ОСОБЕННОСТИ ПОКАЗАТЕЛЕЙ КЛЕТОЧНОГО ИММУНИТЕТА В ЗАВИСИМОСТИ ОТ АКТИВНОСТИ ОЧАГОВ ДЕМИЕЛИНИЗАЦИИ У ДЕТЕЙ С РАССЕЯННЫМ СКЛЕРОЗОМ

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Резюме. РС является распространенным заболеванием центральной нервной системы, которое приводит к инвалидизации и снижению качества жизни. Дебют заболевания у 3-5% пациентов приходится на детский возраст и имеет менее благоприятное течение, по сравнению со взрослыми. РС вызывается активацией аутореактивных эффекторных Т-клеток при срыве периферической толерантности, которая в норме контролируется Т-регуляторными клетками (Treg). Перспективным является исследование экспрессии эктонуклеотидаз CD39 и CD73 в популяциях Treg и Th17 для оценки их супрессивной активности. Цель – оценить содержание основных и малых популяций лимфоцитов и экспрессию эктонуклеотидаз CD39 и CD73 в популяции $CD4^+$ лимфоцитов у детей с РС. Обследовано 111 детей с РС, 66 детей – с контраст негативными очагами на МРТ (1-я группа), 45 детей – с контраст позитивными очагами (2-я группа). Группу сравнения составили 46 условно здоровых детей, сопоставимых по возрасту (3-я группа). Содержание Т-лимфоцитов, В-лимфоцитов, NK-лимфоцитов, Treg ($CD4^+CD25^{high}CD127^{low}$), Thact ($CD4^+CD25^{high}CD127^{high}$), Th17 клеток ($CD3^+CD4^+CD161^+$); экспрессию CD39 и CD73 в Treg, Th17 и Thact проводили методом проточной цитофлуориметрии. Выявлено увеличение содержания Т-хелперов, снижение NK-клеток у пациентов во 2-й группе. Получено увеличение количества Thact и Th17 лимфоцитов у пациентов обеих групп с РС. Количество Treg в 1-й группе было достоверно выше, чем в 3-й группе. Соотношение клеток с экспрессией CD39 и CD73 у пациентов с РС зависело от популяции лимфоцитов также, как и в 3-й группе. Наибольшее содержание $CD39^+$ клеток отмечалось в популяции Treg, а наименьшее в популяции Thact. Для экспрессии CD73 наоборот, наибольшая экспрессия CD73 наблюдалась в Thact клетках, наименьшая в Treg. При

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сравнении групп пациентов получено, что у пациентов 1-й группы было достоверно увеличено количество клеток, экспрессирующих эктонуклеотидазу CD39, а количество supTh17 было сравнимо с 3-й группой. В обеих группах пациентов с РС наблюдалось увеличение количества CD73 в Treg, Thact и Th17. Таким образом, выявлены информативные популяции лимфоцитов ($CD4^+$ клетки, Treg, $CD39^+$Treg, supTh17), которые могут быть использованы для мониторинга состояния детей с рассеянным склерозом.

Ключевые слова: популяции лимфоцитов, $CD4^+$ лимфоциты, Treg, Th17, Thact, CD39, CD73, рассеянный склероз, дети

FEATURES OF PARAMETERS OF CELLULAR IMMUNE DEPENDING ON THE ACTIVITY OF FOCI OF DEMYELINATION IN CHILDREN WITH MULTIPLE SCLEROSIS

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Abstract. MS is a common disease of the central nervous system that leads to disability and reduced quality of life. The debut of disease in 3-5% of patients occurs in childhood and has a less favorable course compared to adults. MS is caused by the activation of autoreactive T cells in the breakdown of peripheral tolerance, which is normally controlled by regulatory T cells (Tregs). It is promising to study expression of CD39 and CD73 in Treg and Th17 populations to assess their suppressive activity. Aim is to evaluate content of major and minor lymphocyte populations and expression of CD39 and CD73 in $CD4^+$ lymphocyte population in children with MS. 111 children with MS were examined, 66 with contrast-negative lesions on MRI (Group 1), 45 with contrast-positive lesions (Group 2). The comparison group consisted of 46 healthy children (Group 3). Content of T, B, NK lymphocytes, Treg ($CD4^+CD25^{high}CD127^{low}$), Thact ($CD4^+CD25^{high}CD127^{high}$), Th17 cells ($CD3^+CD4^+CD161^+$); expression of CD39 and CD73 in Treg, Th17 and Thact was performed by flow cytometry. An increase in content of T helpers, a decrease in NK cells in patients in group 2 was revealed. An increase in number of Thact and Th17 lymphocytes was obtained in patients of both groups with MS. Number of Tregs in group 1 was significantly higher than in group 3. Ratio of cells expressing CD39 and CD73 in MS patients depended on lymphocyte population as well as in the group 3. The highest content of $CD39^+$ cells was observed in Treg population, and the lowest in Thact population. For CD73 expression, on the contrary, the highest expression of CD73 was observed in Thact cells, the lowest in Treg. When comparing groups of patients, it was found that in patients of group 1, number of cells expressing CD39 ectonucleotidase was significantly increased, and number of supTh17 was comparable with group 3. In both groups of MS patients, an increase in CD73 counts in Treg, Thact and Th17 was observed. Thus, informative populations of lymphocytes ($CD4^+$ cells, Treg, $CD39^+$Treg, supTh17) have been identified, which can be used to monitor condition of children with multiple sclerosis.

