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Педиатрический рассеянный склероз: особенности патогенеза, клинической и радиологической картины, современные подходы к диагностике и лечению

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АННОТАЦИЯ

Проанализированы данные об эпидемиологии, клинической картине, диагностике и лечении педиатрического рассеянного склероза, а также об особенностях иммунного и эндокринного статуса пациентов в сравнении с взрослой популяцией больных рассеянным склерозом с использованием баз данных Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka, РИНЦ. Течение рассеянного склероза у детей и взрослых имеет ряд ключевых различий, что может обусловливать необходимость разработки иных подходов к курации, нежели у взрослых. В то же время, несмотря на большое количество исследований, посвящённых педиатрическому рассеянному склерозу, патогенетические основы вышеуказанных различий остаются неясны. Для педиатрического рассеянного склероза характерно более активное течение заболевания, чем во взрослой популяции, а также бóльшая тяжесть обострений. Кроме того, при отсутствии эффективного лечения для детей характерны более быстрое увеличение объёма поражения и ранняя атрофия головного мозга. Несмотря на более быстрый и полный регресс неврологического дефицита после обострений и, как следствие, более медленный темп его накопления, конверсия заболевания во вторично-прогрессирующий рассеянный склероз и достижение нетрудоспособности происходят в более раннем возрасте. Выявленные в иммунологических исследованиях особенности субпопуляционного состава и функциональных отличий лимфоцитов позволяют предположить возможные различия в выборе препаратов, изменяющих течение рассеянного склероза у детей и взрослых. Однако количество исследований иммунного и эндокринного статуса пациентов детского возраста в сравнении с взрослой популяцией ограничено, и их результаты зачастую противоречивы. Таким образом, педиатрический рассеянный склероз представляет собой важную медико-социальную проблему, требующую дальнейшего исследования с целью оптимизации подходов к лечению пациентов с данной патологией.

Ключевые слова: *педиатрический рассеянный склероз, рассеянный склероз, обзор, дети.*

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Pediatric multiple sclerosis: pathogenesis, clinical and radiological features, diagnosis and treatment

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ABSTRACT

Data on the epidemiology, clinical features, diagnosis and treatment of paediatric multiple sclerosis (PMS), as well as characteristics of the immune and endocrine status of children compared with the population with multiple sclerosis (MS) were analysed using the Scopus, Web of Science, MedLine, The Cochrane, EMBASE, Global Health and RSCI databases. The MS course in children and adults has a number of important differences, which may require the development of different treatment approaches than in adults. At the same time, despite the large number of studies on PMS, the pathogenesis of these above differences remains unclear. PMS is characterised by a more active course than in the adult population and by greater severity of exacerbations; in addition, a more rapid increase in lesion volume and early brain atrophy are observed in the absence of effective treatment. Despite a more rapid and complete regression of the neurological deficit after exacerbations and, consequently, a slower rate of its accumulation, conversion to SPMS and achievement of disability occurs at an earlier age. The characteristics of subsets and functional differences of lymphocytes revealed by immunological studies suggest possible differences in the choice of disease-modifying therapies in children and adults. However, the number of studies on the immune and endocrine status of patients with PMS compared with the adult population is limited and the results are often conflicting. PMS is therefore an important medical and social problem that requires further research to optimise approaches to disease-modifying therapies.

Keywords: *pediatric multiple sclerosis, multiple sclerosis, review, children.*

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INTRODUCTION

Multiple sclerosis (MS) is the most common chronic demyelinating disease based on a complex of autoimmune inflammatory and neurodegenerative processes, leading to multiple focal and diffuse lesions of the central nervous system. These processes result in disability and significantly reduced quality of life [1, 2]. In most cases, the disease manifests between the ages of 20 and 40 years [3]. However, an increase in the incidence of MS in the pediatric population has been reported over the past 15 years [4, 5].

