REVIEW ARTICLE

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Paediatric-onset multiple sclerosis (POMS) – diagnosis, treatment and psychological aspects

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Abstract

Introduction and Objective. Paediatric-onset multiple sclerosis (POMS) is a chronic, immune-mediated disease of the central nervous system that manifests before the age of 18. Although relatively rare, it poses unique diagnostic and therapeutic challenges due to differences in immune system maturity, disease presentation, and response to treatment compared to adult-onset MS.

Review Methods. The review systematically synthesizes evidence from various studies to provide a comprehensive overview of POMS, integrating findings on its etiology, diagnosis, treatment, and psychosocial impact.

Brief description of the state of knowledge. The pathogenesis of POMS involves both T and B cell dysregulation, with particular attention paid to the role of IL-17, Epstein-Barr virus infection, HLA-DRB1 phenotype, and environmental factors such as vitamin D deficiency. Diagnostic accuracy has improved through the use of the 2017 McDonald criteria, MRI imaging, cerebrospinal fluid analysis, and detection of specific antibodies. Treatment approaches range from corticosteroids for acute relapses to long-term disease-modifying therapies. First-line immunomodulatory agents, such as interferon-β and glatiramer acetate, are increasingly supplemented or replaced by modern oral medications (e.g., fingolimod, dimethyl fumarate) and monoclonal antibodies (e.g., rituximab, ocrelizumab, natalizumab). In addition to biomedical management, the disease significantly affects the psychological functioning of patients, their cognitive development, and family dynamics. A holistic, multidisciplinary approach that includes psycho-social support is essential for improving long-term outcomes and quality of life for both the children and their caregivers.

Summary. The review presents a comprehensive analysis of current knowledge on the etiology, diagnostic methods, treatment strategies, and the psycho-social impact of POMS.

Key words

POMS, multiple sclerosis, paediatric multiple sclerosis, childhood multiple sclerosis, paediatric onset multiple sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neurodegeneration. While MS predominantly affects young adults, it can also present in paediatric populations, leading to unique diagnostic and therapeutic challenges [1].

One of the most common and troublesome symptoms of MS is fatigue, defined as a significant lack of physical or mental energy that interferes with daily activities. There are four main forms of MS: Relapsing-Remitting (RRMS), Secondary Progressive (SPMS), Primary Progressive (PPMS) and Clinically Isolated Syndrome (CIS), of which the most common (about 85% of diagnoses) is the RRMS (2) While MS is predominantly diagnosed in young adults, it can also manifest in children and adolescents, a form referred to as paediatric-onset multiple sclerosis (POMS). POMS is generally defined as MS with an onset before the age of 16 or 18 years. It is estimated that approximately 3% – 5% of all MS cases begin in childhood or adolescence [2,3]

MS affects about 2.3 million people worldwide, mainly in North America, Western Europe and Asia, and usually begins in early adulthood (2). The global incidence and prevalence of POMS vary across different regions, with the incidence ranging from 0.05 – 2.85 per 100,000 children annually, while prevalence estimates range from 0.69 – 26.92 per 100,000 individuals [1].

Understanding the epidemiology and clinical features of POMS is crucial for developing effective diagnostic and therapeutic strategies tailored to this unique paediatric patient population as there are significant differences in the process of the disease and the treatment process (Tab. 1).

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Table 1. Comparison of differences in MS in adult and paediatric populations (1, 3, 4)

Characteristics	Paediatric Population	Adult Population
Beginning of the disease	10–18 years old	20–40 years old
Clinical processes	More common relapses, longer remissions periods	More common progressions in last stages of the disease
MRI of the brain	More demyelinating lesions mostly in white matter of the brain	Fewer lesions, but more extensive lesions, atrophy of the brain
Axonal Damage	Lower in first stages of the disease, faster regeneration of axons	Higher neurodegeneration, slower regeneration of axons
Reaction for Treatment	Better reaction for immunomodulatory drugs	Higher resistance to current disease treatment models

MATERIALS AND METHOD

A literature search was conducted in electronic databases, including: PubMed/MEDLINE, Scopus, Web of Science. The search included articles published in English during the period January 2020 – May 2025. Some of the articles were older due to the necessary reference to not yet outdated. knowledge. Combinations of the following key words and Medical Subject Headings (MeSH) terms were used: 'paediatric multiple sclerosis', 'childhood multiple sclerosis', 'paediatric-onset multiple sclerosis', 'POMS', 'diagnosis multiple sclerosis children', 'treatment multiple sclerosis children', 'quality of life multiple sclerosis children'. The following were included in the review: original articles, systematic reviews, meta-analyses, clinical guidelines and book chapters that focused on paediatric multiple sclerosis. The following were excluded: conference abstracts, letters to the editor and articles without available full text, studies dealing exclusively with multiple sclerosis in adults. All articles found were pre-screened based on title and abstract. The collected data were qualitatively synthesized, and finally, 87 articles were included in the review..

Etiology and risk factors of MS development. The beginning of the MS disease is usually associated with activation of auto-reactive T-cells, which cross the blood-brain barrier and are transported to the central nervous system (CNS). They are then activated by Antigen Presenting Cells (APCs) and begin to expand and secrete pro-inflammatory cytokines, proteinases, nitrogen oxide and glutamine, which lead to create lesions in CNS [4]

Legroux et al. emphasize the role of T CD4+ cells in the etiology of SM, which is connected to its excretion of IL-17, IL-6, IL-21, IL-23, IL-26, CCL20 and TNF-α (5). Comi et al. underline the role of B-cells in the etiology of MS as they present antigens to T lymphocytes, driving T-cell auto-proliferation, secrete cytokines and chemokines, such as lymphotoxin-α, TNF-α, IL-6 and GM-CSF, which enhance inflammation and produce soluble toxic factors that damage oligodendrocytes and neurons. These processes contribute to the formation of ectopic lymphoid aggregates in the cerebral meninges. They may also be a reservoir for Epstein-Barr virus (EBV) [5,6].

