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Condition of the Immune System in Patients with Various Variants of Cephalgia in an Interictal Period

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Abstract The aim of the present study was to analyze the neurological and immunological aspects of a headache in children. Were examined 24 children with simple migraine, 18 children with migraine with aura and 13 children with tension type headache, with determining the number of circulating T-lymphocytes ($CD3^+$) and their main immune regulating subpopulations of T-helper and T-cytotoxic cells ($CD4^+$, $CD8^+$), B lymphocytes ($CD20^+$), immune regulatory index (IRI), marker of apoptosis ($CD95^+$) in the inter attack period, with remission of somatic diseases. As a result of a comparative analysis of the obtained indicators of the immune system in patients, there was no significant deviation in the cellular immunity parameters relative to control values, which indicates that they have immune homeostasis in the inter attack period.

Keywords A headache, Migraine, Children, Immunology, Cellular immunity

1. Introduction

The problem of a headache in modern neurology remains one of the leading ones [1, 2]. Headache is also one of the most frequent complaints of child age, about which parents treat to the doctor. A wide range of diseases associated with headaches, the diversity of their clinical manifestations, the frequent persistence of the course reflects the urgency of the problem of headaches in pediatrics and neurology [3, 4]. The most frequent types of primary headaches are migraine and tension type headache (TTH) [5], and in 15% of patients, the first attacks occur before the age of 10 years [6].

Despite the huge interest of domestic and foreign researchers in the changes of cellular and humoral immunity accompanying with various pathological conditions, immunological aspects of the pathogenesis of primary cephalgia (an autoimmune component, etc.) in literature practically not discussed, though the close interrelation of NMDA - receptors with immunological indicators is well known. In this regard studying of the immune status of patients with primary headaches is of considerable interest [7-11].

The pathogenesis of cephalgia is complicated and not fully learned. Modern immunology is one of the most actively developing branches of science, continuously expanding its borders by introducing into various areas of clinical medicine [12]. It has been proved that the immune system is not limited to identifying and destroying foreign antigens, an increasingly strong position is taken by the idea of its ability to control non-immune functions of the body [13]. In this regard, a whole new direction has emerged, such as non-infectious immunology. However, the influence of the immune system on the development and progression of primary headaches is not fully understood what an important source of discussion.

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2. Main Body

2.1. Purpose of the Study

To study and determine the state of the immune system in patients with various types of cephalgia in the inter attack period.

2.2. Materials and Methods of Investigation

Forty-two children with a diagnosis of a child migraine enrolled in a study. 24 children with simple migraine — girls 54.2% (13), boys 45.8% (11), respectively; 18 children with migraine with aura- girls 55.5% (10), boys 44.4% (8), respectively and 13 children diagnosed with tension type headache, 38.5% (5) were girls and 46.2% (6) boys. The average age of children was -12.44 ± 0.46.

Based on anamnestic, clinical and neurological data, the third edition of the International Classification of Headache Disorders (ICHD-3) 2013 used for the diagnosis of a migraine. Additionally, the following paraclinical studies were carried out for the purpose of differential diagnosis: MRI, EEG, TCDG, and consultations with narrow specialists.

The assessment of the immunological status was performed according to the recommendations of R.M. Khaitov [14] and 1-level tests for T-cell immunity in the following indicators: the number of circulating T-lymphocytes (CD3) and their main immune regulatory subpopulations of T-helper and T-cytotoxic cells (CD4, CD8), B-lymphocytes (CD20) using monoclonal antibodies, produced by the Research Institute of Immunology of the Ministry of Health of the Russian Federation (Moscow, "Sorbent" company) according to the method of Garib F.Yu. with co-authors [15]. Blood lymphocytes were analyzed in a group of 42 previously diagnosed childhood migraine patients and 13 children with a tension type headache. This is the cross-sectional analysis, which data collection performed in the morning, only in the inter attack period, with remission of somatic diseases.

