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CLINICAL VERIFICATION OF THE ROLE OF INFLAMMATION MARKERS IN CHRONIC BRAIN ISCHEMIA

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Abstract: Persistent neurological, cognitive, and psycho-emotional disorders are determined by a high level of disability and a decrease in the quality of life of patients due to chronic cerebrovascular disorders. According to foreign epidemiological studies, signs of chronic cerebrovascular disorders are detected in 30-40% of individuals over 55 years of age, and in recent years, there has been a trend towards the "rejuvenation" of vascular cerebral pathology.

Keywords: chronic cerebral ischemia, inflammation markers, C-reactive protein, gliofibrillar acidic protein, personalized medicine

Introduction. Chronic cerebral ischemia (CHI) is one of the most pressing problems in modern neurology due to the progressive disruption of cerebral circulation and the development of diffuse changes in brain matter. This condition is characterized by a gradual decrease in brain tissue perfusion due to atherosclerotic damage to the main and intracerebral arteries, leading to the formation of cognitive, motor, and emotional disorders. Epidemiological data indicate a high prevalence of CMI among elderly individuals, with the incidence steadily increasing due to the increase in life expectancy and the frequency of cardiovascular diseases. The socio-economic burden of SMI is determined not only by direct medical expenses but also by significant social support costs for patients with cognitive impairments and dementia. In recent years, the understanding of the pathogenetic mechanisms of chronic cerebral ischemia has significantly expanded. Along with traditional concepts of hemodynamic disorders, neural inflammatory processes, which develop in response to chronic hypoperfusion and can support the progression of the pathological process, are becoming increasingly important. The inflammatory response in CMI is characterized by the activation of microglia, astrocytes, infiltration of peripheral immunocompetent cells, and the release of a wide range of pro-inflammatory mediators. Cytokines, chemokines, adhesion molecules, complement system components, and other biologically active molecules play a key role in initiating and maintaining neural inflammation. Among the most studied markers of systemic inflammation in cerebrovascular diseases, C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and soluble adhesion molecules (sICAM-1, sVCAM-1) should be distinguished. An increase in the concentration of these biomarkers in peripheral blood correlates with the severity of clinical manifestations and disease prognosis.

Neurospecific markers of inflammation, including S100β protein, neuron-specific enolase (NSE), myelin main protein (MBP), gliofibrillar acid protein (GFKB), are of particular interest, reflecting the degree of damage to various brain tissue structures and can serve as indicators of neurodegenerative process activity.

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Modern neural imaging methods, including diffusion-weighted magnetic resonance imaging, perfusion tomography, and functional MRI, allow for the assessment of structural and functional brain changes in CMI and establish their relationship with inflammatory markers. The clinical significance of determining inflammatory markers in CMI is due to the ability to diagnose the disease early, monitor the effectiveness of therapy, and predict the course of the pathological process. Furthermore, understanding the role of inflammatory mechanisms opens up new therapeutic possibilities, including the use of anti-inflammatory drugs, neuroprotectors, and immunomodulators.

A personalized approach to managing patients with SMI should take into account the individual profile of inflammatory biomarkers, which will optimize therapeutic strategies and improve the long-term outcomes of the disease.

This study is aimed at clinical verification of the diagnostic and prognostic significance of various inflammatory markers in chronic cerebral ischemia, establishing their correlations with clinical, neuropsychological, and neuroimaging data, as well as developing algorithms for their use in practical neurology.

The purpose of the study was to study the diagnostic significance of inflammatory markers in the formation of clinical manifestations of chronic cerebral ischemia.

