurological diseases, *Eur J Neurol* **11** (2004), 525–529.
- [36] W.I. McDonald, A. Compston, G. Edan et al., Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis, *Ann Neurol* **50** (2001), 121–127.
- [37] C.H. Wang and K. Walsh, Multiple ring-enhancing lesions in a child with relapsing multiple sclerosis, *J Child Neurol* **17** (2002), 69–72.
- [38] B. Boutin, E. Esquivel, M. Mayer, S. Chaumet, G. Ponsot and M. Arthuis, Multiple sclerosis in children: report of clinical and paraclinical features of 19 cases, *Neuropediatrics* **19** (1988), 118–123.
- [39] S.D. Brass, Z. Caramanos, C. Santos, M.E. Dilenge, Y. Lapierre and B. Rosenblatt, Multiple sclerosis vs. acute disseminated encephalomyelitis in childhood, *Pediatr Neurol* **29** (2003), 227–231.
- [40] Y. Mikaeloff, S. Suissa, L. Vallee et al., First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability, *J Pediatr* **144** (2004), 246–252.
- [41] S. Khan, B.A. Yaqub, C.M. Poser, S.M. al-Deeb and S. Bohlega, Multiphasic disseminated encephalomyelitis presenting as alternating hemiplegia, *J Neurol Neurosurg Psychiatry* **58** (1995), 467–470.
- [42] M. Jan and J.P. Girvin, The Communication of neurological bad news to parents, *Can J Neurol Sci* **29** (2002), 78–82.
- [43] M.M. Jan, Perception of pediatric neurology among non-neurologists, *J Child Neurol* **19** (2004), 1–5.
- [44] R.W. Beck, P.A. Cleary, J.D. Trobe et al., The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group, *N Engl J Med* **329** (1993), 1764–1769.
- [45] A. Assa, N. Watemberg, Y. Bujanover and T. Lerman-Sagie, Demyelinative brainstem encephalitis responsive to intravenous immunoglobulin therapy, *Pediatrics* **104** (1999), 301–304.
- [46] P.S. Sorensen, F. Fazekas and M. Lee, Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis, *Eur J Neurol* **9** (2002), 557–563.
- [47] S.L. Galetta, C. Markowitz and A.G. Lee, Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review, *Arch Intern Med* **162** (2002), 2161–2169.
- [48] L.D. Jacobs, D.L. Cookfair, R.A. Rudick et al., Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG), *Ann Neurol* **39** (1996), 285–294.
- [49] Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group, *Lancet* **352** (1998), 1498–1504.
- [50] J.S. Fischer, R.L. Priore, L.D. Jacobs et al., Neuropsychological effects of interferon beta 1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group, *Ann Neurol* **48** (2000), 885–892.
- [51] E. Waubant, J. Hietpas, T. Stewart et al., Interferon beta-1a in children with multiple sclerosis is well tolerated, *Neuropediatrics* **32** (2001), 211–213.
- [52] Y. Mikaeloff, T. Moreau, M. Debouvierie et al., Interferon-beta treatment in patients with childhood-onset multiple sclerosis, *J Pediatr* **139** (2001), 443–446.
- [53] S. Tenenbaum, S. Martin and N. Fejerman, Disease-modifying therapies in childhood and juvenile multiple sclerosis, *Mult Scler* **7** (2001), S57 (abstract).
- [54] H.L. Weiner and J.A. Cohen, Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects, *Mult Scler* **8** (2002), 142–154.
- [55] B. Banwell and P.E. Anderson, Neuropsychological features of pediatric multiple sclerosis, *Neurology* **58** (2002), A173 (abstract).
- [56] J.H. Noseworthy, C. Lucchinetti, M. Rodriguez and B.G. Weinshenker, Multiple sclerosis, *N Engl J Med* **343** (2000), 938–952.