2.3. Statistical Analysis

Collected data were recorded into previously prepared forms, and the statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 17.0 software package. Continuous values were presented as median and mean±standard deviation, where suitable. Fisher's exact test were used to compare categorical variables among groups. The Mann–Whitney U test was used to compare nonparametric variables. The categorical values were presented as number and percentage. Statistical significance was set at $p<0.05$.

2.4. Results and Discussion

According to anamnestic studies, 23% of children with a diagnosis of a migraine were diagnosed with a burdened perinatal history, with tension type headache (TTH) 6% of children, respectively. In 27% of children with a migraine, the hereditary nature of the disease was observed through the maternal line, whereas with a diagnosis of TTH, these figures were 4%. In 32% of children with a migraine, concomitant chronic somatic diseases of the ENT organs were detected, whereas in TTH this was 8% of children.

During the clinical and neurological examination in the inter attack period, there were no gross focal symptoms, there was a diffuse micro symptomatology of a residual nature, in children with a migraine 26%, in TTH 11% of children; Symptoms of peripheral cervical insufficiency were observed in children with a migraine in 22% of cases, whereas in TTH in 4% of children. The most pronounced symptoms were vegetative disturbances in the form of hyperhidrosis of the palms and feet, meteolability, mood swings in the inter attack period in 28% of children with a migraine and in 9% of children with TTH.

According to paraclinical studies on MRI of the brain, signs of angioencephalopathy were observed in 24% of the examined children with a diagnosis of a migraine, with TTH - in 8% of the children; 9% of children with a migraine had foci of demyelination, with TTH, the incidence was 2% of children and 57% of children did not show any pathological changes. EEG studies of the brain revealed dysfunction of the brainstem structures in 28% of children with a migraine, with TTH it was 9%, increased convulsive activity in 15% of patients with a migraine, with TTH 3%, respectively; diffuse changes in the brain were detected in 34% of children with a migraine, with TTH were 11%.

Transcranial Doppler sonography of the head vessels revealed a lack of blood supply in the vertebrobasilar system in 48% of patients with a migraine, with TTH in 5% of children. The anomaly of vascular development was noted in 12% of children with a migraine, with TTH in 2% of children. In 16% of children with a migraine and in 17% of children with TTH, there were no pathological disorders in the blood supply.

Based on the results of the study in a comparative aspect, conducted in a group of children with a diagnosis of migraine and tension headache, analysis of subjective and objective clinical and neurological parameters, along with the results of paraclinical studies (MRI, EEG, TCD), confirms the literature on the occurrence of headaches migraine pain with pathogenetic mechanisms of vascular genesis. Whereas in TTH, these studies cannot serve as reliable indicators of the connection of this nosology with a vascular genesis.

The results of immunological studies: Baseline indicators of absolute values of leukocytes in the examined groups showed no significant changes. Thus, there is a slight decrease in patients with a tension headache and migraine (6130.77 ± 347.92 and 5845.83 ± 202.49 μl, respectively, with control values of 6900 ± 600.0 μl), together with this with a migraine a small leukocytosis is observed with aura (7066.67 ± 406.80 μl, $P> 0.05$).

Absolute and relative values of lymphocytes show pronounced lymphocytosis in these conditions. Thus, the highest average values of relative indices are observed with tension headache (42.08 ± 1.90% and), slightly less with migraine with aura (41.67 ± 1.55%) and least of all with migraine (39.92 ± 1.21%), relative to the control (32.9 ± 2.2%), the absolute values of lymphocytes with tension headache (576.92 ± 200.22 μl) were significantly reduced as compared to the control (2288.6 ± 260.4 μl) and values in patients with migraine (2333.33 ± 106.60 μl) and migraine from auras (2968.78 ± 204.76 μl, $P <0.05$).

A comparative analysis of the relative and absolute indices of cellular immunity in patients showed the absence of pronounced disorders, with the exception of the absolute values of T-lymphocytes and T-cytotoxic cells in patients with migraine with aura.

