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# CYTOKINE PROFILE AGAINST THE BACKGROUND OF ANTI-EDEMA LYMPHOSTIMULATING AND ANTI-NEUROINFLAMMATORY THERAPY IN PATIENTS WITH HEMORRHAGIC STROKE

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**Summary:** The study found that the content of pro-inflammatory IL-1, IL-6, IL-8 in the blood and the ratio of neutrophils to lymphocytes in patients with hemorrhagic stroke who received anti-edematous lymphotropic and anti-neuroinflammatory therapy significantly decreased on days 5 and 10 of treatment compared with the control group.

**Key words**: neuroinflammation, cerebral edema, hemorrhagic stroke, lymphotropic therapy.

Hemorrhagic stroke (GI) is a global public health problem, one of the main causes of acquired disability worldwide. Despite the fact that HS is almost five times less common than ischemic stroke, it is characterized by a higher level of disability and mortality (from 40 to 50%). GI affects a large percentage of the working-age population and has a high social character [2,5,8].

Blood itself is extremely toxic to brain tissue and leads to focal damage to the central nervous system, which causes neuroinflammation and progression of cerebral edema in the perihematoma space [11,14].

In the acute phase of GI, adverse effects and complications are associated with secondary injury-triggering of neuroinflammatory processes, which is characterized by innate mechanisms such as activation of microglia, which mediates the production of cytokines, damage to the blood-brain barrier (BBB). At the same time, elevated levels of pro- and anti-inflammatory cytokines during the acute phase after hemorrhagic stroke are associated with worse functional outcomes [6,12,15].

To assess the intensity of the neuroinflammation process, the optimal strategy is to measure the level of proinflammatory cytokines IL-1, IL-6, IL-8, which have pathogenetic and prognostic significance [3,7,16].

The results of various scientific studies show that neutrophils are very sensitive to CNS damage and can influence the process of neuroinflammation, being the first immune cell to reach the inflamed tissue. The neutrophil-to-lymphocyte ratio (NLR), as a biomarker of inflammation, can play an important role in the dynamics of neuroinflammation [17].

Glymphatic dysfunction in GI, characterized by impaired interstitial clearance of dissolved substances, requires targeted interventions to enhance drainage function [1,4,10,9,13].

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Anti-neuroinflammatory and anti-edematous lymphotropic therapy aimed at immune-pathogenetic mechanisms can alleviate primary and secondary brain damage after GI, which requires further experimental and clinical studies.

**Purpose of the study**: to evaluate the effect of anti-edematous lymphotropic and anti-neuroinflammatory therapy on the state of cytokines in patients with hemorrhagic stroke.

**Materials and methods of research.** The study included data from patients who were treated in the neurointensive care unit of the Bukhara branch of the Russian Scientific Center for Emergency Medicine in the period 2021-24. The materials of 106 patients with GI were studied, whose age ranged from 49 to 66 years (the average age was 57.5 ± 2.4). All patients underwent standard diagnostic methods (assessment of neurological status during a joint examination by a neurologist and a neurosurgeon, multispiral computed tomography (MSCT), as well as an assessment of the level of interleukins (IL)-1, -6, -8-10 and TNF-alpha, laboratory tests (leukocyte formula, neutrophil-to-lymphocyte ratio index - NSRI), and biochemical blood tests. Neurostatus was assessed using the Glasgow Coma Scale (GCS), with the average score upon admission to hospital being 9.3±2.1. On MSCT, in patients with hemorrhagic stroke, hemispheric hematomas accounted for 69 (65.1%), brainstem hematomas 8 (7.6%), ventricular hematomas 12 (11.3%), and subarachnoid hematomas 17 (16%).

Patients with GI were divided into two groups. The first group is the main one, the patients of which received anti-edematous lymphotropic and anti-neuroinflammatory therapy in the complex of intensive care. For the purpose of anti-edematous lymphotropic therapy, a 2% lidocaine solution - 1 ml, dexamethasone 4 mg, 10% glucose solution 3 ml in one syringe were injected submastoidally on one side (the method was approved at a meeting of the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan, protocol No. 7 dated 09.11.2023) along with anti-neuroinflammatory therapy with sodium diclofenac 75 mg intramuscularly (patent application No. FAP 20240232). Submastoid lymphotropic injections and anti-neuroinflammatory therapy were performed for 5 days, along with conservative treatment, including: antibacterial, anti-edematous, membrane-stabilizing, hemorheological, cerebroprotective and symptomatic therapy.