Research material and methods. The study included patients with clinical manifestations of chronic cerebral ischemia who were observed in outpatient and inpatient settings of the Multidisciplinary Clinic of Samarkand State Medical University (polyclinic department, neurology department, therapy department). The total number of examined patients was n = 77 people aged 45 to 65 (average age - 56.3 ± 5.4), for the period 2024-2025. The study group included patients of both sexes: men - 41 people (53.2%), women - 36 people (46.8%). The inclusion criteria for inclusion in the study were: the presence of clinical signs of chronic cerebral ischemia corresponding to the ICD-10 I67.8 (other specified cerebrovascular diseases) and/or I67.9 (cerebrovascular disease unspecified) diagnosis; age from 45 to 65 years; informed consent of the patient to participate in the study. The exclusion criteria were: acute cerebrovascular disorders in the anamnesis less than 6 months before inclusion in the study; severe dementia; inflammatory and autoimmune diseases in the acute phase; oncological diseases; acute infectious processes; severe somatic pathology in the decompensation stage. Depending on the severity of clinical manifestations of chronic cerebral ischemia, patients of the main group were divided into two groups: 1st group, patients with mild chronic cerebral ischemia 39 people (50.6%), 2nd group, patients with moderate chronic cerebral ischemia 38 people (49.4%). The control group, for comparison of the study indicators, consisted of 31 relatively healthy volunteers who underwent a preventive medical examination in outpatient settings, comparable to the main group by age and sex, without clinical signs of chronic cerebral ischemia and pronounced somatic pathology.

All patients included in the study underwent a comprehensive clinical and laboratory assessment. Clinical assessment included collecting complaints, history of the disease and life, analysis of vascular risk factors (AH, DM, dyslipidemia), standard neurological examination with assessment of focal and diffuse neurological symptoms. The severity of the clinical manifestations of chronic cerebral ischemia was determined based on the clinical and neurological status and corresponded to the generally accepted clinical classification of CMI (mild and moderate degree). Cognitive and psycho-emotional disorders were assessed clinically (presence of complaints about memory decline, attention deficit, fatigue, emotional lability). Laboratory research methods (Laboratory assessment) were aimed at assessing the systemic inflammatory response. In all patients, inflammatory markers were identified in the peripheral venous blood: C-reactive protein (CRP); interleukin-6 (IL-6); tumor necrosis factor-α (TNF-α). Blood sampling was carried out in the morning on an empty stomach. Determination of the concentration of inflammatory markers was carried out by enzyme-linked immunosorbent assay (ELISA) using standard certified reagent sets in accordance with the manufacturer's instructions. The obtained indicators were expressed in mg/l (CRP) and pg/ml (IL-6, TNF-α). Statistical data processing was carried out using the Statistica/SPSS application software package. Quantitative indicators are presented as an average value and standard deviation (M±SD). The normal distribution was checked

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using the Shapiro-Wilk criterion. To compare the quantitative indicators between the groups, Student's t-test or Mann-Whitney's nonparametric test (with abnormal distribution) was used. Correlation analysis was conducted using Pearson's or Spearman's coefficient. Differences at a level of $p<0.05$ were considered statistically significant.

Research results. Clinical analysis of patients with chronic cerebral ischemia revealed significant differences in the severity of neurological symptoms depending on the severity of the disease. In the study group, patients with mild CMI (n=40; 51.9%) were characterized by the predominance of moderately pronounced subjective and objective symptoms, such as headache, dizziness, decreased work capacity, and mild cognitive complaints. The average integral indicator of clinical severity in this group was 3.2±0.6 points. In patients with moderate severity of chronic cerebral ischemia (n=37; 48.1%), the clinical picture was characterized by a greater severity of neurological deficit, including persistent cognitive impairments, emotional-affective disorders, and impaired gait and coordination. The average clinical score in this group was significantly higher and amounted to 6.1±0.8 points, which reflects the progression of the pathological process.

In patients with moderate chronic cerebral ischemia, a statistically significant increase in the severity of the main clinical and neurological symptoms was noted compared to the mild CMI group. The moderate stage of the disease was characterized by a higher frequency of dizziness, asthenic syndrome, cognitive complaints, and emotional disorders ($p<0.01$-0.001). The indicators of the MMSE and MoCA cognitive scales significantly decreased as the clinical course worsened, while the levels of anxiety and depression on the HADS scale increased significantly, reflecting the progression of neuropsychological disorders in CMI.

