PEDIATRIC MULTIPLE SCLEROSIS

Rodica Balasa
First Neurological Clinic, Targu-Mures, Romania

ABSTRACT

Multiple sclerosis is a chronic inflammatory and neurodegenerative disorder which is subject to periodical reconsideration of diagnostic criteria. In the present work the multiple sclerosis cases with onset during childhood are discussed and specific issues regarding diagnosis and treatment of this cathegory of patients are presented.
Key words: multiple sclerosis, young onset, childhood, diagnostic criteria, treatment.

DEFINITION

According to the *„International Pediatric MS Group",* nosologic limits of pediatric multiple sclerosis (PMS) refer to the multiple sclerosis (MS) with onset under the age of 18 years (1). An important number of studies have included PMS patients with onset under the age of 16, 10 or 6 years (2-9).

HISTORY

MS is known as a disease of young to middle adulthood. The *„late-onset"* cases have been well documented. The existence of *„early-onset"* MS (in childhood or adolescence) has been disputed for a long time. Although Charcot in 1868 had some doubts about the occurrence of MS in childhood, his pupil Pierre Marie in 1883 reported cases with early-onset. Over the following years, Schippfer in 1902 and Muller in 1904 presented children with MS. Sporadic MS patients with onset in childhood were reported by Rimbaud et al in 1938 and Carter in 1946 (data quoted by Hanefeld (10)). The trials to systematize MS with childhood onset started at the end of 1950s (11,12).

CLINICAL FEATURES

An estimated 3-5% of all patients with MS had onset before the age of 18 years. Mean age of onset varied between 8.6±1.2 years and 13.5±0.3 years. Gender ratio (female/male) is ~2.1. A family history of MS is reported by 6-8% of PMS (3,8,13-21).

Overall, about 50-70% of children with MS have a polysymptomatic onset, whereas 30-50% have a monosymptomatic onset. From the children with monosymptomatic onset, 10-22% present optic neuritis (ON), ~30% have motor dysfunction, 15-30% have sensory symptoms, 5-15% present ataxia, ~25% have brainstem symptoms and ~10% isolated transverse myelitis. Fatigue (~40%) and cognitive dysfunction (~66%) are severe enough to limit scholastic activities of children with MS (4-10, 20-27).

The risk of MS appearance after ON onset (uni- or bilateral) was smaller in children than in adults in some studies (28,29) but was similar in others (30-33). In a prospective study of ON in children, a percentage of 36% has been diagnosed with MS after 2 years (34).

The majority of PMS patients (~96%) were diagnosed initially with relapsing-remitting MS and only ~4% with primary-progressive MS (8,17,18,35,36). The time span between the initial attack and the second MS-defining event varied between 6 to 12 months (20). The relapse rate reported in retrospective studies ranges from 0.38 a year to 1.0 a year (18,35).

In a prospective study with PMS duration of 8 years or longer, 36 patients (66,7%) had an expanded disability status scale (EDSS) of less than 4, five patients (9,2%) had scores between 4 and 6 and 13 patients (24.1%) had scores greater than 6 (16). The mean time to reach an EDSS score of 4 was 10.8 years and took a mean time of 18.2 years to reach a score of 6 (35). Of 197 PMS patients followed up from first attack in a prospective study, an EDSS score of 4 was reached by 15% of children after a mean observation of 7.8 years (37). In a retrospective group of 83 patients with PMS the median time to an EDSS score of 4 was 14 years and such an outcome occured in 25% of the patients (8). The median times from onset to EDSS score 4, 6 and 7 were 20 years, 29 years and 37 years

respectively, but the patients with PMS took 10 years longer to accrue disability and were about 10 years younger than patients with adult-onset MS with comparable impairment (2).

Secondary-progressive MS was seen in 53.1%, 42.9%, 14.5% and 4.5% patients after mean disease durations of 17.7 years, 12.9 years, 10.0 years and 4.8 years respectively (8,17,35,37). The risk of secondary-progressive MS was associated with a high frequency of relapse and shorter intervals between attacks in the first few years of disease (8,17). The accrual of disability within 1 year of disease onset or a high frequency of relapse in the first 2 years of disease has also been associated with higher EDSS in score at 8 years (16).

PARACLINICAL EXAMINATIONS

In a retrospective study the presence of higher IgG index or of oligoclonal bands in cerebrospinal fluid of 92% PMS patients has been recorded (38).