As the disease progresses, the blood-brain barrier becomes increasingly permeable, allowing autoreactive T and B lymphocytes, as well as other immune cells, to enter the CNS [4]. In addition to demyelination, MS causes direct damage to axons and neurons, leading to ongoing brain shrinkage and permanent neurological impairment. Neurodegenerative processes are driven by the damaging effects of pro-inflammatory cytokines, oxidative stress and mitochondrial dysfunction, all of which play a role in the development of the disease [7].

The most important risk factor of MS is the presence of HLA-DRB1. Sawcer et al. indicate that the patients with this allele have a three-times higher risk of developing MS in comparison to the healthy population [7]. The mechanism of this coincidence is not fully understood, but it is suggested that HLA-DRB1 plays a key-role in presentation of the antigens of CNS and activation of autoreactive T-Cell lymphocytes [5,7].

There is an association between the occurrence of MS and the exposure to sunlight. It was observed that populations living at higher geographical altitudes have a higher prevalence of MS, due to the production of vitamin D which plays a key-role in immune regulation. It promotes the production of anti-inflammatory cytokines and suppresses the production of pro-inflammatory cytokines [8].

EBV is considered to be one of the risk factors of MS development. The mechanism of this coincidence is connected to the latent infection of the virus. Molecular mimicry hypothesis suggests that EBV antigens can be similar to the myelin proteins that provokes the T-Cells to attack patient myelin and provoke demyelination [6].

Clinically, multiple sclerosis can progress along two paths: relapsing or progressive. Most commonly, the disease starts as the relapsing-remitting form of multiple sclerosis, characterized by discrete episodes of neurological dysfunction, followed by partial, complete, or no remission. Over time, the frequency of relapses usually decreases, but gradual deterioration often occurs, leading to continuous progression, known as secondary progressive multiple sclerosis (SPMS) [9].

DIAGNOSTIC METHODS

McDonald Criteria in paediatric MS. The McDonald criteria were established to standardize the diagnosis of multiple sclerosis (MS), and have undergone several revisions to enhance diagnostic accuracy. The 2017 revision introduced significant modifications, particularly relevant to paediatric-onset multiple sclerosis (POMS) [10]. Studies indicate that these criteria perform well in identifying paediatric patients with MS, demonstrating applicability across different age groups. A study by Fadda et al. involving children and youths with acute demyelinating syndromes, found that the 2017 criteria effectively distinguished MS from monophasic demyelination [11]. Hacohen et al. compared the 2017 criteria with earlier versions, such as the 2010 criteria, and found that the updated criteria offer increased sensitivity in diagnosing MS at baseline in paediatric patients. However, this heightened sensitivity may come with a reduction in specificity. A study demonstrated that while the 2017 criteria were more sensitive, they were less specific than the 2010 criteria in predicting conversion to clinically definite MS in children with acquired demyelinating syndromes [10].

Table 2. Features differenting MS, ADEM, MOGAD and NMO in children (22, 25–27)

Clinical feature	MS	ADEM	MOGAD	NMOSD
Age of onset	Usually teenagers, less often younger children.	More common in younger children.	More common in children; ADEM is the most common manifestation of MOGAD in children.	May occur at any age, but is less common in children.
The beginning of the disease	Gradual, symptoms build up over days to weeks.	Sudden onset with rapid progression of symptoms.	Sudden onset, often following infection or vaccination.	Sudden onset with severe symptoms.
Clinical symptoms	Multifocal neurological symptoms, without encephalopathy.	Encephalopathy, multifocal neurological symptoms.	Symptoms similar to ADEM, but often without encephalopathy.	Severe optic neuritis, longitudinal myelitis.
Course of the disease	Relapsing or progressive.	Typically single phase.	Can be monophasic or recurrent.	Usually recurrent.
Brain MRI	Multiple, well-demarcated white matter lesions, often periventricular.	Diffuse, poorly demarcated changes in the white matter.	Large, poorly demarcated white matter lesions similar to ADEM.	Changes in the periventricular, subcortical and medulla oblongata areas.
MRI of the spinal cord	Short changes covering several segments.	Changes may involve several segments.	Long shifts spanning multiple segments.	Long shifts spanning three or more segments.
Cerebrospinal fluid	Oligoclonal bands present in ~90% of cases.	Oligoclonal bands rare.	Oligoclonal bands rare; lymphocytic pleocytosis.	Oligoclonal bands rare; neutrophilic or lymphocytic pleocytosis.
Serum antibodies	No specific antibodies.	No specific antibodies.	Antibodies against MOG present.	Antibodies against aquaporin-4 (AQP4) present.

Differential diagnosis. Diagnosing multiple sclerosis (MS) in children requires careful differentiation from other demyelinating disorders, such as acute disseminated encephalomyelitis (ADEM), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and neuromyelitis optica spectrum disorder (NMOSD). Accurate diagnosis is critical for appropriate treatment and prognosis [12,13]. The major differences are presented in Table 2.

Magnetic resonance imaging (MRI) in paediatric MS diagnosis. MRI plays a crucial role in the application of the McDonald criteria for paediatric MS (14). The 2017 revision emphasizes specific MRI findings, such as the presence of periventricular lesions and 'black holes', which are instrumental in distinguishing MS from other demyelinating conditions in children. These imaging features enhance the diagnostic process and support early intervention strategies [15].

Advanced MRI sequences, such as FLAIR (Fluid-Attenuated Inversion Recovery) and T1 contrast-enhanced MRI, are particularly useful in identifying new foci of the disease and assessing inflammatory activity. The FLAIR sequence allows better visualisation of white matter lesions by eliminating the cerebrospinal fluid (CSF) signal, which facilitates the detection of subtle demyelinating lesions [14]. In particular, the presence of hypointense lesions in T1-weighted images and enhancing foci after contrast administration, significantly increases diagnostic accuracy in MS. In the context of childhood MS, it is also important to differentiate from other similar demyelinating syndromes, such as neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody spectrum disorder (MOGSD), highlighting the importance of advanced imaging techniques in the differential diagnosis [12].