In the analysis of laboratory parameters in patients with chronic cerebral ischemia, significant changes in systemic inflammation markers were revealed, the severity of which increased as the clinical course of the disease worsened. In the group of patients with mild CMI, a moderate increase in the levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) was noted compared to the control group of healthy individuals. The obtained changes were statistically significant ($p<0.001$), which indicates the activation of the inflammatory cascade in the early stages of chronic cerebral ischemia. In patients with a moderate course of SMI, the concentrations of all the studied inflammatory markers were significantly higher both in the mild course group and in the control group ($p<0.001$). The most pronounced differences were found for IL-6 and TNF-α, indicating a progressive nature of the systemic and neural-inflammatory response in the progression of cerebral ischemic damage. Comparative analysis between groups showed a clear gradation of inflammatory marker levels: minimal values were recorded in individuals of the control group, intermediate values in patients with mild CMI, and maximal values in patients with moderate disease progression. These results confirm the dependence of laboratory indicators of inflammation on the clinical severity of chronic cerebral ischemia. Correlation analysis revealed statistically significant positive correlations between CRP, IL-6, and TNF-α levels and the severity of clinical symptoms of the disease. A moderate and strong correlation was noted between the concentration of inflammatory markers and the overall clinical score ($r = 0.52$-0.68; $p<0.01$), as well as the frequency of cognitive and psycho-emotional disorders.

The conducted correlation analysis allowed us to establish statistically significant relationships between the clinical and neurological manifestations of chronic cerebral ischemia and the level of inflammatory markers in the peripheral blood. The obtained data indicate that the severity of clinical symptoms in CMI is directly related to the activation of the systemic inflammatory response. The most pronounced correlations were found between the overall clinical score and the level of all the studied inflammatory markers. Thus, the level of C-reactive protein exhibited a moderate positive correlation with the overall clinical severity of symptoms ($r=0.62$; $p<0.001$), indicating a correlation between the activity of the inflammatory process and the progression of neurological manifestations of the disease. An even closer relationship was noted between the clinical score and the concentration of interleukin-6 ($r=0.68$; $p<0.001$), as well as tumor necrosis factor-α ($r=0.71$; $p<0.001$), which emphasizes the leading role of pro-inflammatory cytokines in the formation of the clinical picture of chronic cerebral

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ischemia. Analysis of individual clinical symptoms showed that memory impairments reliably correlated with an increase in the level of all studied inflammatory markers. The most pronounced correlation was found with the level of TNF-α ($r=0.63$; $p<0.01$), slightly less pronounced - with IL-6 ($r=0.59$; $p<0.01$) and C-reactive protein ($r=0.54$; $p<0.01$). These data confirm the involvement of inflammatory mechanisms in the development of cognitive impairment in patients with chronic cerebral ischemia and reflect the pathogenetic role of systemic inflammation in the damage to neural networks responsible for cognitive functions. Dizziness, as one of the frequent clinical symptoms of CMI, also demonstrated statistically significant positive correlations with levels of CRP ($r=0.48$; $p<0.05$), IL-6 ($r=0.52$; $p<0.05$), and TNF-α ($r=0.55$; $p<0.05$). The moderate strength of the identified correlations indicates the participation of the inflammatory component in the formation of vestibulo-atactic disorders, however, it emphasizes the multifactorial nature of this symptom.

Data reflecting the relationship between emotional lability and inflammation markers deserve special attention. It was established that an increase in the levels of TNF-α and IL-6 was accompanied by an increase in emotional-affective disorders ($r=0.60$ and $r=0.57$, respectively; $p<0.01$), which may indicate the involvement of inflammatory mediators in the pathogenesis of psycho-emotional disorders in chronic cerebral ischemia. The correlation with the level of SRE was also statistically significant, but less pronounced ($r=0.51$; $p<0.01$). Overall, the results of the correlation analysis demonstrate the presence of stable and statistically significant relationships between the level of inflammatory markers and the clinical manifestations of chronic cerebral ischemia.

Conclusions: The conducted study showed that chronic cerebral ischemia is accompanied by clinically significant activation of inflammatory processes, the severity of which increases as the clinical course of the disease worsens. A significant increase in the levels of inflammatory markers in patients with chronic cerebral ischemia compared to the control group, as well as their progressive increase during the transition from the mild to moderate stage of the disease, was established. The identified statistically significant correlations between inflammation indicators and the clinical severity of neurological and cognitive impairments confirm the pathogenetic role of the inflammatory component in the formation of the clinical picture of chronic cerebral ischemia. The obtained results justify the expediency of using inflammatory markers in the comprehensive clinical assessment of patients with chronic cerebral ischemia and open up prospects for improving the diagnosis and monitoring of the course of the disease.

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