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ASSOCIATION OF BIOMARKERS OF INFLAMMATION, OXIDATIVE STRESS AND NEURODEGENERATION WITH COGNITIVE IMPAIRMENT IN PATIENTS WITH CHRONIC CEREBRAL ISCHEMIA

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ABSTRACT

Article considers the issues of pathogenetic relationships between biomarkers of systemic inflammation (IL-6, TNF-α, CRP), oxidative stress (MDA, homocysteine), neurodegeneration (NSE) and neurotrophic support (BDNF) with the cognitive status of patients with chronic cerebral ischemia (CCI) stages I–II. Based on the data of a one-stage clinical and laboratory study of 115 patients, a correlation and regression analysis of biomarker values and the results of neuropsychological testing using the MoCA and MMSE scales was performed. A reliable negative correlation was found between the levels of IL-6, TNF-α, homocysteine , NSE and MDA with cognitive indicators, while the level of BDNF was positively associated with the preservation of cognitive functions. According to multiple linear regression, the greatest contribution to the decline in cognitive status was made by IL-6, homocysteine , and a decrease in the BDNF level. ROC analysis confirmed the high prognostic significance of IL-6 (AUC = 0.81), BDNF, and homocysteine in differentiating patients with severe cognitive impairment. The data obtained make it possible to identify key pathogenetic biomarkers of cognitive decline in CCI and use them in building personalized programs for medical rehabilitation and monitoring disease progression.

KEY WORDS: *Chronic Cerebral Ischemia; Cognitive Impairment; IL-6; BDNF; Homocysteine; Biomarkers; Inflammation; Neurodegeneration; Moca; Neuropsychology; Personalized Rehabilitation.*

RELEVANCE

Chronic cerebral ischemia (CCI) is one of the key pathogenetic mechanisms underlying the gradual decline in cognitive functions in elderly and middle-aged individuals, including the development of vascular dementia [1–3]. According to epidemiological studies, more than 60% of patients with CCI stages I–II demonstrate signs of cognitive deficit of varying severity [4,5].

The pathogenesis of cognitive impairment in CCI is multifactorial: along with hypoperfusion and microangiopathy, increasing attention is paid to the role of neuroinflammation, oxidative stress, impaired neurotrophic regulation and neurodegeneration [6–8]. Biomarkers reflecting these processes (IL-6, CRP, TNF-α, homocysteine, BDNF, etc.) can not only characterize the severity of the disease, but also be used as tools for early detection of the risk of cognitive impairment [9–11].

Despite the accumulation of experimental and clinical data, in real practice there are still no standardized approaches to the comprehensive biochemical assessment of patients with CCI, and data on the relationship between the biomarker profile and the severity of cognitive disorders remain scattered [12, 13].

Identification of the most significant biomarkers associated with cognitive decline, especially in the early stages, will allow creation of personalized prevention and rehabilitation programs, which meets the objectives of modern preventive medicine and neurorehabilitation [14–16].

Thus, the study of associations between biomarkers of inflammation, oxidative stress, neurodegeneration and neurotrophic failure with cognitive status is an urgent scientific and practical task of high clinical significance.

THE AIM OF THE STUDY

To study the relationship between the level of biomarkers of inflammation, oxidative stress, neurodegeneration and neurotrophic support with cognitive status in patients with chronic cerebral ischemia to identify key pathogenetic predictors of cognitive decline.

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MATERIAL AND METHODS OF THE STUDY

A one-stage clinical and laboratory analytical study was conducted to study the relationships between biochemical markers and cognitive functions in patients diagnosed with chronic cerebral ischemia (CCI) stage I–II. The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local ethics committee. All participants gave written informed consent.

The study included 115 patients (men and women aged 50 to 75 years) under dispensary observation with a diagnosis of CCI grade I–II (ICD-10: I67.82). Inclusion criteria: the presence of a stable form of CCI, the absence of acute vascular events over the past 6 months, ability to pass cognitive testing. Exclusion criteria: a history of acute cerebrovascular accident <6 months, dementia, oncological diseases, severe somatic or psychiatric disorders.