In the Russian Federation, the term "pediatric multiple sclerosis" (pMS) is defined as MS manifested before the age of 18 years. In some countries, due to different age classifications, MS manifests before the age of 16 years [6]. Currently, the peculiarities of the course of MS in children are described, which may require the development of different treatment approaches than in adults. However, the pathogenesis of these differences remains unclear despite the large number of studies in pMS. All these factors underscore the importance of further research into the peculiarities of pMS.

The incidence of pMS ranges from 0.05 to 2.85 per 100,000 children per year. The prevalence is 3%–10% of the total number of MS cases, with absolute values ranging from 0.69 to 26.9 per 100,000 children [4, 7, 8]. Thus, pMS has an orphan prevalence. The average age of onset of PMS is 11–13 years [8, 9]. The ratio of girls to boys before age 10–12 is 1:1, rapidly reaching 3:1 after puberty, as in adults [3, 10].

PECULIARITIES OF THE CLINICAL PICTURE OF PEDIATRIC MULTIPLE SCLEROSIS

During childhood and adolescence, the remitting form of MS is predominant (85%–100% of cases) [4, 11]. The progressive course of the disease in childhood, especially from its onset, should always prompt a more thorough differential diagnosis and the exclusion of competing diagnoses [12].

Several authors observed a tendency toward a higher frequency of exacerbations in children, especially at the disease's onset [13, 14]. A recent study showed that 41.6% of patients with pMS meet the criteria for highly active MS [15]. In some cases, ADEM-like exacerbations[1] of the disease occur, accompanied by impaired consciousness, epileptic seizures, and fever [11, 16]. Such exacerbations are particularly characteristic of patients younger than 12 years [7, 17, 18].

In addition, prepubertal children are more likely to have polysymptomatic exacerbations of the disease, whereas monosymptomatic exacerbations predominate in children over 12 years of age, as in adults [11, 15]. Furthermore, the brainstem and cerebellum are often involved in the pathological process, manifested by symptoms [15, 19–21].

Several literature sources point to the greater severity of exacerbations in pMS compared with adults, especially in children younger than 12 years [15, 19–21]; however, patients in this age group are characterized by faster and more complete regression of neurological deficits [22].

Despite high disease activity, especially in the early stages, pMS patients show a slower accumulation rate of neurological deficits than adult patients [23]. These features are usually due to extensive reparative processes after relapse, which can be explained by the greater ability of the developing brain to repair and synthesize myelin and by greater neuroplasticity [24]. Alternatively, an increased propensity of pMS patients to accumulate cognitive deficits is reported [25–27] and is currently under active investigation.

When MS changes to secondary progressive MS, marked by steadily increasing disability, the possibilities for effective treatment are significantly reduced. Literature indicates that the duration of the disease before its conversion to secondary progressive MS in pediatric patients is, on average, 10 years longer than in patients with a later onset [11]. Nevertheless, disability occurs at an earlier age [12, 28], leading to an increase in the level of disability in the most able-bodied population.

DIFFERENTIAL DIAGNOSIS

Diagnosing MS in adults and children involves distinct approaches. For example, to establish the diagnosis of MS in adults, the Mac Donald's (2017)

[1]ADEM, acute disseminated encephalomyelitis.

Table 1. Mac Donald's (2017) diagnostic criteria [29]

Number of clinical attacks	Number of foci associated with objective clinical manifestations	Additional data for diagnosis
≥2	≥2	Not required
≥2	1 and significant anamnestic data on previous attacks, demonstrating the lesion of a specific anatomical zone	Not required
≥2	1, absence of significant history suggesting other foci	Presence of spatial dissemination in the form of recurrent clinical attack OR according to magnetic resonance imaging (MRI) data
1	≥2	Presence of temporal dissemination in the form of recurrent clinical attack OR MRI findings OR detection of oligoclonal immunoglobulin (Ig) class G bands in cerebrospinal fluid
1	1	Presence of spatial dissemination in the form of recurrent clinical attack OR according to MRI AND Presence of temporal dissemination in the form of repeated clinical attack OR according to MRI data OR detection of oligoclonal IgG bands in cerebrospinal fluid
Spatial and temporal dissemination criteria according to MRI data		
Spatial dissemination	One or more T2-hyperintense foci typical of MS in two or more of the four zones: – Periventricularly – Cortically or juxtacortically – Infratentorially – In the spinal cord	
Temporal dissemination	Simultaneous presence of contrast-enhancing and noncontrast-enhancing T2-hyperintense foci on an MRI scan OR A new T2-hyperintense or contrast-positive focus compared with the previous MRI scan (regardless of date)	

