

PEDIATRIC MULTIPLE SCLEROSIS: CLINICAL, DIAGNOSIS AND THERAPEUTIC APPROACH

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Abstract

Multiple Sclerosis (MS) in pediatric age accounts for about 10% of cases of multiple sclerosis, defining as infantile form that onset before 10 years of age, and adolescent form that at the beginning between 10 and 18 years. The current diagnostic criteria for MS in McDonald's adult age can be applied to the pediatric age if the initial presentation of the disease is not an acute encephalopathy.

As for adults, the triggering factor of the inflammatory process in the CNS is related to an immunological alteration on the basis of which T cells play a fundamental role in particular in relation to various antigenic stimuli. The diagnostic evaluation is based on the history, physical examination, blood tests, liquor and neuroimaging.

In pediatric early-onset forms, MOG (glycoprotein oligodendrocyte anti-myelin) and MBP (basic anti-myelin protein) are often present.

The initial symptoms of MS vary significantly, often with difficulty in detecting modest symptoms such as changes in sensitivity. Often the initial symptom may be an encephalopathy (like ADEM) or an optic neuropathy with onset with a convulsive episode. The course is generally relapsing-remitting.

The EDSS score, disability index, in pediatric forms is generally lower than in adults.

Patients with MS in children should be considered for treatment with both beta interferon and glatiramer acetate, as first-line drugs, unless there is a specific contraindication to the use of the two products.

The knowledge gained on the use of DMTs in adults (early and long-term) is in favor of their early use even in pediatric age.

Keywords: Adolescent, Diagnosis, Multiple Sclerosis, Clinical Approach, Pediatric.

Nosology

Multiple Sclerosis (MS) in pediatric age accounts for about 10% of cases of multiple sclerosis, defining as infantile form that onset before 10 years of age, and adolescent form that at the beginning between 10 and 18 years (1). The current diagnostic criteria for MS in McDonald's adult age can be applied to the pediatric age if the initial presentation of the disease is not an acute encephalopathy. In this case (in relation to the guidelines of the international group of pediatric SM study - 2013) the ADEM is classified, by definition monophasic, which can last up to 3 months unlike the CIS which can be monofocal or plurifocal (2).

Proposed Revision of the McDonald's Diagnostic Criteria (2010) For Multiple Sclerosis (October 2017) (The Lancet Neurology –Volume17, No.2, p162-173)

1. In the presence of CIS (clinically isolated syndrome) the presence of oligoclonal bands together with clinical and neuroradiological criteria (MRI) of "diffusion in space" allows to perform a diagnosis of multiple sclerosis even without the previously requested diffusion in time

2. The presence of MR lesions (symptomatic or asymptomatic) is such as to meet the RM criteria for diffusion in space and time

3. The spread of lesions in space can also be demonstrated by cortical lesions and not only by juxtacortical lesions

4. The diagnosis of a progressive primary form no longer provides for the distinction between symptomatic and asymptomatic lesions and can also be performed taking into account cortical lesions

5. At the time of diagnosis we can only temporarily hypothesize the type of course that will be subsequently revalued according to the characteristics of the pathology

CLINICAL CRITERIA ADEM

IPMSSG (International Pediatric Multiple Sclerosis Study Group) – 2013

- A first polyphochal clinical event of the CNS with presumed inflammatory demyelinating cause
- Encephalopathy that can not be explained by fever
 - MRI and clinical status unchanged after three months
 - Abnormalities of MRI during the acute phase
 - Typical findings on cerebral MRI: including widespread and poorly demarcated lesions involving brain white matter; T1 hypodense lesions of white matter are rare; Deep gray matter lesions may be present

ADEM VS PEDIATRIC MULTIPLE SCLEROSIS (1)

EZIOPATOGENETIC MECHANISMS

As for adults, the triggering factor of the inflammatory process in the CNS is related to an immunological alteration on the basis of which T cells play a fundamental role in particular in relation to various antigenic stimuli. In

younger children there was a reduced production of BO in the liquor with a higher percentage of neutrophils than older children (> 11 years) and adults, an index of prevalent and massive innate immune response to the first clinical event. In pediatric early-onset forms, MOG (glycoprotein oligodendrocyte anti-myelin) and MBP (basic anti-myelin protein) are often present (3). Environmental factors without any doubt are fundamental conditions for the development of the disease. Several studies have shown evidence of increased HIV seropositivity in patients with MS (independently of the HLA-DRB1 status). Instead, remote infection of CMV and HSV-1 in HLA-DRB1 positive individuals has been observed to reduce the risk of MS by more than 70% while this risk is increased by more than 4-fold in HLA-DRB1 negative individuals. (4) With reference to vaccinations, no correlation was found between the hepatitis B vaccine and subsequent development of MS while exposure to secondhand smoke is a significant risk element for the onset of the disease (about twice the control population) (5,6). Unlike the adult, the effect of Vitamine D for the development of the disease is not known, while a direct correlation with the risks of relapse has been observed. The most studied genetic risk factor is HLA-DRB1 which, if present, increased the probability of development of the disease from 2 to 4 times as in adults. (7)

