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Review article

Pediatric multiple sclerosis and fulminant disease course: Features and approaches to treatment – A case report and review of the literature

Dániel Sandi [a], Edit Bereg [b], Tamás Biernacki [a], Erika Vörös [c], Péter Klivényi [a], Csaba Bereczki [b], László Vécsei [a,d], Krisztina Bencsik [a,*]

[a] Department of Neurology, University of Szeged, Szeged, Hungary
[b] Department of Pediatrics, University of Szeged, Szeged, Hungary
[c] Department of Radiology, University of Szeged, Szeged, Hungary
[d] MTA-SZTE Neuroscience Research Group, University of Szeged, Szeged, Hungary

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ABSTRACT

Multiple sclerosis (MS) is the autoimmune, neurodegenerative disease of the central nervous system (CNS). Typically, it affects the young adult population, however, up to 10% of the cases, it can develop in childhood. Atypical manifestations, such as the tumefactive variant (tMS) or acute disseminated encephalomyelitis (ADEM), especially coupled with fulminant disease course, are even more rare and pose a considerable differential diagnostic and therapeutic challenge. Recently, the therapeutic strategy on the use of disease modifying therapies (DMTs) in MS has shifted to the direction of a more individualized approach, that takes the personal differences heavily into account, in particular regard to the activity and prognosis of the disease. Despite this change has only been applied to adults yet, it is plausible to predict, that it will soon be applied to pediatric patients as well, particularly, as several randomized studies are under way concerning DMTs in pediatric populations. To our best knowledge, we are the first to report a successful natalizumab treatment of pediatric fulminant tMS, in case of a 13.5 years old girl. We feel that this report demonstrates the need of early and adequate treatment in such an aggressive case, because it can reverse the course of a possibly fatal disease.

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1. Introduction

Multiple sclerosis (MS) is an autoimmune, demyelinating, neurodegenerative disease of the central nervous system (CNS). Usually it starts in young adulthood, as the majority of the patients are aged between 20 and 45 years at disease onset [1,2]. However, in a smaller proportion of cases, the disease manifests itself before the age of 18 years. Atypical manifestations of demyelination are even more rare in children: there are very few data regarding these phenomena. The options of treatment in pediatric onset MS (POMS), atypical manifestations variants in particular, are by far not as established as in adults, mainly due to the relatively low number of patients and the difficulty of pediatric studies (both non-interventional and interventional) (see Table 1).

In this short review, we aim to give a comprehensive summary of the latest findings in POMS, atypical variants and therapeutic approaches. Also, we aim to share our own experience on the field via a case-report.

2. Pediatric-onset multiple sclerosis versus adult-onset multiple sclerosis

2.1. Epidemiology

The reported prevalence of POMS varies between 0.4 and 10.4% of all MS cases, with the later examinations yielding higher rates, possibly due to the development of better diagnostic tools and criteria [3]. MS onset before puberty (before 10–12 years of age) is extremely rare, accounting for less than 1% of all cases [4–6]. The mean age at disease onset tends to be around 14 years [4]. The annual incidence rate of POMS varies between 0.07 and 2.90/100.000 [7,8]. The female-male ratio tends to be even higher than in adults, approximately 4–5:1 in POMS regarding onset around puberty, but interestingly in younger onset patients (before the age of 10–12 years) the distribution is near equal [4,9]. This highlights the possible role of sex hormones in the development of the disease [10].

* Corresponding author at: Semmelweis str. 6, 6720 Szeged, Hungary.
E-mail address: bencsik.krisztina@med.u-szeged.hu (K. Bencsik).

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Table 1
The summary of differences of pediatric-onset multiple sclerosis in epidemiology, clinical manifestations and MRI features as compared to adult-onset multiple sclerosis MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; POMS, pediatric-onset multiple sclerosis; DMT, disease modifying therapy.