diagnostic criteria are currently used to diagnose MS in adults (Table 1), which can be applied to children aged 12 years and older if the first clinical episode was not ADEM-like [29, 30]. In other cases, the specific criteria of the Pediatric International Study Group (Table 2) [30], which optimize and adapt the criteria for diagnosing MS and other demyelinating diseases to the pediatric population, are used to diagnose pMS.

The above criteria are used in most clinical studies of pMS [28]. The main differences between the Pediatric International Study Group criteria and the Mac Donald's (2017) criteria are the need to follow a special algorithm for diagnosing MS in children with a first ADEM-like attack and the inability to establish a diagnosis of MS in children younger than 12 years with a single clinical attack, even if the MRI pattern meets the criteria for temporal and spatial dissemination. In addition, the presence of oligoclonal IgG in the cerebrospinal fluid of patients younger than 12 years of age is not considered evidence of temporal dissemination.

The basic principle of differential diagnosis of pMS can be formulated as follows: the less typical the case and the younger the child, the more thorough the differential diagnosis should be [31]. In addition to considering other demyelinating diseases (e.g., opticoneuromyelitis spectrum diseases, ADEM, and diseases associated with antibodies to myelin-oligodendrocyte glycoprotein), pMS should be differentiated from diseases wherein CNS lesions may resemble MS. These include vasculitis, including systemic connective tissue diseases, neurosarcoidosis, leukodystrophies, inherited metabolic disorders, and CNS lesions of infectious etiology (Table 3) [28]. The

Table 2. Diagnostic criteria for pMS [30 with modifications]

Nosologic form	Diagnostic criteria
ПРС	Any of the following: – Two or more nonencephalopathic (i.e., not consistent with ADEM) clinical episodes of CNS lesions of inflammatory demyelinating etiology separated by more than 30 days and involving more than one region of the CNS. – A nonencephalopathic episode typical of MS, accompanied by an MRI image that meets the Mac Donald's (2010) criteria for spatial dissemination, with the detection of a new T2 hyperintense focus on one of the subsequent MRI images. – An ADEM-like episode followed by an ADEM-unrelated clinical attack 3 months or more after debut, accompanied by new focal changes on MRI consistent with spatial dissemination according to Mac Donald's (2010) criteria. – First clinical episode not consistent with ADEM accompanied by an MRI image that meets the Mac Donald's (2010) criteria for temporal and spatial dissemination (only applicable in children aged ≥12 years).

incidence of other demyelinating diseases in children is relatively higher than in adults [12]. Therefore, similar to adult patients, pMS is a diagnosis of exclusion [8].

MRI is the primary tool for early diagnosis, disease monitoring, and assessment of treatment response in pMS [33]. CT scanners at 1.5 and 3.0 Tesla are most effective for the above tasks [34]. In addition to examining the brain, conducting an MRI of the spinal cord, especially the cervical cord, holds significant importance because focal lesions are frequently observed [23]. At initial diagnosis, the presence of temporal and spatial dissemination of focal CNS changes should be assessed (Table 1). Subsequently, monitoring MRI activity and the dynamics of focal changes becomes paramount to assess disease progression and the efficacy of antiretroviral therapy. Intravenous contrast agents containing gadolinium are used to detect active foci.