The second group of patients was the control group, which received standard therapy. Comparison of clinical and laboratory parameters was carried out in three stages: the first stage - upon admission, the second stage: -5th day, the third stage - 10th day of intensive therapy.

In order to assess the parameters of systemic immunity in the blood serum, the content of cytokines (IL-1, TNF-α, IL-6, IL-8, IL-10) was studied with a set of reagents (Vector-Best) by the method of solid-phase enzyme-linked immunosorbent assay (ELISA).

**Results and discussion:** to determine the indicators accepted as physiological norms, 12 practically healthy donors (average age 25.1±2.1 years) were examined, Table 1.

Table 1.

Content of cytokines in the blood serum of practically healthy individuals.

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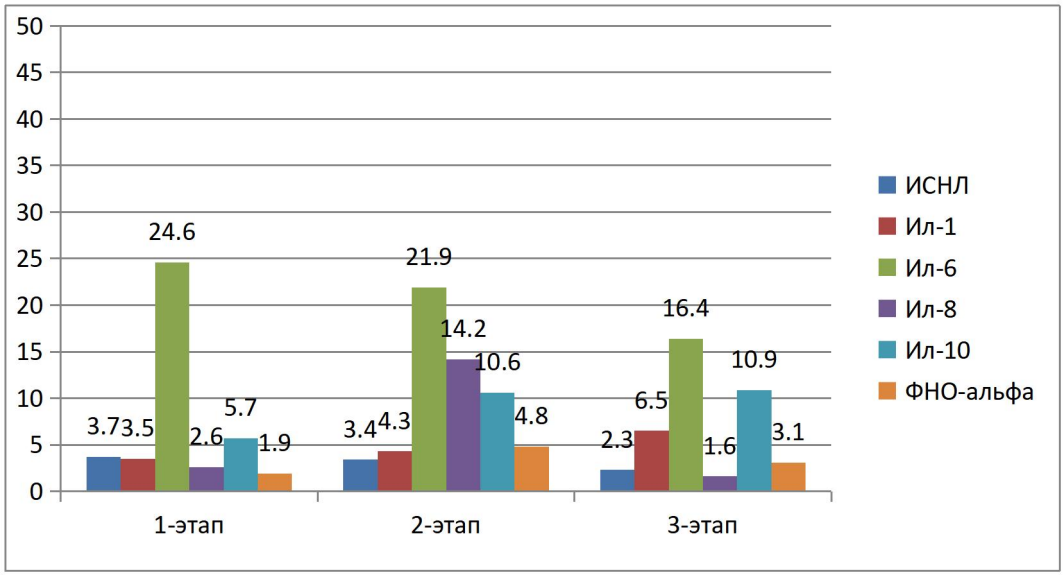
| Cytokines | Cytokine content (pg/ml) M±m |
|---|---|
| IL-1β | 1,88±0,23 |
| IL -6 | 2,33±0,50 |
| IL -8 | 2,53±0,90 |
| IL -10 | 1,89±0,16 |
| TNF-α | 1,98±0,43 |

The cytokine status was assessed in patients with GI on the first day and dynamically on the 5th-10th days of stay in the neurointensive care unit. The content of all cytokines in both groups upon admission of patients to the hospital - on the first day were characterized by an increase compared to practically healthy individuals (Table 1). At the same time, the highest concentration of the proinflammatory cytokine IL-6 was noted. Both in our work and in other studies, the concentration of proinflammatory cytokines directly correlated with the hematoma volume and ISNL [2]. When examining on the 5th and 10th days of treatment in the main group using lymphotropic anti-edematous and antineuroinflammatory therapy, the indicators of blood proinflammatory cytokines IL-1, IL-6 and IL-8 were significantly lower, and the level of anti-inflammatory cytokine IL-10 was higher compared to the indicators studied upon admission ($p<0.05$), (graph 1). Moreover, a direct correlation of the proinflammatory cytokine IL-6 with ISNL.




**Graph 1.** Dynamics of ISNL and cytokine indices in the main group of patients with GI who underwent lymphotropic anti-edematous and anti-neuroinflammatory therapy.

