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Treatment of Immunological Disorders in the Acute Period of Hemorrhagic Stroke

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Abstract In order to study the effectiveness of reflexology in correcting immunological disorders in the acute period of hemorrhagic stroke, a clinical and immunological examination of 45 patients was performed (on the 2nd day of the patients' stay in the hospital and 15 days after the start of the early rehabilitation course). In the main group of patients (30 people), in whom the basic complex of rehabilitation measures was optimized by including reflexology, a reliable improvement in a number of indicators of cellular and humoral immunity was noted: a decrease in leukocytes in the peripheral blood ($p<0.05$), an increase in the content of lymphocytes ($p<0.05$), relative and absolute indicators of the content of T-lymphocytes (CD3+) ($p<0.01$ and $p<0.05$, respectively), immunoregulatory cells T-helpers (CD4+) ($p<0.05$), a decrease in the number of B-lymphocytes to normal values ($p<0.01$) and an increase in the level of IgG ($p<0.05$). In the control group (15 people), where standard treatment was carried out, such a pronounced dynamics of the indicators was not observed. Thus, the conducted complex clinical immunological study of the effectiveness of non-drug correction of immunological disorders in the acute period of ischemic stroke showed the high effectiveness of acupuncture, with the relative simplicity and safety of its use.

Keywords Acute period of hemorrhagic stroke, Acupuncture, Reflexotherapy, Immune status, Cellular and humoral immunity

1. Introduction

Due to the high mortality rate after stroke, which remains one of the highest in the world [10], optimization of early rehabilitation of strokes has acquired particular importance in recent decades. Moreover, in 68% of cases, the cause of death in patients who have suffered a stroke at the age of over 60 years are complications that join the main pathological process, while the direct severity of the stroke is only 32% [2,3]. In the very near future after the onset of the most severe forms of stroke, complications develop that occur due to gross extensive damage to brain structures. Somatic complications caused by immobility of patients, autonomic dysfunction and infection develop at a relatively later time [2], therefore their prevention and treatment are of primary practical importance.

In recent years, an important role in the pathogenesis of hemorrhagic stroke has been given to immunological mechanisms, since the interaction of the nervous and immune systems, carried out according to the principle of mutual regulation, determines the risk of dysfunction of one of them in the pathology of the other [6,8,11], aggravating the clinical picture and contributing to neurological deficit. One of the main autoimmune processes in the pathogenesis of stroke is damage to the endothelium of the vascular wall, which occurs with the participation of immune factors and is associated with the deposition of immune complexes on the inner surface of the vessels [1].

The literature describes mainly various medicinal methods for correcting immunological disorders in patients who have suffered an ischemic stroke: recombinant IL-2 (roncoleukin) [5], cortexin [9], tactivin [7]. For effective rehabilitation of patients with arterial hypertension who have suffered a hemorrhagic stroke, a combined use of the standard hyperbaric oxygenation method and immunoprotection with actovegin according to the standard scheme in the basic complex of rehabilitation treatment has been proposed [4]. However, in addition to the high cost of immunomodulatory drugs, their use carries a risk of developing side effects, which can significantly limit their use. Centuries of experience in acupuncture allow it to be classified as a method that restores immune status.

The aim of the study was to investigate the possible effectiveness of reflexology in correcting immunological disorders in the acute period of hemorrhagic stroke.

2. Materials and Methods of Research

A clinical and immunological examination of 45 patients (22 women and 23 men) in the acute period of hemorrhagic stroke, treated in the neuroreanimation department for

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patients with acute cerebrovascular accidents of the Bukhara branch of the Russian Scientific Center of Medical Care, was performed. The age of the patients ranged from 44 to 81 years (the average age was 64.3 ± 1.8 years). Stroke in the left middle cerebral artery basin was diagnosed in 12 patients, in the right middle cerebral artery basin in 18 patients, and in the vertebrobasilar basin in 15 patients. The clinical diagnosis was made on the basis of anamnestic information, the results of subjective and objective neurological symptoms, and data from additional research methods (computer tomography of the brain, duplex scanning of the main arteries of the head, cerebrospinal fluid analysis) in accordance with the ICD 10 revision. The severity of neurological symptoms, assessed using the NIHSS scale, averaged 6.05±0.42 points. To assess the possible impact of acupuncture on immune status indicators, a clinical and immunological study was conducted in two groups of patients, representative in terms of gender, age, and severity of neurological symptoms (Table 1).