The MRI picture in pMS has several distinctive features compared with that of adult MS patients. There is a tendency for a more significant number of focal changes at disease onset [32, 35], with a remarkably rapid increase in the early years of the disease in the absence of effective treatment [32]. In addition, a larger size of foci is observed, frequently accompanied by perifocal edema. This may reflect a tendency in children to experience edematous reactions and immaturity of the blood–brain barrier and microglia [35, 36]. A higher frequency of infratentorial lesions [3, 35, 36] and a decrease in gray matter volume, total brain volume, and thalamic volume [37, 38] are characteristic findings consistent with clinical data.

Several studies showed that brain atrophy is possible in children with MS, even at the earliest stages of the disease, leading to disruption of normal brain growth and development [39, 40]. However, despite the abovementioned negative features, a reduction in lesion volume or signal intensity up to complete regression of some foci occurs more frequently in children with pMS than in adults. This may indicate a less profound and/or more reversible demyelination process and a greater recovery potential of the pediatric brain [3, 9].

A paired cerebrospinal fluid and serum oligoclonal IgG assay may be used to confirm temporal dissemination in patients 12 years of age or older who have one clinical episode and MRI findings that do not meet this criterion [29]. In this case, oligoclonal IgG bands are detected in the cerebrospinal fluid in 40%–90% of cases, according to different authors [8, 28, 41]. Even lower detection of intrathecal IgG synthesis (27%) was reported in patients younger than 10 years [42]. In addition, the IgG index may be elevated in the cerebrospinal fluid [12].

A positive MRZ reaction, a polyspecific intrathecal humoral immune response against measles (M), rubella (R), and varicella-zoster (Z) viruses, is detected in the majority of patients with MS (70%) and is significantly less frequent in neurosarcoidosis (9%) and autoimmune encephalitis (11%). The specificity of this test for MS patients is 92% [43].

Mild lymphocytic pleocytosis, which can be neutrophilic in children younger than 10 years [8], and hyperproteinuria [44] may be seen in a general cerebrospinal fluid analysis. If these parameters are significantly elevated, a more thorough differential

Table 3. Differential diagnosis of pMS [32]

Genesis of the disease	Nosologic forms
Demyelinating diseases	Clinically isolated syndrome, ADEM, optic neuromyelitis spectrum disorders, optic neuritis, transverse myelitis, postvaccinal encephalitis, and acute necrotizing encephalopathy
Other inflammatory diseases	Systemic lupus erythematosus, neurosarcoidosis, Sjögren syndrome, antiphospholipid syndrome, Behçet disease, and primary (isolated) CNS vasculitis
Mitochondrial diseases	Myoclonic epilepsy with red fiber rupture, mitochondrial encephalopathy with lactate acidosis and seizures, Leber hereditary optic neuropathy, Leigh syndrome, and Kearns−Sayre syndrome
Leukodystrophies	Metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe disease, Pelizaeus−Merzbacher leukodystrophy, Refsum disease, leukoencephalopathy with disappearance of white matter, leukoencephalopathy with predominant brainstem and spinal cord involvement and increased lactate content, Wilson disease, Fabry disease, and Alexander disease
Genetic metabolic disorders	Congenital metabolic disorders, aminoaciduria
Infectious diseases	Neuroborreliosis, herpetic encephalitis, human immunodeficiency virus infection, neurocysticercosis, streptococcal infection, brain abscess, neurosyphilis, progressive multifocal leukoencephalopathy, and Whipple disease
Vascular diseases	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Moyamoya disease, internal carotid artery dissection
Endocrine pathologies	Thyroid diseases, diabetes mellitus
Deficiency conditions	Vitamin B12, vitamin E, and folic acid deficiency
Newly formed tumors	Lymphoma, astrocytoma, medulloblastoma, metastasis
Toxic lesions	Radiation damage, effects of chemotherapy (methotrexate, cyclosporine, cytarabine), extrapontine myelinolysis
Others	Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis

diagnosis should be made with infectious pathology and acute inflammatory conditions [12], including ADEM, autoimmune encephalitis, and vasculitis.