Keywords: lymphocytes subsets, $CD4^+$ subsets, Treg, Th17, Thact, CD39, CD73, multiple sclerosis, children

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating disease, which is based on a complex of autoinflammatory and neurodegenerative processes leading to multiple focal and diffuse lesions of the central nervous system (CNS), resulting in disability of patients. There are about 2.8 million people with MS in the world. Since 2013, the prevalence of MS has increased in all regions of the world, in Russia it ranges from 51 to 100 cases per 100,000 population [15]. There are 2 main forms of MS: relapsing-remitting (RR) and primary progressive. The onset of MS disease in 3-5% of patients begins before the age of 16 [8]. MS in children is different from the disease in adults and has its own characteristics. Children are less likely to develop primary or secondary progressive multiple sclerosis; 98% of children with MS have a RR form of the course. Children have more frequent relapses and disability occurs 10 years earlier than adults [1, 8].

The etiopathogenesis of MS is not fully understood. It is believed that the disease occurs in a genetically determined individual under the influence of adverse

environmental factors [5]. There are over 200 genes associated with MS. Understanding of the process and the significance of certain genes is proven only for a few associated loci, such as variants of HLA-A*02:01 and HLA-DRB1*15:01, as well as genes encoding the α-chains of IL-2 and IL-7 receptors [11]. MS is caused by the activation of peripheral autoreactive effector T cells (Teff), which migrate to the CNS and initiate the pathological process [5]. Most Teff is discarded in the thymus (central tolerance), a small amount of Teff is released to the periphery. Normally, regulatory T cells (Treg) control peripheral tolerance mechanisms by downregulating the activity of various cell types, including Teff, cytotoxic $CD8^+$T cells, and antigen presenting cells (APCs), through intercellular contact and the secretion of suppressor cytokines [10].

When peripheral tolerance is disrupted, which involves genetic factors, environmental factors, including infectious agents (Epstein-Barr virus) and microbiota, cell clones are formed that, due to molecular mimicry, are capable of causing damage in the CNS [12, 14]. After entering the CNS, Teff ($CD8^+$T cells, Th1 and Th17 cells) and B lymphocytes activate cellular and humoral immunity reactions, secreting cytokines that cause the activation of CNS resident immune cells (microglia, astrocytes, macrophages), which also produce cytokines, amplifying functions of APC [8].

It is known that Teff in the CNS, in addition to Tregs, can be regulated by other regulatory cells: type 1 T regulatory cells (Tr1), $CD8^+$Tregs, NK cells, and B regulatory cells. Thus, an increase in the number of NK cells is associated with remission with effective therapy with daclizumab and IFNβ [3]. In patients with MS, it has been shown that Treg, as well as Tr1, have a reduced suppressor activity in relation to the inhibition of Teff proliferation [3]. The suppressor activity of Tregs can be assessed by the amount of CD39 and CD73 ectonucleotidase expressed on their surface.

CD39 and CD73 are enzymes expressed on the surface of immune cells that sequentially dephosphorylate pro-inflammatory ATP to adenosine, which has anti-inflammatory properties. To date, there are conflicting data regarding the expression of CD39 in Treg in patients with MS. Some studies have shown that the frequency of $CD39^+$ cells in the Treg population is reduced [4], in others, on the contrary, both their content and ATPase activity are increased, regardless of immunomodulatory treatment [2, 7]. In this regard, **the aim of this study** is to evaluate the content of major and minor lymphocyte populations, as well as the expression of CD39 and CD73 in the $CD4^+$ lymphocyte population in children with MS.

