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Paediatric multiple sclerosis — current diagnosis and treatment

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system that mostly affects younger adults. However, the first symptoms of MS can appear in children and adolescents before the age of 18, and we call this paediatric MS (PMS).

It is estimated that paediatric MS accounts for 3-5% of the general population of patients with MS. Despite the fundamental similarities to adult MS, PMS has many distinctive features. Paediatric MS has a milder course compared to adults, but leads to significant disability at an early age. PMS is relapsing-remitting in 95-98% of cases; the primary progressive manifestation is much less common than in adults. The differential diagnosis of MS in children should include other childhood demyelinating diseases, mitochondrial and metabolic diseases, connective tissue diseases, and neuroborreliosis. Differentiating acute disseminated encephalomyelitis (ADEM) from the first onset of MS remains the biggest challenge. Over the past 10 years, understanding of the epidemiology, pathophysiology, diagnosis, and treatment of MS in children has significantly expanded. The diagnostic criteria leading to earlier diagnosis and initiation of disease-modifying therapy (DMT) have changed, and the number of drugs used in children has increased. However, many important issues require further research. This review discusses the current state of knowledge regarding the epidemiology, diagnosis, and treatment of multiple sclerosis in children.

Key words: multiple sclerosis, development age, epidemiology, diagnosis, treatment

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Introduction

Multiple sclerosis is a disease primarily affecting adults, with the first symptoms usually appearing in the third or fourth decades of life. However, paediatric MS is being diagnosed more and more often. It is defined as multiple sclerosis with onset before the age of 18 (sometimes before the age of 16) [1, 2]. This disorder was previously known as early onset MS (EOMS), paediatric onset MS (POMS), or juvenile MS.

It is estimated that paediatric MS accounts for 3-5% of the general population of patients with MS. Despite the fundamental similarities to adult MS, PMS has many distinctive features, and the course of the disease is different to that in adults [4]. There have been far fewer studies, natural history data, and reports regarding the diagnosis and treatment of PMS. The establishment of the International Paediatric MS Study Group (IPMSSG) in 2005 brought about significant development of research and expanded knowledge about PMS [5]. Over the past 15 years, international and collaborative studies have identified an increasing number of genetic and environmental risk factors for paediatric MS. Identifying these factors has helped to better understand the pathophysiology of PMS and may contribute to treatment progress.

Over the years, the diagnostic criteria have changed several times, new drugs have been introduced, and the methods of differential diagnosis have improved [6–9].

This review presents the current state of knowledge regarding pathogenesis, epidemiology and course of the disease, and discusses the criteria for diagnosis and differential diagnosis as well as treatment of multiple sclerosis in children.

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Epidemiology

MS is a rare disease in the paediatric population. The prevalence and incidence of paediatric MS is not fully known. In a systematic review covering the period 1965 to 2018, 19 population MS studies were identified, which included 1,439 people aged ≤ 19 [10]. Incidence of multiple sclerosis in children ranged from 0.05 to 2.85 per 100,000 children per year, with most studies showing incidences of < 1 per 100,000, while prevalence ranged from 0.7 to 26.9 per 100,000 children [10]. Prevalence is highest in children aged 13 to 16 [3]. This wide range of incidence and prevalence rates can be a consequence of applying different diagnostic criteria and adopting different age limits among the examined paediatric cohorts from 15 to 18 years of age. Studies have shown that disease onset during the paediatric period occurs in 3-5% of individuals with multiple sclerosis [11–13].

In the paediatric population before adolescence, the number of sick girls and boys is relatively equivalent [14, 15]. In adolescents > 10 years of age, a more pronounced female dominance is observed. Given that the female to male ratio increases to 2-3:1, this suggests that the onset of menstruation may play a role in the pathogenesis of multiple sclerosis [14]. Prepubertal MS is a rare diagnosis, comprising less than 1% of all cases [13]. To date, no epidemiological studies have been conducted in Poland to cover the child population of MS.

Genetic and environmental risk factors for the development of paediatric MS

Children who develop MS are influenced by the same genetic and environmental risk factors that support the development of MS in adults. This suggests that childhood MS is the same disease as MS in adults. Studies on monozygotic twins show a 25% match for the development of MS. The risk ratio for dizygotic twins is similar to that of first-degree relatives: 2-5% [16–18]. Certain immunologic human leukocyte antigen (HLA) genes are associated with an increased risk of the development of MS, including haplotypes HLA -DRB1 * 1501, DQA1 * 0102, and DQB1 * 0602 [18]. The HLA-DR15 haplotype has been strongly associated with early disease onset in the MS population [17]. In addition to genetic factors, environmental factors contribute significantly to the increased risk of developing MS in children. Widely recognised factors include a previously recognised infection with Epstein-Barr Virus (EBV) as well as exposure to cigarette smoke. A history of EBV infection is associated with a 2-4-fold increase in the risk of MS in both adults and children [19–21]. With increased identification of genetic and environmental risk factors, additional studies can be done to determine combined risk. For example, in a cohort of children presenting with an initial acquired demyelinating syndrome, more than half of the study participants (57%) with the presence of HLA-DRB1 * 1501 allele, remote EBV infection, and low vitamin D were ultimately confirmed as having MS [19].

The role of vitamin D deficiency in PMS is not entirely clear, but it has been documented that low levels of vitamin D are associated with an increased susceptibility to PMS [19]. Lower vitamin D levels are also associated with a higher rate of relapse in children [20]. The increased risk of multiple sclerosis in smokers has also been confirmed, and the greater the cumulative dose (i.e. the duration and number of cigarettes smoked) the greater the risk [22]. Parental smoking and passive exposure to smoke are associated with a doubled risk of MS in children [23]. Female obesity at the age of 18 is another risk factor known to double the risk of MS. An association between obesity and an increased risk of the failure of multiple sclerosis treatment in girls has also been demonstrated [25]. To date, no clear relationship has been found between diet and the risk of MS, and the effect of table salt on the occurrence of MS has not been confirmed [26]. There is limited evidence suggesting that childhood head trauma is also a risk factor of MS [27].

Symptoms and clinical course

The symptoms of multiple sclerosis in older children and adults are similar. However, if the disease begins before the age of 10, the course differs from that in adults. Sometimes the onset of the disease is acute or subacute (with consciousness disorders and fever), often with partial seizures [4, 28]. The first symptoms are predominantly sensory disturbances, impaired coordination of movements (such as walking). After some time, cognitive and emotional disorders can occur, such as excessive irritability and emotional lability [29].

