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CLINICO-IMMUNOLOGIC DISORDERS IN THE ACUTE PERIOD OF ISCHEMIC STROKE

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Abstract

To study the immune status of patients in the acute period of ischemic stroke a clinical and immunological observation of 45 patients was performed. On the 2nd day of the disease the increase in the leukocyte count ($p < 0.01$), the decrease in lymphocytes ($p < 0.05$), T-lymphocytes (CD3 +) ($p < 0.01$), T-helpers (CD4 +) ($P < 0.01$) and cytotoxic T-lymphocytes (CD 8+) ($p < 0.05$), the increase in the number of Blymphocytes (CD20 +) ($p < 0.05$) and disgammaglobulinemia due to the tendency to hyperfunction IgA and IgM ($p > 0.05$) and an increase in IgG ($p < 0.05$) were observed. Deviation of the immune status of normal values was more pronounced with increasing severity of neurological symptoms and infarct size. Thus, these studies demonstrate the involvement of the immune system in a complex set of reactions involved in the development of cerebral infarcts and suggest an increased susceptibility of these patients to the development of infectious complications.

Key words: ischemic stroke, immune status.

Introduction

According to the medical service of state statistics, vascular diseases of the cerebral vessels occupy the second place in the structure of mortality from diseases of the circulatory system (39%) and total mortality of the population (23.4%). The annual mortality from stroke in the world remains one of the highest. Complications associated

with the main pathological process are more often the cause of death than the immediate severity of stroke . In stroke survivors over the age of 60, complications are the cause of death in 68% of cases, and the immediate severity of vascular brain damage is only in 32%. Complications directly caused by gross extensive damage to brain structures develop in the very near term after the occurrence of the most severe forms of stroke. At a relatively late date, somatic complications develop, due to the immobility of patients, vegetative dysfunction and infection, therefore, their treatment and prevention are of paramount practical importance. The interaction of the nervous and immune systems, carried out on the principle of mutual regulation, determines the risk of disruption of the functions of one of them in the pathology of the other. Recently, in the pathogenesis of ischemic stroke (IS), great importance has been attached to immunological mechanisms, including the autoimmune process, which aggravates the clinical picture and contributes to neurological deficiency. The formation of antibodies to DNK in the acute period of IS occurs as a result of intense destructive processes in the brain, accompanied by cellular decay, violation of tissue homeostatic processes, and these indicators correlate with the severity of the pathological process and the degree of regression of the neurological defect – the higher the level of antibodies to DNK, the more pronounced the neurological defect. The main one in the pathogenesis of stroke is damage to the vascular wall endothelium, which occurs with the participation of immune factors and is associated with the settling of immune complexes on the inner surface of the vessels [8,9,10].

According to the Federal State Statistics Service, vascular diseases of the cerebral vessels occupy the second place in the structure of mortality from diseases of the circulatory system (39%) and total mortality of the population (23.4%). Annual mortality from stroke in Russia remains one of the highest in the world [5]. Complications associated with the main pathological process in stroke survivors over the age of 60 are the cause of death in 68% of cases, and the immediate severity of vascular brain damage is only in 32% [1]. Somatic complications caused by immobility of patients, vegetative dysfunction and infection develop at a relatively late date, therefore their treatment and prevention are of paramount practical importance [1,2].The interaction of the nervous and immune systems, carried out on the principle of mutual regulation, determines the risk of disruption of the functions of one of them in the pathology of the other [3, 4].

Analysis of the literature data on the parameters of the immune status in cerebrovascular pathology revealed that its development is accompanied by leukocytosis

in combination with relative lymphopenia, suppression of the T-cell link of the immune system (decrease in mature CD3+, immunoregulatory CD4+, cytotoxic CD8+-Tlymphocytes) and activation of the humoral immune response with an increase in the blood content in-lymphocytes (CD19+, CD20+), Ig A, M, G and circulating immune complexes (CEC) [2, p. 58].Studies devoted to the study of the relationship of immunological parameters with specific characteristics of stroke, such as the assessment of neurological deficit on the NIHSS scale and the volume of the infarction focus, have yielded contradictory results [6,7], which requires further research in this direction.

