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REVIEW ARTICLE

Dilemmas in the differential diagnosis of pediatric multiple sclerosis

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Summary

Multiple sclerosis (MS) is a chronic, inflammatory, and neurodegenerative disease of the central nervous system (CNS). It typically presents in early or middle adulthood, and pediatric-onset MS (POMS), defined by the first MS attack occurring before the age of 18, is less common. Current data from the Danish Multiple Sclerosis Registry indicates that nearly 3% of patients had the onset before the age of 18. In comparison with adult-onset MS, POMS patients typically have a more inflammatory-active disease course, resulting in more frequent relapses, but slower long-term disability accumulation. In POMS, diagnostic dilemmas may include differentiating MS from acute disseminated encephalomyelitis (ADEM) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), both of which most commonly occur among children and share some clinical and imaging features with MS. Inherited leukodystrophies should be considered in the differential diagnosis only in select cases, as their hallmark clinical feature—a progressive disease course—distinguishes them from the typically non-progressive acquired demyelinating syndromes, including neuromyelitis optica spectrum disorder. It's important to remember that magnetic resonance imaging (MRI) of the brain and spinal cord is essential for establishing a timely and accurate diagnosis of POMS. MRI helps exclude alternative diagnoses, allowing for the prompt initiation of effective treatment.

Keywords: multiple sclerosis, diagnosis, pediatric-onset

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, neuroinflammatory and neurodegenerative disease of the central nervous system (CNS). MS typically presents in early or middle adulthood. Pediatric-onset MS (POMS), defined as the first MS attack occurring before the age of 18, is less common. Pediatric-onset multiple sclerosis (POMS) is estimated to account for approximately 2% to 10% of all MS cases, with disease onset before the age of 10 occurring in only 0.2% to 0.7% of cases (1). Current data from the Danish Multiple Sclerosis Registry, with onsets between 2003 and 2022, indicates that 2.89% of patients had the onset before the age of 18 (2). In the recent meta-analysis, an estimated global incidence of POMS was 0.87 per 100,000 individuals per year (3).

In the French KidbioSEP cohort, the mean age of onset was 11.8 ± 3.7 years. The study also suggested that the number of children experiencing their first attack before the age of 11 may be higher than previously estimated (4). Younger children present with encephalopathy, seizures, and multifocal deficits, more often than children over the age of 12 and adults. Moreover, in children under 12, T2-hyperintense lesions tend to be larger and confluent. Conversely, clinical presentations and imaging findings of older children are usually similar to those of adults (5). The clinical presentation of POMS is very heterogeneous and depends, first of all, on the location of the demyelinating plaques that affect predilection sites, that is, the optic nerve, brain and spinal cord (6). As already mentioned, in children with the first attack after the age of 11, the clinical picture of POMS does not differ significantly from adult MS. However, in younger children, symptoms of encephalopathy may occur more often, accompanied by a disturbance in the state of consciousness and epileptic seizures, followed by headache, nausea and vomiting (7). Studies to date indicate that the majority of POMS patients—approximately 50% to 70%—present with a multifocal, or polysymptomatic, disease onset, while a mono-focal presentation occurs in 30% to 50% of cases. However, the multifocal presentation most often occurs before the age of 12, while the mono-focal presentation of the disease occurs most often after the age of 10 (8).

In comparison with adult-onset MS, POMS patients typically have a more inflammatory-active disease course, resulting in more frequent relapses but slower long-term disability accumulation (9). These features are generally attributed to the extensive post-relapse recovery that can be at least partly attributed to a higher ability for myelin repair/synthesis and greater plasticity of the developing brain (10). Immunological changes that occur throughout the lifespan impact the clinical manifestations of MS, such as relapse frequency, severity, and recovery. Children have larger and higher proportions of naive T cells and higher B-cell functional capacities, resulting in more robust immune responses to antigens than adults, which may amplify the inflammatory pathology of MS and explain why most POMS cases present with a relapsing-remitting course (2). Approximately 98% of patients with POMS present with a relapsing-remitting disease course (11). Although progressive-onset multiple sclerosis is rare in childhood and the transition to a secondary progressive phenotype occurs over a longer period, patients with POMS still reach ambulatory disability milestones at younger chronological ages than those with adult-onset MS due to their earlier disease onset (12, 13).