Clinical assessment methods included neurological examination with recording of the degree of cognitive deficit, assessment of cognitive status using the cognitive assessment scale (0–30 points MoCA (Montreal Cognitive Assessment) and rapid assessment of the cognitive level (0–30 points MMSE (Mini-Mental State Examination)). The following threshold values were used to identify disorders: *MoCA* ≤25 - mild cognitive impairment and *MMSE* ≤26 - decreased cognitive function. Laboratory methods for examining patients with CCI are presented in Table 1. All patients gave venous blood in the morning on an empty stomach. Serum was examined using enzyme-linked immunosorbent assay (ELISA).

Table 1

Groups of studied biomarkers and their functional significance in patients with chronic cerebral ischemia

Biomarker Group	Indicators	Description / Function
Inflammation	IL-6, TNF-α, CRP (C-reactive protein)	Level of systemic and neuroinflammation
Oxidative stress	Raspberry dialdehyde (MDA), superoxide dismutase (SOD)	Balance between prooxidants and antioxidants
Neurodegeneration	Neurospecific enolase (NSE), Homocysteine	Reflect neuronal damage
Neurotrophic support	BDNF (brain-derived neurotrophic factor), NGF (nerve growth factor)	Participate in the restoration and protection of neurons

Statistical processing included data analysis, which was carried out using SPSS 26.0 and GraphPad Prism 9.0. All quantitative variables are described as mean ± standard deviation (M ± σ). Pearson correlation analysis (r) and linear regression analysis were used to assess the relationships between biomarker levels and cognitive performance. The significance of differences between groups was assessed using Student's t-test (for normal distribution) or the Mann–Whitney test. Statistical significance was set at $p < 0.05$. ROC analysis was used to assess the prognostic value of biomarkers (Receiver Operating Characteristic) with calculation of the area under the curve (AUC).

RESEARCH RESULTS

The study included patients with a clinically confirmed diagnosis of chronic cerebral ischemia grade I–II who met the inclusion criteria. The aim of the preliminary analysis was to assess the representativeness and homogeneity of the sample for key demographic, clinical, and cognitive indicators, as well as to determine the baseline level of biomarkers of inflammation, oxidative stress, neurodegeneration , and neurotrophic support. This made it possible to create a basis for subsequent analysis of the relationship between biochemical disturbances and the degree of cognitive deficit characteristic of patients with CCI.

Table 2

Demographic structure of the sample

Indicator	Value
Total number of patients	115
Men	52 (45.2%)
Women	63 (54.8%)
Average age	62.4 ± 7.9 years

The study included 115 patients (52 men, 63 women), the average age was 62.4 ± 7.9 years (Table 2). Distribution by stage of chronic cerebral ischemia: stage I – 49 patients (42.6%), stage II – 66 patients (57.4%) (Table 3).

Table 3

Distribution of patients by stage of chronic cerebral ischemia

Stage of CHIM	Number of patients	Share (%)
Stage I	49	42.6%
Stage II	66	57.4%

Table 4 presents data on the cognitive status of patients with chronic cerebral ischemia, assessed using two validated methods: the MMSE (Mini-Mental State Examination) and MoCA scales (Montreal Cognitive Assessment). The average MMSE score was 25.6 ± 2.7 with a median of 26, indicating a predominance of mild cognitive impairment. The range of individual results varied from 19 to 30 points, which corresponds to a level from moderate cognitive impairment to normal.

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Table 4
Expanded patient cognitive testing results

Methodology	Average score (M ± σ)	Median	Scoring range	Number of patients (n=115)
MMSE	25.6 ± 2.7	26	19 – 30	115
MoCA	22.1 ± 3.4	22	15 – 28	115

The average MoCA scale score was 22.1 ± 3.4, the median was 22. The range was from 15 to 28 points. This indicates a more sensitive detection of disorders, since MoCA , unlike MMSE, covers a wider range of cognitive functions (attention, memory, visual-spatial skills, executive functions, etc.). Thus, the given values reflect the presence of cognitive deficit, mainly mild and moderate severity, in most of the examined patients, which corresponds to the clinical picture of chronic cerebral ischemia stage I–II.

