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REVIEW ARTICLE

Pediatric Multiple sclerosis

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Abstract:
Multiple sclerosis (MS) is considered as the major cause of acquired neurological insult in young adults and the most common demyelinating disease of the central nervous system (CNS). It is an inflammatory disease characterized by multiple areas of demyelination, rupture of the blood-brain barrier and diffused disorder of the white matter. MS is relatively rare in childhood. However, 3-10% of children develop the first episode of MS before the 16th year of age. Diagnosis of MS in childhood requires clinical and laboratory data, that localize the demyelinating episodes of the CNS, helping to exclude other pathological conditions. The therapeutic options vary and mainly focus on the use of steroids and intravenous immunoglobulins, while recent data suggest the use of interferon. In this review, we present the latest bibliographic data concerning the epidemiological characteristics, the etiology, the clinical course, the available diagnostic methods and the main treatment options of MS.

Keywords: *multiple sclerosis, demyelinating disorders, childhood*
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Introduction

Multiple sclerosis (MS) is considered as the major cause of acquired neurological insult in young adults and the most common demyelinating disease of the central nervous system (CNS) [1]. It is an inflammatory disease, which is characterized by multiple areas of demyelination, rupture of the blood-brain barrier and diffused disorder of the white matter. MS is relatively rare in childhood 2. Although the disease usually affects people between the third and fourth decade of life, MS is increasingly diagnosed in children [3,4]. This is mainly a result of the early clinical suspicion, as well as the contribution of magnetic resonance imaging (MRI). Childhood MS represents 10% of all MS cases [5,6].

In pediatric population, compared with adults, MS has a higher number of recurrences [7,8].

The etiology is still unclear, although it is generally considered that MS is a result of environmental factors affecting genetically predisposed people. The clinical presentation may be misleading, while the safety and efficacy of therapeutic options are not well documented in children [9].

In this review, we present the latest bibliographic data concerning the epidemiological characteristics, the etiology, the clinical course, the available diagnostic methods and the main therapeutic options of MS.

Epidemiological data

MS is considered relatively rare in childhood. However, 3-10% of children develop the first episode of MS before the 16th year of age [10]. The incidence

of MS is 1,35–2.5:100.000 in childhood and 0,4–1,4:100.000 in infants and young children, with significant variations among countries [11,12,13]. Regarding the age of onset of MS in childhood, most frequently reported age is 9-13 years old [7].

The ratio between the genders varies according to age. Thus, in ages before 6 years old, the proportion female: male is 0,8:1, it increases to 1,6:1 in ages 6-10 years old and to 2,1:1 in children older than 10 years. However, in adulthood the ratio female: male is approximately 3:1 [7]. The higher incidence in females probably reflects a hormonal factor affecting the pathogenesis of MS. Sexual hormones and other neuroendocrine factors act as regulators of the immune response. While in MS low estrogen level diverts the immune system to Th1 response, the great increase of female hormones during pregnancy leads to a temporary shift to Th2 immune response [14]. Additionally, there is a higher recurrence risk (up to double) during the first months after labor [15].

Etiology

The etiology of the disease still remains unclear. It is considered that MS is a result of environmental factors affecting genetically predisposed people. This theory is supported by the fact that about 6-21% of children diagnosed with MS has a first, second or third degree relative with MS [8,16]. The prevalence of MS in general population is approximately 0,2%. First degree relatives of patients with MS have a 20-40 times higher risk (5%) compared with general population [1,17]. Monozygotic twins have a 30% risk of MS, while dizygotic twins have only 2,4% [18,19]. The risk increases along with the number of affected relatives and the younger age of disease onset [20]. In addition, some leukocyte antigens (HLA DRB1 * 1501, DQA1 * 0102, DQB1 * 0602) have been associated with an increased risk of MS [21-24]. More recently, there has been reported a correlation of gene polymorphisms ST8SIA1 with MS. ST8SIA1 gene is located on chromosome 12p12 and encodes the ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1 [25].

Several causative environmental factors have been associated with MS, including viral infections, low levels of vitamin D and smoking. The exact role of viral infections in the development of MS is not clear. Environmental factors may be involved in the pathogenesis of MS through a variety of mechanisms [1]:

a) a transient or persistent infection can activate self-reactive T cells through the mechanism of molecular mimicry or other non-specific mechanisms.

b) transient CNS infection can trigger a sequence of events that facilitate "self-immunity" (rupture of the blood-brain barrier, release of CNS antigens).

c) recurrent CNS infections can predispose to recurrent episodes of inflammation and demyelination.

d) a persistent CNS viral infection probably stimulates inflammatory processes harmful to oligodendrocytes or has a direct harmful effect on them.