Materials and methods

We examined 111 children with MS at the age of 16 (14.2-17.5) years. MS patients were divided into groups based on clinical and anamnestic data and magnetic resonance imaging (MRI) results: group 1 – patients with contrast-negative demyelination foci (without active foci), n = 66; Group 2 – with contrast-positive foci of demyelination (with active foci), n = 45. We also examined 46 conditionally healthy children, comparable in age and with no deviations in the results of standard clinical and biochemical blood tests. The examination of all groups of children was carried out in accordance with the ethical and regulatory documents of the Russian Federation. The study was approved by the local ethical committee. Before the study, informed consent was obtained from the parents in accordance with the Declaration of Helsinki. Venous blood samples for the study were obtained by taking from the cubital vein on an empty stomach in BDVacutainer® tubes with K_2EDTA anticoagulant.

The content of the main and small populations of lymphocytes, as well as the study of the number of lymphocytes with the expression of CD39 and CD73 ectonucleotidase, was carried out by laser flow cytometry (Novocyte, ACEA Biosciences, USA). A panel of monoclonal antibodies conjugated to various fluorochromes was used: CD4-FITC (cat. A07750, Beckman Coulter, USA), CD127-PE (cat. IM 10980U, Beckman Coulter, USA), CD25-PC7 (cat. A52882, Beckman Coulter, USA), CD161-PE (cat. IM 3450, Beckman Coulter, USA), CD3-PC5 (cat. A07749, Beckman Coulter, USA), CD39-APC-Cy7 (Clone A1, cat. RT2241130 Sony Biotechnology, USA), CD73-APC-Cy7 (Clone AD2, cat. RT2320110, Sony Biotechnology, USA). The number of cells with $CD39^+$ and $CD73^+$ in Treg ($CD4^+CD25^{high}CD127^{low}$), activated T helpers (Thact – $CD4^+CD25^+CD127^{high}$), Th17 lymphocytes ($CD4^+CD161^+CD3^+$) was assessed using stepwise gating. To isolate Tregs and Thacts carrying CD39 and CD73, first, the "lymphoid" region was isolated according to the parameters of direct (FSC) and side (SSC) light scattering, $CD4^+$ positive lymphocytes were isolated, among $CD4^+$ cells, Tregs were isolated by markers ($CD4^+CD25^{high}CD127^{low}$) and Thact ($CD4^+CD25^{high}CD127^{high}$). Within the selected Treg and Thact regions, the percentage of cells carrying CD39 and CD73 was evaluated. Within the isolated region of Th17 cells ($CD3^+CD4^+CD161^+$), the number of cells expressing CD39 and CD73 was also evaluated.

The obtained data were statistically processed using the Statistica 10.0 program (StatSoft; USA). Descriptive statistics of quantitative traits are presented in the format: median (lower and upper quartiles) – Me ($Q_{0.25}$-$Q_{0.75}$). The significance of differences between groups was assessed using the nonparametric Mann–Whitney U test. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

The content of lymphocyte populations in patients with MS in groups without active foci and with active foci was assessed in comparison with apparently healthy children (Table 1). A significant increase in the relative content of T lymphocytes due to the population of T helpers was found in patients with active foci compared with healthy children. The content of NK cells was significantly reduced in patients with active lesions compared with apparently healthy children and compared with patients without active lesions.

In patients with MS in both groups, the content of small helper populations was also significantly increased. An increase in the population of Thact lymphocytes and an increase in the absolute number of Th17 lymphocytes were obtained. It is interesting to note that the number of Tregs in patients without active lesions was significantly higher than in the group of apparently healthy children. While in patients with active foci, the number of Treg was significantly lower than the comparison group.

As mentioned above, both Treg lymphocytes and NK cells are involved in the regulation of autoreactive lymphocyte clones in MS patients. In our study, in patients without active lesions, the number of Treg significantly increased and the number of NK lymphocytes was increased relative to patients with active lesions, which is a good prognostic sign for patients with MS [3].

TABLE 1. RELATIVE AND ABSOLUTE CONTENT OF MAJOR AND MINOR POPULATIONS OF LYMPHOCYTES IN CHILDREN WITH MS COMPARED WITH HEALTHY CHILDREN, Me ($Q_{0.25}$-$Q_{0.75}$)