		Pediatric-onset MS	Adult-onset MS
Epidemiology	Sex ratio	Before the age of 12 years, female-male ratio 1:1, after the age of 12 years, female-male ratio 4–5:1	The female-male ratio is approximately 3:1
	Clinical course	98% of the patients have RRMS, PPMS is extremely rare	The rate of PPMS patients is approximately 10%
Clinical presentation	Somatic symptoms	Relapses tend to be monofocal, polyfocal relapses occur more often before the age 12 years. Brainstem symptoms are seen often	Brainstem symptoms are not as often present as in POMS
	Cognitive symptoms	Linguistic skills, executive functions are more often present, problems with mathematic skills are unique to pediatric-onset patients. Conceptual reasoning is not affected	The most commonly affected cognitive domains are information processing speed, visual and verbal memory and attention. Conceptual reasoning may be affected
	Relapse rate	The annualized relapse rate is higher.	The annualized relapse rate is lower.
	Severity of, and recovery from relapses	Relapses tend to be more severe, yet complete or near-complete recovery from relapses is more often in pediatric patients.	Severe relapses occur less often than in POMS, yet the recovery from the relapses tend to be worse
	Disability	The time to reach the threshold associated with irreversible neurologic damage is ~10 years longer, patients reach SPMS state ~10 years younger	Patients reach EDSS: 4 points ~10 years earlier than in POMS.
MRI parameters	Localisation	Infratentorial (mainly brainstem) lesion load is higher in POMS patients.	Infratentorial lesions occur less often in adults.
	Atrophy	Regional atrophy, most prominently the atrophy of the thalami is more pronounced	Global atrophy is the most prominent in adults
Management	DMTs	There are no data from randomized-control studies; most of the DMTs considered off-label in most countries	There are several DMTs available with data from randomized-control studies

2.2. Clinical manifestations

Overwhelming majority of pediatric MS patients develop the relapsing-remitting (RRMS) course of the disease, up to 98% of the patients; the primary progressive course (PPMS) is extremely rare [4,11]. Relapses occur more frequently in POMS than in adults, the annualized relapse rate was consequently shown to be higher in many assessments, even during longer follow-up periods (up to 6 years) [12,13]. There are also evidences, that the first attack interval is shorter. The relapses tend to be severe more often in children than in adults [8,14]. Yet, the recovery from these relapses are usually far better: nearly all children reach complete or near-complete recovery from the attacks [8,14–16]. Moreover, several examinations consequently reported, that the median time to conversion to SPMS is approximately 10 years longer in POMS as well as the time to acquire EDSS score 4 [4,5,17–19]. However, once EDSS score 4 is reached, there is no difference in the disability progression between children and adults [4,5,17–19]. It was also evident from these data, that POMS patients reach the secondary progressive (SPMS) stage 10 years younger than adult-onset MS patients [4,5,17–19]. There are also some differences regarding the clinical symptoms between children and adults. The initial relapses tend to be monofocal, and attacks involving the brainstem and the cerebellum are more often seen in POMS [8,17,20]. However, in children under the age of 10 years, attacks can be multifocal often, leading to difficulties in differential diagnosis from ADEM and other neurological conditions [4,7,9,21]. Other signs, as fever, headache, vomiting, altered mental status and seizures are present far more often in POMS than in adults [4,22]. Cognitive impairment is a frequent and substantial symptom of MS both in children and adults. Yet, the psychological profile is different than in adults: linguistic skills are much more often affected in children, as are several executive functions, yet dysfunction in conceptual reasoning, which is considered to be a rather MS-specific phenomenon, is less prevalent in children [23–28]. In addition, POMS patients seem to be vulnerable to deficits in mathematic skills, which are not seen in adults [25].

2.3. MRI presentation

The MRI characteristics of pediatric MS are not as clear as in adult-onset MS. Initially, it was established that children with MS suffer from a lower lesion burden [11]. Some reports state even, that pediatric patients less often meet the criteria for dissemination in space [29]. However, recent assessments proved that the T2 lesion burden is similar in POMS and in adults [21,30]. Furthermore, Waubant et al. concluded that lesion burden on MRI scans at presentation and disease activity on follow-up scans in POMS patients is significantly higher, than adults at the same disease stage in the same population [31]. They also concluded, that infratentorial lesions (including the brainstem) are significantly more prevalent in children [31]. In accordance to this, another assessment found that despite the overall T1 lesion burden is lower in POMS, when evaluated regionally, POMS patients showed a significantly higher T1 lesion burden in the infratentorial area [21]. These findings correlate very well with the fact, that brainstem signs are more frequently seen in children, than in adults [9].

Several studies proved, that the negative effect on brain volume and on brain maturation is severe in POMS: global brain volume (as well as in adult onset MS) is significantly lower compared to the healthy population [30,32]. It seems that on the regional level, the thalamus is the most vulnerable in pediatric patients [32]. Also, it seems, that this relative thalamic brain volume loss (and of the corpus callosum) is also indicative of cognitive dysfunction in POMS [33].

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