Cytomegalovirus infection, measles, rubella, mumps, whooping cough, herpes simplex virus type 1, shingles and Parvovirus B19 have not been correlated with high risk for MS. However, the infection by Epstein-Barr virus (EBV) increases 3-5 times the risk of developing MS [26,27]. There has been some concern that vaccination may precipitate the onset of multiple sclerosis or lead to relapses. However, tetanus, hepatitis B and influenza virus vaccinations have not been associated with onset or relapses of MS [28-30].

Epidemiological studies support the idea that vitamin D may be a natural inhibitor of MS [31]. Exposure to sunlight and sufficient dietary intake of vitamin D even from childhood reduces the risk of MS. The oral supplementary administration of vitamin D does not fully reproduce the beneficial effect of exposure to solar radiation, since it has been proven that the latter stimulates neuro-endocrine and immunomodulatory processes which influence inflammatory cell trafficking and apoptosis [31].

Smoking is another strong causative factor for MS. The relative risk of developing the first MS episode is double in smokers' children than in general population and increases when children are exposed to smoking for a period longer than 10 years [32]. Hedstrom et al. found a significant correlation between smoking and the existence of two specific genetic risk factors, the presence of HLA-DRB*15 and the absence of HLA-A*02 [33].

Clinical Presentation

Presenting symptoms in pediatric MS include hemiparesis or paraparesis (30%), unilateral or

bilateral optic neuritis (10-22%), focal sensory loss (15-30%), ataxia (5-15%), diplopia, dysarthria, or bowel/bladder dysfunction. Polyregional symptoms are reported in 30% of patients. Encephalopathy is less common and suggests consideration of acute disseminated encephalomyelitis (ADEM) [5,30,34,35].

Two main clinical manifestations of acute CNS demyelination have been reported:

a) The first that occurs more often in young patients (< 10 years old) is described by the non-specific term "acute encephalitis", including fever, altered level of consciousness, impaired mental function, diplegia, hemiplegia, cerebellar or brainstem dysfunction and optic neuritis. Seizures are quite uncommon but described in 22% of children aged less than 6 years old, indicative of a more aggressive disease course [36,37]. Other less common manifestations include symptoms from basal ganglia or spinal involvement [30,38].

b) The second occurs more often in adolescence, accompanied or not by neurological symptoms, such as optic neuritis, hemiparesis, brainstem dysfunction and sensory disturbances. Altered level of consciousness or diminished mental function are rarely reported [37].

Fatigue is notable in 40% of children with MS, with typical worsening of symptoms during the afternoon and lasts from days to weeks [36]. Fatigue in MS patients is attributed to dysfunction of the immune system, neuro-endocrine and neuro-transmitting alterations, sleep disorders, pain and drug side effects [39]. Usually, there is no triggering factor for fatigue. However, in some cases an acute infection or a metabolic disorder act as triggering factors. Cognitive impairment has also been reported in 30-66% of children with MS and are more prominent with early onset [40,41]. Cognitive and memory impairment present within the first two years from onset of childhood Ms, while in adulthood MS the cognitive impairment is usually gradual [42,43].

Optic neuritis (ON) is the first manifestation of MS in 14-35% of children, while 50% of patients will experience at least one episode during their lifetime [1]. Patients with ON present with unilateral reduced visual acuity, painful eye movements, reduced color perception, scotomas, with or without other CNS symptoms [34]. Bilateral ON, compared to unilateral ON, has been correlated with increased risk of developing MS in children [44].

Diagnostic evaluation

The diagnostic approach of MS in children includes clinical examination, immunological testing, cerebrospinal fluid (CSF) testing, evoked potentials and MRI.

CSF analysis reveals pleiocytosis in 66% of patients with MS [45]. Total protein level in CSF is within 100-150 mg/l. Oligoclonal bands are confirmed in 75% of children with MS [17,46]. However, the absence of oligoclonal bands in children does not exclude the diagnosis of MS. Moreover, the presence of oligoclonal bands in CSF is also reported in other inflammatory and infectious CNS diseases [47,48].