The multimodal evoked potentials in PMS patients have found out subclinical demyelinated lesions. In 46% of PMS patients, spatial dissemination was detected by visual, auditory and somatosensory evoked potentials before the second clinical attack. Evoked potentials may constitute an important tool for earlier diagnosis of PMS (39).

Application of adult magnetic resonance imaging (MRI) criteria is problematic in children, particularly those under the age of 10 (40). There are many possible reasons why the MRI appearance of MS in children may differ from that in adults: a) the subclinical phase of the MS disease process is inherently brief in PMS and thus there may be fewer, pre-existing lesions notable on MRI changes obtained at the time of the first demyelinating event; b) the full myelin maturation may influence the regional proclivity for MS lesions, particularly in the very young MS patients; c) immunologic maturity and inflammatory nature of lesions differ between children and adults; d) children differ from adults in their innate capacity for myelin repair, leading to fundamental differences in the MRI appearance of lesion evolution (41).

MRI features of PMS have the following particularities: a) demyelinating lesions are large, with perilesional edema, sole presence and nondisseminated in space; b) enhancing gadolinum lesions are present only in ~20% of the patients. Serial MRIs 3 to 6 months after an initial demyelinating event in childhood has been advocated (34,41-44).

MR spectroscopy, magnetization transfer and diffusion tensor imaging provide new tools to examine the relationships among neuro-axonal loss, myelin disruption and immune-mediated processes (45-46).

Serological studies have demonstrated a high prevalence of Epstein-Barr virus in PMS patients (47-49). In a study, Chlamidia pneumoniae intrathecal antibodies in children with MS has been found (50).

DIFERENTIAL DIAGNOSIS

After the first clinical attack induced by a demyelinating lesion of central nervous system, the diagnosis of PMS is very difficult. The younger a child and the more atypical the initial clinical, laboratory and neuroimaging features, the more care is needed in establishing the diagnosis of PMS (1,51,52).

First of all, PMS must be differentiated from acute disseminated encephalomyelitis (ADEM). This disease, wich is frequent in childhood, may have at onset the same symptomatology as PMS and has monophasic, recurrent or multiphasic evolution. However, there are distinct criteria for diagnosis of ADEM (1,52-57).

Second, PMS must be differentiated from neuromyelitis optica, which has known criteria for positive diagnosis (58,59).

Third, PMS must be differentiated from other central nervous system diseases: a) infectious (neuroborreliosis, HIV encephalomyelitis, progressive multifocal leukoencephalopaty, subacute sclerosing panencephalitis, neurosyphilis, parasitosis, etc.); b) neoplasms (lymphoma, astrocytoma, medulloblastoma, metastases, etc.); c) inflammatory/noninfectious (systemic lupus erythematosus, Behcet disease, isolated angiitis, neurosarcoidosis, Sjögren disease, etc.); d) neurometabolic/neurogenetic leukoencephalopathies (adrenoleukodystrophy, metachromatic leukodystrophy, Krrabe disease, Pelizaeus-Merzbacher disease, Wilson disease, Fabry disease, etc.); e) mitochondrial disorders (Leber disease, Leigh disease, Kearns-Sayre syndrome, etc.); f) vitamin deficiencies (vitamin B12, vitamin E, folate, celiac disease, etc.); g) vascular diseases (Moyamoya disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, etc.) (52).

TREATMENT

Treatment for relapses

Corticosteroids in adequate dosage are well tolerated by the children and adolescents. This

treatment requires careful monitoring of blood pressure, urine glucose, serum potassium and administration of gastric protection. The risk of side effects increases with prolonged use and total cumulative dose (60).

Plasmapheresis has been proposed when the children fail to recover after treatment with high dose corticosteroids or to avoid side effects of frequent pulses of steroids (60-62).

Intravenous immunoglobulins have been somewhat helpful to children with MS who do not improve after high dose corticosteroids (63-65).

Disease-modifying therapy

Immunomodulatory therapy may be used in PMS but efficacy and tolerability data are extremely limited, especially in children under the age of 10 years (60, 63-65, 7-73).

Interferon beta-1b (Betaseron/Betaferon) has been used with good results in some studies (66-68). In other studies, interferon beta-1a (Avonex or Rebif) has been used, also with good results (69-72). *Glatiramer acetate* (Copaxone) appeared to be safe and well tolerated, with good results in PMS (63,73,74).

There is no accepted definition of *management for progressive forms or poor responders* in PMS. The experience with *immunosupressive agents* (cyclophosphamide, mitoxantrone, methotrexate etc.) is not satisfactory and no conclusions regarding its safety and eficacy in PMS can be made at this time (60).