On the 5th day of the study, patients with GI without lymphotropic and antineuroinflammatory therapy showed an increase in the level of proinflammatory cytokine IL-6 and INSL compared to admission ($p<0.05$). A comparative analysis on the 10th day of

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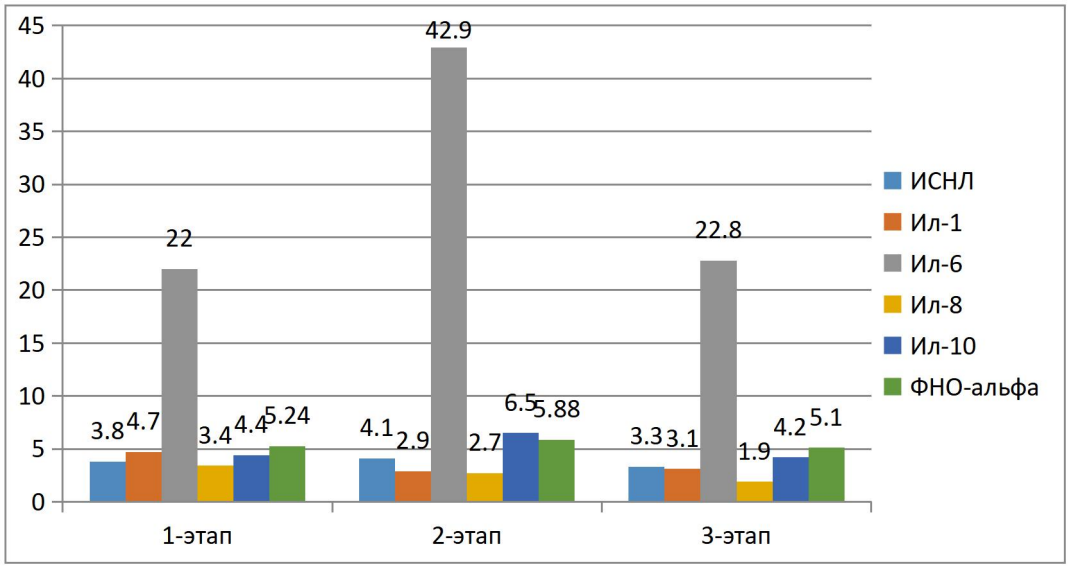
the study showed no significant differences compared to their content upon admission (graph 2).




**Graph 2.** Dynamics of ISNL indices and blood cytokines in patients with GI in the control group.

Dynamic changes in the content of CSF cytokines in HS in patients of the main group who were given, along with standard therapy, additional anti-edematous lymphotropic and anti-inflammatory therapy (pg/ml).

**Table 2.**

| Interleukin | 1st day | 5th day | 10th day |
|---|---|---|---|
| IL-1β | 17,6±2,36 | 11,4 ±1,25 * | 8,3±2,19** |
| IL-6 | 144,9±6,23 | 114,2 ±2,27 * | 62,7±2,83** |
| IL-8 | 85,2±3,15 | 54,2 ±1,83* | 32,7±4,6** |
| IL-10 | 32,5±3,86 | 27,9±1,46* | 20,5±3,14** |
| TNF-α | 1,2±0,64 | 3,1 ± 0,72 | 2,4±0,73 |

**Note:** *- significantly significant decrease on day 5 ($p<0.05$), **- significantly significant decrease on day 10 compared to the cytokine content upon admission (day 1) ($p<0.001$).

Dynamic changes in the content of CSF cytokines in GI in patients of the comparison group who received standard therapy without the use of anti-edematous lymphotropic and anti-inflammatory therapy (pg/ml).

**Table 3.**

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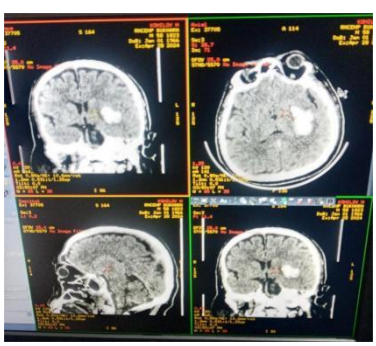
Динамические изменения содержания цитокинов ЦСЖ при ГИ у больных группы сравнения, которым применена стандартная терапия без использования противоотечной лимфотропной и противонейвоспалительной терапии (пг/мл).