Parameter	Patients without active foci n = 66	Patients with active foci n = 45	Comparison group n = 46
CD3, %	74.6 (69.4-78.8) p = 0.14	76.9 (72.4-80.3) p = 0.003	72.4 (67.9-75.3)
CD3, cells/μL	1302 (986-1744) p = 0.014	1344 (1134-1794) p = 0.089	1617 (1237-1850)
CD4, %	39.8 (37.0-48.6) p = 0.103	43.3 (39.3-48.9) p = 0.004	38.4 (35.2-44.6)
CD4, cells/μL	730 (535-945) p = 0.036	804 (616-1094) p = 0.52	857 (717-1016)
CD8, %	26.4 (22.2-31.0) p = 0.42	25.9 (23.3-30.3) p = 0.45	26.3 (24.1-31.9)
CD8, cells/μL	500 (337-633) p = 0.01	473 (383-630) p = 0.013	618 (415-804)
B lymphocytes, %	13.2 (10.7-17.5) p = 0.44	12.2 (9.2-17.4) p = 0.17	13.5 (12.1-17.5)
B lymphocytes, cells/μL	239 (189-367) p = 0.012	215 (137-319) p = 0.003	304 (252-370)
NK, %	11.9 (8.9-16.7) p = 0.62	9.4 (6.5-12.0)* p = 0.012	14.2 (8.3-17.2)
NK, cells/μL	212 (133-316) p = 0.046	180 (102-270)* p = 0.000	263.9 (177-402)
Treg, % from CD4	9.3 (7.5-10.9) p = 0.024	3.7 (3.1-4.6) p = 0.004	7.7 (7.2-9.4)
Treg, cells/μL from CD4	63 (48-86) p = 0.46	76 (53-95) p = 0.09	67.3 (54-89)
Thact, % from CD4	21.7 (15.5-27.3) p = 0.000	18.9 (12.9-24.9) p = 0.000	14.1 (9.9-16.5)
Thact, cells/μL from CD4	149 (104-196) p = 0.016	153 (92-207) p = 0.014	117.1 (83-139)
Th17, % from CD4	21.2 (16.9-25.7) p = 0.000	20 (15.8-25.6) p = 0.004	17.1 (14.0-19.4)
Th17, cells/μL from CD4	151 (109-188) p = 0.81	167 (131-208) p = 0.21	150.2 (118-172)

Note. *, $p < 0.05$ between groups of patients with MS.

In children with MS, an analysis of the number of cells expressing CD39 and CD73 ectonucleotidase showed that the content of populations with the highest and lowest number of $CD39^+$ and $CD73^+$ cells in lymphocyte populations is comparable to that in conditionally healthy children [13]. Thus, the highest content of $CD39^+$ cells was noted in the Treg population and amounted to Me-34.5 (29.5-44.6) %, and the smallest number in the Thact population was Me-3.5 (1.8-5.7) %. The reverse situation was observed for CD73 expression. The highest expression of CD73 was in Thact cells -Me-21.9 (16.4-28.9) %, and the lowest in Treg -Me-13.2 (9.6-20.9) %.

An analysis of the expression of ectonucleotidase in the populations of Th17, Thact and Treg lymphocytes in patients without active foci (n = 42), with active foci (n = 26) and in the group of apparently healthy children (n = 34) is shown in Figure 1.

When comparing the expression of ectonucleotidase in groups of patients with MS with a group of apparently healthy children, a significant increase in cells expressing CD39 in Treg in patients without