In patients whose initial episode includes encephalopathy the use of disease-modifying therapy (DMT) should be delayed until a second or third attack with more typical MS features has occured to avoid giving DMT to a child with ADEM or its variants (60).

Symptomatic therapy

Initial management of spasticity utilizes daily stretching and physical therapy. If stretching exercises are insufficient, progressive titration of antispastic medication can be considered. *Baclofen* is the drug of choice for monotherapy. If the patients do not tolerate baclofen, *tizanidine, diazepam* or *clonazepam* can be used. All these drugs must be utilized in pediatric doses and should be carefully monitored. For patients resistent to the previously mentioned antispasticticity interventions, selective botulinum toxin A infections can be considered (60,75-77).

Many children with MS complain of *fatigue.* A study showed amantadine to be safe and efficient in treating fatigue of PMS. If amantadine is not effective, *modafinil* should be considered (60, 78, 79).

Until now, there are no studies regarding treatment of tremor, ataxia, paroxistic symptoms, cognitive or autonomic disturbances in children with MS. For all those aspects the neurological literature has appealed to the drugs used in adult forms of MS (60).

CONCLUSIONS

The use of standardized definition for PMS greatly facilitates clinical care and promotes a platform for future researches (80).

REFERENCES

1. **Krupp LB, Banwell B, Tenembaum S –** (for the International Pediatric MS Study Group). Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; 68(Suppl 2): S7-S12.
2. **Renoux C, Vukovisic S, Mikaeloff Y et al –** Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007; 356: 2603-2613.
3. **Sindern E, Haas J, Strok E et al –** Early onset MS under the age of 16: clinical and paraclinical features. *Acta Neurol Scand* 1992; 86: 280-284.
4. **Guilhoto LM, Osorio CA, Machado LR et al –** Pediatric multiple sclerosis: report of 14 cases. *Brain Dev* 1995; 17: 9-12.
5. **Cole GF, Stuart CA –** A long perspective on childhood multiple sclerosis. *Dev Med Child Neurol* 1995; 37: 661-666.
6. **Selcen D, Anlar B, Renda Y –** Multiple sclerosis in childhood: report of 16 cases. *Eur Neurol* 1996; 36; 79-84.
7. **Ruggieri M, Polizzi A, Pavone L et al –** Multiple sclerosis in children under 6 year of age. *Neurology* 1999; 53: 478-484.
8. **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.
9. **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.
10. **Hanefeld F –** Pediatric multiple sclerosis: a short hystory of a long story. *Neurology* 2007; 68 (Suppl 2): S3-S6.
11. **Low NL, Carter S –** Multiple sclerosis in children. *Pediatrics* 1956; 18: 24-30.
12. **Gall JC, Hayles AB, Siekert RG et al –** Multiple sclerosis in children. A clinical study of 40 cases with onset in childhood. *Pediatrics* 1958; 21: 703-709.
13. **Duquette P, Murray TJ, Pleines J et al –** Multiple sclerosis in childhood: clinical profile in 125 patients. *J Pediatr* 1987; 111: 359-363.
14. **Ghezzi A, Deplano V, Faroni J et al –** Multiple sclerosis in childhood: clinical featues of 149 cases. *Mult Scler* 1997; 3: 43-46.