Although POMS patients have relatively slower physical disability progression, the early and frequent neuroinflammatory attacks can result in impaired brain development and poorer cognitive performance when compared to adult-onset MS patients or non-MS peers (14, 15). These impairments can have long-term consequences, including a lower likelihood of pursuing higher education, lower annual earnings, frequent sick days during work life, and early enrollment into disability pension programs (16). Very recently, it has been emphasized that acquired demyelinating syndromes (ADS), such as MS and myelin oligodendrocyte glycoprotein antibody disease (MOGAD), often cause cognitive impairment and fatigue in children and adults (17). POMS is associated with worse cognitive impairment in adulthood compared to adult-onset MS and reduced participation in university education and employment. However, the impact of POMS on school participation remains unknown to date. Therefore, efforts toward early diagnosis, discovery of early predictors of long-term outcomes, and appropriate early drug intervention are highly warranted (18).

A group of neurological disorders characterized by acute or subacute onset of neurological deficits associated with the evidence of inflammatory demyelination of the central nervous system (CNS), including the optic nerves, is collectively named ADS (19), with acute disseminated encephalomyelitis (ADEM), occurring in 22-32% of children with ADS. It could be represented as one of neuroinflammatory diseases, such as AQP4-NMOSD, MOGAD, ADEM with encephalopathy, or a monophasic disease (20), or MS. Furthermore, it has to be emphasized that only 20% of pediatric ADS cases are ultimately diagnosed with POMS (21).

In POMS, diagnostic dilemmas may include differentiating MS from monophasic acute disseminated encephalomyelitis (ADEM) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) (20), both of which most commonly occur among children and share some clinical and imaging features with MS. Inherited leukodystrophies should be considered in the differential diagnosis only in select cases, as their hallmark feature—a progressive disease course—is uncommon among other acquired demyelinating syndromes (ADS) (22).

PATHOHISTOLOGY AND IMMUNOPATHOGENESIS IN MS

Demyelinated regions, i.e., lesions or plaques, in the gray and white matter of the CNS, form the pathological basis of MS. Nowadays, plaques of demyelination are known to involve both white and gray matter, including the nuclei, cortex, and spinal cord. Plaques indicate damage and loss of oligodendrocytes and myelin sheaths (23, 24). At the very beginning of the disease, both neurons and axons are partly preserved. However, later on, with the progression of the disease, there is neuroaxonal damage. Inflammation is most pronounced in the acute stages of the disease but can be detected in all stages. In addition to the demyelination process, remyelination can also be detected initially. In the initial stage of the disease, in the pathohistological findings, macrophages with CD8+ T lymphocytes are the most abundant, and plasma cells and B lymphocytes can also be found (23, 24).

Studies have shown that with the progression of the disease and neuroaxonal damage, there is a deterioration in the degree of disability and the occurrence of brain atrophy. In the pathohistological findings, diffuse fields of B and T lymphocytes, astrocytes, and microglia can be detected. In addition, damage to axons and myelin can also be seen. All these processes damage the white and gray matter of the brain and spinal cord and the consequent reduction in brain volume, i.e., atrophy (23, 24, 25). In the later course of the disease, sclerotic lesions are created in the white matter plaques under the influence of astrocytes. Postmortem analysis of MS brains, compared to those of healthy controls, showed a 19% to 24% reduction in the cross-sectional area of the spinal cord at the cervical, thoracic, and lumbar levels. Gray matter atrophy was from 17 to 21%, and white matter from 19% to 24% (24). The density of axons in patients was lower by 57% to 62% compared to healthy controls. Demyelination affected between 11% and 13% of white matter and 24% to 48% of gray matter (24).