Thus, the mean values of the relative index of the total pool of CD3+ lymphocytes in patients with tension headache do not practically differ from the mean values of the control group (53.38 ± 0.94% and 53.6 ± 1.5%, respectively), also there is a slight but not significant increase in the absolute values of the index (1367.08 ± 98.84 and 1207.8 ± 129.8 μl, respectively).

Table 1. Characteristics of cellular immunity in patients with primary headaches (%, M ± m)

Indicators	Healthy child (n=30)	Tension type headache (TTH) (n=13)	Migraine (n=24)	Migraine with aura (n=18)
Lymphocytes, μl	6900 ± 600,0	6130,77 ± 347,92	5845,83 ± 202,49	7066,67 ± 406,80
Lymphocytes, μl,%	32,9 ± 2,2	42,08 ± 1,90*	39,92 ± 1,24*	41,67 ± 1,55*
Lymphocytes, μl	2288,6 ± 260,4	576,92 ± 200,22*	2333,33 ± 106,60•	2968,78 ± 204,76*
$CD3^+$ (%)	53,6 ± 1,5	53,38 ± 0,94	51,54 ± 0,91	50,83 ± 0,80
$CD3^+$, μl	1207,8 ± 129,8	1367,08 ± 98,84	1193,67 ± 51,31•	1519,78 ± 115,24*
$CD4^+$ (%)	28,2 ± 1,0	29,23 ± 0,68	27,96 ± 0,69	27,11 ± 0,47
$CD4^+$, μl	633,9 ± 66,6	750,23 ± 59,90	647,08 ± 27,98	806,00 ± 61,41
$CD8^+$ (%)	23,4 ± 1,0	24,15 ± 0,74	23,58 ± 0,71	23,72 ± 0,75
$CD8^+$, мкл	532,9 ± 59,6	616,85 ± 43,94	546,58 ± 27,34	713,83 ± 58,14*
IRI ($CD4^+/CD8^+$)	1,2 ± 0,1	1,22 ± 0,06	1,23 ± 0,05	1,19 ± 0,05
$CD20^+$ (%)	18,6 ± 0,5	20,23 ± 0,45*	20,79 ± 0,29*	20,50 ± 0,46*
$CD20^+$, μl	435,7 ± 57,2	521,69 ± 42,56	488,04 ± 24,95	593,00 ± 39,44
$CD95^+$ (%)	23,6 ± 2,2	22,54 ± 0,63	24,79 ± 0,68	23,39 ± 0,71

Note: * - p <0.05 - the significance of differences relative to healthy individuals;
● - p <0.05 - the significance of differences in the dynamics of the disease

There is also some (unreliable) decrease in both absolute values of CD3+ lymphocytes relative to the control group (1207.8 ± 129.8 and 1193.67 ± 51.31%, respectively) and relative indicators of CD3 + lymphocytes in patients with a migraine (53, 6 ± 1.5% and 51.54 ± 0.91%, respectively).

The somewhat contradictory position is noted in the initial values of the relative and absolute indicators of the total pool of T-lymphocytes in migraine with aura, i.e. with a slight decrease in relative indices of CD3 + lymphocytes (50.83 ± 0.80%, with a control of 53.6 ± 1.5%), there are reliably high absolute values of this indicator both in relation to control values and values observed in patients with migraine (1519.78 ± 115.24; 1207.8 ± 129.8 and 1193.67 ± 51.31 μl, respectively).

The mean absolute values of the T-helper population of T-lymphocytes shows that the direction of changes in the mean values showed a slight increase in patients with tension headache and migraine with aura (750.23 ± 59.90 and 806.00 ± 61.41 μl, accordingly, the indices of CD4 + lymphocytes in patients with a migraine (647.08 ± 27.98 μl) relative to control values (633.9 ± 66.6 μl) practically do not change.