For differential diagnosis with seropositive diseases of the opticoneuromyelitis spectrum, conducting a serum analysis for antibodies to aquaporin-4 and myelin-oligodendrocyte glycoprotein proves valuable [12, 45]. However, the latter biomarker can be detected in diseases associated with antibodies to myelin-oligodendrocyte glycoprotein. In some cases, it can be found in the blood of patients with MS [24] and ADEM [46]. Moreover, blood tests for antinuclear antibodies with immunoblot and other markers of systemic autoimmune disease, thyroid hormone, and vitamin B_{12} are useful [45].

EXACERBATION TREATMENT

The principle of treatment of exacerbations in pMS does not differ from that in adult MS patients. The leading group of drugs is glucocorticoids, most commonly in pulse therapy with methylprednisolone 20–30 mg/kg per day for 3–5 days [8, 12, 47, 48]. However, other glucocorticoids (prednisolone, dexamethasone) may be administered in doses equivalent to the above [8, 12].

In complete recovery, oral glucocorticoids are not necessary [32]. However, in patients with residual neurologic deficits, prednisolone may be administered at a starting dose of 1 mg/kg per day with a tapering of 5 mg every 2 days until complete withdrawal [48].

For the treatment of exacerbations that do not respond to glucocorticoid therapy, especially those associated with severe motor and visual impairment, the simultaneous or sequential use of plasmapheresis (usually five sessions every other day) [47, 49] and intravenous immunoglobulin at a dose of 0.4 mg/kg per day for 2–5 days [12, 47] is appropriate.

RELAPSE THERAPY

Currently, two MS disease-modifying drugs (DMDs) are approved for use in children: subcutaneous interferon beta-1a and fingolimod.

Subcutaneous interferon beta-1a is classified as a first-line DMD and is approved for use in children based on the results of the retrospective REPLAY clinical trial [50]. The drug's efficacy and safety

profile practically not differ from those in the adult population [24, 50]. According to the instructions, a dose of 22 mcg subcutaneously three times per week is usually prescribed between 12 and 16 years of age, followed by a change to a dose of 44 mcg subcutaneously three times per week starting at 16 years of age. In actual clinical practice, the dose is selected individually depending on the tolerability and efficacy of the drug. The most common adverse events are flu-like symptoms, reactions at the site of administration, increased activity of aminotransferases, and leukopenia. When prescribing the drug, possible induction of anxiety-depressive syndrome should be considered.

Several authors analyzed data using first-line DMD therapy in the pediatric population. After a mean follow-up of 3.9 years, 114 (44.2%) of 258 patients switched to another DMD due to refractory disease (27.9%) or poor tolerability of the first-line drug (16.3%) [51]. After 12.5 years of follow-up of a group of 97 patients, it was found that 84.5% of them required a change in therapy, with 58% requiring a change to a second-line agent [52].

Escalation of therapy became more readily available with the approval of fingolimod, a second-line agent, for use in children older than 10 years based on the results of the PARADIGMS clinical trial [53, 54]. Administered at a dose of 0.5 mg/day, the drug showed greater efficacy than intramuscular interferon beta-1a, with an average annualized exacerbation rate of 0.12 in the fingolimod group versus 0.67 in the interferon group. The most common adverse events were headache, upper respiratory tract infection, leukopenia, and increased aminotransferase activity. One case of macular edema and one case of atrioventricular block were reported [53]. Before fingolimod is prescribed and during its use, the safety monitoring plan detailed in the fingolimod package insert should be strictly followed.

The TERIKIDS clinical trial of teriflunomide showed conflicting results. The drug was 55% more effective than placebo in preventing the increase in volume of focal brain lesions. However, after 96 weeks of the study, no statistically significant reduction in the risk of relapse was found with teriflunomide compared with placebo [55]. Nevertheless, the European Medicines Agency approved teriflunomide for use in children aged 10 to 17 years in July 2021 [24].