It is crucial to emphasize that axon damage is the primary pathophysiological mechanism of disease progression and neurological disability. It is believed to occur very early in MS, even during radiologically isolated syndrome (RIS), and POMS patients have a greater degree of acute axonal damage than adults (24). This was also shown by pathohistological studies, which were conducted on autopsy tissues of nineteen children and adolescents with POMS and clinically isolated syndrome (CIS) (25). This study showed that acute axon damage is 50% higher in children and adolescents (age range from 4 to 17 years) than in adult patients (26, 27).

HOW TO ESTABLISH THE DIAGNOSIS OF POMS?

Although guidelines have evolved over the years, the critical role of magnetic resonance imaging (MRI) has remained consistently recognized. MRI is highlighted as the most valuable tool for diagnosing POMS. It has also been generally accepted that MRI is mandatory for demonstrating dissemination in time and space.

The diagnostic criteria proposed by Krupp et al., widely used since 2013, have evolved gradually since 2004, incorporating advancements—particularly in MRI technology—along the way (28). Krupp's diagnostic criteria for POMS are presented in **Table 1**.

Table 1. Diagnostic criteria for POMS by Krupp et al.

One of the following is necessary:
Two or more non-encephalopathic CNS events: Occurring at least30 days apart Affecting more than one area of the CNS
One non-encephalopathic CNS event and MRI features, according to 2010 Revised McDonald criteria for DIS and DIT
One ADEM episode followed three or more months later by: A non-encephalopathic clinical event New MRI lesions fulfilling 2010 Revised McDonald DIS criteria

CNS central nervous system; MRI magnetic resonance imaging; DIS dissemination in space; DIT dissemination in time; ADEM acute disseminated encephalomyelitis.
Adapted from Krupp et al. (28)

The current diagnostic criteria for adult MS patients (29) can be fully applied in children older than 12 years **(Table 2)** since the 2017 McDonald criteria are being increasingly validated in children who had not presented an ADEM as the first demyelinating event (4). However, in children below the age of 12, there is a diagnostic concern to using the 2017 McDonald criteria because, in this population, there is a higher probability that the first neurological event related to MS can have a picture of ADEM. Therefore, it is of utmost importance to emphasize that in the Franch cohort, the 2017 McDonald criteria were validated, and it was demonstrated that they could also be used in children below the age of 12 who had not had an ADEM presentation (4). Thus, for children below the age of 12, after excluding ADEM patients, the 2017 McDonald criteria have acceptable sensitivity and specificity. Conversely, it is important to recognize that including ADEM patients significantly reduces sensitivity and specificity.

The diagnostic algorithm involves the integration of all typical clinical and paraclinical characteristics that form the basis of a typical clinical picture (30). The main paraclinical indicators in POMS are brain and spinal cord MRI and, additionally, CSF examination (29). Clinical and paraclinical features should confirm dissemination in space and time to establish a diagnosis, and it is also necessary to exclude all other CNS diseases of differential diagnostic importance. MRI in the pediatric population enables quick and simple confirmation of dissemination in time and space and, thus, rapid diagnosis. Characteristic predilection localizations of changes on MRI are periventricular white matter, deep white matter,

Table 2. The 2017 McDonald criteria for dissemination in space (DIS) and time (DIT)

DIS demonstration requires one or more T2 lesions in at least 2 of 4 areas of the CNS: - Periventricular - Juxtacortical/cortical - Infratentorial - Spinal cord
DIT can be defined by one of the following: - A new T2 and/or gadolinium-enhancing lesion(s) on a follow-up MRI, compared to a baseline scan, irrespective of the timing of the baseline MRI - Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time - CSF-specific oligoclonal bands

CNS central nervous system; MRI magnetic resonance imaging; CSF cerebrospinal fluid;
Adapted from Thompson et al. (29)

juxtacortical regions, corpus callosum, and infratentorial regions of the brain (brainstem and cerebellum), as well as changes in the spinal cord, optic nerve, and cortical lesions (31, 32). It must be emphasized that infratentorial and contrast-enhancing lesions at baseline MRI scans are more frequent in children than in adult-onset MS (4).