Machado-Rivas et. al discussed changes in white matter microstructure in children with early-onset multiple sclerosis (POMS). Patients with POMS, compared to healthy controls, showed higher values of radial diffusion coefficient (cRD) and mean diffusion coefficient (cMD) in lesioned areas, as well as reduced fractional anisotropy factor (cFA). These changes are indicative of microstructural damage, which is more pronounced in lesions compared to healthy tissue, as well as in the entire white matter compared to healthy controls [16]. De Mol et. al focuses on the impact of genetic risk on white matter microstructure in children, which may have important implications for the early diagnosis of MS. Using magnetic resonance imaging (MRI) diffusion tensor imaging (DTI), two types of areas in the white matter were identified: 'pits' (potholes): areas of reduced fractional anisotropy (FA), indicating degenerative changes and 'hills' (molehills): areas of increased FA, suggesting increased microstructural integrity [17].

Cerebrospinal fluid analysis (CSF). This analysis is an important part of the diagnosis of multiple sclerosis (MS), both in adults and children. A study by McKay et al. found that children with MS were more likely than adults to have positive oligoclonal bands (OCB) in the PMR, indicating intrathecal production of immunoglobulin G (IgG) (18). A 2020 review article discussed the importance of microRNAs (miRNAs) in the PMR as potential biomarkers of MS. It was noted that miRNA levels in the PMR are altered in patients with MS, which may help in the diagnosis and monitoring of disease progression [19].

Bianchi et al. studied changes within the visual junction in patients with various demyelinating diseases, including MS. Although the main focus was on changes in brain structures, the study highlighted the importance of monitoring changes in the PMR, such as the presence of oligoclonal striations and inflammatory markers, in the diagnosis of MS. Analysis of these markers can provide valuable information on disease activity and help differentiate MS from other conditions of similar aetiology. In the paediatric context, monitoring of PMR lesions may be particularly important due to the differences in clinical presentation and disease course in this age group [20].

Serological markers. In the diagnosis of multiple sclerosis (MS), no specific serological markers have been identified to confirm the presence of the disease unequivocally. However, to distinguish MS from other demyelinating disorders, such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), the detection of antibodies to MOG (MOG-IgG) is important. The presence of MOG-IgG is suggestive of MOGAD, which is relevant in both adults and

Table 3. Summary of diagnostic methods in MS

Diagnostic Area	Description
2017 McDonald Criteria	MRI plays a key role in diagnosing paediatric MS. Periventricular lesions and 'black holes' are characteristic findings. Techniques such as FLAIR and contrast-enhanced MRI help assess inflammatory activity. Imaging protocols need to be adjusted to the age of the child (29,30).
Advanced MRI Techniques	Diffusion Tensor Imaging (DTI) assesses white matter microstructure. Paediatric-onset MS (POMS) shows increased radial (cRD) and mean (cMD) diffusivity and decreased fractional anisotropy (cFA). A study also found a correlation between genetic MS risk and white matter changes ('pits' and 'hills'), particularly in the corpus callosum. (32,33)
CSF – Oligoclonal Bands (OCB)	OCBs are more frequently present in children than in adults with MS, and are associated with higher disability scores (EDSS). Their detection is essential for diagnosis and prognosis in paediatric MS (34).
miRNA in CSF	Changes in miRNA levels in CSF may serve as potential biomarkers for MS diagnosis and disease monitoring. However, more research is needed. They are considered supportive markers alongside OCBs and inflammatory markers (35).
CSF in Differential Diagnosis	CSF analysis may reveal antibodies, such as anti-AQP4 and anti-MOG, assisting in the differentiation between MS and diseases like NMOSD and MOGAD. This is particularly relevant in transverse myelitis and other demyelinating conditions. (36,37)
MOG-IgG	Detection of myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) is essential to diagnose MOGAD and distinguish it from MS. This has major implications for treatment decisions, especially in children with atypical presentations (38,39).

children, influencing the choice of appropriate treatment [21].

An article published in 2021 discusses myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which can manifest in both adults and children as central nervous system demyelination. In the diagnosis of MOGAD, the detection of serum antibodies to MOG is important in distinguishing this disease from MS and other disorders, such as neuromyelitis optica spectrum disorder (NMOSD). The presence of these antibodies in the PMR can also provide information on the local inflammatory response in the central nervous system [22].

TREATMENT OF MULTIPLE SCLEROSIS IN CHILDREN

Corticosteroids. Corticosteroids play a key role in the treatment of MS relapses. Their mechanism of action involves reducing inflammation, including decreasing the release of pro-inflammatory cytokines, limiting intrathecal IgG synthesis, and stabilizing the permeability of the blood-brain barrier. Administering corticosteroids during a relapse results in a faster resolution of neurological symptoms; however, there is no evidence suggesting that steroids affect the natural course of the disease. In relapse treatment with corticosteroids, they are typically administered intravenously (methylprednisolone), while for milder relapses, they are given orally (prednisone or methylprednisolone) [23].

Intravenous immunoglobulin. Another treatment option for PMS relapses is intravenous immunoglobulin (IVIG) infusions. IVIG, with its anti-inflammatory properties, can be helpful in managing acute relapses of multiple sclerosis and in preventing new relapses. In the reported case, IVIG treatment alone, followed by its combination with interferon, significantly improved visual acuity in a child with optic neuritis. This highlights the growing role of IVIG in the treatment of multiple sclerosis [24].

Immunomodulating treatment. IFNβ and glatiramer acetate are the first medications approved by the FDA and EMA for use as a disease-modifying therapy (DMT) in MS in children. IFN acts by generating the transcription complex interferon-stimulated gene factor 3 (ISGF3). This is achieved by activating Janus kinases (JAK1) and tyrosine kinases (TYK2). IFNβ down-regulates major histocompatibility complex (MHC) class II. Moreover, it stimulates the production of interleukin 10, shifts the balance of T lymphocytes towards anti-inflammatory T-helper 2 cells, and also causes a decrease in matrix metalloproteinases (MMPs) (25). In treating MS, IFN-β-1a, IFN-β-1b and pegIFN-β1a are used [24, 25].