EPIDEMIOLOGY

The prevalence rates of occurrence of pediatric MS vary from 2.2% to 4.4% of all MS cases (in some centers this percentage reaches up to 10%). In general, the onset before 10 years is rare and constitutes about 20% of pediatric cases. (7,8). The incidence of pediatric MS is 0.51/100000 /year while for other forms of acute demyelination it is 1.66/100000/year (optic neuritis, ADEM, transverse myelitis). Before the 6 years the male-female ratio is 0.8: 1 while in the following years it is similar to the adult forms (9,10)

CLINICAL CHARACTERISTICS AND DIAGNOSTIC APPROACH

SM in pediatric age involves multiple social and personal problems. In particular mood disorders, concern for the future, relational disorders, cognitive impairment (present in about 30-70% of children) in particular in the domains concerning memory, attention, executive functioning and evidenced mainly with poor performance school (11). The EDSS score, disability index, in pediatric forms is generally lower than in adults. Generally, the value of 4 is reached after about 20 years in pediatric MS versus 10 years of adult form. It should be considered that this score, an index of specific disabling neurological deficits, however, is generally reached in an age of about 10 years younger than in adults with greater damage to the family and to work. (12). The initial symptoms of MS

vary significantly, often with difficulty in detecting modest symptoms such as changes in sensitivity. Often the initial symptom may be an encephalopathy (like ADEM) or an optic neuropathy with onset with a convulsive episode. The course is generally relapsing-remitting with a recurrence rate ranging between 0.38% and 0.87% in the first 10 years. (13). In general, pediatric multiple sclerosis, especially in the smallest patient, presents atypical features such as fever, encephalopathy, absence of BO, increase in liquor leukocytes. The diagnostic evaluation is based on the history, physical examination, blood tests, liquor and neuroimaging (14).

The differential diagnosis must be made with:

- Endocrine disorders: thyroid disorder, diabetes mellitus
- Autoimmune diseases: systemic lupus erythematosus (SLE), neurosarcoidosis, Sjögren's syndrome, antiphospholipid antibody syndrome (APLAS), Behçet's disease, isolated angiitis
- Mitochondrial diseases: MERRF (Myoclonic epilepsy with ragged-red fibers), MELAS (mitochondrial encephalomyopathy with lactic acidosis ()), hereditary optic neuropathy of Leber (LHON), Leigh's syndrome, Kearns-Sayre syndrome
- Leukodystrophy: metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease, Refsum disease, leukoencephalopathy with involvement of the brainstem and spinal cord and high levels of lactate, Wilson's disease, Fabry's disease, Alexander's disease
- Genetic/metabolic diseases: errors of metabolism, aminoacidurie
- Infectious pathology: Neuroborreliosis (Lyme disease), HSV encephalitis, HIV infection, neurocysticercosis, poststreptococcal infection, abscess, neurosyphilis, progressive multifocal leukoencephalopathy (PML), Whipple's disease
- Vascular pathology: autosomal dominant cerebral arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), Moyamoya disease, carotid dissection
- Other demyelinating diseases: clinically isolated syndrome, ADEM, optic neuritis, transverse myelitis, NMO, postvaccination, acute necrotizing encephalopathy
- Nutritional Deficit: vitamin B12, vitamin E or folate deficiency; celiac disease
- Neoplasia: lymphoma, astrocytoma, medulloblastoma, metastasis
- Toxic alterations: radiation, chemotherapy (methotrexate, cyclosporine, cytosine-arabioside), extrapainin myelinosis
- Other: Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis

The examination of the liquor in pediatric SM varies according to age. Generally, before the age of 11 years a neutrophilia is present, then an increase in lymphocytes is shown. BOs are usually present in older children or adolescents (unlike ADEM where the BO positivity ranges from 0% to 29%). The IgG index is elevated in 68% of patients over 11 years of age. (15). In pediatric MS, MRI lesions (T2 hyperintensity) may be more rare than in adults, whereas other lesions (T1) are more common in the trunk and cerebellum. The periventricular white matter lesions are not specific to MS, as they are also observed in other CNS demyelinating diseases such as NMO. Other instrumental investigations in pediatric MS are the ENP and the OCT. Visual evoked potentials often indicate a previous and asymptomatic lesion of the optic nerves.

Therapeutic Approach

Although the treatment of MS and I-II line therapies approved for the treatment of MS are widely used in the age groups that include children and adolescents, most of them are used in the "off-label" because they are never formally evaluated in these age group.