Younger children will often show multifocal symptoms, but with adolescence it becomes more common to reveal a single focal symptom, similarly to adults [4]. The most commonly reported symptoms in children include sensory (15–30%), motor (30%), and brainstem dysfunction (25–41%) [30]. Children of prepubertal age are more likely to show polysymptomatic attacks and more prominent motor and brainstem involvement (diplopia, facial weakness), sphincter dysfunction, and cognitive disturbances [15]. Diagnosis is often delayed because children are less able to express subtle symptoms such as paraesthesia or unilateral visual impairment [31].

Patients with paediatric MS have a greater accumulation of new magnetic resonance imaging (MRI) lesions [32], an earlier age of reaching disability milestones [4], and greater long-term cognitive impairment [33] compared to adult-onset MS.

The course of multiple sclerosis in children is typical for relapsing-remitting forms, although a shorter interval between the initial and subsequent relapses is observed, as well as a higher relapse rate compared to MS in adults [34, 35]. About 40% of children experience a second episode of demyelination within a year of the first presentation, 60% within two years, and 66% within three years [31]. Despite the higher rate of relapses,

in the initial period of the disease there is usually a complete remission of symptoms [4]. This is due to the high plasticity of the central nervous system in children, the possibility of development, and regeneration of brain damage.

The average time to reach 4 points on the EDSS scale is definitely longer in developmental age (20 *vs* 10 years in adults) [36]. However, over the years, children with MS entering adulthood are often permanently disabled. Although the time to reach the threshold of irreversible damage of motor neurons causing disability is about 10 years longer in children and adolescents with MS than in adults with MS, disability occurs at a younger age than in adults with MS [4, 37].

The clinical course in 95-98% of paediatric MS patients is relapsing-remitting, compared to 85-90% in adults [3, 4, 30]. Less than 3% of paediatric MS cases are reported as primary progressive, compared to 10-15% in the adult population [4, 38]. Because primary progressive MS (PPMS) is rare in children, leukodystrophy, inborn error of metabolism, mitochondrial diseases, and neuromyelitis optica can be misdiagnosed. MS should be ruled out in every child with continuous disability without specific attacks [7].

Diagnosis

MS is historically defined as neurological symptoms disseminated in time (DIT) and space (DIS). The diagnostic criteria for MS in adults have been refined over time [39–42]. The current McDonald criteria display a high sensitivity and specificity for the diagnosis of paediatric MS when applied to children ≥ 11 years of age without features suggestive of ADEM [9, 43].

Diagnosis of multiple sclerosis in children begins with the diagnosis of CIS (clinically isolated syndrome) or sporadic ADEM (acute disseminated encephalomyelitis). When first-line clinical symptoms persist for more than 24 hours, with no evidence of encephalopathy, but with possible inflammatory demyelination, CIS is diagnosed. To confirm the diagnosis, it is necessary to confirm at least two clinical episodes due to demyelination at least 30 days apart.

The diagnosis of PMS is always a challenge, especially before puberty. Reasons include the atypical clinical picture and the results of laboratory and imaging tests, as well as a wide spectrum of diseases occurring in this age group, which should be taken into account in differential diagnosis. In the case of diffuse changes in white matter in children, it is necessary to perform a basic test panel, which includes [44]:

- Cerebrospinal fluid (CSF): Oligoclonal bands (OCBs), IgG index, cell count, protein, glucose, HSV, Lyme Disease
- Serum: Complete blood cell (CBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein, NMO antibodies (in cases of optic neuritis and/or longitudinally extensive transverse myelitis), antinuclear panel (including SSA, SSB), thyroid-stimulating hormone, vitamin B12
- Imaging: Brain and cervical spine MRI with and without gadolinium
- Other: Ophthalmology (if optic neuritis)
- Neuroimaging plays an essential role in the diagnosis and monitoring of paediatric MS [32, 45, 46]. The presence of one or more T2 hyperintense lesions typical of multiple sclerosis in at least two of the following regions of the CNS: periventricular, cortical or juxtacortical, infratentorial or spinal cord, indicates dissemination in space (DIS). The simultaneous presence of enhancing and non-enhancing lesions at any time, or the presence of new or enlarging hyperintense lesions in the MRI image, indicate dissemination in time (DIT), which is also used in the monitoring of the disease course [45,46]. Compared to adults, children tend to demonstrate more T2 lesions, with the number of lesions increasing rapidly in the first few years of the disease (Fig. 1 and Fig. 2). IPMSSG recommends an MRI scan every six months to monitor the progression of the disease and the growth of new lesions [33].

A diagnosis of paediatric MS must meet the diagnostic criteria proposed by the International Paediatric MS Study Group (IPMSSG) [5, 43]. For the diagnosis of paediatric MS and other acute demyelinating diseases, certain conditions have to be met (Tab. 1):

Differential diagnosis

Differential diagnosis of central nervous system demyelination in children is a real challenge. This includes acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), optic neuritis, transverse myelitis, neuromyelitis optica (NMO), and various infectious and metabolic and

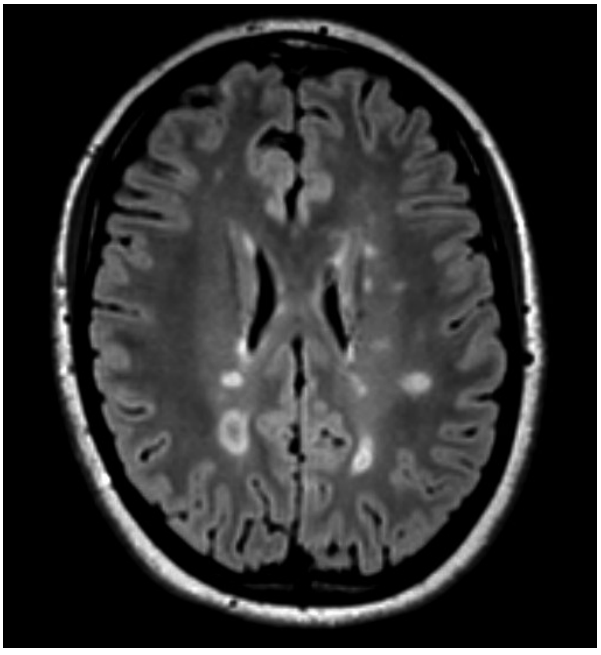

Figure 1. Brain MRI showing multiple gadolinium-enhancing periventricular and juxtacortical lesions

