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Characteristics of the Immune Status in Patients in the Acute Period of Ischemic Stroke

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Abstract

To study the immune status of patients in an acute period of ischemic stroke, a clinical and immunological observation of 45 patients was performed. At the 2nd day after the onset of the disease, an increase in the leukocyte count ($p<0.01$) and a decrease in lymphocytes ($p<0.05$), T-lymphocytes (CD3+) ($p<0.01$), T-helpers (CD4+) ($p<0.01$) and cytotoxic T-lymphocytes (CD8+) ($p<0.05$) were observed. There was also a tendency to decrease the content of natural killers (NK cells, CD16+) and cells that express the receptors for IL-2 (CD25+) ($p>0.05$). In the humoral immunity an in- crease in the number of B-lymphocytes (CD20+) ($p<0.05$) and dysgammaglobulinaemia due to the ten- dency to hyperfunction IgA and IgM ($p>0.05$) and an increase in IgG ($p<0.05$) was observed. Deviation of the immune status of normal values was more pronounced with increasing severity of neurological symptoms and infarct size. With a moderate and severe stroke on the NIHSS scale and the infarct size of more than 15 mm, more pronounced lymphopenia ($p<0.05$) was noted with a significant decrease in the T-lymphocyte (CD3+) ($p<0.05$), T-lymphocyte subpopulations (CD4+; $p<0.05$) and CD8+; $p<0.005$), as well as NK cells (CD16+) and cells expressing receptors for IL-2 (CD25+) ($p>0.05$). Thus, these studies demonstrate the involvement of the immune system in a complex set of reactions involved in the development of cerebral accidents and suggest an increased susceptibility of these patients to the de- velopment of infectious complications.

Keywords: ischemic stroke, immune system, immune status, cellular and humoral immunity.

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The lack of immune status changes against standard therapy requires an immune-corrective therapy (in case of violations of basic parameters of the immune system).

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 rate from stroke in the world remains one of the highest [9]. Complications joining the main pathological process are more often the cause of death than the immediate severity of stroke [2].

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% [2]. 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 [2], 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 [5, 8, 10]. Recently, in the pathogenesis of ischemic stroke (AI), 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 DNA in the acute period of AI occurs as a result of intense destructive processes in the brain, accompanied by cellular decay, disruption 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 DNA, the more pronounced the neurological defect [3].

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 [1].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+ T-lymphocytes) and activation of the humoral immune response with an increase in blood B-lymphocytes (CD19+, CD20+), IgA, IgM, IgG and circulating immune complexes (CEC) [4, 6].

In extremely severe stroke, there was a more pronounced degree of lymphopenia, a decrease in the indicators of the T-link of immunity (T-lymphocytes, T-helpers) [7] and activation of the humoral

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response (an increase in the level of IgA and CEC). Immune status indicators correlated with functional outcome: the more severe the degree of disability (3-4 degrees on the Rankin scale), the lower the levels of T-lymphocytes, T-helper cells, IgM and higher IgA [4]. In a study conducted by A. Hug et al. [12], 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, was studied. The main factor determining the development of lymphocytopenia mainly due to natural killers (NK) in the 1st and 4th days after stroke was the volume of infarction, which was an independent early predictor of the development of respiratory tract infections. However, in another study, there was no statistically significant relationship between the volume of the infarction focus and the content of T-lymphocytes after a stroke [11].

Thus, the inconsistency of the literature data and the lack of information about the state of the immune system in dynamics against the background of basic AI therapy 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 in dynamics against the background of ongoing therapy, the dependence of the main indicators of immunity on the severity of neurological symptoms and the size of the focus of cerebral infarction.

Materials and methods of research

A clinical and immunological examination of 45 patients (22 women and 23 men) in the acute period of AI who were treated in the neurological department for patients with ONMC of the neuro-intensive care unit of the Bukhara branch of the RNCMP was performed. The age of the patients ranged from 44 years to 81 years (mean age 64.3±1.8 years).Stroke was diagnosed in 12 patients in the basin of the left medial cerebral artery, in 18 − in the basin of the right medial cerebral artery, in 15 – in the vertebrobasilar basin. 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 and 15 days after the start of the early rehabilitation course. Mononuclear cells were isolated from venous blood at a density gradient of ficoll–verografin (p=1,077).

Phenotyping of peripheral blood lymphocytes was carried out by indirect immunofluorescence using monoclonal antibodies to CD3+, CD4+, CD8+, CD20+, CD16+, CD25+ differentiation clusters

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(FGBI SSC Institute of Human Immunology and Genomics of the Republic of Uzbekistan, Sorbent Ltd., Tashkent), the fluorescent label FITZ (fluorescence isothiocyanate) 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. 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.