Numerous diagnostic criteria for POMS have been proposed throughout history. However, the first widely accepted official criteria emerged following the establishment of the International Multiple Sclerosis Study Group for children and adolescents (33). The majority of clinicians have relied on the criteria established by the International Study Group for Multiple Sclerosis in Children (28). It is necessary to monitor and follow the diagnostic protocol in order to make an accurate diagnosis of the disease.

Brain MRI lesions in POMS are typically small (less than 1 cm) ovoid-shaped areas with sharp borders and a homogeneous hyperintensity on T2-weighted sequences of at least 3mm in the long axis (34, 35). It is important to remember that these lesions usually appear larger because of the inflammatory edema, which is usually huge in children. Demyelinating lesions are present in both white and gray matter, especially in the cortical regions and deep gray matter (36).

Periventricular lesions are T2-hyperintense cerebral white matter lesions bordering the lateral ventricles without white matter in between, including the corpus callosum. The FLAIR sequences are the first choice for their detection because they show abnormalities even when standard T2-weighted images are normal (34, 37). It is important to emphasize that periventricular lesions are present in 86% of children with MS (38). Similarly, brainstem lesions are frequently present in 61% of POMS, significantly more often than in subjects with monophasic ADS (38). In total, infratentorial lesions are almost 25% more frequent in POMS compared to adult-onset MS (39).

Spinal cord lesions are hyperintense lesions, which show well-defined margins and are typically located in the cervical region, extending up to two vertebrae (40, 41). As already mentioned, POMS present a more elevated inflammatory component as adult-onset MS. Thus, contrast-enhancing lesions at baseline MRI scans are present at up to 70% of POMS (38). In contrast, enhancing lesions are present in only 10% of children with monophasic ADS (38).

Finally, very recently the group of experts recommended the following regarding MRI in POMS: a) The same standardized brain and spinal cord MRI protocols should be used for POMS as in adult-onset MS; b) In order to exclude non-MS diagnosis at onset, Gd-enhanced images are useful; c) For children with spinal cord manifestations or with inconclusive brain MRI, it is indicated to perform complete spinal cord MRI; d) Spinal cord MRI at baseline could be useful at baseline for all POMS; e) An innovative optic nerve MRI protocol is not recommended in POMS (42).

DIFFERENTIAL DIAGNOSIS

As already mentioned, ADS includes several CNS inflammatory conditions, such as ADEM, MS, MOGAD, and AQP4+ NMOSD. Although their clinical presentation and MRI findings may have certain similarities, it is important to mention that, for example, MOGAD is more common prepuberally than MS. Thus, presentation before the age of 11 speaks instead in favor of MOGAD, being a red flag of MS. Advancements in serological testing, recent development of cell-based assays for AQP-4 IgG and MOG-IgG have significantly improved differential diagnosis between MOGAD and AQP-4+NMOSD, and MS (43, 44).

A key consideration in the differential diagnosis of a potential POMS onset attack is acute ADEM, an inflammatory demyelinating disorder of the CNS that primarily affects children. It is characterized by polyfocal symptoms and encephalopathy, which are associated with typical MRI findings. ADEM is rare, but 0.07 to 0.9 per 100,000 children are affected by this disorder every year (19). Although it can affect people at any age, ADEM is more common in children, with a median age of onset at the age of 5 to 8. A male preponderance had been shown in most studies, with a male-to-female ratio ranging from 1:0.8 to 2.3:1 (19). In the last decade, to characterize the range of ADS, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) produced consensus clinical and radiologic diagnostic criteria defining ADEM as an ADS (Table 3) (28). A key development in recent years is the recognition of the association of MOG-IgG with ADEM, as well as with multiphasic ADEM (MDEM) and ADEM followed by recurrent optic neuritis (ADEM-ON) (Table 3) (45, 46, 47). ADEM is very rarely the first manifestation of MS or NMOSD (less than 10%) (45).