| Интерлейкини | 1-е сутки | 5-е сутки | 10-е сутки |
|---|---|---|---|
| IL-1β | 18,1±2,46 | 22,6 ±2,15* | 11,2±2,36** |
| IL-6 | 142,8±5,92 | 148,6 ±6,18* | 94 ,6±2,73** |
| IL-8 | 84,3±3,25 | 92,6 ±3,64 * | 52,6±3,37** |
| IL-10 | 32,5±3,86 | 37,9±1,38 * | 26,2±3,35** |
| TNF-α | 4,4±0,58 | 6,7 ± 0,63 * | 3,4±0,52** |

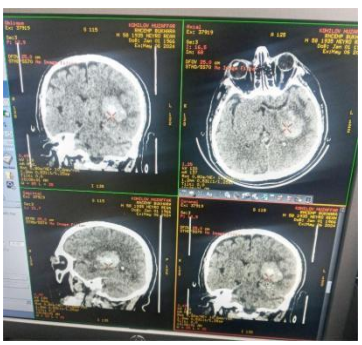
**Note:** *- significantly increased on day 5 ($p<0.05$), **- significantly decreased on day 10 compared to cytokine content on day 5 ($p<0.001$).

The study found that standard therapy did not lead to a statistically significant decrease in the concentration of key proinflammatory cytokines (IL-1β, IL-8 and IL-6) in patients with GI, and an increase in the level of interleukins on the 5th day coincides with the progression of cerebral edema and neuroinflammation in these patients on these days. Thus, standard therapy does not provide a sufficient effect on the level of proinflammatory interleukins that initiate the neuroinflammatory process, thereby maintaining the progression of cerebral edema.

The analysis of the obtained data of the MSCT study revealed that all patients in both groups had parenchymatous and ventricular hemorrhages on the primary MSCT. In addition, the compaction of the grooves of the cerebral cortex, narrowing of the basal cistern were signs of intracranial hypertension with phenomena of impaired consciousness. In patients of the main group, against the background of lymphotropic anti-edematous and anti-neuroinflammatory therapy, on the second and third MSCT, regression of cerebral edema was evidenced by the resorption of the hematoma, the appearance of signs of improvement in the architectonics of the cerebral cortex, restoration of normal sizes of the basal cisterns and ventricles of the brain (Figures 1). All these manifestations corresponded to the indicators of the ISNL, blood cytokines, GCS and positive neurological changes.



A)



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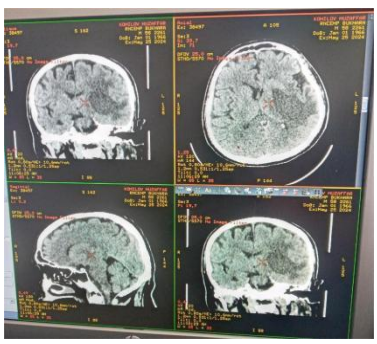

C)

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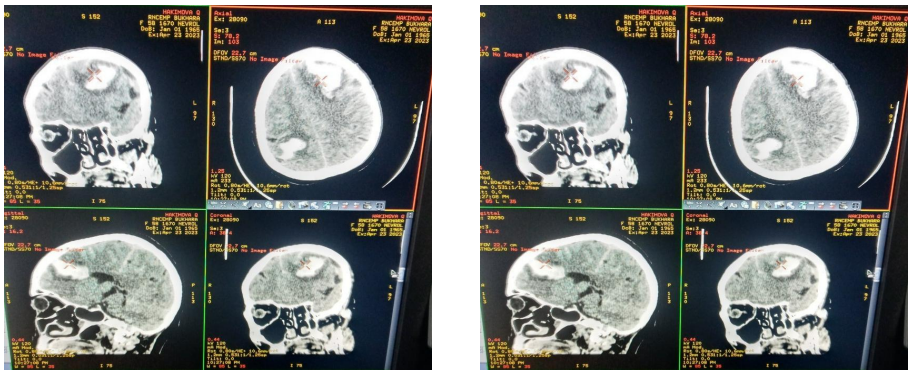
**Figure 1.** MSCT of a patient with hemorrhagic stroke of the main group (A – upon admission, B – on the 5th day, C – after the 10th day).

In patients in the control group, the above-mentioned changes on MSCT of the brain appeared noticeably slowly compared to the main group (Figure 2).



