

Indicators of Neurobiomarkers in Patients with Chronic Cerebral Ischemia Who Have Had a Coronavirus Infection

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Abstract

Annotation: The causes of the development of cerebrovascular diseases in COVID-19 may be a significant deterioration in the rheological properties of blood, activation of hemostasis, changes in the atrombogenic properties of the vascular wall endothelium. Thrombocytopenia and elevated levels of fibrinogen, D-dimer and coagulation factor VIII are most often observed in COVID-19. Changes in the indicators of neurobiomarkers, namely antibodies to gliadin-fibrillar acid protein (GFAP), S-100 protein, to serotonin and dopamine receptors in CHEM indicate the severity of this disease. The aim of the study was to study the features of neurological and biochemical parameters in patients with CHEM who had a coronavirus infection, to assess the number and prognostic value of markers of brain damage: antibodies to GFAP, serotonin, dopamine receptors and S-100 protein.

Keywords: chronic cerebral ischemia, COVID-19, antibodies to GFAP, serotonin, dopamine receptors, S-100 protein.

Vascular diseases of the brain are an urgent medical and social problem. They occupy a leading place in the structure of morbidity and mortality in economically developed countries. Mortality from cerebrovascular diseases in economically developed countries is 11-12% and is second only to mortality from heart diseases and tumors of all localizations.

Cerebrovascular pathology is one of the most frequent comorbid conditions in patients with COVID-19, being found in approximately 12% of infected [14, 85, 100]. The study of comorbid diseases among the deaths of COVID-19 showed that out of 2000 cases, 228 patients had chronic cerebral ischemia (ChCI) [16]. Vascular cognitive impairment is an important medical and social problem [2,17].

Chronic cerebral ischemia (ChCI) is a multifactorial disease, the main pathogenetic factor of which is atherosclerosis of the stem and cerebral vessels [6].

The main reasons for the possible development and progression of ChCI in patients who have undergone COVID-19 include [56, 81, 84, 95]: disorders of the rheological properties of blood caused by the infectious process, as well as coagulopathy, which, in turn, contribute to platelet disorders and disorders of blood clotting factors; pronounced in COVID-19

cytokine storm; development of hypoxia of various organs, including the brain; macro- and microangiopathies: endotheliitis, endothelial thrombo-inflammatory [4].

Chronic cerebral ischemia is one of the most common causes of stroke, dementia and disability. Chemical therapy is based on small focal and diffuse ischemic changes in brain tissue, manifested by a complex of neurological and neuropsychological diseases [2, 4, 12].

The causes of the development of cerebrovascular diseases in COVID-19 may be a significant deterioration in the rheological properties of blood, activation of hemostasis, changes in the atrombogenic properties of the vascular wall endothelium [5]. Thrombocytopenia and elevated levels of fibrinogen, D-dimer and coagulation factor VIII are most often observed in COVID-19 [1,8].

Changes in the indicators of neurobiomarkers, namely antibodies to glial fibrillar acid protein (GFAP), S-100 protein, serotonin and dopamine receptors in CHEM indicate the severity of this disease [4,19].

Glial-fibrillar acidic protein (GFAP — glial-fibrillar acidic protein). The literature provides information about the increase in GFAP in neurodegenerative

processes [9,13]. At the same time, in Alzheimer's disease, frontotemporal dementia, its amount is increased in blood serum and cerebrospinal fluid [10]. An increase in the number of antibodies to GFAP in the body is a sign of astrocyte activation and reactive gliosis in response to trauma, ischemia or neurodegenerative processes [15,16]. GFAP is responsible for the cytoskeleton of glial cells and provides their mechanical strength. It also participates in neuroglial cooperation [16].

The S-100 protein is considered a glial biomarker and has neurospecific properties. Some authors recognize this protein as one of the early markers of brain damage in patients with hypertension [10,18]. The literature reports a significant increase in the number of antibodies to the S-100 protein in serum with moderate cognitive impairment and Alzheimer's disease [4,7,18]. The level of S-100 protein in the blood makes it possible to assess the degree of brain damage in stroke, traumatic brain injury and other conditions leading to neurological diseases.

Antibodies to serotonin receptors have the highest expression in the brain and enhance cellular apoptosis and protein oxidation [2,5]. According to the data, these receptors are important in learning and memory processes. An increase in the number of antibodies to these receptors in the blood was also found in Alzheimer's disease [8,16]. Antibodies to dopamine receptors are directly involved in cognitive dysfunction and depressive states [5,19]. An increase in antibodies against these receptors in the blood leads to a decrease in their number. A decrease in the markers of the dopaminergic system is accompanied by a deterioration in the frontal function of the cortex, a decrease in attention and

memory, and metabolic disorders in certain areas of the cortex [14,20].