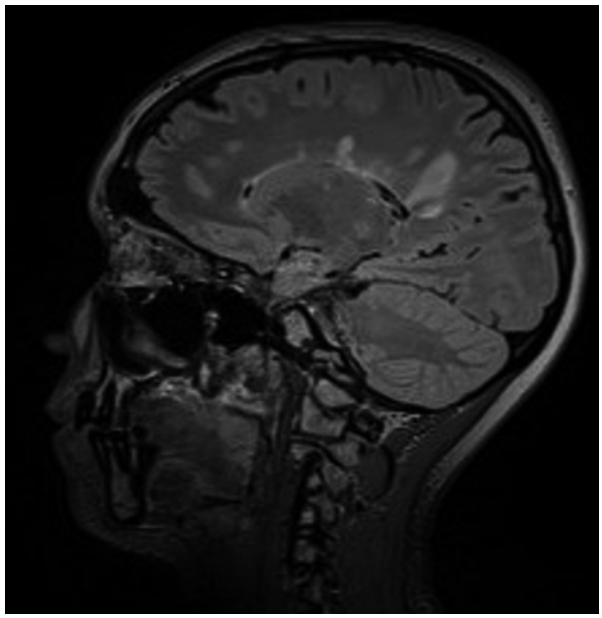

Figure 2. Brain MRI T2 FLAIR sagittal image with demyelinating plaques arranged perpendicular to the corpus callosum showing the typical Dawson fingers

rheumatological conditions [7, 47]. It is believed that most of these conditions result from the dysregulation of the immune system caused by an infectious agent in a genetically susceptible person [47]. In the presence of symptoms of focal damage to the central nervous system in a child with simultaneous changes in white matter, the broadest possible differential diagnosis should be carried out to clarify the cause. The diagnosis of MS requires confirmation of dissemination of the demyelinating process in time and space as well as the exclusion of other diseases and syndromes [7, 44]. Attention should be paid to unusual symptoms, which include fever, encephalopathy, severe psychosis, progressive course of the disease, refractory epileptic seizures, involvement of other systems (including the peripheral nervous system), lack of oligoclonal bands, and significantly increased leukocyte counts in the cerebrospinal fluid [47].

The more the unusual features found, and the younger the child is, the more carefully the diagnosis of multiple sclerosis should be considered.

Detailed neurological history and evaluation, results of laboratory tests of serum and cerebrospinal fluid, as well as neuroimaging tests, can provide data allowing for the differentiation of acute demyelinating diseases of the central nervous system from other disease entities [44, 48].

Differentiating between PMS and ADEM is particularly difficult [49–51]. Errors in the diagnosis of ADEM in patients with MS may affect up to 27% of cases [48]. According to the definition, apart from encephalopathy, ADEM features headaches, meningitis symptoms, convulsions and multifocal, defective neurological symptoms [48]. In 50-70% of cases, ADEM is preceded by an infection or vaccination. It most often affects children between the ages of 5 and 8, and rarely occurs in adulthood when the peripheral nervous system is more often affected in the form of acute polyradiculoneuropathy. In cerebrospinal fluid, lymphocytic pleocytosis, increased protein concentration, and transiently appearing oligoclonal bands are found.

In MRI study, the lesions are diffuse, less demarcated, asymmetrically involving white and grey matter, more often in the area of basal ganglia [51, 52]. Contrast enhancing lesions are described in 30-100% of cases depending on the stage of the disease, and can cover the entire focus or an irregular part of it [49, 53]. The course of ADEM as an immune disease is usually monophasic and the symptoms tend to disappear spontaneously within 1-6 months [53].

MOG antibody disease (MOG, myelin oligodendrocytes glycoprotein), only identified in recent years, is another disease that causes great difficulties in the differential diagnosis of paediatric MS [7, 54, 55]. MOG-AD is an inflammatory demyelinating disease of the CNS characterised by a monophasic or relapsing course, which does not meet the typical criteria for MS and occurs in the presence of MOG antibodies detected in the blood serum. MOG antibodies have been identified in a range of acquired demyelinating syndromes in the paediatric population, including in acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM) [49, 54]. The median age of onset is 30, but the disease also manifests itself in children; there is a slight predominance in females. Identifying MOG antibodies is helpful in the differential diagnosis of multiple sclerosis with ADEM. 30-40% of paediatric patients suffering from inflammatory demyelinating conditions of the CNS produce intermittent anti-MOG autoantibodies, the decrease of which is associated with a more favourable prognosis for ADEM patients [54, 55].

The diagnostic criteria developed by IPMSSG (Tab. 1) help in the differential diagnosis of MS and other demyelinating diseases in children. Other diseases and syndromes requiring differentiation from childhood MS are listed in Table 2.

Treatment of paediatric MS

Treatment of relapse

Treatment of MS relapse in children is similar to that in adults. Intravenous (IV) pulse of methylprednisolone (20–30 mg / kg / day for 3–5 days) is a typical regimen [56, 57]. No further glucocorticoid is needed if patients recover completely. However, oral prednisolone starting with 1 mg/kg/day and decreasing by 5 mg every two days is used for patients with residual disability [57]. For patients who experience recurrence during glucocorticoid tapering, repeated treatment with IV methylprednisolone at the same doses is suggested [57]. Intravenous immunoglobulin infusions are only recommended if treatment with methylprednisolone fails [56]. The recommended dose is 0.2–0.4 g / kg for 2–5 days. Therapeutic

Table 1. Diagnostic criteria for paediatric MS and other immune-mediated CNS demyelinating disorders [3, 42]

For a diagnosis of paediatric CIS, all of the following criteria are required to be met

- A monofocal or polyfocal clinical CNS event with presumed inflammatory demyelinating cause
- Absence of a prior clinical history of CNS demyelinating disease (e.g. absence of past optic neuritis (ON), transverse myelitis (TM) and hemispheric or brain-stem related syndromes)
- No encephalopathy (i.e. no alteration in consciousness or behaviour) that cannot be explained by fever
- A diagnosis of MS based on baseline MRI features (as recently defined) are not met