A) B)

**Figure 2**. MSCT of a patient with hemorrhagic stroke in the control group (A – upon admission, B – after 10 days).

Venous congestion and venous stasis indicate intracranial hypertension and cerebral edema in GI. The use of anti-edematous lymphotropic and anti-inflammatory therapy contributed to a more rapid improvement in the ophthalmological picture compared to standard therapy, which is associated with additional stimulation of the glymphatic function - the drainage system of the central nervous system.

Since the fundus condition reflects the degree of intracranial hypertension and cerebral edema, it can be concluded that anti-edematous lymphotropic and anti-inflammatory therapy effectively corrects these conditions in GI by suppressing the neuroinflammatory response and eliminating glymphatic dysfunction. These results are consistent with the literature.

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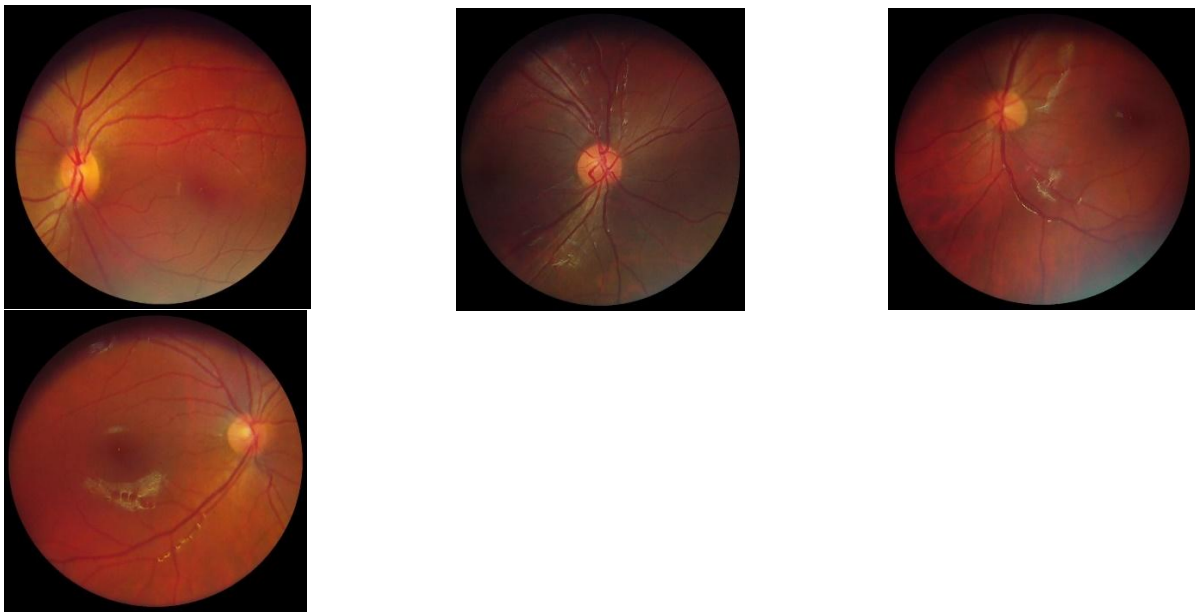

A B C D

**Figure 3.** The condition of the fundus and optic nerve head in a healthy (A), patient and a patient with hemorrhagic stroke upon admission (B), against the background of anti-edematous lymphotherapy for 5 days (C) and 10 days (D).

Our study showed that GI is accompanied by an imbalance in the content of both pro- and anti-inflammatory cytokines in the blood. On the first day, the direction of pathological changes in patients with different outcomes does not differ, characterized by an increase in the blood concentration of proinflammatory cytokines IL-1β, IL-6, IL-8 and anti-inflammatory cytokine IL-10. On the 5th and 10th days of the study, in the group using lymphotropic anti-edematous and anti-neuroinflammatory therapy, these indicators were significantly lower in comparison with the group who did not receive lymphotropic and anti-neuroinflammatory therapy. There was also a reliable significant improvement in the clinical picture in patients of the main group, which shows the feasibility of including lymphotropic anti-edematous and anti-neuroinflammatory therapy in the standard treatment of patients with GI.

**Conclusions.** Anti-edematous lymphotropic and anti-neuroinflammatory therapy against the background of basic treatment increases the effectiveness of standard intensive therapy of patients with GI. Prevents the progression of cerebral edema in patients with GI against the background of a decrease in the concentration of proinflammatory cytokines in the blood.

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