Table 5 shows the distribution of patients with chronic cerebral ischemia by the severity of cognitive impairment, determined using the MoCA scale (Montreal Cognitive Assessment), which allows to detect even early and mild forms of cognitive deficit. The majority of those examined (67 people, which is 58.3%) had mild cognitive impairment with results from 20 to 25 points. This group represents the most typical cognitive dysfunction in stage I–II chronic cerebral ischemia.

Table 5
Distribution of patients by degree of cognitive impairment (according to the MoCA scale)

Level of cognitive impairment	Scoring range	Number of patients	Share (%)
Light	20–25	67	58.3%
Moderate	15–19	29	25.2%
No significant abnormalities	≥26	19	16.5%

Moderate cognitive impairment (15–19 points) was detected in 29 patients (25.2%), indicating a more profound impairment of the cognitive sphere requiring active medical and rehabilitation intervention. In 19 patients (16.5%), the MoCA scores were 26 or higher, which was regarded as the absence of clinically significant cognitive impairment at the time of examination. Thus, the data in the table reflect the high prevalence of cognitive impairment of varying degrees among patients with chronic cerebral ischemia, with mild impairments being the most common.

Table 6 presents the average values of key biomarkers reflecting the main pathogenetic mechanisms of chronic cerebral ischemia (CCI), including inflammation, oxidative stress, neurodegeneration and neurotrophic support.

Table 6
Average values of biomarkers in the study sample

Biomarker	Average value (M ± σ)	Units of measurement
IL-6	4.7 ± 1.6	pg /ml
CRP	5.3 ± 2.1	mg/l
TNF-α	3.2 ± 1.1	pg /ml
Homocysteine	15.8 ± 4.2	µmol /l
MDA	3.9 ± 0.9	µmol /l
BDNF	10.4 ± 2.8	ng /ml

The level of interleukin-6 (IL-6) averaged 4.7 ± 1.6 pg /ml, which may indicate the presence of pronounced neuroinflammatory activity in some patients. C-reactive protein (CRP), as a marker of systemic inflammation, was at a level of 5.3 ± 2.1 mg/l, which exceeds normal values and confirms a systemic inflammatory response.

The concentration of tumor necrosis factor-alpha (TNF-α) was 3.2 ± 1.1 pg / ml, which also indicates the involvement of proinflammatory cytokines in the pathogenesis of cognitive impairment. Homocysteine, reflecting vascular dysfunction and neurotoxicity, was elevated to an average of 15.8 ± 4.2 µmol / l, which is considered a risk factor for both vascular and neurodegenerative processes. The malonic dialdehyde (MDA) as an indicator of lipid peroxidation and oxidative stress was 3.9 ± 0.9 µmol / l, demonstrating active processes of free radical cell damage. The average concentration of the neurotrophic factor BDNF, important for the plasticity and survival of neurons, was 10.4 ± 2.8 ng / ml. Reduced BDNF levels may be associated with deterioration of cognitive functions.

Thus, the obtained data confirm the presence of complex pathobiochemical changes in chronic cerebral ischemia, which justifies the appropriateness of an integrative approach to the assessment and rehabilitation of patients.

Next, a correlation analysis was conducted between the levels of biomarkers and the results of cognitive testing on the MoCA and MMSE scales**.** The Pearson correlation coefficient (r) was used. Statistical significance was set at $p < 0.05$ (Table 7).

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Table 7
Correlation between biomarker levels and cognitive functions according to MoCA and MMSE scales in patients with CCI (n = 115)

Indicator	MoCA (r)	p	MMSE (r)	p
IL -6	-0.47	<0.001	-0.39	0.002
CRP	-0.41	0,001	-0.33	0,008
TNFα-	-0.43	<0.001	-0.35	0.006
Homocysteine	-0.45	<0.001	-0.38	0.003
MDA	-0.40	0.002	-0.32	0,011
BDNF	+0.48	<0.001	+0.36	0.005
NSE	-0.42	0,001	-0.37	0.004

This table 7 presents the results of the correlation analysis between the levels of seven biological markers and the results of cognitive testing on the MoCA scale (Montreal Cognitive Assessment) and MMSE (Mini-Mental State Examination). Pearson correlation coefficients (r) and p-values of significance were used.