The purpose of this clinical and immunological analysis was to study the state of the immune status in patients in the acute period of AI, the dependence of the main indicators of immunity on the severity of neurological symptoms and the size of the focus of cerebral infarction.

Material and methods of research

Clinical and immunological examination of 45 patients (22 women and 23 men) aged from 44 years to 81 years (average age 64.3 ± 1.8 years) in the acute period of AI, who were treated in the Bukhara State Medical Institute, was performed.

The clinical diagnosis was made on the basis of anamnestic information, the results of subjective and objective neurological symptoms, and data from additional examination methods (CT or MRI of the brain, duplex MAG scanning, analysis of cerebrospinal fluid) in accordance with ICD 10 revision. The severity of neurological symptoms assessed on the NIHSS scale averaged 6.37 ± 0.75 points.

The immunological study was conducted on the 2nd day of the patients' stay in the hospital. Mononuclear cells were isolated from venous blood at a density gradient of ficoll – verografin (p = 1,077). Phenotyping of peripheral blood lymphocytes was performed by indirect immunofluorescence using monoclonal antibodies to CD3+, CD4+, CD8+, CD20+, CD16+, CD25+ differentiation clusters, the FITZ fluorescent label was used.The smears were counted using a luminescent microscope "Lumam-P8" using a combination of light filters. The concentration of serum immunoglobulins was determined by Mancini radial immunodiffusion using monospecific antiserums (N.F. Gamalei Research Institute of Epidemiology and Microbiology, Moscow). The indicators of 20 practically healthy individuals, representative by gender and age, were used as normative values.

To identify a possible relationship between the severity of immunological disorders and the severity of neurological symptoms, the immune status indicators of patients with mild severity on the NIHSS scale (from 3 to 8 points, 27 people) and with moderate and severe severity (over 8 points, 18 people) were compared. In order to study the possible influence of the size of the infarction focus on immunological parameters, 2 groups of patients were compared: the first – with the size of the focus (according to the results of

CT or MRI of the brain) up to 15 mm (25 people) and the second – more than 15 mm (20 people).

Statistical data processing was carried out using the Microsoft Office 2013 (Excel) and Statistica 6.0 software package. Quantitative variables are presented as an average value ± standard error of the average value (X ± mx), the Student's t-test was used to assess the statistical significance of the observed differences.

Results and their discussion

The study showed that in the acute period of AI, on the 2nd day from the onset of the disease, there was a quantitative and qualitative change in the immune status: a significantly pronounced increase in the content of leukocytes (p 0.01) and a decrease in lymphocytes (p 0.05) compared with the indicators of relatively healthy individuals. Pronounced suppression of the T–cell link of the immune system was manifested in the form of a significant decrease in the relative level of mature T-lymphocytes (CD3+) (p < 0.01) and the subpopulation composition of Tlymphocytes with a significant decrease in the relative and absolute values of T-helper cells (CD4+) and cytotoxic T-lymphocytes (CD8+) (p 0.01 and p 0.05, respectively) (Table 1).

There was also a tendency to decrease the content of natural killers (NK cells, CD16+) and cells expressing receptors for IL-2 (CD25+) (p 0.05). In the humoral link of immunity, there was a significant increase in the number of B-lymphocytes (CD20+) (p 0.05) and dysgammaglobulinemia due to the tendency to hyperfunction of IdA and IgM (p 0.05) and a significant increase in IgG content (p 0.05) (Table 1). Thus, the analysis of the results showed that the development of acute cerebrovascular pathology is accompanied by leukocytosis in combination with lymphopenia, suppression of the T-cell link of the immune system and activation of the humoral immune response. These observations indicate the active participation of immunological mechanisms in the pathogenesis of AI.