Skarlis et al. described a study involving 27 patients with POMS. There was a significant decrease in the number of relapses (mean ± SD: 2.0 ± 1.0 vs 1.2 ± 1.6; p = 0.002), annualized relapse rate (ARR) (mean ± SD: 1.5 ± 0.7 vs 0.4 ± 0.5; p = 0.0001), and progression in the Expanded Disability Status Scale (EDSS) (mean ± SD: 1.5 ± 0.8 vs 0.9 ± 0.7; p = 0.005) after treatment with any first-line therapy. Additionally, a significant decrease in patients with disease activity on MRI was demonstrated (59% vs 18.5%; p = 0.0020 [26].

Glatiramer acetate consists of synthetic copolymers of amino acids, such as L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. The function of the copolymers is to mimic basic myelin protein (MBP) and act as a T cell receptor antagonist. As a result, the cytokine and T cell profile changes to anti-inflammatory [27]. Clinical trials have been completed on the drug, but none have focused exclusively on paediatric patients [28, 29].

Modern oral drugs. Fingolimod is a functional antagonist of the G-protein-coupled sphingosine-1-phosphate receptors (S1PR) S1P1P1, S1P2, S1P3 and S1P4 (30). Fingolimod acts by reversibly inhibiting central memory T cells and naive T cells in lymph nodes. Therefore, it reduces the influx of autoreactive T cells into the CNS. In one randomized study, L. Krupp et al. compared the effects of fingolimod with IFN β. Fingolimod showed a significant effect ($p \leq 0.05$) on all items of the PedsQL scale, except for social functioning (fingolimod 1.30; IFN β -1.27), compared to IFN β. The percentage of patients who achieved significant clinical improvement was higher with fingolimod. Additionally, by analyzing the number of relapses over the two years before the study, a reduction was found in the number of relapses in the case of fingolimod [31].

D.L. Arnold et al. compared the same group of patients concerning MRI T2 MS lesion activity during fingolimod and IFN β. A greater reduction in lesions was also achieved in patients treated with fingolimod (62.8% relative reduction; $p<0.001$) compared with IFN β. Fingolimod and IFN β were also compared concerning brain volume reduction. A reduction in the annualised rate of brain atrophy (ARBA) was shown in patients treated with fingolimod, compared to patients treated with IFN β (−0.48% vs -0.80%) [32].

Dimethylfumarate (DMF) has immunomodulatory and neuroprotective effects. It is associated with both nuclear factor and erythroid factor 2-related factor 2 (Nrf2)-

dependent and independent molecular pathways. DMF affects the composition of immune cells in the mixture and redirects their phenotype towards an anti-inflammatory. Moreover, it is correspondingly a substance that protects axons, myelin and neurons [33].

P. Vermerch et al. in their randomized study examined the efficacy of DMF versus IFN-β-1a in the treatment of paediatric MS. The percentage of patients without new hyperintense or T2-enhancing lesions on MRI at week 96 was 16.1% (95% CI, 8.0%-27.7%) for DMF and 4.9% (95% CI, 0.6%-16.5%) for IFN-β-1a, respectively. Compared with DMF, patients treated with IFN-β-1a had 62% more hyperintense MRI lesions at week 96 (95% CI, 37.9%-76.7%; P < 0,001). Furthermore, the IFN-β-1a group had a higher relapse rate. The risk ratio for relapse for DMF vs. IFNβ-1a was 0.574 (95% CI, 0.329–1.001; P =.05), but it was not statistically significant [34].

The above-described studies related to both first-line therapy and modern oral drugs are presented in Table 4.

Table 4. Comparison of first-line therapies and modern oral drugs in MS (47, 54, 55, 57)

	Agent	Research	No. of patients	Age
First-line therapies	IFNβ	Ch. Skarlis et al. (2023)	27	up to 18
	Glatiramer acetate	NA	NA	NA
Modern oral medications	Fingolimod	L. Krupp et al. (2022) D.L. Arnold et al. (2020)	214	10-18 (median 15,3)
	Dimethyl-fumarate	P. Vermerch et al. (2022)	150	10–17 (median 15,0)

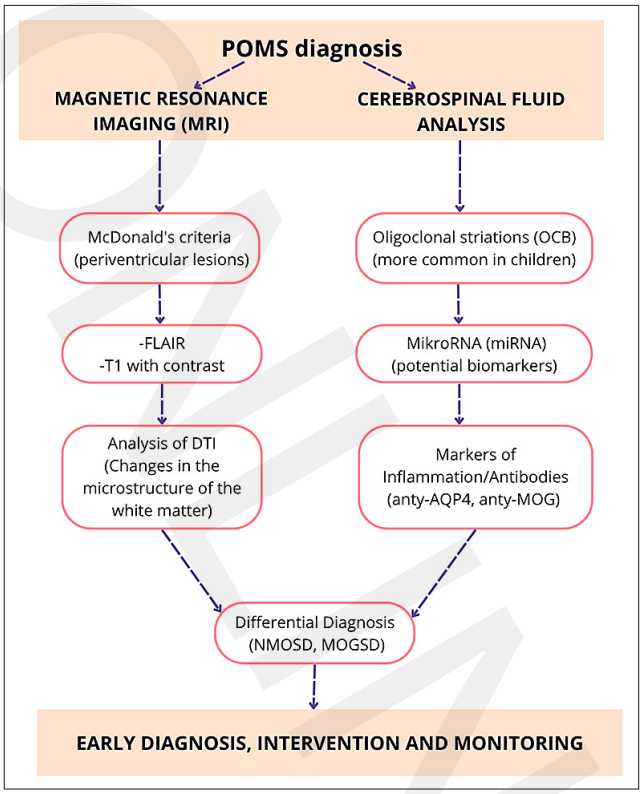

Figure 1.