15. **Dale RC, de Sousa C, Chong WK et al** – Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. *Brain* 2000; 123: 2407-2422.
16. **Ghezzi A, Pozzilli C, Liguori M et al** – Prospective study of multiple sclerosis with early onset. *Mult Scler* 2002; 8: 115-118.
17. **Boiko A, Vorobeychik G, Paty D et al** – Early onset multiple sclerosis: a longitudinal study. *Neurology* 2002; 59: 1006-1010.
18. **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.
19. **Brass SD, Caramanos Z, Santos C et al** – Multiple sclerosis vs acute disseminated enchephalomyelitis in childhood. *Pediatr Neurol* 2003; 29: 227-231.
20. **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.
21. **Shiraishi K, Higuchi Y, Ozawa K et al** – Clinical course and prognosis of 27 pacients with childhood onset of multiple sclerosis in Japan. *Brain Dev* 2005; 27: 224-227.
22. **Hanefeld F, Bauer HJ, Christen HJ et al** – Multiple sclerosis in childhood: report of 15 cases. *Brain Dev* 1991; 13: 410-416.
23. **Ozakbas S, Idiman E, Balkan B et al** – Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. *Brain Dev* 2003; 25: 233-236.
24. **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.
25. **Banwell BL, Anderson PE** – The cognitive burden of multiple sclerosis in children. *Neurology* 2005; 64: 891-894.
26. **MacAllister WS, Belman AL, Milazzo M et al** – Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* 2005; 64: 1422-1425.
27. **MacAllister WS, Boyd JR, Holland NJ et al** – The psychosocial consequences of pediatric multiple sclerosis. *Neurology* 2007; 68(Suppl 2): S66-S69.
28. **Visudhiphan P, Chiemchanga S, Santadusit S** – Optic neuritis in children: recurence and subsequent development of multiple sclerosis. *Pediatr Neurol* 1995; 13: 293-295.
29. **Lucchinetti CF, Kiers L, O' Duffy A et al** – Risk factors for developing multiple sclerosis after childhood optic neuritis. *Neurology* 1997; 49: 1413-1418.
30. **Rükonen 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. **Morales DS, Siatkowski RM, Howard CW et al** – Optic neuritis in children. *J Pediatr Ophthalmol Strabismus* 2000; 37: 254-259.
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, Buneic JR et al** – The clinical features, MRI findings and outcome of optic neuritis in children. *Neurology* 2006; 67: 258-262.
35. **Deryck O, Ketelaer P, Dubois B** – Clinical characteristic and long-term prognosis in early onset multiple sclerosis. *J Neurol* 2006; 253: 720-723.
36. **Rostasy K** – Multiple sclerosis in children: clinical, diagnostic and therapeutic aspects. In: Minagar A (Ed) – *The neurobiology of multiple sclerosis*. Academic Press, London, UK, 2007: 269-279.
37. **Mikaeloff Y, Caridade G, Assi S et al** – Prognostic factors for early severity in a childhood multiple sclerosis cohort. *Pediatrics* 2006; 118: 1133-1139.
38. **Pohl D, Rostasky K, Reiber H et al** – CSF characteristics in early-onset multiple sclerosis. *Neurology* 2004; 63: 1966-1967.
39. **Pohl D, Rostasy K, Treiber-Held S et al** – Pediatric multiple sclerosis: detection of clinically silent lessions by multimodal evoked potentials. *J Pediatr* 2006; 149: 125-127.
40. **Hahn CD, Shroff MM, Blaser SI et al** – MRI criteria for multiple sclerosis: evaluation in a pediatric cohort. *Neurology* 2004; 62: 806-808.
41. **Banwell B, Shroff M, Ness JM et al** – MRI features of pediatric multiple sclerosis. *Neurology* 2007; 68(Suppl 2): S46-S53.
42. **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.
43. **Balassy C, Bernert G, Wober-Bingal C et al** – Long-term MRI observation of childhood-onset relapsing-remitting multiple sclerosis. *Neuropediatrics* 2001; 32: 28-37.
44. **Triulzi F** – Neuroradiology of multiple sclerosis in children. *Neurol Sci* 2004; 25(Suppl 4): S340-S343.
45. **Bruhn H, Frahm J, Merboldt KD et al** – Multiple sclerosis in children: cerebral metabolic alterations monitored by localized proton magnetic resonance spectroscopy in vivo. *Ann Neurol* 1992; 32: 140-150.
46. **Mazzapesa DM, Rocca MA, Falini A et al** – A preliminary diffusion tensor and magnetization transfer magnetic resonance imaging study of early-onset multiple sclerosis. *Arch Neurol* 2004; 61: 366-368.
47. **Alotaibi S, Kennedy J, Tellier R et al** – Epstein-Barr virus in pediatric multiple sclerosis. *JAMA* 2004; 291: 1875-1879.
48. **Pohl D, Krone B, Rostasy K et al** – High seroprevalence of Epstein-Barr virus in children with multiple sclerosis. *Neurology* 2006; 67: 2063-2065.
49. **Banwell B, Krupp L, Kennedy J et al** – Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. *Lancet Neurol* 2007; 6: 773-781.
50. **Rostasy K, Reiber H, Pohl D et al** – Chlamidia pneumoniae in children with MS: frequency and quality of intrathecal antibodies. *Neurology* 2003; 61: 125-128.
51. **Krupp LB, Hertz DP** – Pediatric multiple sclerosis. *Neurology* 2007; 68(Suppl 2): S1-S2.
52. **Hahn JS, Pohl D, Rensel M et al** – Differential diagnosis and evaluation in pediatric multiple sclerosis. *Neurology* 2007; 68(Suppl 2): S13-S22.
53. **Tenembaum, Chitnis T, Ness J et al** – Acute disseminated encephalomyelitis. *Neurology* 2007; 68(Suppl 2): S23-S36.
54. **Rust RS** – Multiple sclerosis, acute diseminated encephalomyelitis and related conditions. *Semin Pediatr Neurol* 2000; 7: 66-90.
55. **Dale RC** – Acute disseminated encephalomyelitis. *Semin Pediatr Infect Dis* 2003; 14: 90-95.
56. **Garg RK** – Acute disseminated encephalomyelitis. *Postgrad Med J* 2003; 29: 11-17.
57. **Jones CT** – Childhood autoimmune neurologic diseases of the central nervous system. *Neurol Clin* 2003; 21: 745-764.
58. **Wingerchuk DM, Weinshenker BG** – Neuromyelitis optica: clinical predictors of relapsing course and survival. *Neurology* 2003; 60: 848-853.
59. **Wingerchuk DM, Lennon VA, Pittock SJ et al** – Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006; 66: 1485-1489.
60. **Pohl D, Waubant E, Banwell B et al** – Treatment of pediatric multiple sclerosis and variants. *Neurology* 2007; 68(Suppl 2): S54-S65.
61. **Takahashi I, Sawaishi Y, Takeda O et al** – Childhood multiple sclerosis treated with plasmapheresis. *Pediatr Neurol* 1997; 17: 83-87.
62. **Weng WC, Yang CC, Yu TW et al** – Multiple sclerosis with childhood onset: report of 21 cases in Taiwan. *Pediatr Neurol* 2006; 35: 327-334.
63. **Krupp LB, MacAllister WS** – Treatment of pediatric multiple sclerosis. *Curr Treat Options Neurol* 2005; 7: 191-199.
64. **Chabas D, Green AJ, Waubant E** – Pediatric multiple sclerosis. *Neuro RX* 2006; 3: 264-275.
65. **Banwell B, Ghezzi A, Bar-Or A et al** – Multiple sclerosis in children: clinical diagnosis, therapeutic strategies and future direction. *Lancet Neurol* 2007; 6: 887-902.
66. **Adams AB, Tyor WR, Holden KR** – Interferon beta-1b and childhood multiple sclerosis. *Pediatr Neurol* 1999; 21: 481-483.
67. **Schilling S, Haestel C, Spencer J** – Follow-up of interferon beta-1b treatment in a 15-year-old patrient with secondary progressive multiple sclerosis. *Neuropediatrics* 2002; 33: A31.
68. **Banwell B, Reder AT, Krupp L et al** – Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. *Neurology* 2006; 66: 472-476.
69. **Waubant E, Hieptas J, Stewart T et al** – Interferon beta-1a in children with multiple sclerosis. *Neuropediatrics* 2001; 32: 211-213.
70. **Mikaeloff Y, Moreau T, Debouverie M et al** – Interferon treatment in patients with childhood-onset multiple sclerosis. *J Pediatr* 2001; 139: 443-446.
71. **Pohl D, Rostasy K, Görtnes J et al** – Treatment of early onset multiple sclerosis with subcutaneus interferon beta-1a. *Neurology* 2005; 65: 888-890.