For paediatric MS, one of the following criteria is required to be met

- Two or more CIS separated by more than 30 days involving more than one area of CNS
- One CIS associated with MRI findings consistent with the 2017 McDonald criteria for dissemination in space (DIS) and in which a follow-up MRI shows at least one new enhancing or nonenhancing lesion consistent with criteria for dissemination in time (DIT)
- One ADEM attack followed by one CIS, three or more months after symptom onset, that is associated with new MRI lesions that fulfill the 2017 revised McDonald DIS criteria
- A first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2017 McDonald criteria for dissemination in space and dissemination in time (applies only to children ≥ 11 years old)

For paediatric NMO, all of the following criteria are required to be met

- Optic neuritis
- Acute myelitis
- At least two of these three supportive criteria:
    * contiguous spinal cord MRI lesion extending over three vertebral segments
    * brain MRI not meeting diagnostic criteria for MS
    * aquaporin IgG seropositive status

For paediatric ADEM, all of the following criteria are required to be met

- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after onset
- Brain MRI is abnormal during the acute (three-month) phase
- Typically on a brain MRI:
    *diffuse, poorly demarcated, large (> 1–2 cm) lesions involving predominantly cerebral white matter;
    * deep grey matter lesions (e.g. thalamus or basal ganglia) may be present
    *T1-hypointense lesions in the white matter are rare

Table 2. Differential diagnosis of paediatric multiple sclerosis

Demyelinating	Clinically isolated syndrome, ADEM, optic neuritis, transverse myelitis, NMO, postvaccination, acute necrotising encephalopathy
Inflammatory	Systemic lupus erythematosus (SLE), neurosarcoidosis, Sjögren syndrome, antiphospholipid antibody syndrome (APLAS), Behçet Disease, isolated angiitis
Mitochondrial	Myoclonic epilepsy with ragged red fibres (MERRF), mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS), Leber hereditary optic neuropathy (LHON), Leigh syndrome, Kearns-Sayre syndrome
Leukodystrophy	Metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe Disease, Pelizaeus-Merzbacher Disease, Refsum Disease, vanishing white matter, leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate levels, Wilson's Disease, Fabry Disease, Alexander Disease
Genetic/metabolic	Inborn errors of metabolism, aminoacidurias
Infectious	Neuroborreliosis (Lyme Disease), HSV encephalitis, HIV infection, neurocysticercosis, poststreptococcal infection, abscess, neurosyphilis, progressive multifocal leukoencephalopathy (PML), Whipple Disease
Vascular	Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Moyamoya Disease, carotid dissection
Endocrine	Thyroid disorder, diabetes mellitus
Nutritional	Vitamin B12, vitamin E, or folate deficiency; coeliac disease
Neoplastic	Lymphoma, astrocytoma, medulloblastoma, metastases
Toxic	Radiation, chemotherapy (methotrexate, cyclosporine, cytosine-arabinoside), extrapontine myelinosis
Other	Langerhans cell histiocytosis, haemophagocytic lymphohistiocytosis

Table 3. Ongoing clinical trials of disease-modifying therapies in paediatric-onset multiple sclerosis [62]

Study trial/NCT	Drug	Brief title	Primary endpoint	Status
CONNECT NCT02283853	Dimethyl fumarate	Phase 3 efficacy and safety study of bg00012 in paediatric subjects with relapsing-remitting multiple sclerosis (RRMS)	% Free of new / enlarging T2 foci	Enrolment complete
TERIKIDS NCT02201108	Teriflunomide	Efficacy, safety and pharmacokinetics of teriflunomide in paediatric patients with relapsing forms of multiple sclerosis	Time to first relapse	Enrolment complete
LemKids NCT03368664	Alemtuzumab	Efficacy, safety, and tolerability of alemtuzumab in paediatric patients with RRMS with disease activity on prior DMT	New or enlarging T2-bright foci	Enrolment ongoing
NCT04075266	Ocrelizumab	Study of ocrelizumab in children and adolescents with relapsing-remitting multiple sclerosis	Serum concentration of ocrelizumab and Levels of CD19+ B-cell count in blood	Enrolment ongoing
NCT03958877	Peginterferon Beta-1a	Safety, tolerability, and efficacy of BIIB017 (Peginterferon Beta-1a) in paediatric participants for treatment of relapsing-remitting multiple sclerosis	Annualised relapse rate (ARR) at week 96	Enrolment ongoing
NCT03870763	Dimethyl fumarate and Peginterferon Beta-1a	Efficacy and safety of dimethyl fumarate (Tecfidera) and Peginterferon Beta-1a (Plegridy) for treatment of relapsing-remitting multiple sclerosis in paediatric participants	Time to first relapse	Enrolment ongoing
PASSAGE NCT01442194	Fingolimod or other DMT	Safety study in patients with multiple sclerosis treated with fingolimod or other approved disease-modifying therapies	For each of the selected, number of patients with a reported event since study start	Enrolment ongoing

plasma exchange can only be used in acute, severe relapses when there is no success with steroid treatment [56, 58].

Disease-modifying therapy (DMT)

Treating paediatric MS is challenging given high disease activity and the lack of safety and efficacy data for most disease-modifying therapies (DMT) in children [2]. Evidence of DMT's effectiveness in reducing relapse rates and disease progression in children with MS is primarily based on observational studies. The number of approved DMT drugs for use in children and adolescents with MS is limited [1]. None of these drugs, except for fingolimod (PARADIGMS study), have been evaluated in a paediatric population in randomised, double-blind studies with a control group receiving active treatment [59, 60]. We are currently awaiting the results of further randomised, controlled TERIKIDS (teriflunomide), LemKids (alemtuzumab), and CONNECT (dimethyl fumarate vs interferon beta-1a) and other studies [61, 62] (Tab. 3).