TARGETED TREATMENT

Rituximab. A chimeric anti-CD20 monoclonal antibody the action of which is based on the depression of B cells and combining with CD3+ T cells that have the CD20 antigen on their surface, and are pro-inflammatory [35]. The study by M. Breu et al. included 61 patients whose median age at the first symptoms of MS was 14.9 years, and the median age at diagnosis – 15.2 years. Patients received rituximab (41 patients), IFN β (7 patients), fingolimod (3 patients), dimethyl fumarate (1 patient), and glatiramer acetate (1 patient). The median number of doses in patients receiving rituximab was 5. The most common regimen was 500 mg or 1,000 mg infusion every 6 months. One relapse occurred in 6 patients. ARR decreased from 0.60 (95% CI 0.38–0.92) to 0.03 (95% CI 0.01–0.07) during rituximab treatment. Moreover, the EDSS correspondingly decreased from 1 to 0 (p=0.027), and the rate of new T2 lesions per year decreased from 1.25 (95% CI 0.70–2.48) to 0.08 (95% CI 0.03–0.25) [36].

Daclizumab. An anti-CD25 antibody that inhibits IL-2 binding to its receptor, reducing T-cell activation. Unfortunately, due to numerous cases of fatal encephalitis, it was withdrawn from the market [40].

Alemtuzumab. A human IgG1 anti-CD52 monoclonal protein that targets B and T cells, as well as monocytes and macrophages [61]. One of the clinical case series evaluated the use of alemtuzumab in the treatment of MS in children and adolescents. Patients aged 14 and 16 years received intravenous alemtuzumab at a dose of 60 mg for 5 days, followed by a dose of 36 mg for 3 days after a year. The patients did not develop secondary autoimmunity. Moreover, there was no radiological deterioration or recurrence [37].

Ocrelizumab. A human monoclonal IgG1 anti-CD20 antibody with a mechanism of action of the antibody which is remarkably analogous to rituximab. Although approved for use in MS in adults, data on the use of ocrelizumab in children are limited [38]; however, a study investigating the safety and use of ocrelizumab in POMS is currently ongoing [39]. C. B. Amirov et al. assessed the efficacy of ocrelizumab in the treatment of relapsing-remitting MS (P-RRMS) in children. Then patients were followed for more than 12 months during the treatment. The median follow-up time was 28.3 months (min: 15 months, max: 46 months). Interestingly, the mean ARR decreased from 2.01 (±0.71) to 0 during follow-up (p < 0.0001). MRI of the patients was assessed and showed no MS activity [38].

Natalizumab. A monoclonal antibody against the α4-integrin component of cell adhesion molecules α4β1 and α4β7. These cells are involved in migration across the blood-brain barrier. Natalizumab therapy reduces ARR and MRI changes, and is well tolerated among patients [40]. A study by F. Palavra et al. included 27 patients with POMS who had a mean age of 14.8 (± 2.8) years. Patients were treated with IFNβ-1a (8 patients), IFNβ-1b (2 patients), pegIFNβ-1a (1 patient), natalizumab (4 patients), glatiramer acetate (5 patients), teriflunomide (1 patient), and fingolimod (1 patient). In 5 cases, it was decided not to undertake any treatment. 33.3% of participants (9 patients) achieved the status of No Evidence of Disease Activity-3 (NEDA-3) after 12 months from the

diagnosis of MS. The criterion of no clinical relapses was met by 21 patients. Interestingly, all patients met the criterion of no progression of neurological disability. Unfortunately, 16 patients did not meet the MRI criterion of no disease activity. All patients treated with natalizumab achieved NEDA-3 (φC = 0.742) indicating the importance of this antibody in the treatment of POMS [41].

Ofatumumab. A human monoclonal antibody that binds to a distinct loop epitope on the CD20 molecule [45]. Through complement-dependent cytotoxicity, ofatumumab induces B-cell lysis [40, 42].

A summary of biological therapies applied in paediatric SM is provided in Figure 2.

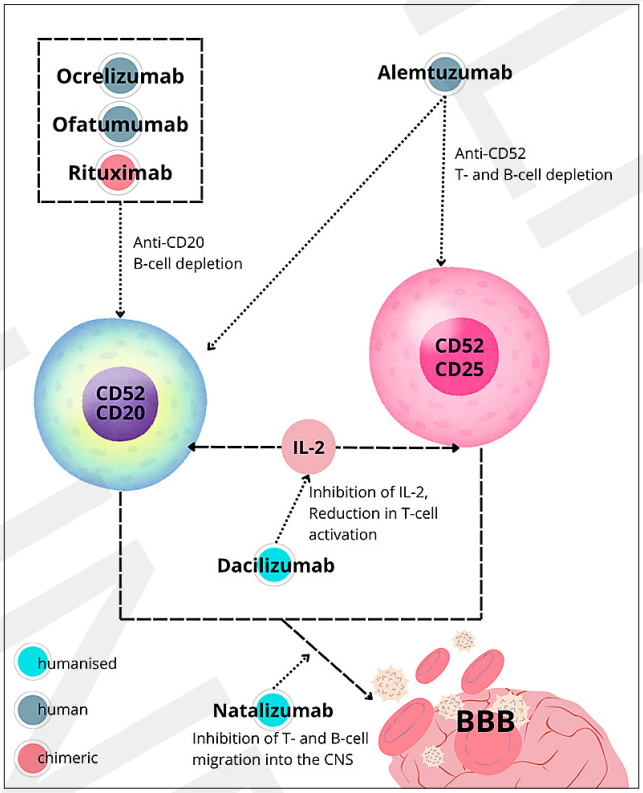

Figure 2.

IMPACT OF PMS ON THE QUALITY OF LIFE OF CHILDREN AND THEIR FAMILIES

Children with a diagnosis of multiple sclerosis (MS) are characterized by a reduced quality of life, due to the need for frequent hospitalizations, chronic treatment, and the co-occurrence of psychiatric disorders. Cognitive deficits, chronic fatigue and psychological symptoms figure clearly in the clinical picture of paediatric MS (43). Up to one-third of patients under the age of 18 may be affected. Although the most common form of the disease is the projection-remission form, psychological symptoms can be present during periods of disease remission. The consequence of these disorders is a significant reduction in daily life functioning and a deterioration in overall quality of life [44].