Table 1. Indicators of immune status in patients in the acute period of ischemic stroke on the 2nd day from the onset of the disease compared with healthy individuals

Indicators	Healthy (n =20)	Patients with IS (n = 45)	P
SPaul, men/women, abs., %	11/9 55/45	23/22 51/49	p > 0,05
Age	61,6 ± 2,2	64,3 ± 1,8	p > 0,05
Leukocytes, 10^9/l	5,2 ± 1,4	7,6 ± 0,72	p < 0,01
Lymphocytes, %	30,0 ± 4,8	27,6 ± 2,44	p < 0,05
T-lymphocytes (CD3+), %	57,0 ± 4,6	47,4 ± 0,59	p < 0,01

T-lymphocytes (CD3+), x 10^9/l	1,0 ± 0,39	1,0 ± 0,09	p > 0,05
B-lymphocytes (CD20+), %	12,0 ± 3,1	17,27 ± 3,8	p < 0,05
B-lymphocytes (CD20+), x 10^9/l	0,24 ± 0,06	0,38 ± 0,12	p < 0,05
T-helpers (CD4+), %	40,2 ± 5,1	32,7 ± 2,59	p < 0,01
T-helpers (CD4+), x 10^9/l	1,2 ± 0,32	0,92 ± 0,07	p < 0,05
T-cytotoxic/suppressors (CD8+),%	21,2 ± 4,1	15,7 ± 1,36	p < 0,05
T-cytotoxic/suppressors (CD 8+), x 10^9/l	0,6 ± 0,08	0,52 ± 0,03	p > 0,05
IRI	2,04 ± 0,6	2,12 ± 0,06	p > 0,05
NK (Natural Killers) (CD16+), %	10,2 ± 1,2	8,2 ± 0,41	p > 0,05
CD25+, %	10,4 ± 0,9	9,1 ± 0,65	p > 0,05
Ig A, g/l	1,62 ± 0,2	1,82 ± 0,07	p > 0,05
Ig M, g/l	1,22 ± 0,14	1,27 ± 0,04	p > 0,05
Ig G, g/l	12,6 ± 1,2	13,6 ± 0,36	p < 0,05

When comparing the immune status in groups of patients with varying degrees of stroke severity (Table. 2) it was noted that the indicators of the severity of lymphopenia and reduction of T-lymphocytes (CD3+) were significantly lower (p 0.05) in moderate and severe stroke compared with the group of patients with mild course.

There was also a significant difference in the comparison groups of Tlymphocyte subpopulations (CD4+) (p 0.05) and (CD 8+) (absolute values) (p 0.005) correlating with the severity of the course. In severe AI, there was a more pronounced decrease in NK cells (CD16+) and cells expressing receptors for IL-2 (CD25+) (p 0.05). When analyzing the indicators of the humoral link of immunity, there was no significant difference in the content of B-lymphocytes and immunoglobulins, depending on the severity of IS.

Thus, a decrease in the content of T-lymphocytes (CD3+), T-helper cells (CD4+), T-cytotoxic lymphocytes (CD8+), NK cells (CD16+) is an indirect sign of the severity of AI, the threat of complications and the possibility of an unfavorable outcome of IS.

Table 2. Average indicators of immune status depending on the severity of neurological symptoms on the NIHSS scale and on the size of the stroke.

Indicator	Light degree severity on the scale	Moderate and severe degree severity on the scale	P1	The size of the hearth is up to 15 mm in	The size of the hearth is more than 15 mm in	P2