Encouraging results from a phase II clinical trial of dimethyl fumarate showed a significant reduction in the average annual number of exacerbations by 84% compared with baseline. A Phase III study in 156 patients (CONNECT) is ongoing.

Clinical trials on the use of monoclonal antibodies (natalizumab, anti-B-cell therapy [ocrelizumab and ofatumumab], alemtuzumab, and siponimod) in the pediatric population continue [24]. All of their results have yet to be published.

DISCUSSION

Considering the differences in clinical and radiological manifestations of MS between adults and children, the need to enhance treatment approaches and explore factors that determine the course of MS in the pediatric population is of particular interest.

One such factor worth investigating is the patient's endocrine status, given the dynamic changes in the endocrine profile as children grow and develop. Important gender differences in inflammatory activity and the nature of disease progression have been observed in adult patients. For example, women with relapsing forms of the disease have a higher frequency of exacerbations. In contrast, men with a lower frequency of exacerbations have a poorer initial recovery from relapses and a faster rate of progression [56].

Changes in the hormonal background in a woman's body during normal pregnancy, such as increased levels of estrogen, progesterone, glucocorticoids, and activated vitamin D, result in a decreased number of MS exacerbations during pregnancy, especially during the third trimester [57].

In the postpartum period, an apparent increase in the recurrence rate occurs. This is due to a dramatic decrease in estrogen, progesterone, and glucocorticoid levels. In fact, a phenomenon similar to the immune reconstitution inflammatory syndrome is observed after childbirth. During this period, an increase in the levels of hormones involved in lactation mechanisms is observed, which may play a role in the resurgence of disease activity [58].

During lactation, prolactin, oxytocin, progesterone, and glucocorticoids are elevated. The role of prolactin in the pathogenesis of MS

remains unclear. Prolactin was shown to protect against excitotoxicity and potentiate remyelination [59]. Conversely, an increase in prolactin levels in MS patients compared with healthy volunteers was observed, potentially contributing to B-cell autoreactivity. Hyperprolactinemia was also shown to be associated with clinical relapses of MS, especially in patients with hypothalamic lesions and/or optic neuritis [60]. However, some authors reported no significant association of prolactin with the disability severity, clinical forms, and gender of MS patients [61].

Furthermore, controversy exists regarding the effect of lactation on the course of MS. For example, some authors suggest that lactation protects against relapses and that healthy breastfeeding women may have a lower subsequent risk of developing MS. Conversely, some suggest that lactation does not suppress the disease and does not affect relapses [57].

Based on evidence of MS stabilization during pregnancy, attempts were made to treat MS with estrogens. Open clinical trials involving estriol and other equivalent sex hormone combinations in patients with phases I and II MS, as well as a double-blind phase II trial of estriol in combination with glatiramer acetate or placebo, were conducted. These trials demonstrated a significant reduction in the severity of delayed-type hypersensitivity reactions to tetanus anatoxin, a decrease in the level of interferon γ in peripheral mononuclear cells, and a reduction in the frequency of relapses and the number of new contrast-positive foci on MRI, compared with the pretreatment and placebo groups [62–64].

Further research and application of estrogens in treating MS are complicated by the extreme variability of their effects. On the one hand, the anti-inflammatory effects of estrogens were shown in the model of experimental autoimmune encephalomyelitis and other autoimmune diseases. On the other hand, estrogens can induce inflammation in chronic autoimmune diseases. The variant of process development depends on many factors: the ratio of cell populations involved in the process at different stages of the disease, the target organ and the specificity of its microenvironment, the reproductive status of a woman, and the level of basal estrogen secretion and expression of its receptors [65].