Therefore, in addition to symptomatic and disease-modifying treatment, a holistic and individually tailored therapeutic approach that includes psychosocial support is necessary. Cognitive dysfunction, in addition to motor disability and disease flares, can significantly affect the educational abilities and school achievement of patients. The review conducted by Slávka Mrosková et al. showed that multiple sclerosis significantly impacts the quality of life (QoL) of paediatric patients, with the greatest negative effects observed in the school and emotional domains. Findings indicate that children with multiple sclerosis have lower levels of general intelligence (IQ), with earlier age of onset correlating with more severe reductions in IQ values [45].

Patients with multiple sclerosis (MS) often have co-occurring psychiatric disorders, such as anxiety, mood disorders and depression. A study by Aloni et al. found that children with MS had significantly higher rates of clinical anxiety (78.1%) compared to healthy controls (27.3%). In addition, the percentage of patients meeting criteria for clinical depression was 43.8% in the group of children with MS, while there were no cases of depression among healthy control subjects (0%). These results underscore the significant impact of MS on children's mental state and indicate the need for comprehensive care that includes psychological and psychiatric support [46].

The diagnosis of a chronic illness in a child poses a significant challenge for both the patient and the family, negatively affecting the mental health of caregivers [43,44]. Studies have shown that the mothers of children with multiple sclerosis (MS) have a higher prevalence of somatic illnesses and mood and anxiety disorders, compared to mothers of healthy children – before, during and after diagnosis [47]. Unfortunately, available data on the impact of a child's illness on the psychological state of parents is limited. Further research in this area is needed, as the psychological and emotional support of parents plays a key role in the comprehensive care of children with multiple sclerosis. Proper support for parents can not only improve their well-being, but also have a positive impact on the course of the disease and the child's quality of life [48, 49].

DISCUSSION AND CONCLUSIONS

Multiple sclerosis (MS) is a disease primarily affecting the young adult population, therefore few studies have focused on the paediatric population affected by the disease. For that reason, the presented review attempts to summarize the available knowledge on the paediatric onset of multiple sclerosis (POMS). An important development in improving the diagnosis of POMS was the 2017 revision of the McDonald criteria, especially for children aged 11 years and older [10]. Both Thopmson et al. in their paper and the current review cite papers that support the usefulness of the McDonald criteria in the diagnosis of MS in children [9–11]. It is important to always be aware of the limitations of the McDonald criteria – including that they should not be used in children at the onset of acute disseminated encephalomyelitis [10, 14]. It is important for future studies to emphasize the role the adaptation of imaging protocols in MS to the age of the patient [30]. Studies, including by De Mol et al., suggest that even subtle microstructural changes (identified by DTI) may be associated with genetic risk, opening new perspectives in the early detection and monitoring of MS in children [17,

50]. In the paediatric population, differential diagnosis is more important than in adults. Including the differentiation with ADEM, MOGAD, NMOSD, which when combined with the use of McDonald criteria and MRI diagnosis, can significantly improve the effectiveness of the overall diagnostic process [12, 13].

Currently, there is a wide range of MS therapies for children, but the basis for treating relapses still remains GCSs [23]. The rapid anti-inflammatory effect and ability to accelerate the resolution of neurological symptoms is the main feature of GCSs, prompting their use in the therapy of MS relapses in children. However, it should be remembered that their role is limited to the treatment of symptomatic relapses, and does not affect the long-term course of the disease. Therefore, they should not be recommended for long-term therapy because of potential adverse effects associated with prolonged therapy [23, 51].

The first oral DMT in POMS was fingolimod, which was more preferable than previous therapies in terms of method of administering the drug [30]. The superior efficacy of fingolimod is be highlighted for improving the quality of life and reducing relapses (Krupp et al.), reducing lesion activity on MRI (Arnold et al.), and slowing brain atrophy (Arnold et al.) [31, 32]. Dimethyl fumarate (DMF), a drug with dual immunomodulatory and neuroprotective effects, shows better control of lesion activity on MRI, as highlighted by the results of a study by Vermerch et al. comparing DMF with IFN-β-1a [34]. The introduction of these oral drugs has changed the paradigm for the treatment of paediatric MS, offering greater efficacy, convenience of use, and potentially better adherence (no need for injection), which is particularly important in the paediatric population.

Targeted treatments, particularly monoclonal antibodies, are revolutionizing MS therapy in children, offering superior efficacy in controlling disease activity and potentially reducing disability progression. For instance, despite the lack of formal EMA/FDA approval for paediatric MS (as opposed to ocrelizumab for adults), rituximab is often used off-label and has shown strong efficacy [36]. Ocrelizumab with a mechanism analogous to rituximab is approved for adults with MS, but data for children are limited [38]. Studies on the safety and efficacy of ocrelizumab in POMS are currently in progress. Daclizumab, despite its proven efficacy, has been withdrawn from the market due to cases of fatal encephalitis [40], highlighting the continued need to monitor all POMS therapies. Alemtuzumab, while promising, is a drug that has been poorly studied in the paediatric population, and has an intensive effect profile and requires monitoring for autoimmunity. There is a need for longer studies on the safety of these potent drugs in children's developing bodies since for many of the modern drugs, data are still limited and often come from smaller case series or studies that were not designed exclusively for children. The growing number of therapeutic options challenges clinicians to optimally select a drug for a given patient, taking into account age, disease course, genetics and preferences.

In addition to symptomatic and disease-modifying treatment, a holistic and individually tailored therapeutic approach that includes psychosocial support is essential [44, 45]. Available data on the impact of a child's illness on the psychological state of the parents is limited. There is a need for further research in this area because proper psychological and emotional support for parents can not only improve their well-being, but also positively affect the course of the disease and the child's quality of life [49].