First-line treatment

It is recommended to start MS treatment in children with interferon beta (IFN-beta), or glatiramer acetate (GA) [6, 63–65]. The safety profile of these drugs is favourable for children. Observational studies have demonstrated efficacy, and no serious adverse events have been reported for IFN beta-1b treatment [65]. The most common adverse events include a flu-like syndrome (35%), abnormal liver function tests (26%) and injection site reaction (21%) [65]. The multi-centre international REPLAY study assessing the safety, tolerability, and efficacy of IFN beta-1a in children with MS (44 and 22 μg, three times a week) showed very good effects and excellent tolerance [66]. The annual relapse rate was 1.79 before treatment and 0.47 during treatment. Experience with glatiramer acetate is very limited. GA is estimated to have approximately the same efficacy as IFN-beta, which is why possible adverse effects and injection tolerance should be taken into account when selecting treatment [64, 67].The safety and efficacy of dimethyl fumarate and teriflunomide have not been established in children and adolescents with multiple sclerosis. Caution should be exercised when using these drugs, taking into account known side effects in adults [6]. The FOCUS study assessing the effect of dimethyl fumarate on MRI activity in a paediatric population showed a reduction in the development of new T2 hyperintense lesions [68]. Although the data showed a decrease in disease activity on MRI, there was no reduction in the number of relapses in a population of children with MS [69]. The open, randomised, and controlled CONNECT trial comparing dimethyl fumarate to interferon beta-1a in a paediatric population is under way [61].We are also waiting for the results of the TERIKIDS study, a randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of teriflunomide in multiple sclerosis in children [61].

Second-line treatment

In children after failure of first-line therapy or rapidly developing severe MS, escalation to more effective second-line therapies such as natalizumab or fingolimod can be considered [54]. These indications result from the extrapolation of data from studies involving adult patients. Regarding PMS,

safety, efficacy, and tolerability data for most of these therapies is scarce and based only on a small retrospective series of cases [6, 58].

The only exception is fingolimod, which in May 2018 was approved by the FDA for the treatment of children 10 years and older with relapsing-remitting MS. The registration of fingolimod in children was based on the PARADIGMS phase 3 study (n = 215) comparing fingolimod to interferon beta-1a in children and adolescents [55]. Patients were randomly assigned to a group that once a day received oral fingolimod (n = 107, 0.5 mg or 0.25 mg, depending on patient weight), or intramuscular interferon (IFN) beta-1a (n = 108) once a week. Compared to IFN beta-1a, fingolimod reduced the annual frequency of T2 lesions by 52.6% ($p < 0.001$) and the number of Gd + lesions by 66.0% ($p < 0.001$). Treatment with fingolimod compared to IFN beta-1a significantly reduced MRI activity and slowed the loss of brain volume [59].

Recommendations for the use of other drugs are based only on observational studies. These studies showed that natalizumab is an effective treatment in children with active MS and has a good safety profile, comparable to the adult population [69–73]. In a series of 14 paediatric cases of multiple sclerosis treated with rituximab, none of the patients had a subsequent relapse [74]. The most common side effects include hypogammaglobulinemia and infusion reactions [75, 76]. Cyclophosphamide, an alkylating agent, has been shown to effectively reduce the frequency of relapses in children with aggressive MS [77]. Although it is an effective drug, there is a significant risk of secondary malignancies, infections, and infertility [77].

If IFN or GA is not effective, IPMSSG recommends switching to fingolimod. In contrast, natalizumab is recommended for the treatment of rapidly developing severe PMS [61]. For patients who cannot take natalizumab (high index JC virus and associated risk of PML), the available options include switching to one of the other infusion DMTs (ocrelizumab, rituximab) or to one of the oral DMTs (dimethyl fumarate. teriflunomide). However, these drugs have more side effects in children than do interferon beta or glatiramer acetate [1].

In Poland, INF and GA are recommended and reimbursed as part of the first-line treatment with no age limit, whereas treatment with beta-1a peginterferon, dimethyl fumarate, and teriflunomide is only refunded from the age of 12.

As for the second-line therapy in Poland, only natalizumab and fingolimod are reimbursed, which can be administered from the age of 12 after failure of first-line drug therapy or in the case of rapidly developing severe MS.

Prognosis of multiple sclerosis in children

The course of paediatric MS in the initial stages is milder than in adults. 90% of children with MS have no symptoms of physical disability for five years from the first relapse [29]. The remaining 10% require outpatient assistance after an average of three years. Some of these children develop significant walking impairment or wheelchair dependency during the first five years [29]. This result has not been shown to be related to age at onset of symptoms, but is more likely to occur in children with multifocal onset, persistent neurological deficit after the first relapse, disability progression between relapses, and/or frequent relapses in the first two years of the disease [29, 78]. The psychosocial complications of multiple sclerosis include a sense of self-awareness, worries about the future, problems with family and friends, mood disorders, and cognitive impairment [79–82]. These handicaps are unrelated to physical disability. It is estimated that c.30-48% of children with multiple sclerosis have affective disorders [83]. The most common psychiatric disorders include major depression, anxiety disorder, a combination of anxiety and depression, panic attacks, bipolar disorder, and adjustment disorder [81]. It is estimated that cognitive impairment occurs in c.30-75% of children with multiple sclerosis, depending on which definition is used and at which point in time the child is evaluated [81–84]. The disability mainly concerns such functions as memory, complex attention, processing speed, verbal understanding, and executive functioning. A younger age at the beginning of symptoms correlates with a lower intelligence quotient (IQ) [82, 84]. Children with multiple sclerosis appear to be prone to cognitive decline more quickly than adults with multiple sclerosis [82]. In school-aged children, cognitive decline manifests in poor school performance. A significant percentage of paediatric patients with multiple sclerosis require different types of help or a changed school programme due to cognitive impairment [84].

Thus, despite the slower development of irreversible disability in children with multiple sclerosis, the age at which the disease progresses significantly and irreversible neurological deficits appear, is 10 years lower than in the adult population [28].

References

1. Fisher KS, Cuascut FX, Rivera VM, et al. Current Advances in Pediatric Onset Multiple Sclerosis. Biomedicines. 2020; 8(4), doi: 10.3390/biomedicines8040071, indexed in Pubmed: 32231060.
2. Krysko KM, Graves JS, Rensel M, et al. US Network of Pediatric MS Centers. Real-World Effectiveness of Initial Disease-Modifying Therapies in Pediatric Multiple Sclerosis. Ann Neurol. 2020; 88(1): 42–55, doi: 10.1002/ana.25737, indexed in Pubmed: 32267005.
3. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. BMC Neurol. 2018; 18(1): 27, doi: 10.1186/s12883-018-1026-3, indexed in Pubmed: 29523094.
4. Renoux C, Vukusic S, Confavreux C, et al. Adult Neurology Departments KIDMUS Study Group. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007; 356(25): 2603–2613, doi: 10.1056/NEJMoa067597, indexed in Pubmed: 17582070.
5. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis

Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013; 19(10): 1261–1267, doi: 10.1177/1352458513484547, indexed in Pubmed: 23572237.
6. Rensel M. Long-Term Treatment Strategies of Pediatric Multiple Sclerosis, Including the use of Disease Modifying Therapies. Children (Basel). 2019; 6(6), doi: 10.3390/children6060073, indexed in Pubmed: 31159312.
7. Galardi MM, Gaudioso C, Ahmadi S, et al. Differential Diagnosis of Pediatric Multiple Sclerosis. Children (Basel). 2019; 6(6), doi: 10.3390/children6060075, indexed in Pubmed: 31163654.
8. An Q, Fan CH, Xu SM. Childhood multiple sclerosis: clinical features and recent developments on treatment choices and outcomes. Eur Rev Med Pharmacol Sci. 2018; 22(17): 5747–5754, doi: 10.26355/eurrev_201809_15843, indexed in Pubmed: 30229853.
9. Wong YuY, de Mol CL, van der Vuurst de Vries RM, et al. Real-world validation of the 2017 McDonald criteria for pediatric MS. Neurol Neuroimmunol Neuroinflamm. 2019; 6(2): e528, doi: 10.1212/NXI.0000000000000528, indexed in Pubmed: 30697581.
10. Jeong A, Oleske DM, Holman J. Epidemiology of Pediatric-Onset Multiple Sclerosis: A Systematic Review of the Literature. J Child Neurol. 2019; 34(12): 705–712, doi: 10.1177/0883073819845827, indexed in Pubmed: 31185780.
11. Boiko A, Vorobeychik G, Paty D, et al. University of British Columbia MS Clinic Neurologists. Early onset multiple sclerosis: a longitudinal study. Neurology. 2002; 59(7): 1006–1010, doi: 10.1212/wnl.59.7.1006, indexed in Pubmed: 12370453.
12. Bigi S, Banwell B. Pediatric multiple sclerosis. J Child Neurol. 2012; 27(11): 1378–1383, doi: 10.1177/0883073812452784, indexed in Pubmed: 22914372.
13. Gadoth N. Multiple sclerosis in children. Brain Dev. 2003; 25(4): 229–232, doi: 10.1016/s0387-7604(03)00035-4, indexed in Pubmed: 12767451.
14. Wang CX, Greenberg BM. Pediatric Multiple Sclerosis: From Recognition to Practical Clinical Management. Neurol Clin. 2018; 36(1): 135–149, doi: 10.1016/j.ncl.2017.08.005, indexed in Pubmed: 29157395.
15. Huppke B, Ellenberger D, Rosewich H, et al. Clinical presentation of pediatric multiple sclerosis before puberty. Eur J Neurol. 2014; 21(3): 441–446, doi: 10.1111/ene.12327, indexed in Pubmed: 24330201.
16. Oksenberg JR, Baranzini SE, Sawcer S, et al. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. Nat Rev Genet. 2008; 9(7): 516–526, doi: 10.1038/nrg2395, indexed in Pubmed: 18542080.
17. Banwell BL. Pediatric multiple sclerosis. Curr Neurol Neurosci Rep. 2004; 4(3): 245–252, doi: 10.1007/s11910-004-0045-1, indexed in Pubmed: 15102351.
18. Ramagopalan SV, Knight JC, Ebers GC. Multiple sclerosis and the major histocompatibility complex. Curr Opin Neurol. 2009; 22(3): 219–225, doi: 10.1097/WCO.0b013e32832b5417, indexed in Pubmed: 19387341.
19. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol. 2011; 10(5): 436–445, doi: 10.1016/S1474-4422(11)70045-X, indexed in Pubmed: 21459044.
20. Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. Ann Neurol. 2010; 67(5): 618–624, doi: 10.1002/ana.21972, indexed in Pubmed: 20437559.
21. Ascherio A, Munch M. Epstein-Barr virus and multiple sclerosis. Epidemiology. 2000; 11(2): 220–224, doi: 10.1097/00001648-200003000-00023, indexed in Pubmed: 11021623.
22. Hedström AK, Olsson T, Alfredsson L. Smoking is a major preventable risk factor for multiple sclerosis. Mult Scler. 2016; 22(8): 1021–1026, doi: 10.1177/1352458515609794, indexed in Pubmed: 26459151.
23. Mikaeloff Y, Caridade G, Tardieu M, et al. KIDSEP study group. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain. 2007; 130(Pt 10): 2589–2595, doi: 10.1093/brain/awm198, indexed in Pubmed: 17827175.
24. Rotstein DL, Cortese M, Fung TT, et al. Body size and risk of MS in two cohorts of US women. Neurology. 2009; 73(19): 1543–1550, doi: 10.1212/WNL.0b013e3181c0d6e0, indexed in Pubmed: 19901245.
25. Langer-Gould A, Brara SM, Beaber BE, et al. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. Neurology. 2013; 80(6): 548–552, doi: 10.1212/WNL.0b013e31828154f3, indexed in Pubmed: 23365063.
26. McDonald J, Graves J, Waldman A, et al. A case-control study of dietary salt intake in pediatric-onset multiple sclerosis. Mult Scler Relat Disord. 2016; 6: 87–92, doi: 10.1016/j.msard.2016.02.011, indexed in Pubmed: 27063630.
27. Montgomery S, Hiyoshi A, Burkill S, et al. Concussion in adolescence and risk of multiple sclerosis. Ann Neurol. 2017; 82(4): 554–561, doi: 10.1002/ana.25036, indexed in Pubmed: 28869671.
28. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology. 2002; 59(12): 1922–1928, doi: 10.1212/01.wnl.0000036907.37650.8e, indexed in Pubmed: 12499484.
29. Mikaeloff Y, Suissa S, Vallée L, et al. KIDMUS Study Group. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr. 2004; 144(2): 246–252, doi: 10.1016/j.jpeds.2003.10.056, indexed in Pubmed: 14760270.
30. Banwell B, Ghezzi A, Bar-Or A, et al. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol. 2007; 6(10): 887–902, doi: 10.1016/S1474-4422(07)70242-9, indexed in Pubmed: 17884679.
31. Ruggieri M, Iannetti P, Polizzi A, et al. Italian Society of Paediatric Neurology Study Group on Childhood Multiple Sclerosis. Multiple sclerosis in children under 10 years of age. Neurol Sci. 2004; 25 Suppl 4: S326–S335, doi: 10.1007/s10072-004-0335-z, indexed in Pubmed: 15727227.
32. Yeh EA, Weinstock-Guttman B, Ramanathan M, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. Brain. 2009; 132(Pt 12): 3392–3400, doi: 10.1093/brain/awp278, indexed in Pubmed: 19892770.
33. McKay KA, Manouchehrinia A, Berrigan L, et al. Long-term Cognitive Outcomes in Patients With Pediatric-Onset vs Adult-Onset Multiple Sclerosis. JAMA Neurol. 2019 [Epub ahead of print], doi: 10.1001/jamaneurol.2019.1546, indexed in Pubmed: 31206130.
34. Gorman MP, Healy BC, Polgar-Turcsanyi M, et al. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009; 66(1): 54–59, doi: 10.1001/archneurol.2008.505, indexed in Pubmed: 19139299.
35. Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord. 2014; 3(2): 186–193, doi: 10.1016/j.msard.2013.06.004, indexed in Pubmed: 25878006.