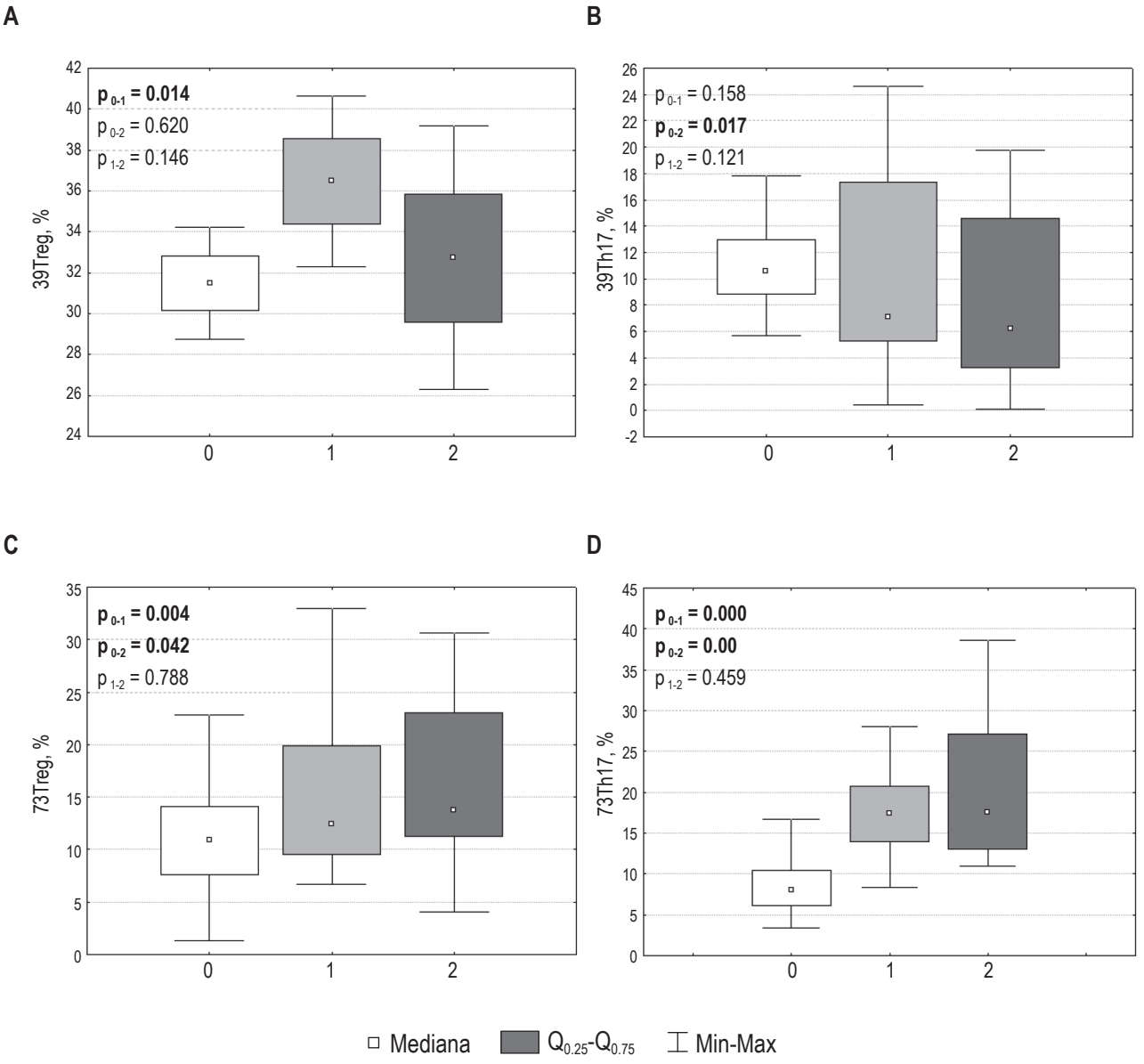

Figure 1. Relative content of CD39 and CD73 in the populations of Th17 lymphocytes and Treg in patients with MS of the group of apparently healthy children

Note. 0, group of apparently healthy children; 1, group of MS patients without active lesions; 2, group of MS patients with active lesions.
p, reliability between groups of patients and conditionally healthy children. (A) % of Treg expressing CD39. (B) % of Th17 expressing CD39. (C) % of Treg expressing CD73. (D) % of Th17 expressing CD73.

active foci was shown (Figure 1A). The number of CD39$^+$Th17 lymphocytes was significantly reduced in patients with MS with active lesions compared with apparently healthy children (Figure 1B). As for patients without active lesions, the number of Th17 expressing CD39$^+$ was comparable to that of apparently healthy children. It is known that the Th17 population expressing CD39 ectonucleotidase (supTh17) has suppressor properties [6]. Thus, in children with MS in the group with active foci, a decrease in the content of supTh17 was revealed. For Thact, a significant decrease in the number of cells expressing CD39 was found in patients of both groups with MS, and in the group of patients with active foci, this decrease was more significant ($p_{0\text{-}1} = 0.000$, $p_{0\text{-}2} = 0.000$). At the same time, the expression of CD73 in the populations of Treg (Figure 1C), Thact ($p_{0\text{-}1} = 0.000$, $p_{0\text{-}2} = 0.000$) and Th17 (Figure 1D) was significantly higher in both groups of patients relative to the control group.

The greatest differences in the content of the main and small populations of lymphocytes in children with MS relative to conditionally healthy children were found in patients with active foci of demyelination according to MRI and consisted in an increase in the content of T lymphocytes, T helpers and a decrease in the content of NK cells. More significant differences were revealed when assessing small populations of lymphocytes, namely: a decrease in Treg in patients with active foci, while an increase in this regulatory population was detected in patients without active foci. In patients without active foci, in addition to an increase in the number of Treg, the content of cells expressing CD39 ectonucleotidase increased, and the amount of supTh17 was comparable with the group of conditionally healthy children. As for the increase in CD73 ectonucleotidase in Treg, Thact, and Th17 in patients with active foci, this can be regarded as a compensatory mechanism in response to a decrease in the regulatory populations of lymphocytes – Treg, NK cells, and supTh1.

Conclusion

Thus, informative populations of lymphocytes (CD4$^+$ cells, Treg, CD39$^+$Treg, supTh17) have been identified, which can be used to monitor the condition of children with multiple sclerosis.

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