A comparative analysis of the relative values of CD4 + lymphocytes showed insignificant visible changes in mean values (increase) in patients with a tension headache (29.23 ± 0.68%), and a slight decrease in patients with migraine (27.96 ± 0.39%) and in patients with migraine with aura (27.11 ± 0.47%) relative to the values in the control (28.2 ± 1.0%). Since T-helpers determine the intensity and direction of immunological reactions, their reduction in peripheral blood is possibly related to the recycling of lymphocytes and the participation of these cells in immunological reactions in areas of inflammation.

An identical picture is also observed in the assessment of changes in the relative indicators of the T-cytotoxic cell subpopulation of T-lymphocytes, namely, the initial values of CD8 + lymphocytes with a tension headache was 24.15 ± 0.74%, with migraine 23.58 ± 0.71% and migraines with aura of 23.72 ± 0.75%, which are slightly different from the control values - 23.4 ± 1.0%.

More significant abnormalities are observed in absolute values of CD8 + lymphocytes, i.e., there is an increase in the latter in all pathologies, but only in migraine patients with aura they have a statistically significant difference (713.83 ± 58.14 μl, P <0.05) relative to the values in the control (532.9 ± 59.6 μl), which is not observed with tension headache (616.85 ± 43.94 μl) and with migraine (546.58 ± 27.74 μl) (P> 0.05).

The observed picture of the initial values of the relative indices of T-lymphocyte T-helper and T-cytotoxic lymphocyte subpopulations leads to unexpressed changes in the IRI values like with a tension headache (1.22 ± 0.06), with a migraine (1.23 ± 0.05) and migraine with aura (1.19 ± 0.05) with IRI in the control - 1.2 ± 0.1.

Since apoptosis is one of the immune regulatory mechanisms, the next step in the study was to evaluate the expression of CD95 on blood lymphocytes as a membrane marker of readiness for apoptosis. The study of apoptosis processes is an integral part of the study of immune pathological processes. To understand and determine the level of inflammation in the body at the moment, i.e. the moment of determining the indicators of cellular immunity in our patients, we studied the level of apoptotic readiness of lymphoid cells on the content of CD95+ lymphocytes.

The obtained results show a slight decrease in the average indices of this marker in the groups of patients with tension and migraine headache with aura (22.54 ± 0.63%, 23.39 ± 0.71%, respectively) relative to the values in the control (23.6 ± 2.2%) and a slight increase in patients with migraine (24.79 ± 0.68%). In general, CD95 lymphocytes are expressed by activated CD4 + and CD8+ T-cells, while

resting T-lymphocytes do not express the Fas-ligand, and considering the state of subpopulation T-lymphocyte cells in our patients at the time of the study, it is possible to explain the lack of significant changes in the parameters of apoptosis factor.

At the same time, there is a significant increase in the average values of B-lymphocytes in all groups of examined patients. So, with headache tension to 20.23 ± 0.45%, with a migraine 20.79 ± 0.29%, with a migraine with aura 20.50 ± 0.46%. Considering that B-lymphocytes are producers of immune globulins, the observed situation indicates that the transferred or ongoing inflammatory process in the body.

It is proved that in the development of cephalgia are important as stem and hypothalamic region of the brain involved in turn and in the modulation of the immune response [16]. Secretory products of immune cells, possessing neurotropic action, can influence the processes underlying the headache onset: hyperexcitability of the cortex, peripheral and central sensitization, neurogenic inflammation [17, 18].

Therefore, there is a possibility of modification of the course unit under the influence of an imbalance in the immune system. In turn, a cascade of reactions that implements the manifestations cephalgia, may contribute to the development of immune disorders.

3. Conclusions

As a result of a comparative analysis of the obtained results of the immune system in patients with migraine, migraine with aura and tension type headache, there were no significant deviations of cellular immunity indicators relative to control values, except for a significant increase in B-lymphocytes, which indicates a postponed inflammatory process and indicates the integrity they have an immune homeostasis in the interictal period.

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