36. Ness JM, Chabas D, Sadovnick AD, et al. International Pediatric MS Study Group. Clinical features of children and adolescents with multiple sclerosis. Neurology. 2007; 68(16 Suppl 2): S37–S45, doi: 10.1212/01.wnl.0000259447.77476.a9, indexed in Pubmed: 17438237.
37. Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. Ann Neurol. 2002; 51(4): 475–480, doi: 10.1002/ana.10147, indexed in Pubmed: 11921053.
38. Miller D, Leary S. Primary-progressive multiple sclerosis. The Lancet Neurology. 2007; 6(10): 903–912, doi: 10.1016/s1474-4422(07)70243-0.
39. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001; 50(1): 121–127, doi: 10.1002/ana.1032, indexed in Pubmed: 11456302.
40. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005; 58(6): 840–846, doi: 10.1002/ana.20703, indexed in Pubmed: 16283615.
41. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69(2): 292–302, doi: 10.1002/ana.22366, indexed in Pubmed: 21387374.
42. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2): 162–173, doi: 10.1016/S1474-4422(17)30470-2, indexed in Pubmed: 29275977.
43. Krupp LB, et al. B Banwell Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology. 2007; 68(16): S7–12, doi: 10.1212/WNL.0000000000002877.
44. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology. 2017; 89(3): 269–278, doi: 10.1212/WNL.0000000000004117, indexed in Pubmed: 28615429.
45. Jurkiewicz E, Kotulska K. [Neuroimaging of multiple sclerosis in children]. Neurol Neurochir Pol. 2011; 45(2): 152–160, doi: 10.1016/s0028-3843(14)60027-x, indexed in Pubmed: 21574120.
46. Dębska J, Kotulska-Józwiak K, Pawliszak P, et al. Spinal cord lesions in children and adolescents with multiple sclerosis - Magnetic resonance imaging. Neurol Neurochir Pol. 2017; 51(1): 77–81, doi: 10.1016/j.pjnns.2016.11.008, indexed in Pubmed: 28038775.
47. Hahn JS, Pohl D, Rensel M, et al. International Pediatric MS Study Group. Differential diagnosis and evaluation in pediatric multiple sclerosis. Neurology. 2007; 68(16 Suppl 2): S13–S22, doi: 10.1212/01.wnl.0000259403.31527.ef, indexed in Pubmed: 17438234.
48. Tenembaum S, Chitnis T, Ness J, et al. International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology. 2007; 68(16 Suppl 2): S23–S36, doi: 10.1212/01.wnl.0000259404.51352.7f, indexed in Pubmed: 17438235.
49. Alper G, Heyman R, Wang Li. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: comparison of presenting features. Dev Med Child Neurol. 2009; 51(6): 480–486, doi: 10.1111/j.1469-8749.2008.03136.x, indexed in Pubmed: 19018840.
50. Dale RC, de Sousa C, Chong WK, et al. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000; 123 Pt 12: 2407–2422, doi: 10.1093/brain/123.12.2407, indexed in Pubmed: 11099444.
51. Callen DJA, Shroff MM, Branson HM, et al. Role of MRI in the differentiation of ADEM from MS in children. Neurology. 2009; 72(11): 968–973, doi: 10.1212/01.wnl.0000338630.20412.45, indexed in Pubmed: 19038851.
52. Ketelslegers IA, Neuteboom RF, Boon M, et al. Dutch Pediatric MS Study Group. A comparison of MRI criteria for diagnosing pediatric ADEM and MS. Neurology. 2010; 74(18): 1412–1415, doi: 10.1212/WNL.0b013e3181dc138b, indexed in Pubmed: 20335562.
53. O'Mahony J, Bar-Or A, Arnold DL, et al. Canadian Pediatric Demyelinating Disease Network. Masquerades of acquired demyelination in children: experiences of a national demyelinating disease program. J Child Neurol. 2013; 28(2): 184–197, doi: 10.1177/0883073812443006, indexed in Pubmed: 22573735.
54. Jarius S, Paul F, Aktas O, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J Neuroinflammation. 2018; 15(1): 134–1399, doi: 10.1186/s12974-018-1144-2, indexed in Pubmed: 29724224.
55. Wynford-Thomas R, Jacob A, Tomassini V. Neurological update: MOG antibody disease. J Neurol. 2019; 266(5): 1280–1286, doi: 10.1007/s00415-018-9122-2, indexed in Pubmed: 30569382.
56. Ghezzi A, Banwell B, Boyko A, et al. The management of multiple sclerosis in children: a European view. Mult Scler. 2010; 16(10): 1258–1267, doi: 10.1177/1352458510375568, indexed in Pubmed: 20685764.
57. Lattanzi S, Cagnetti C, Danni M, et al. Oral and intravenous steroids for multiple sclerosis relapse: a systematic review and meta-analysis. J Neurol. 2017; 264(8): 1697–1704, doi: 10.1007/s00415-017-8505-0, indexed in Pubmed: 28492970.
58. Chitnis T, Ghezzi A, Bajer-Kornek B, et al. Pediatric multiple sclerosis: Escalation and emerging treatments. Neurology. 2016; 87(9 Suppl 2): S103–S109, doi: 10.1212/WNL.0000000000002884, indexed in Pubmed: 27572854.
59. Chitnis T, Arnold DL, Banwell B, et al. PARADIGMS Study Group. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. N Engl J Med. 2018; 379(11): 1017–1027, doi: 10.1056/NEJMoa1800149, indexed in Pubmed: 30207920.
60. Deiva K, Huppke P, Banwell B, et al. Consistent control of disease activity with fingolimod versus IFN β-1a in paediatric-onset multiple sclerosis: further insights from PARADIG. J Neurol Neurosurg Psychiatry. 2020; 91(1): 58–66, doi: 10.1136/jnnp-2019-321124, indexed in Pubmed: 31467033.
61. Waubant E, Banwell B, Wassmer E, et al. IPMSSG. Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. Neurology. 2019; 92(22): e2538–e2549, doi: 10.1212/WNL.0000000000007572, indexed in Pubmed: 31043474.
62. https://clinicaltrials.gov.
63. Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology. 2016; 87(9 Suppl 2): S97–S9S102, doi: 10.1212/WNL.0000000000002823, indexed in Pubmed: 27572869.
64. Narula S, Hopkins SE, Banwell B. Treatment of pediatric multiple sclerosis. Curr Treat Options Neurol. 2015; 17(3): 336, doi: 10.1007/s11940-014-0336-z, indexed in Pubmed: 25680425.
65. Banwell B, Reder AT, Krupp L, et al. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. Neurology. 2006; 66(4): 472–476, doi: 10.1212/01.wnl.0000198257.52512.1a, indexed in Pubmed: 16505297.