Abnormal evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways. In a study of 156 children with MS, evoked potentials were examined in 85 (55%) and abnormal findings were reported in 56% of them, while just 40% had vision disturbances [49].

Cranial MRI exhibits discrete T2 lesions in cerebral white matter, particularly periventricular regions as well as brainstem, cerebellum, and juxtacortical and deep gray matter. Alternatively, tumefactive T2 lesions are also seen. Spine MRI typically shows partial-width cord lesions restricted to 1-2 spine segments.[50]. Recent data suggest that children have much more lesions in the initial MRI compared to adults, especially in brainstem and cerebellum. This fact has been associated with poorer prognosis [51].

According to a recent study, the presence of two of the following has 85% sensitivity and 98% specificity for the diagnosis of MS in childhood: 1) presence of $\geq$ 5 lesions, 2) $\geq$ 2 periventricular sites and 3) $\geq$ 1 lesions in brainstem [52]. Moreover, the coexistence of any of the following criteria can distinguish the first MS episode by an ADEM episode: presence of "black holes" in T1 sequences, presence of $\geq$ 2 periventricular lesions and absence of diffuse bilateral lesions [53].

The principle criteria for diagnosis of MS is the establishment of dissemination in time and place of lesions, meaning that episodes affecting separate sites within the central nervous system have occurred at least 30 days apart. MRI can substitute for 1 of these clinical episodes.

Dissemination in time of magnetic resonance lesions requires: 1 gadolinium-enhancing lesion at least 3 mo after the onset of the clinical event, or a new T2 lesion compared with a reference scan done at least

Table I. Clinical and MRI findings that may distinguish ADEM from first MS episode.

	ADEM	MS
Age	<10 yr	>10 yr
Stupor/coma	+	–
Fever/vomiting	+	–
Family history	No	20%
Sensory complaints	+	+
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
MRI imaging	Widespread lesions: basal ganglia, thalamus, cortical gray-white junction	Isolated lesions: periventricular white matter, corpus callosum
CSF	Pleocytosis (lymphocytosis)	Oligoclonal bands
Response to steroids	+	+
Follow-up	No new lesions	New lesions

30 days after onset of the clinical event. In the case of recurrent stereotyped clinical episodes at the same neurologic site, criteria for MRI definition of dissemination in space are 3 features from the following: (1) 1 gadolinium-enhancing lesion or 9 T2 MRI lesions, (2) 1 or more infratentorial lesions, (3) 1 or more juxtacortical lesions, or (4) 3 or more periventricular lesions (a spinal cord lesion can replace some of these brain lesions) [54].

Primary progressive MS can be diagnosed after 1 yr of a progressive deficit and 2 of the following: (1) a positive brain MRI, (2) a positive spinal cord MRI, and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation but who do not meet all of the diagnostic criteria can be classified as having possible MS [54].

Differential diagnosis

Like adult MS, pediatric MS can be diagnosed following 2 demyelinating episodes localizing to distinct CNS regions, clinical semiology lasting >24 hr and separated by >30 days, provided no other plausible explanation exists. Alternatively, accumulation of T2 or gadolinium-enhancing lesions in the brain or spine >3 mo later can demonstrate dissemination in time, enabling MS diagnosis after the 1st event. MS is relatively rare in childhood, therefore the differential diagnosis include the following [54,55]:

1) Systemic diseases complicated by CNS involvement that follow a relapsing-remitting course (eg, systemic vasculitis)

2) Diseases of the brain and spinal cord confined to selected physiological systems and usually following a progressive course (eg, the hereditary cerebellar ataxias)

3) Disorders affecting one anatomical site and with either a relapsing-remitting or progressive course (especially, tumours and other structural lesions)

4) Monophasic disorders affecting many neuroantaomical sites (eg, acute disseminated encephalomyelitis-ADEM)

5) Non-organic symptoms that, intentionally or otherwise, mimic the clinical features of MS (so-called functional or somatisation disorders)

ADEM is a self-limited syndrome characterized by encephalopathy, polyregional neurologic deficits, and diffuse multifocal MRI T2 abnormalities followed by subsequent clinical improvement and resolution of MRI T2 lesions. However, 10-25% of pediatric MS patients present with an ADEM phenotype and then experience multiple relapses with accumulation of MRI T2 lesions. ADEM usually occurs following a viral infection but may appear following vaccination, bacterial or parasitic infection, or even appear spontaneously without any obvious triggering factor. However, MS can also be triggered by an immunological stimulus. Some features that may help distinguish an initial acute episode of demyelination from a 1st attack of MS in children are seen in table [34]. Final diagnosis of MS is based on follow-up evaluation and subsequent MRIs.