72. **Tenenmbaum SN, Segura MJ** – Interferon beta-1a treatment in childhood and juvenile-onset multiple sclerosis. *Neurology* 2006; 67: 511-513.
73. **Ghezzi A, Amato MP, Capobianco M et al** – Disease-modifying drugs in childhood-juvenile multiple sclerosis: results of an italian cooperative study. *Mult Scler* 2005; 11: 420-424.
74. **Kornek B, Bernet G, Balassy C et al** – Glatiramer acetat treatment in patients with childhood and juvenile onset multiple sclerosis. *Neuropediatrics* 2003; 34: 120-126.
75. **Goldstein EM** – Spasticity management: an overview. *J Child Neurol* 2001; 16: 16-23.
76. **Krach LE** – Pharmacotherapy of spasticity: oral medications and intrathecal baclofen. *J Child Neurol* 2001; 16: 31-36.
77. **Wagstaff AJ, Bryson HM** – Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; 53: 435-452.
78. **Krupp LB, Coyle PK, Doscher C et al** – Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline and placebo. *Neurology* 1995; 45: 1956-1961.
79. **Stankoff B, Waubant E, Confavreux C et al** – Modafinil for fatigue in MS: a randomized placebo-controlled dauble-blind study. *Neurology* 2005; 64: 1139-1143.
80. **Belman AL, Chitnis T, Renoux C et al** – Chellenges in the classification of pediatric multiple sclerosis and future direction. *Neurology* 2007; 68: S70-S74.