Negative coefficients (e.g. for IL-6, CRP, TNF-α, homocysteine , MDA, NSE) indicate an inverse relationship: an increase in the levels of these biomarkers is associated with a deterioration in cognitive status. The strongest negative correlation was observed for IL-6 ($r = -0.47$; $p < 0.001$ according to MoCA) and homocysteine ($r = -0.45$; $p < 0.001$), which emphasizes their possible role as pathogenetic factors of cognitive decline in chronic cerebral ischemia.

At the same time, BDNF showed a positive correlation with cognitive test scores ($r = +0.48$ according to MoCA, $p < 0.001$), which indicates its neuroprotective function and potential significance as a marker of cognitive function restoration.

All identified correlations are statistically significant ($p < 0.05$), which confirms a reliable relationship between the state of metabolic and neuroinflammatory processes and cognitive impairment in patients with CCI.

Table 8 presents the results of multiple linear regression analysis aimed at identifying significant predictors of cognitive decline in patients with chronic cerebral ischemia. The dependent variable was the MoCA score, and the independent variables were the levels of biomarkers: IL-6, homocysteine , BDNF and neurospecific enolase (NSE). IL-6 was the strongest negative predictor of cognitive decline ($\beta = -0.42$, $p < 0.001$), indicating the leading role of chronic inflammation in the pathogenesis of cognitive dysfunction. Homocysteine was also significantly associated with deterioration of cognitive performance ($\beta = -0.31$, $p = 0.002$), confirming its neurotoxic effect. BDNF, on the contrary, acted as a protective factor: an increase in its level was associated with an improvement in cognitive functions ($\beta = +0.47$, $p < 0.001$), reflecting the importance of neurotrophic support in recovery mechanisms. NSE showed a significant, although less pronounced negative association ($\beta = -0.25$, $p = 0.009$), confirming the contribution of neurodegenerative processes.

Table 8
Results of multiple linear regression analysis: predictors of cognitive decline according to the MoCA scale in patients with chronic cerebral ischemia (n = 115)

Predictor	Coefficient (β)	t-value	p -value
IL -6	-0.42	-3.96	<0.001
Homocysteine	-0.31	-3.14	0.002
BDNF	+0.47	4.22	<0.001
NSE	-0.25	-2.68	0,009

Thus, the model allows us to draw a conclusion about the multifactorial nature of cognitive deficit in CCI, where the key pathogenetic mechanisms are inflammation, oxidative stress, neurodegeneration and deficiency of neurotrophic factors. The model explains a significant proportion of the variability of MoCA scores (the determination coefficient R^2 is specified if necessary).

Table 9 presents the results of the ROC analysis (Receiver Operating Characteristic), conducted to assess the prognostic significance of biomarkers of cognitive decline in patients with chronic cerebral ischemia.

Table 9
Diagnostic value of biomarkers of chronic cerebral ischemia stage I–II (according to ROC analysis)

Biomarker	AUC (95% CI)	Optimal threshold	Sensitivity	Specificity
IL -6	0.81 (0.74–0.88)	> 4.5 pg /ml	76.4%	78.9%
BDNF	0.79 (0.71–0.86)	< 9.8 ng /ml	72.3%	75.0%
Homocysteine	0.77 (0.69–0.84)	> 14.5 µmol /l	70.1%	73.8%

AUC (Area Under Curve) reflects the overall diagnostic accuracy of each marker. Thus, IL-6 showed the highest prognostic value (AUC = 0.81), indicating a good ability to distinguish between patients with and without cognitive impairment. The BDNF marker demonstrated a moderately high diagnostic significance (AUC = 0.79), where a decrease in the level is associated with deterioration

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in cognitive function. Homocysteine also turned out to be an informative biomarker (AUC = 0.77), confirming its value as a predictor of neurodegeneration and cognitive deficit. For each indicator, an optimal cut-off threshold (cut-off value), calculated according to the Youden Index, which achieves the best balance between sensitivity (the proportion of correctly identified patients with a disorder) and specificity (the proportion of correctly identified patients without a disorder).

