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Multiple Sclerosis on behalf SFSEP

Update on pediatric-onset multiple sclerosis

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INFO ARTICLE

Article history:
Received 11 March 2018
Received in revised form
29 March 2018
Accepted 4 April 2018
Available online xxx

Keywords:
Pediatric multiple sclerosis
ADEM
Diagnostic criteria
Prognosis
Cognitive impairment

ABSTRACT

Pediatric-onset multiple sclerosis (POMS) has distinctive features compared with adult-onset multiple sclerosis (AOMS), and warrants caution despite being a rare form of MS. POMS diagnostic criteria are somewhat different from those used in AOMS, with acute disseminated encephalomyelitis being a key differential diagnosis of MS in children. Other differential diagnoses that have to be ruled out before diagnosing MS include demyelinating syndromes, autoimmune and systemic pathologies, and infectious, genetic, metabolic and neoplastic diseases. Compared with AOMS, POMS has several different clinical, biological and imaging findings. At onset, high-level inflammatory activity is mainly reported, and patients with POMS are also at high risk of developing early physical disabilities and early cognitive impairment. Yet, treating patients with POMS is challenging due to a lack of randomized controlled trials. Some of the disease-modifying drugs currently prescribed are analogous to therapies used in adults, and are associated with good tolerability in pediatric patients. However, a few clinical trials dedicated to POMS are now in progress, and the future outlook is to improve the long-term prognosis of POMS patients with early effective and safe treatments.

1. Introduction

Pediatric-onset multiple sclerosis (POMS) refers to children and adolescents aged < 18 years. Among MS cases in general, the prevalence of POMS is low, with rates close to 3–4% (reports range from 2.7% to 10.5%, according to the study) [1–5]. However, the development of new diagnostic tools and therapeutic issues has recently been associated with an increase in published reports relating to this form of disease. Thus, in the present update, positive and differential diagnoses of POMS are summarized and presented. In addition, the various distinctive features of POMS compared with adult-onset MS (AOMS) are described in terms of their clinical and paraclinical characteristics; the evolution and prognosis of patients affected by the disease are also summarized. Finally, the therapeutic management of this young population is discussed.

2. Diagnostic criteria

As is the case with adults, a positive diagnosis of POMS should only be determined if there is no better explanation.

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https://doi.org/10.1016/j.neurol.2018.04.003

Table 1 – Diagnostic criteria for clinically isolated syndrome (CIS), multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM).

	2012 IPMSSG criteria [8]	2017 McDonald criteria [16]
CIS	First monofocal or multifocal central nervous system (CNS) clinical demyelinating event with no encephalopathy unless due to fever	Monophasic monofocal or multifocal CNS clinical demyelinating event with no fever or infection lasting $\geq$ 24 hours
MS	$\geq$ 2 non-encephalopathic CNS demyelinating events involving more than one area of CNS separated by $\geq$ 1 month One clinical demyelinating event consistent with MS with DIS and DIT according to 2010 McDonald criteria[a] (DIT by a single MRI only applies to children aged $\geq$ 12 years without ADEM) ADEM followed 3 months later by non-encephalopathic clinical events with new lesions on brain MRI consistent with MS	Criteria applicable in patients aged $\geq$ 11 years with no better explanation after carefully excluding differential diagnoses (such as ADEM, NMOSD): MS diagnosis could be made after $\geq$ 2 clinical attacks with objective clinical evidence of $\geq$ 2 lesions After $\geq$ 2 clinical attacks with objective clinical evidence of a single lesion, DIS is indicated by another clinical attack implicating a different CNS location or by MRI[a] After one multifocal attack (not ADEM), DIT is indicated by another clinical attack (separated by $\geq$ 1 month) or by MRI[a] or CSF-OCB positivity[b] After one monofocal attack, DIS is indicated by another clinical attack implicating a different CNS location or by MRI[a]; DIT is indicated by another clinical attack or by MRI[a], or CSF-OCB positivity[b]
ADEM: Monophasic Multiphasic	First polyfocal clinical CNS event suggests demyelinating disease with encephalopathy not explained by fever and no new symptoms, signs or MRI findings after 3 months New ADEM event $\geq$ 3 months after initial event associated with new or re-emergence of previous clinical/MRI findings independently of corticosteroid therapy delivery	Typical presentation of ADEM No details

NMOSD: neuromyelitis optica spectrum disorder; DIS: dissemination in space; DIT: dissemination in time; MRI: magnetic resonance imaging.
[a] See Table 2 for 2010 and 2017 revised McDonald criteria.
[b] Presence of oligoclonal bands in cerebrospinal fluid.

More important, the diagnostic criteria for the pediatric population differ from those for adults, particularly in children aged < 11 years. The difficulty in children is related to the wider range of possible atypical clinical presentations compared with adults. Postinfectious and post-vaccinal demyelinating events are frequently observed in children, and are commonly associated with acute disseminated encephalomyelitis (ADEM). Recently, a set of criteria was proposed specifically for this patient population by the International Pediatric Multiple Sclerosis Study Group (IPMSSG). The first consensus definitions for pediatric MS were published in 2007 [6] and, in 2011, the International Panel on MS proposed a revised version of the McDonald criteria, taking into account the particularity of pediatric MS [7]. Later, in 2012, the IPMSSG criteria were submitted (Table 1) [8]. In cases of non-encephalopathic central nervous system (CNS) clinical events, the same definitions as used for adults may be used.

2.1. *Acute disseminated encephalomyelitis*

Monophasic ADEM is defined as the first multifocal CNS event associated with encephalopathy that is not explained by fever. There are also magnetic resonance imaging (MRI) findings typical of ADEM: poorly defined lesions; large lesions measuring 1–2 cm; and hyperintense lesions in cerebral white matter and gray matter (thalamus, basal ganglia); however, contrary to MS in general, T1-weighted hypointense lesions are rare. For a diagnosis of monophasic ADEM, no new symptoms and/or new MRI lesions are evident after 3 months. Unlike in adults, ADEM is commonly seen in the pediatric population. It is noteworthy that myelin oligodendrocyte glycoprotein (MOG)-antibody-associated disease has recently emerged, with either an ADEM presentation or severe optic neuritis, mainly in the pediatric population in comparison to adults and is now among the differential diagnoses of MS [9,10].

In the other hand, the term ''recurrent ADEM'', used in the 2007 IPMSSG criteria, was dropped from the 2012 version. The key point is the difference between ''multiphasic ADEM'' and MS. If new events of ADEM associated with new or previous clinical and MRI findings appear at least 3 months after the initial event, then a diagnosis of multiphasic ADEM may be applied. Contrary to the 2007 IPMSSG criteria, in the 2012 IPMSSG version, these events could happen independently of the time of corticosteroid treatment. On the other hand, if, 3 months after a first episode of ADEM, a child presents with a non-encephalopathic clinical event with new lesions on brain MRI suggestive of MS, then a diagnosis of pediatric MS may be applied.

2.2. *Clinically isolated syndrome (CIS)*

CIS, defined as the first clinical CNS demyelinating event suggestive of MS, can be either monofocal or multifocal. One important point in the definition of CIS is that encephalopathy should be absent unless it is due to fever. The likelihood of having MS rather than ADEM is increased if two of the three following criteria are met: absence of diffuse bilateral lesion pattern; presence of black holes; and at least two periventricular lesions [11].

Please cite this article in press as: Ruet A. Update on pediatric-onset multiple sclerosis. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2018.04.003