Table 3. Criteria for acute disseminated encephalomyelitis (ADEM) and relapsing disorders following ADEM

ADEM	• Single polyfocal clinical CNS event with a presumed inflammatory cause • Encephalopathy that cannot be explained by fever, with MRI which typically presents with diffuse, poorly limited, large >1–2 cm lesions predominantly involving cerebral white matter; T1 hypointense white matter lesions are very rare; deep gray matter lesions (e.g., thalamus or basal ganglia) can be present • No new symptoms, signs, or MRI findings after three months of initial presentation of ADEM
Multiphasic ADEM (MDEM)	New event of ADEM three months or more after the initial event that can be associated with new or re-emergence of prior clinical and MRI findings
ADEM-ON	At least one subsequent attack of optic neuritis, without encephalopathy, with potential other neurological manifestations at least three months after initial ADEM
ADEM-MS	ADEM is followed three months later by a non-encephalopathic clinical event with new lesions on brain MRI consistent with MS; very rare
ADEM-NMOSD	ADEM is followed three months later by ON, myelitis, or area postrema syndrome, fulfilling NMOSD diagnostic criteria, commonly AQP4-IgG negative

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; ON, optic neuritis; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; AQP4, aquaporin 4. Adapted from Pohl et al. (45).

CONCLUSION

MS is a chronic, neuroinflammatory, and neurodegenerative disease of CNS that rarely affects children in whom the onset can occur prior to the age of 18. The differential diagnosis of POMS can be broad. Thus, it may pose diagnostic dilemmas, especially at the initial presentation. Acquired demyelinating disorders, such as ADEM, NMOSD, and MOGAD, which are currently precisely defined unique disorders, continue to overlap with MS. This is due to certain similarities regarding clinical presentation and MRI. Early and accurate diagnosis is crucial, as it enables the prompt initiation of effective treatment.

Author Contributions

JD, JJ, BN, TP, and SM conceived and wrote the paper, revised it for important intellectual content, and approved the final submission.

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DILEME U DIFERENCIJALNOJ DIJAGNOZI PEDIJATRIJSKE MULTIPLE SKLEROZE

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Sažetak

Multipla skleroza (MS) je hronična, inflamatorna i neurodegenerativna bolest centralnog nervnog sistema (CNS). Obično se javlja u ranom ili srednjem odraslom dobu, a MS sa pedijatrijskim početkom (POMS), definisan prvim napadom MS koji se javlja pre 18. godine, je manje čest. Aktuelni podaci iz Danskog registra multiple skleroze pokazuju da je skoro 3% pacijenata imalo početak pre 18. godine. U poređenju sa MS kod odraslih, pacijenti sa POMS-om obično imaju aktivniji tok bolesti, što dovodi do češćih relapsa, ali sporijeg dugoročnog pogoršanja onesposobljenosti. Kod POMS-a, dijagnostičke dileme mogu uključivati razlikovanje MS od akutnog diseminovanog encefalomijelitisa (ADEM) i bolesti povezane sa antitelom na mijelina oligodendrocitni glikoprotein (MOGAD), od kojih se oba najčešće javljaju kod dece i imaju slične pojedine kliničke i radiološke karakteristike u poređenju sa MS. Nasledne leukodistrofije se takođe mogu uzeti u obzir u diferencijalnoj dijagnozi, ali samo u određenim slučajevima, jer je njihova klinička karakteristika progresivan tok bolesti, neuobičajen za druge gore navedene stečene demijelinizacione sindrome, uključujući bolesti iz spektra neuromijelitisa optika. Treba imati na umu da je magnetna rezonanca mozga i kičmene moždine ključna za postavljanje pravovremene i tačne dijagnoze POMS, nakon isključivanja alternativnih dijagnoza, što omogućava hitan početak efektivnog lečenja.

Ključne reči: multipla skleroza, dijagnoza, početak bolesti u detinjstvu

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