	NIHSS n=27	NIHSS n=18		diameter n=25	diameter n=20	
Leukocytes, 10^9/l	7,18 ± 0,7	7,75 ± 1,02	> 0,05	7,82 ± 0,74	6,55 ± 0,84	> 0,05
Lymphocytes, %	33,4 ± 3,04	22,3 ± 3,4	< 0,05	29,9 ± 3,1	24,8 ± 4,72	< 0,05
T- lymphocytes, % (CD3+), %	48,0 ± 0,79	45,13 ± 0,79	< 0,05	48,33 ± 0,8	47,6 ± 0,78	> 0,05
T- lymphocytes, % (CD3+), x 10^9/l	1,01 ± 0,07	0,72 ± 0,17	< 0,05	1,02 ± 0,07	0,77 ± 0,08	< 0,05
B- lymphocytes, % (CD20+), %	17,13 ± 0,26	17,28 ± 0,31	> 0,05	17,13 ±0,27	17,45 ± 0,25	> 0,05
B- lymphocytes, % (CD20+), x 10^9/l	0,24 ± 0,12	0,30 ± 0,20	> 0,05	0,25 ± 0,12	0,28 ± 0,20	> 0,05
T- helpers (CD4+), %	33,0 ± 0,53	30,63 ± 0,73	< 0,05	33 ± 0,56	29,12 ± 0,65	< 0,05
T- helpers (CD4+), x 10^9/l	0,9 ± 0,06	0,71 ± 0,13	< 0,05	0,9 ± 0,07	0,74 ± 0,07	< 0,05
Cytotoxic/Suppressors (CD 8+), %	15,8 ± 0,39	14,25± 0,37	> 0,05	15,47 ±0,39	13,6± 0,38	< 0,05
Cytotoxic/Suppressors (CD 8+), x 10^9/l	0,55 ± 0,02	0,46 ± 0,06	<0,005	0,55 ± 0,03	0,46 ± 0,03	< 0,005
IRI	2,04 ± 0,04	2,11 ± 0.06	> 0,05	2,07 ± 0,04	2,06 ± 0.07	> 0,05
NK (natural killers) (CD16+), %	7,67 ± 0,23	6,88 ± 0,44	> 0,05	7,4 ± 0,28	7,08 ± 0,42	> 0,05
CD25+, %	9,8 ± 0,5	8,13 ± 0,85	> 0,05	9,73 ± 0,57	9,23 ± 0,71	> 0,05
Ig A, g/l	1,18 ± 0,07	1,02± 0,09	> 0,05	1,78 ± 0,08	1,82± 0,07	> 0,05
Ig M, g/l	1,18 ± 0,03	1,16 ± 0,03	> 0,05	1,18 ± 0,03	1,28 ± 0,03	> 0,05
Ig G, g/l	13,2 ± 0,27	13,33 ± 0,4	> 0,05	13,3 ± 0,3	13,4 ± 0,34	> 0,05

Focus Comparison of immunological indicators in patients depending on the size of the cerebral infarction focus (Table. 2) showed a more pronounced immunosuppression (decreased leukocyte count (p 0.05) and more pronounced lymphocytopenia (p <0.05)) with large focal sizes. With a significant difference, the content of absolute indicators of T lymphocytes (CD3+) was reduced, as well as a decrease in immunoregulatory cells of Thelpers (CD4+) (P<0.05) and T-cytotoxic lymphocytes (CD8+) (P<0.005). Indicators reflecting the state of humoral immunity indicated a slight tendency to increase the content of B-lymphocytes (CD20+), immunoglobulins A, M and G (p 0.05) with the size of the infarction focus more than 15 mm. Thus, the results indicate that with large foci of infarction, immunosuppression develops, which is manifested by a more pronounced decrease in leukocytes, lymphocytes, T-lymphocytes (CD3+), T-helper cells (CD4+) and T-cytotoxic cells (CD8+) and a tendency to increase B-lymphocytes with activation of production immunoglobulins.

Thus, these studies prove the involvement of the immune system in a complex set of reactions involved in the development of brain infarcts. The deviation of the immune status indicators from normal values turned out to be more pronounced with an increase in the severity of neurological symptoms and the size of the heart attack focus. The data obtained in our study on the development of pronounced immunological disorders in the acute period of AI suggest an increased susceptibility of these patients to the development of infectious complications, and therefore the assessment of the parameters of the immune system in such patients and their correction are of great practical importance in the complex of early rehabilitation measures.

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