The patients in the control group (15 people) received only standard therapy (medication, physiotherapy, exercise therapy). In the patients in the main group (30 people), the basic therapy was optimized by including reflexology. In order to correct immunological disorders, daily injections were made (in addition to the standard acupuncture regimen, which was compiled depending on the existing neurological deficit) to acupuncture points with an immunoregulatory effect: on the channels of the large intestine (GI (II) 11 Qu-chi, GI (II) 4 He-gu), stomach (E (III) 36 Zu-sanli), spleen (RP (IV) 6 San-yin-jiao), kidneys (R (VIII) 3 Tai-si), san-jiao (TR (X) 5 Wai-guan), liver (F (XII) 3 Tai-chong) (on both sides) and the anterior median meridian (J (XIV) 17 Tan-zhong and J (XIV) 6 Qihai). Additionally, points on the auricle (22, 55 and 101) were pricked on one side, alternating the sides of the impact (day on the right, day on the left). Reflexotherapy procedures were prescribed from the 2nd-3rd day of the patient's stay in the hospital (in the absence of contraindications), the duration of the impact was 20-30 minutes using the harmonizing method, the course consisted of 10-12 procedures.

An immunological study was conducted on the second 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 on a Ficoll-Verografin density gradient (p=1.077). Phenotyping of peripheral blood lymphocytes was performed by indirect immunofluorescence using monoclonal antibodies to differentiation clusters CD3+, CD4+, CD8+, CD20+, CD16+, CD25+ (Institute of Human Immunology and Genomics of the Republic of Uzbekistan), the fluorescent label FITC (fluoresceinate isothiocyanate) was used. Smears were counted using a Lumam-P8 fluorescent microscope, using a combination of light filters. The concentration of serum immunoglobulins was determined by the Mancini radial immunodiffusion method using monospecific antisera. The indicators of 20 practically healthy individuals, representative by gender and age, were used as normative values.

Statistical data processing was performed using the Microsoft Office 2013 (Excel) and Statistica 6.0 software packages. Quantitative variables are presented as mean ± standard error of the mean (X±mx); Student's t-test was used to assess the statistical significance of the observed differences.

3. Results of the Study and Their Discussion

In the control group, on the 15th day of the patients' stay in hospital, a tendency ($p>0.05$) towards a slight decrease in leukocytes and lymphocytes in the peripheral blood was noted, compared with the results obtained at the beginning of treatment (Table 2). An insignificant increase ($p>0.05$) in the content of the relative number of T-lymphocytes (CD3+) was also noted. The difference between the quantitative characteristics of the subpopulation indicators CD4+ and CD8+ before and after treatment was also not significant ($p>0.05$). A tendency towards an increase in the content of NK cells (CD16+) and CD25+ ($p>0.05$) was observed. The dynamics of the humoral immunity state is represented by a reliable ($p<0.05$) decrease to the norm of elevated B-lymphocytes (CD20+) and a slight tendency to increase IgA and IgG, the content of IgM remained virtually unchanged ($p>0.05$). Thus, a comparative analysis of the immunological examination in the control group showed that there were no significant changes in the immune status against the background of the generally accepted standard treatment of hemorrhagic stroke.

Table 1. Characteristics of patients

Sign		Main group (n=30)	Control group (n=15))	p
Age, years		62,4±1,45	64,4±2,14	>0,05
Gender male/female, %		50,0/50,0	53,3/46,7	>0,05
Stroke localization, %	basin of the left middle cerebral artery	23,3	26,6	>0,05
	basin of the right middle cerebral artery	40,0	33,3	
	vertebrobasilar basin	36,6	40,0	
Severity of neurological symptoms according to the NIHSS scale, points		6,03±0,48	6,06±0,8	>0,05

In the main group of patients, in whom the basic complex of rehabilitation measures was optimized by including reflexotherapy (Table 3), a significant decrease in leukocytes in the peripheral blood ($p<0.05$) and a significant increase in the lymphocyte content ($p<0.05$) were noted. A significant increase in the relative and absolute indicators of the quantitative content of T-lymphocytes (CD3+) ($p<0.01$) and immunoregulatory T-helper cells (CD4+) ($p<0.05$) was also noted. A tendency toward an increase in the indicators of cytotoxic T-lymphocytes (CD8+), natural killers (NK cells, CD16+), IRI and a tendency toward a decrease in CD25+ cells expressing receptors for IL-2 ($p>0.05$) were recorded. From the humoral side of the immune system, a reliable ($p<0.01$) decrease in the number of B-lymphocytes to normal values with an unexpressed dynamics of increase in IgA production ($p>0.05$) and a reliable increase in the level of IgG ($p<0.05$) was noted. Thus, almost all indicators of the immune status under the influence of treatment using acupuncture approached normal values. The normalization of the content of lymphocytes, T-lymphocytes (CD3+), T-helpers (CD4+) and B-lymphocytes in the peripheral blood is especially indicative. Whereas in the control group, where standard treatment was carried out, such a pronounced dynamics of the indicators was not observed, and such important indicators of the immune status as T-lymphocytes (CD3+), T-helpers (CD4+), NK cells (CD16+) remained below normal.