Research 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 (p0.01) and a decrease in lymphocytes (p0.05) compared with the indicators of relatively healthy individuals (Table 1).

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 AI (n=45)	p
Gender	Male	11 (55%)	23 (51%)	>0,05
	female	9 (45%)	22 (49%)	>0,05
Age		61,6±2,2	64,3±1,8	>0,05
Leukocytes, 109/l		5,2±1,4	7,6±0,72	<0,01
Lymphocytes, %		30,0±4,8	27,6±2,44	<0,05
T-lymphocytes (CD3+), %		57,0±4,6	47,4±0,59	<0,01
T-lymphocytes (CD3+), ×109/l		1,0±0,39	1,0±0,09	>0,05

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B-lymphocytes (CD20+), %	12,0±3,1	17,27±3,8	<0,05
B-lymphocytes (CD20+), ×109/l	0,24±0,06	0,38±0,12	<0,05
T-helpers (CD4+), %	40,2±5,1	32,7±2,59	<0,01
T-helpers (CD4+), ×109/l	1,2±0,32	0,92±0,07	<0,05
T-cytotoxic/suppressors (CD8+), %	21,2±4,1	15,7±1,36	<0,05
T-cytotoxic/suppressors (CD8+), ×109/l	0,6±0,08	0,52±0,03	>0,05
IRI	2,04±0,6	2,12±0,06	>0,05
NK − Natural Killers (CD16+), %	10,2±1,2	8,2±0,41	>0,05
CD25+, %	10,4±0,9	9,1±0,65	>0,05
IgA, g/l	1,62±0,2	1,82±0,07	>0,05
IgM, g/l	1,22±0,14	1,27±0,04	>0,05
IgG, g/l	12,6±1,2	13,6±0,36	<0,05

The results of the study also demonstrate pronounced suppression of the T–cell link of the immune system in AI patients: a significant decrease in the relative level of mature T-lymphocytes (CD3+) ($p<0.01$) and the subpopulation composition of T-lymphocytes, which was characterized by a significant decrease in the relative and absolute indicators of T-helper cells (CD4+) and cytotoxic T-lymphocytes (CD8+) (p0,01 and p0,05, respectively).

There were no significant differences in the calculation of the immunoregulatory index (IRI) ($p>0.05$). There was also a tendency to decrease the content of natural killers (NK cells, CD16+) and cells expressing receptors for IL-2 (CD25+) ($p>0,05$). A significant increase in the number of B-lymphocytes (CD20+) ($p>0.05$) and dysgamaglobulinemia was observed in the humoral link of immunity due to the tendency to hyperfunction of IdA and IgM ($p>0.05$) and a significant increase in IgG content ($p>0.05$).

As a result, 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 humoral immune response, which is consistent with the data obtained in other studies [4, 6]. These observations testify to the active participation of immunological mechanisms in the pathogenesis of AI. When comparing immunological parameters in groups of patients with varying degrees of stroke severity (Table. 2) it was noted that the severity of lymphopenia and a decrease in T-lymphocytes (CD3+) depended on the severity of the course of AI: the indicators were significantly lower ($p<0.05$) in moderate and severe stroke compared with the group of patients with mild disease.

There was also a significant difference in the comparison groups of absolute indices of T-lymphocyte subpopulations (CD4+) ($p<0.05$) and (CD8+) ($p<0.005$) correlating with the severity

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of the course. In severe AI, a more pronounced decrease in NK cells (CD16+) and cells expressing receptors for IL-2 (CD25+) (p>0,05) was revealed. 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 AI.

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 AI.

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

Indicators	Mild severity (n=27)	Moderate and severe severity (n=18)	p
Leukocytes, 109/l	7,18±0,7	7,75±1,02	>0,05
Lymphocytes, %	33,4±3,04	22,3±3,4	<0,05
T-lymphocytes (CD3+), %	48,0±0,79	45,13±0,79	<0,05
T-lymphocytes (CD3+), ×109/l	1,01±0,07	0,72±0,17	<0,05
B-lymphocytes (CD20+), %	17,13±0,26	17,28±0,31	>0,05
B-lymphocytes (CD20+), ×109/l	0,24±0,12	0,30±0,20	>0,05
T-helpers (CD4+), %	33,0±0,53	30,63±0,73	<0,05
T-helpers (CD4+), ×109/l	0,9±0,06	0,71±0,13	<0,05
T-cytotoxic/suppressors (CD8+), %	15,8±0,39	14,25±0,37	>0,05
T-cytotoxic/suppressors (CD8+), ×109/l	0,55±0,02	0,46±0,06	<0,005
IRI	2,04±0,04	2,11±0,06	>0,05
NK − Natural Killers (CD16+), %	7,67±0,23	6,88±0,44	>0,05
CD25+, %	9,8±0,5	8,13±0,85	>0,05
IgA, g/l	1,18±0,07	1,02±0,09	>0,05
IgM, g/l	1,18±0,03	1,16±0,03	>0,05
IgG, g/l	13,2±0,27	13,33±0,4	>0,05