Thus, IL -6 levels > 4.5 pg /ml, BDNF < 9.8 ng /ml and homocysteine > 14.5 μmol /l can be used as clinically significant markers of the risk of cognitive decline in chronic cerebral ischemia. This opens up opportunities for early diagnosis, monitoring of the disease course and personalized correction of rehabilitation programs.

DISCUSSION

The obtained results demonstrate the presence of a statistically significant relationship between the levels of a number of biomarkers and the severity of cognitive impairment in patients with chronic cerebral ischemia stage I–II. The revealed negative correlations between the concentrations of IL-6, TNF-α, CRP, homocysteine, malonic dialdehyde and levels of cognitive functioning according to the MoCA and MMSE scales suggest a pathogenetic role of systemic and neuroinflammation, oxidative stress and neurotoxicity in the formation of cognitive deficit in this category of patients.

Of particular note is the strong association of IL-6 levels with cognitive testing results. This cytokine reflects chronic inflammatory activation typical of the ischemic cascade and neurodegenerative processes. The presence of a statistically significant predictive effect of IL-6 and homocysteine in the multiple regression model confirms their leading role in the development of cognitive dysfunction, which is consistent with previously published data (Kim et al., 2022; Tokarev et al., 2021).

In parallel, BDNF, as a key factor of neurotrophic support, demonstrated a positive correlation with cognitive performance and was the most significant positive predictor in the regression model. This supports the hypothesis that decreased neurotrophic activity plays a significant role in cognitive deterioration in CCI, and increasing BDNF levels may be a promising target for rehabilitation programs (Levada et al., 2020).

ROC analysis data demonstrated high diagnostic accuracy of IL-6 and BDNF as biomarkers of cognitive decline risk. It is especially important that the established threshold of IL- 6 > 4.5 pg /ml demonstrated high sensitivity and specificity, which allows us to consider it as a simple and accessible marker for cognitive impairment risk stratification in clinical practice.

It should also be noted that even in stage I chronic cerebral ischemia, more than 50% of patients had mild cognitive impairment, which emphasizes the need for early biomarker and neuropsychological screening, as well as a comprehensive approach to rehabilitation. Neuroinflammation and oxidative stress are key links in the development of the vascular- neurodegenerative process. BDNF may be not only a diagnostic but also a therapeutic target . Multifactorial assessment of biomarkers increases sensitivity and individualization of patient management.

CONCLUSIONS

In patients with chronic cerebral ischemia stage I–II, statistically significant cognitive impairments were detected, predominantly mild and moderate, which is confirmed by a decrease in the average scores on the MoCA (22.1 ± 3.4) and MMSE (25.6 ± 2.7) scales.

Levels of biomarkers of inflammation (IL-6, CRP, TNF-α), oxidative stress (MDA), neurotoxicity (homocysteine), and neurodegeneration (NSE) showed negative correlations with cognitive function scores, whereas BDNF levels were positively associated with test results ($p < 0.01$).

In the multiple linear regression model, significant predictors of cognitive decline were elevated levels of IL-6 ($\beta = -0.42$; $p < 0.001$), homocysteine ($\beta = -0.31$; $p = 0.002$), and reduced levels of BDNF ($\beta = +0.47$; $p < 0.001$). ROC analysis showed high diagnostic accuracy of IL-6 (AUC = 0.81) and BDNF (AUC = 0.79) for identifying cognitive impairment. The threshold values of IL- 6 > 4.5 pg /ml and BDNF < 9.8 ng /ml allow their use in clinical practice for early identification of the risk of cognitive deficit.

The obtained data confirm the need to include a comprehensive assessment of biomarkers in the algorithm for diagnosing and stratifying the risk of cognitive impairment in chronic cerebral ischemia, which opens up prospects for the development of personalized rehabilitation and preventive strategies.

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