Table 2. Immune status indicators in the control group before and after treatment

Indicators	Before treatment	After treatment	p
Leukocytes, 109/l	6,96±0,97	6,10±0,7	>0,05
Lymphocytes, %	27,10±5,90	26,90±2,5	>0,05
T-lymphocytes (CD3+), %	47,80±0,70	48,80±0,60	>0,05
T-lymphocytes (CD3+), ×109/l	0,77±0,13	0,71±0,06	>0,05
B-lymphocytes (CD20+), %	17,27±3,80	10,80±1,4	<0,05
B-lymphocytes (CD20+), ×109/l	0,31±0,20	0,10±0,01	<0,05
T-helpers (CD4+), %	33,10±0,55	35,0±0,46	>0,05
T-helpers (CD4+), ×109/l	0,71±0,08	0,77±0,04	>0,05
T-cytotoxic/suppressor (CD8+), %	15,10±0,44	15,50±0,63	>0,05
T-cytotoxic/suppressor (CD8+), ×109/l	0,47±0,04	0,46±0,03	>0,05
IRI	2,11±0,04	2,07±0,08	>0,05
NK (natural killer) (CD16+), %	7,0±0,33	6,88±0,29	>0,05
CD25+, %	9,0±0,76	9,63±0,65	>0,05
IgA, g/l	1,46±0,06	1,51±0,06	>0,05
IgM, g/l	1,23±0,04	1,25±0,03	>0,05
IgG, г/л	13,40±0,26	13,70±0,18	>0,05

Table 3. Immune status indicators in the main group of patients receiving acupuncture, before and after treatment

Indicators	Before treatment	After treatment	p
Leukocytes, 109/l	7,60±0,72	6,0±0,60	<0,05
Lymphocytes, %	28,60±2,44	34,33±1,80	<0,05
T-lymphocytes (CD3+), %	47,40±0,90	52,90±1,0	<0,01
T-lymphocytes (CD3+), ×109/l	0,82±0,09	1,10±0,10	<0,05
B-lymphocytes (CD20+), %	17,17±2,80	10,20±1,50	<0,01
B-lymphocytes (CD20+), ×109/l	0,24±0,11	0,15±0,02	<0,05
T-helpers (CD4+), %	32,70±0,59	38,67±0,66	<0,05
T-helpers (CD4+), ×109/l	0,92±0,07	1,0±0,08	>0,05
T-cytotoxic/suppressor (CD8+), %	15,50±0,36	16,38±0,45	>0,05
T-cytotoxic/suppressor (CD8+), ×109/l	0,54±0,03	0,64±0,04	>0,05
IRI	2,04±0,05	2,12±0,06	>0,05
NK (natural killer) (CD16+), %	7,39±0,29	8,20±0,41	>0,05
CD25+, %	9,70±0,53	9,10±0,45	>0,05
IgA, g/l	1,46±0,08	1,54±0,07	>0,05
IgM, g/l	1,24±0,03	1,29±0,04	>0,05
IgG, g/l	12,80±0,32	13,90±0,36	<0,05

Against the background of significant improvement in immune status indicators in the main group, a more significant regression of neurological deficit on the NIHSS scale was noted by an average of 4.6 points (up to 1.43±0.14 points, $p<0.001$), while in the control group, less pronounced positive dynamics were noted - by 2.6 points (up to 3.5±0.54, $p<0.05$). No complications were noted during reflexotherapy procedures.

Thus, the conducted complex clinical and immunological study of the effectiveness of non-drug correction of immunological disorders in the acute period of hemorrhagic stroke showed high efficiency of acupuncture, with relative simplicity and safety of its use. Correction of immunological disorders in the acute period of hemorrhagic stroke seems very important, since it is a prevention of the development of infectious complications, and, therefore, accelerates the process of early rehabilitation.

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