The IPMSSG, in this regard, produced the following document:

- Patients with MS in children should be considered for treatment with both beta interferon and glatiramer acetate, as first-line drugs, unless there is a specific contraindication to the use of the two products
- If the decision to start a disease modifying therapy has been taken, the therapy should be started as quickly as possible, even if you are facing recent re-exacerbations or during re-exacerbation and concomitant treatment with steroids

Clinical monitoring.

- Assess the state of health, tolerability, adherence to treatment (neurologist, pediatrician, other health care provider every 4 months approximately)
 - Neurological evaluation every 6 months
 - Neurological evaluation in case of re-exacerbation
 - Magnetic resonance at least on an annual basis
 - Magnetic resonance of the spinal cord at baseline and subsequently based on clinical evolution

In case of inadequate response to therapy, the various options involve switching to II line drugs, rather than switching from interferon to copolymer or vice versa. Natalizumab, on the basis of available data (class IV) in children with MS has proven effective in reducing clinical and MRI relapse in most cases to the point that this drug may represent a viable alternative for pediatric patients to meet the criteria of active disease during treatment (20,21). In conclusion, children and adolescents with MS are at high risk for developing severe physical sequelae and accumulating cognitive impairment. The knowledge gained on the use of DMTs in adults (early and long-term)

is in favor of their early use even in pediatric age. From the widely expressed considerations, the position of a greater emphasis on safety aspects, especially with new drugs in pediatric age, is increasingly clear. Of the treatments described above, the published studies provided most of the information for beta interferons. Data on other therapies are limited or non-existent in children.

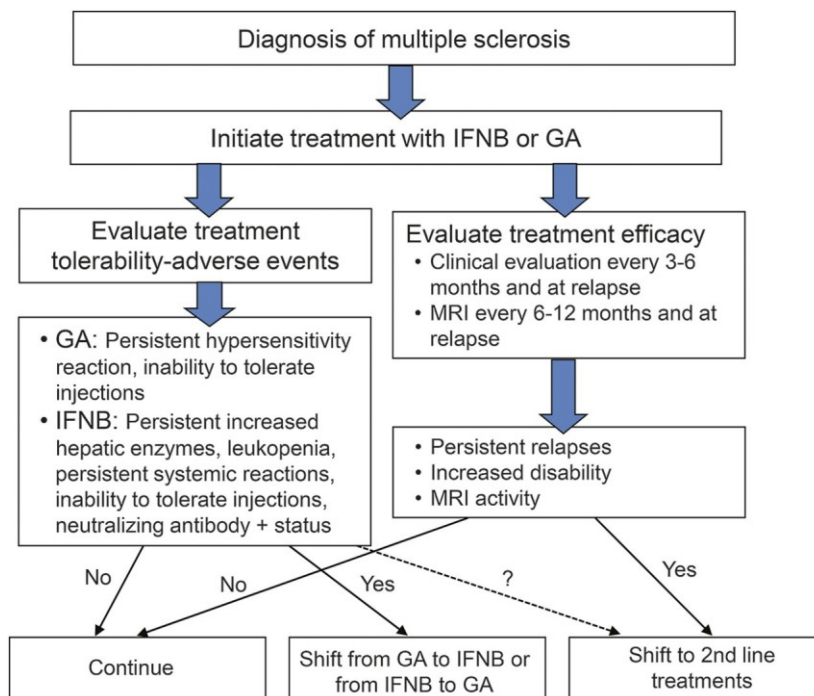
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Table 1: ADEM VS PEDIATRIC MULTIPLE SCLEROSIS

Typical features	ADEM	MS
Demographic	More frequently younger age groups (<10 years); no gender predilection	More frequently adolescents; girls predisposed more than boys
Prior flu-like illness	Very frequent	Variable
Encephalopathy	Required in definition	Rare early in the disease
Seizures	Variable	Rare
Discrete event	A single event can fluctuate over the course of 12 weeks	Discrete events separated by at least 4 weeks
MRI shows large lesions involving gray and white matter	Frequent	Rare
MRI shows enhancement	Frequent	Frequent
Longitudinal MRI findings	Lesions typically either resolve or show only residual findings*	Typically associated with development of new lesions
CSF pleocytosis	Variable	Extremely rare, white blood cell count almost always <50
Oligoclonal bands	Variable	Frequent
Response to steroids	Appears favorable	Favorable

* A subset of patients with acute disseminated encephalomyelitis (ADEM) fail to have a self-limited disease course and instead experience additional relapses and accumulate lesions on neuroimaging. Subsequently, these patients are reclassified as multiple sclerosis (MS).

Figure-1 : THERAPEUTIC FLOW CHART

Angelo Ghezzi e al. Neurology, August 30, 2016; 87 (9 Supplement 2)