66. Tenembaum SN, Banwell B, Pohl D, et al. REPLAY Study Group. Subcutaneous interferon Beta-1a in pediatric multiple sclerosis: a retrospective study. J Child Neurol. 2013; 28(7): 849–856, doi: 10.1177/0883073813488828, indexed in Pubmed: 23666046.
67. Kornek B, Bernert G, Balassy C, et al. Glatiramer acetate treatment in patients with childhood and juvenile onset multiple sclerosis. Neuropediatrics. 2003; 34(3): 120–126, doi: 10.1055/s-2003-41274, indexed in Pubmed: 12910434.
68. Alroughani R, Das R, Penner N, et al. Safety and Efficacy of Delayed-Release Dimethyl Fumarate in Pediatric Patients With Relapsing Multiple Sclerosis (FOCUS). Pediatr Neurol. 2018; 83: 19–24, doi: 10.1016/j.pediatrneurol.2018.03.007, indexed in Pubmed: 29681490.
69. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. JAMA Neurol. 2013; 70(4): 469–475, doi: 10.1001/jamaneurol.2013.923, indexed in Pubmed: 23420110.
70. Ghezzi A, Pozzilli C, Grimaldi LME, et al. Italian MS Study Group. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. Mult Scler. 2013; 19(8): 1106–1112, doi: 10.1177/1352458512471878, indexed in Pubmed: 23401129.
71. Ghezzi A, Moiola L, Pozzilli C, et al. MS Study Group-Italian Society of Neurology. Natalizumab in the pediatric MS population: results of the Italian registry. BMC Neurol. 2015; 15: 174, doi: 10.1186/s12883-015-0433-y, indexed in Pubmed: 26407848.
72. Alroughani R, Ahmed SF, Behbehani R, et al. The Use of Natalizumab in Pediatric Patients With Active Relapsing Multiple Sclerosis: A Prospective Study. Pediatr Neurol. 2017; 70: 56–60, doi: 10.1016/j.pediatrneurol.2017.01.017, indexed in Pubmed: 28389054.
73. Arnal-Garcia C, García-Montero MaR, Málaga I, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. Eur J Paediatr Neurol. 2013; 17(1): 50–54, doi: 10.1016/j.ejpn.2012.09.004, indexed in Pubmed: 23021975.
74. Salzer J, Lycke J, Wickström R, et al. Rituximab in paediatric onset multiple sclerosis: a case series. J Neurol. 2016; 263(2): 322–326, doi: 10.1007/s00415-015-7979-x, indexed in Pubmed: 26603152.
75. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol. 2014; 51(1): 114–118, doi: 10.1016/j.pediatrneurol.2014.02.007, indexed in Pubmed: 24768216.
76. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014; 83(2): 142–150, doi: 10.1212/WNL.0000000000000570, indexed in Pubmed: 24920861.
77. Makhani N, Gorman MP, Branson HM, et al. Cyclophosphamide therapy in pediatric multiple sclerosis. Neurology. 2009; 72(24): 2076–2082, doi: 10.1212/WNL.0b013e3181a8164c, indexed in Pubmed: 19439723.
78. Gusev E, Boiko A, Bikova O, et al. The natural history of early onset multiple sclerosis: comparison of data from Moscow and Vancouver. Clin Neurol Neurosurg. 2002; 104(3): 203–207, doi: 10.1016/s0303-8467(02)00039-2, indexed in Pubmed: 12127655.
79. Till C, Noguera A, Verhey LH, et al. Cognitive and Behavioral Functioning in Childhood Acquired Demyelinating Syndromes. J Int Neuropsychol Soc. 2016; 22(10): 1050–1060, doi: 10.1017/S1355617716000308, indexed in Pubmed: 27903328.
80. Amato MP, Goretti B, Ghezzi A, et al. Multiple Sclerosis Study Group of the Italian Neurological Society. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. Neurology. 2010; 75(13): 1134–1140, doi: 10.1212/WNL.0b013e3181f4d821, indexed in Pubmed: 20876467.
81. Amato MP, Goretti B, Ghezzi A, et al. MS Study Group of the Italian Neurological Society. Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. Neurology. 2014; 83(16): 1432–1438, doi: 10.1212/WNL.0000000000000885, indexed in Pubmed: 25217060.
82. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. Neurology. 2005; 64(5): 891–894, doi: 10.1212/01.WNL.0000152896.35341.51, indexed in Pubmed: 15753431.
83. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997; 36(7): 980–988, doi: 10.1097/00004583-199707000-00021, indexed in Pubmed: 9204677.
84. Cardoso M, Olmo NR, Fragoso YD. Systematic Review of Cognitive Dysfunction in Pediatric and Juvenile Multiple Sclerosis. Pediatr Neurol. 2015; 53(4): 287–292, doi: 10.1016/j.pediatrneurol.2015.06.007, indexed in Pubmed: 26233264.