Management

In children, an acute episode of MS is usually managed with intravenous methylprednisolone, in dose ≤ 30 mg/kg or according to others up to 40 mg/kg for children ≤ 30 kg, and 1gr per day for children >30 kg, for 3-5 days. It is generally accepted that treatment with corticosteroids speeds up recovery from relapses. The exact mechanism of action of corticosteroids in MS remains unclear [56]. Possible mechanisms of action are the reduction of edema, stabilization of the blood-brain barrier, reduction of cytokines that promote inflammation and the induction of T-cells' apoptosis [57]. The exact frequency of intravenous corticosteroid administration has not been clarified yet, but it is generally considered that the administration should not exceed three times per year [58].

Plasmapheresis is a well-established therapeutic option in a variety of autoimmune neurological disorders. It is considered that the beneficial action of plasmapheresis is attributed to the removal of circulating inflammatory mediators including cytokines, autoantibodies and immune complexes. Plasmapheresis is more beneficial when administered within 4-6 weeks from symptoms' onset. There are few reports with small number of children who underwent plasmapheresis. However, the results are encouraging [59,60].

Intravenous g-globulin (IVIg) is a blood fractioned derivative consisting of condensed immunoglobulin IgG, derived from plasma tank of < 3,000-10,000 people. Due to its immunomodulatory properties, it has been used in various autoimmune diseases. The use of IVIg is suggested in pediatric patients with MS whose symptoms regress after days or weeks after discontinuation of steroids. The proposed dosage regimen is an initial loading dose of IVIg (0.4 g/Kg body weight/day, for 5 consecutive days) and additional booster dose infusions (0.4 g/Kg body weight/booster dose, every 6 weeks up to 1 year) as a maintenance treatment [61]. Another treatment regimen that has been proposed is the administration of IVIg in dosage 1 g/kg/day per month for two days for children weighing <50kg and for 4-5 days for children weighing >50kg [62,63].

Based on large clinical studies in adult patients with MS, the FDA (US Food and Drug Administration) and the EMA (European Medicines Agency) have approved disease-modifying drugs for the treatment of the recurrent form of MS. These include: interferon-b (IFN-β), glatiramer acetate, the monoclonal antibody natalizumab and the chemotherapeutic agent mitoxantrone.

Interferon-Beta (IFN-β) is a relatively small protein (about 1/10 of the size of immunoglobulin IgG), which carries out its complex action by inducing various genetic and metabolic processes [64]. Interferon is used in MS, because it is considered that lessens the production of IgG via direct effect in plasmacells and in the function of Natural Killer cells [65]. Additionally, interferon inhibits the proliferation of T-lymphocytes and reduces the production of pre-inflammatory cytokines, redirecting the immune response from the inflammatory Th1 to Th2 type [66]. The IFN-β stabilizes the blood-brain barrier, reducing the migration of inflammatory cells, probably through decreasing endothelial adhesion molecules (ICAM and VCAM) and the production of chemokines and matrix metalloproteinases [67-69].

Latest data suggest treatment with IFN-β or glatiramer acetate immediately after the diagnosis of MS. The effectiveness of these medications is considered to be higher during the early phases of the inflammatory disease compared to later phases. Current data indicate that IFN-β and glatiramer acetate are safe and well tolerated in pediatric population [70]. Treatment with IFN-β significantly reduces the risk of relapse during the first two years of the disease [71]. The appropriate dosage has not been yet established, but according to the current European Consensus, initial treatment with IFN-β is proposed to begin with 25-50% of adult dose gradually increased within 2-3 months to full adult dose [72]. Both intramuscular and subcutaneous forms of IFN-β1a and IFN-β1b have been used. Several retrospective studies propose the administration of intramuscular IFN-β1a at a dose of 30mg once daily, and subcutaneous IFN-β1a at a dose of 22 or 44mg three times daily [73-78].