REFERENCES

1. Yan K, Balijepalli C, Desai K, Gullapalli L, Druyts E. Epidemiology of paediatric multiple sclerosis: A systematic literature review and meta-analysis. Multiple Sclerosis and Related Disorders. 2020;44.
2. Alroughani R, Boyko A. Paediatric multiple sclerosis: a review. BMC Neurol. 2018;18:27.
3. Brola W, Steinborn B. Paediatric multiple sclerosis – current status of epidemiology, diagnosis and treatment. Neurol Neurochir Pol. 2020;54(6):508–17.
4. Comi G, Bar-Or A, Lassmann H, Uccelli A, Hartung HP, Montalban X, et al. The role of B cells in Multiple Sclerosis and related disorders. Ann Neurol. 2021;89(1):13–23.
5. Palle P, Monaghan KL, Milne SM, Wan ECK. Cytokine Signaling in Multiple Sclerosis and Its Therapeutic Applications. Med Sci (Basel). 2017;5(4):23.
6. Ruprecht K. The role of Epstein-Barr virus in the etiology of multiple sclerosis: a current review. Expert Rev Clin Immunol. 2020;16(12):1143–57.
7. Mey GM, Mahajan KR, DeSilva TM. Neurodegeneration in multiple sclerosis. WIREs Mech Dis. 2023;15(1):e1583.
8. Balasooriya NN, Elliott TM, Neale RE, Vasquez P, Comans T, Gordon LG. The association between vitamin D deficiency and multiple sclerosis: an updated systematic review and meta-analysis. Multiple Sclerosis and Related Disorders. 2024;90:105804.
9. Li EC, Zheng Y, Cai MT, Lai QL, Fang GL, Du BQ, et al. Seizures and epilepsy in multiple sclerosis, aquaporin 4 antibody-positive neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein antibody-associated disease. Epilepsia. 2022;63(9):2173–91.
10. Hacohen Y, Brownlee W, Mankad K, Chong WK 'Kling', Thompson A, Lim M, et al. Improved performance of the 2017 McDonald criteria for diagnosis of multiple sclerosis in children in a real-life cohort. Mult Scler. 2020;26(11):1372–80.
11. Fadda G, Brown RA, Longoni G, Castro DA, O'Mahony J, Verhey LH, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. Lancet Child Adolesc Health. 2018;2(3):191–204.
12. Shahriari M, Sotirchos ES, Newsome SD, Yousem DM. MOGAD: How It Differs From and Resembles Other Neuroinflammatory Disorders. AJR Am J Roentgenol. 2021;216(4):1031–9.
13. Wei S, Xu L, Zhou D, Wang T, Liu K, Gao F, et al. Differentiation of MOGAD in ADEM-like presentation children based on FLAIR MRI features. Mult Scler Relat Disord. 2023;70:104496.
14. Wong YYM, de Mol CL, van der Vuurst de Vries RM, van Pelt ED, Ketelslegers IA, Catsman-Berrevoets CE, et al. Real-world validation of the 2017 McDonald criteria for paediatric MS. Neurol Neuroimmunol Neuroinflamm. 2019;6(2):e528.
15. Wattjes MP, Ciccarelli O, Reich DS, Banwell B, de Stefano N, Enzinger C, et al. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. 2021;20(8):653–70.
16. Machado-Rivas F, Jaimes C, Scherrer B, Benson LA, Gorman MP, Warfield SK, et al. Evaluation of white matter microstructure in paediatric onset multiple sclerosis with diffusion compartment imaging. J Neuroimaging. 2022;32(6):1098–108.
17. de Mol CL, Neuteboom RF, Jansen PR, White T. White matter microstructural differences in children and genetic risk for multiple sclerosis: A population-based study. Mult Scler. 2022;28(5):730–41.
18. McKay KA, Wickström R, Hillert J, Karrenbauer VD. Cerebrospinal fluid markers in incident paediatric-onset multiple sclerosis: a nationwide study. Sci Rep. 2021;11(1):18528.
19. Martinez B, Peplow PV. MicroRNAs in blood and cerebrospinal fluid as diagnostic biomarkers of multiple sclerosis and to monitor disease progression. Neural Regen Res. 2020;15(4):606–19.
20. Bianchi A, Cortese R, Prados F, Tur C, Kanber B, Yiannakas MC, et al. Optic chiasm involvement in multiple sclerosis, aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein-associated disease. Mult Scler. 2024;30(6):674–86.
21. Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated

disease: International MOGAD Panel proposed criteria. Lancet Neurol. 2023;22(3):268–82.
22. Marignier R, Hacohen Y, Cobo-Calvo A, Pröbstel AK, Aktas O, Alexopoulos H, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. Lancet Neurol. 2021;20(9):762–72.
23. Lattanzi S, Cagnetti C, Danni M, Provinciali L, Silvestrini M. Oral and intravenous steroids for multiple sclerosis relapse: a systematic review and meta-analysis. J Neurol. 2017;264(8):1697–704.
24. Mavridi A, Bompou ME, Redmond A, Archontakis-Barakakis P, Vavougios GD, Mitsikostas DD, et al. Current and Emerging Treatment Options in Paediatric Onset Multiple Sclerosis. Sclerosis. 2024;2(2):88–107.
25. Xavier A, Campagna MP, Maltby VE, Kilpatrick T, Taylor BV, Butzkueven H, et al. Interferon beta treatment is a potent and targeted epigenetic modifier in multiple sclerosis. Front Immunol. 2023;14:1162796.
26. Skarlis C, Markoglou N, Gontika M, Bougea A, Katsavos S, Artemiadis A, et al. First-line disease modifying treatments in paediatric-onset multiple sclerosis in Greece: therapy initiation at more advanced age is the main cause of treatment failure, in a retrospective observational study, with a cohort from a single Multiple Sclerosis Center. Neurol Sci. 2023;44(2):693–701.
27. Kasindi A, Fuchs DT, Koronyo Y, Rentsendorj A, Black KL, Koronyo-Hamaoui M. Glatiramer Acetate Immunomodulation: Evidence of Neuroprotection and Cognitive Preservation. Cells. 2022;11(9):1578.
28. Teva Takeda Pharma Ltd. Copaxone Subcutaneous Injection Syringe Special Drug Use-Result Investigation (All-Case Investigation) 'Prevention of Relapse of Multiple Sclerosis'. clinicaltrials.gov. 2024. Report No.: NCT03209479.
29. IMPULS Endowment Fund. Czech Pharmaco-epidemiological Real World Data Study Focused on Effectiveness of Different Disease Modifying Drugs. clinicaltrials.gov. 2023. Report No.: NCT05762003.
30. Yang T, Tian X, Chen CY, Ma LY, Zhou S, Li M, et al. The efficacy and safety of fingolimod in patients with relapsing multiple sclerosis: A meta-analysis. Br J Clin Pharmacol. 2020;86(4):637–45.
31. Krupp L, Banwell B, Chitnis T, Deiva K, Gaertner J, Ghezzi A, et al. Effect of fingolimod on health-related quality of life in paediatric patients with multiple sclerosis: results from the phase 3 PARADIGMS Study. BMJ Neurol Open. 2022;4(1):e000215.
32. Arnold DL, Banwell B, Bar-Or A, Ghezzi A, Greenberg BM, Waubant E, et al. Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIGMS study. J Neurol Neurosurg Psychiatry. 2020;91(5):483–92.
33. Højsgaard Chow H, Talbot J, Lundell H, Marstrand L, Gøbel Madsen C, Bach Søndergaard H, et al. Dimethyl fumarate treatment of primary progressive multiple sclerosis: results of an open-label extension study. Mult Scler Relat Disord. 2023;70:104458.
34. Vermersch P, Scaramozza M, Levin S, Alroughani R, Deiva K, Pozzilli C, et al. Effect of Dimethyl Fumarate vs Interferon β-1a in Patients With Paediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA Netw Open. 2022;5(9):e2230439.
35. Filippini G, Kruja J, Del Giovane C. Rituximab for people with multiple sclerosis. Cochrane Database Syst Rev. 2021;11(11):CD013874.
36. Breu M, Sandesjö F, Milos RI, Svoboda J, Salzer J, Schneider L, et al. Rituximab treatment in paediatric-onset multiple sclerosis. European Journal of Neurology. 2024;31(5):e16228.
37. Riera R, Torloni MR, Martimbianco ALC, Pacheco RL. Alemtuzumab for multiple sclerosis. Cochrane Database Syst Rev. 2023;6(6):CD011203.
38. Bibinoğlu Amirov C, Saltık S, Yalçınkaya C, Tütüncü M, Saip S, Siva A, et al. Ocrelizumab in paediatric multiple sclerosis. European Journal of Paediatric Neurology. 2023;43:1–5.
39. Mar S, Valeriani M, Steinborn B, Schreiner T, Waubant E, Filippi M, et al. Ocrelizumab dose selection for treatment of paediatric relapsing–remitting multiple sclerosis: results of the OPERETTA I study. J Neurol. 2025;272(2):137.
40. Samjoo IA, Drudge C, Walsh S, Tiwari S, Brennan R, Boer I, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J Comp Eff Res. 2023;12(7):e230016.
41. Palavra F, Silva D, Fernandes C, Faustino R, Vasconcelos M, Pereira C, et al. Clinical predictors of NEDA-3 one year after diagnosis of paediatric multiple sclerosis: an exploratory single-center study. Front Neurosci. 2023;17.
42. Hauser SL, Cross AH, Winthrop K, Wiendl H, Nicholas J, Meuth SG, et al. Safety experience with continued exposure to ofatumumab in patients with relapsing forms of multiple sclerosis for up to 3.5 years. Mult Scler. 2022;28(10):1576–90.
43. Tarantino S, Proietti Checchi M, Papetti L, Monte G, Ferilli MAN, Valeriani M. Neuropsychological performances, quality of life, and psychological issues in paediatric onset multiple sclerosis: a narrative review. Neurol Sci. 2024;45(5):1913–30.
44. Ghai S, Kasilingam E, Lanzillo R, Malenica M, van Pesch V, Burke NC, et al. Needs and Experiences of Children and Adolescents with Paediatric Multiple Sclerosis and Their Caregivers: A Systematic Review. Children (Basel). 2021;8(6):445.
45. Mrosková S, Klímová E, Majerníková Ľ, Tkáčová Ľ. Quality of Life of Children and Adolescents with Multiple Sclerosis – A Literature Review of the Quantitative Evidence. Int J Environ Res Public Health. 2021;18(16):8645.
46. Aloni R, Asher G, Ben-Ari A, Menascu S. Unveiling the Psychological Consequences of Illness Perception in Paediatric Multiple Sclerosis: A Parent-Child Study. Children (Basel). 2024;11(8):929.
47. Tarantino S, Proietti Checchi M, Papetti L, Monte G, Ferilli MAN, Valeriani M. Parental Experiences in Paediatric Multiple Sclerosis: Insights from Quantitative Research. Children (Basel). 2024;11(1):71.
48. Kaplan SH, Shaughnessy M, Fortier MA, Vivero-Montemayor M, Masague SG, Hayes D, et al. The role of parental health and distress in assessing children's health status. Qual Life Res. 2022;31(12):3403–12.
49. O'Mahony J, Marrie RA, Laporte A, Brown A. Addressing Health-Related Quality of Life Among Children With Multiple Sclerosis. Int J MS Care. 2023;25(1):35–42.
50. Ehtesham N, Rafie MZ, Mosallaei M. The global prevalence of familial multiple sclerosis: an updated systematic review and meta-analysis. BMC Neurol. 2021;21:246.
51. Cahyadi M, Mesinovic J, Chim ST, Ebeling P, Zengin A, Grech L. Medication and bone health in multiple sclerosis: A systematic review and meta-analysis. J Manag Care Spec Pharm. 2023;29(12):1331–53.