Therefore, the study of the endocrine status of patients with pMS is of particular interest. As previously noted, the sex structure of the morbidity changes dramatically after puberty. It quickly reaches the values of the adult population, suggesting an important role of changes in hormonal background, particularly during menarche, in the pathogenesis of MS [9, 12, 66]. Several studies showed an association between early menarche and an increased risk of developing MS, as well as its early onset [67-69]. In addition, the role of sex hormones in the mechanism of disease exacerbations was suggested based on the more frequent development of MS relapses during perimenarche compared with postmenarche [70].

A Russian study showed increased prolactin levels in adolescents with MS and juvenile rheumatoid arthritis compared with healthy adolescents. Prolactin levels in patients with MRI signs of MS activity were significantly higher than those without such signs [71]. However, the number of studies investigating the role of changes in hormonal status in the course of MS is limited.

The study of the immune status of patients with pMS and the search for possible differences in adult patients remains highly relevant. Several studies were conducted on individual subpopulations of T- and B-lymphocytes in pMS patients, but the results are inconclusive. Thus, I. Mexhitaj et al. showed an increase in the concentration of effector T helper cells ($CCR2^+CCR5^+CD4^+$), their abnormally increased proinflammatory response induced by Th1 and Th17 cytokines, and a decrease in the function of T regulators in children with MS compared with adult MS patients and healthy children [72].

In contrast, a study by B. Balint et al. revealed no differences between children and adults with MS, demonstrating a weakening of the suppressive function of T regulators in both groups. However, it noted a significant decrease in the concentration of naive T cells compared with healthy children and an increase in the concentration of memory T cells in patients with pMS [73].

Another study by A. Schwarz et al. showed an increase in the concentration of naive B cells in adults and children with MS compared with healthy volunteers aged 1−55 years and an increase in the number of plasmoblasts in the blood of children with pMS. The subpopulation composition of B-lymphocytes in cerebrospinal fluid differed between children and adults with MS. Thus, cerebrospinal fluid samples

obtained from children exhibited high concentrations of nonswitched memory B cells and plasmoblasts, whereas switched memory B cells and plasmocytes predominated in the cerebrospinal fluid of adult patients [74]. Larger comparative studies, including both pediatric and adult groups and covering all major lymphocyte subpopulations, were not found in the existing literature.

Vitamin D levels are currently shown to have an impact on MS activity. It should be assessed in all children with newly diagnosed MS as one of the few modifiable risk factors for developing and relapsing pMS [12]. The active form of vitamin D, 1,25-dihydroxycholecalciferol, has a number of immunomodulatory properties. Some of its identified effects include suppression of differentiated dendritic cells and prevention of dendritic cell differentiation and migration to lymph nodes, helping to increase dendritic cell tolerance [75]. In addition, 1,25-dihydroxycholecalciferol prevents proliferation of activated B cells and increases their apoptosis [76].

In mice, vitamin D receptor agonists reduce levels of proinflammatory interleukin-17 [77] and inhibit the development of proinflammatory type 1 T helper cells [78]. Finally, vitamin D receptor agonists promote the induction and function of $CD4^+CD25^+$ lymphocyte T regulatory cells [79]. In a study involving 110 patients with pMS, every 10 ng/mL increase in vitamin D levels was associated with a 34% reduction in the relapse rate. The recommended target blood level for vitamin D is 60–100 ng/mL [80].

CONCLUSIONS

The course of MS in children and adults has a number of significant differences. pMS is characterized by a more active disease course and more severe exacerbations than the adult population. In addition, there is a more rapid increase in lesion volume and early brain atrophy occur without effective treatment. Despite a more rapid and complete regression of neurological deficits after exacerbations, leading to an accumulation slower rate, the transition of the disease to secondary progressive MS and disability occurs at an earlier age.

The peculiarities of the subpopulation composition and functional differences of lymphocytes revealed in immunological studies suggest possible differences in the choice of DMD therapy for treating MS in children and adults. However, the number of studies on pediatric patients' immune and endocrine status compared with the adult population is limited, and their results often need to be revised.

Thus, pMS is a significant medical and social problem that requires further research to optimize approaches to treating patients with this pathology.

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