Patients treated with IFN-β rarely present with severe adverse effects [73,76,78,79]. Most frequently reported side effect in 65% of patients is the development of flu-like syndrome, followed by leukopenia (8-27%), thrombocytopenia (16%), anemia (12%) and transient increase of liver enzymes (21-33%). Complications at the injection site in cases of subcutaneous administration include local reactions (> 66%), abscesses (6%) and necrosis at the injection site (6%) [73,76,78,79]. Due to possible adverse effects during treatment, hematological parameters and liver function should be measured at

the beginning of treatment and every 3-6 months [7]. In case that liver enzymes remain elevated (more than double) despite the reduction of the dose, the possibility of discontinuation of the specific therapeutic regimen should be considered [80]. Thyroid hormones profile should also be mesured annually. The presence of neutralizing antibodies against IFN-β significantly reduces the effectiveness of treatment and is indicative of discontinuation [81].

Glatiramer acetate is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine. The drug has been designed to mimic the human major basic protein (MBP), and it is believed that it induces the response against myelin from suppressor T-lymphocytes and affects the function of antigen-presenting cells [82]. It also redirects immune response to Th3 and Th2 type and helps the function of regulatory (Treg) cells, while probably has immunomodulatory properties to B-lymphocytes and neuroprotective actions through increasing the production of "brain-derived neurotrophic factor (BDNF) [80,82-88]. It has been reported that therapy with glatiramer acetate reduces the risk of recurrence by about 30% compared to placebo therapy. Indications of administration to pediatric population are limited and the dose is the same with adults (20 mg/day) [89-91]. Severe side effects include syncope, hypertension, pancreatitis, gastrointestinal and hematological disorders and complications from CNS. Glatiramer acetate should not be combined with the natalizumab due to an increased risk of developing progressive multifocal leukoencephalopathy (PML) [80]. It is generally believed that glatiramer acetate has more favorable profile of side effects compared to other treatment options in patients with MS.

At least one third of children with MS require administration of an immunomodulatory agent. Drugs that target lymphocyte subtypes (cladribine, alemtuzumab) or interfere with lymphocyte myelin interaction (fingolimod, natalizumab) are promising agents in trials in adult patients with MS. However, experience in the use of these drugs in pediatric population is limited. Natalizumab therapy has been associated with the risk of developing progressive multifocal encephalopathy (CNS infection with human polyomavirus JC) [34].

Prognosis

Several studies have indicated that a poor prognosis is related to male gender, a late age at onset, motor, cerebellar, and sphincter involvement at onset, a progressive course at onset, a short inter-attack interval, a high number of early attacks, and a relevant early residual disability [92]. The presence of T1 gadolinium-enhancing lesions at onset, the appearance of new T2 lesions or of T1 gadolinium-enhancing lesions 3 months after onset have been associated with a greater degree of disability during the course of the disease [93]. On the contrary, there has not been reported a significant correlation with the patient's gender and the age of onset of the symptoms [94,95]. The occurrence of seizures seems to be correlated with poor prognosis [96].

Children with chronic disease have an increased risk of developing chronic fatigue syndrome, emotional, cognitive and learning disorders. Teenagers with MS often report difficulties in high-level cortical functions and in multiple processes organization. Cognitive dysfunction may occur early during the course of disease up to 65% of patients [97]. Children have a higher risk due to the modern and rapidly-evolving development and maturation. Within 10-15 years, about 70% of patients with the relapsing form of the disease may develop progressive disability, in the absence of a new episode (secondary progressive MS) [30,94]. Children have a more prolonged recurrent phase and also 76% of pediatric patients maintain their motor functions 5 years after the initial diagnosis 6,30. About 40-60% of children will relapse within the first year from onset, reflecting the fact that children have more relapses compared to adults [36,98,99].

According to McAlpine and Compston, the average relapse rate is 0.3 to 0.4 recurrences per year, but the gap between the first symptoms and the first relapse shows significant variations [11]. In 30% of patients, the relapse occurs in the first year from the disease onset, in 20% in two years, in 20% within 5-9 years and in 10% between 10-30 years. Kurtzke et al. mention that one of the most important prognostic factors of long-term disability is the degree of disability in the first 5 years after the onset of symptoms [100].

In conclusion, the early onset of MS in childhood is an increasingly recognized clinical entity due to the strong clinical suspicion and the available diagnostic methods. The course of the disease in the susceptible pediatric population shows frequent exacerbations and remissions. The early diagnosis and treatment

lead to a better prognosis. The diagnostic and therapeutic approach of MS in children is a strong challenge for the child neurologist.

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