Comparison of indicators of the immune status in patients depending on the size of the focus of cerebral infarction (Table. 3) showed more pronounced immunosuppression − a decrease in the content of leukocytes (p0.05) and more pronounced lymphocytopenia (p<0.05) with large sizes of the focus. With a significant difference, the content of absolute indicators of T-lymphocytes (CD3+) was reduced, as well as a decrease in immunoregulatory T-helper cells (CD4+) (p<0.05) and T-cytotoxic lymphocytes (CD8+) (p<0.005). The decrease in the content of NK cells (CD16+) and CD25+ compared to patients with a small infarction was unreliable (p>0,05).

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Indicators reflecting the state of humoral immunity indicated a slight tendency to an increase in the content of B-lymphocytes (CD20+), immunoglobulins A, M and G (p0.05) 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 immunoglobulin production.

On the 15th day of the patients' stay in the hospital, a repeated immunological examination was performed (Table. 4), which showed a significant decrease in the level of B-lymphocytes (p0.05) against the background of basic therapy (medication, physiotherapy and exercise therapy). There was no significant change in other immunological parameters.

Table 3. Average indicators of immune status depending on the size of the stroke focus

Indicators	The size of the hearth is up to 15 mm in diameter (n=25)	The size of the hearth is more than 15 mm in diameter (n=20)	p
Leukocytes, 109/l	7,82±0,74	6,55±0,84	>0,05
Lymphocytes, %	29,9 ±3,1	24,8±4,72	<0,05
T-lymphocytes (CD3+), %	48,33±0,8	47,6±0,78	>0,05
T-lymphocytes (CD3+), ×109/l	1,02±0,07	0,77±0,08	<0,05
B-lymphocytes (CD20+), %	17,13±0,27	17,45±0,25	>0,05
B-lymphocytes (CD20+), ×109/l	0,25±0,12	0,28±0,20	>0,05
T-helpers (CD4+), %	33±0,56	29,12±0,65	<0,05
T-helpers (CD4+), ×109/l	0,9±0,07	0,74±0,07	<0,05
T-cytotoxic/suppressors (CD8+), %	15,47±0,39	13,6±0,38	<0,05
T-cytotoxic/suppressors (CD8+), ×109/l	0,55±0,03	0,46±0,03	<0,005
IRI	2,07±0,04	2,06±0,07	>0,05
NK − Natural Killers (CD16+), %	7,4±0,28	7,08±0,42	>0,05
CD25+, %	9,73±0,57	9,23±0,71	>0,05
IgA, g/l	1,78±0,08	1,82±0,07	>0,05
IgM, g/l	1,18±0,03	1,28±0,03	>0,05
IgG, g/l	13,3±0,3	13,4±0,34	>0,05

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Table 4. Indicators of immune status in patients with acute ischemic stroke before and after treatment

Indicators	Before treatment	After treatment	P
Leukocytes, 109/l	7,6±0,72	6,9±0,7	>0,05
Lymphocytes, %	27,6±2,44	26,9±2,5	>0,05
T-lymphocytes (CD3+), %	47,4±0,59	48,8±0,6	>0,05
T-lymphocytes (CD3+), ×109/l	1,0±0,09	0,71±0,06	>0,05
B-lymphocytes (CD20+), %	17,27±3,8	10,8±1,4	<0,05
B-lymphocytes (CD20+), ×109/l	0,38±0,12	0,1±0,01	<0,05
T-helpers (CD4+), %	32,7±2,59	34±0,46	>0,05
T-helpers (CD4+), ×109/l	0,92±0,07	0,87±0,04	>0,05
T-cytotoxic/suppressors (CD8+), %	15,7±1,36	15,5±0,63	>0,05
T-cytotoxic/suppressors (CD8+), ×109/l	0,52±0,03	0,46±0,03	>0,05
IRI	2,12±0,06	2,07±0,08	>0,05
NK − Natural Killers (CD16+), %	8,2±0,41	7,68±0,29	>0,05
CD25+, %	9,1±0,65	9,63±0,65	>0,05
IgA, g/l	1,82±0,07	1,51±0,06	>0,05
IgM, g/l	1,27±0,04	1,25±0,03	>0,05
IgG, g/l	13,6±0,36	13,7±0,18	>0,05

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.

In this regard, the assessment of the parameters of the immune system in such patients is of great practical importance in the complex of early rehabilitation measures. The absence of changes in the immune status in dynamics against the background of standard therapy requires, when detecting violations of the main parameters of the immune system, an immunologist's consultation and immunocorrective therapy.

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