The purpose of the study. To study the features of neurological and biochemical parameters in patients with ChCI who have had a coronavirus infection, to assess the number and prognostic value of markers of brain damage: antibodies to GFAP, serotonin, dopamine receptors and S-100 protein.

The results of the study. To achieve this goal, 56 patients participated in the study, including 36 (54.5%) patients with a diagnosis of ChCI who had a history of COVID-19 as representatives of the main group and 20 patients in the comparison group (45.5%) with a diagnosis of ChCI who had no history of COVID-19 infection. All patients underwent neurological examination, a general blood test and a biochemical blood test. All the patients in our study were treated at the Central Clinical Hospital №2 of the Main Department of Medicine under the Administration of the President of the Republic of Uzbekistan. The patients were aged 48-82 years (mean age 63.2 ± 1.5 years) ($P=0.42$), observation was carried out for 1 year (2020-2021). Among the observed patients, there were more women than men, this ratio was 1.8:1.

When analyzing the complaints (Fig. 1) presented by patients, we noted that the frequency of their occurrence was higher in patients of the main group, so the most frequent were: fatigue (in 95% of patients), headache (58%), impaired concentration (67%), memory impairment (87%) and hair loss (63%). Whereas in the comparison group their frequency was 72%, 36%, 48%, 40% and 32%, respectively, which was significantly lower ($P<0.05$).

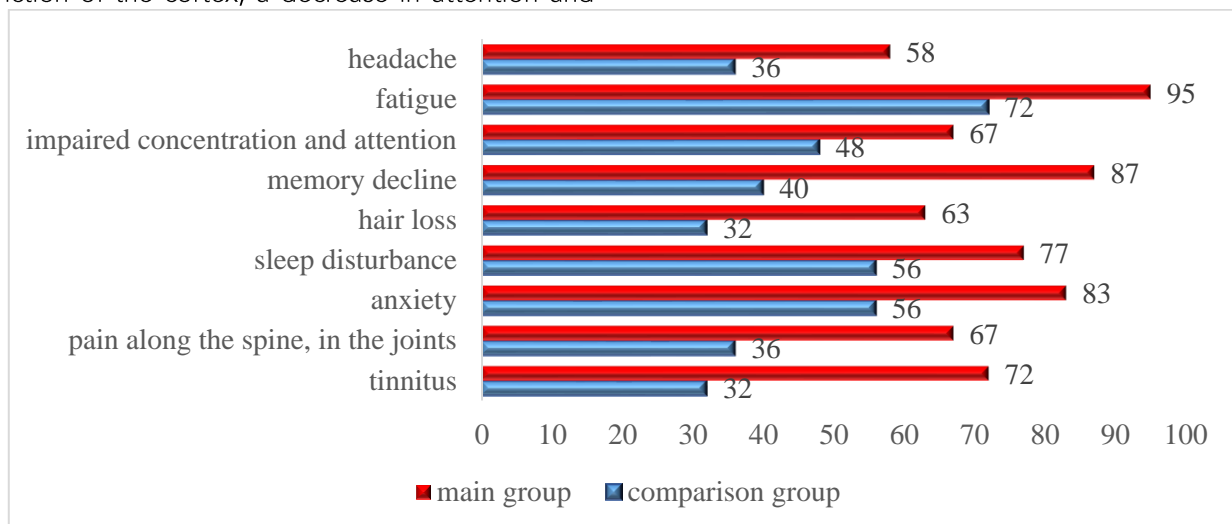


Fig.1. Frequency of complaints made by patients with ChCI, depending on the presence of a history of covid infection

When studying the neurological status in patients of the main group, a higher percentage of the incidence of focal symptoms is noted (Fig. 2) in relation to the indicators in the comparison group ($P<0.05$). Thus, coordination disorders were observed in 83.3% in the main group and 73.0% in the comparison group, the presence of reflexes of oral automatism (pathological) – in 76% and 53%,

respectively, the revival of tendon reflexes – in 68% and 52% of patients, anisoreflexia - 42% and 23%, violations of convergence and accommodation – 42% and 23% respectively. Central paresis of the facial nerve was almost 2 times more common in patients of the main group, which was a significantly significant indicator (34% vs. 15%; $P<0.05$) in relation to the comparison group.

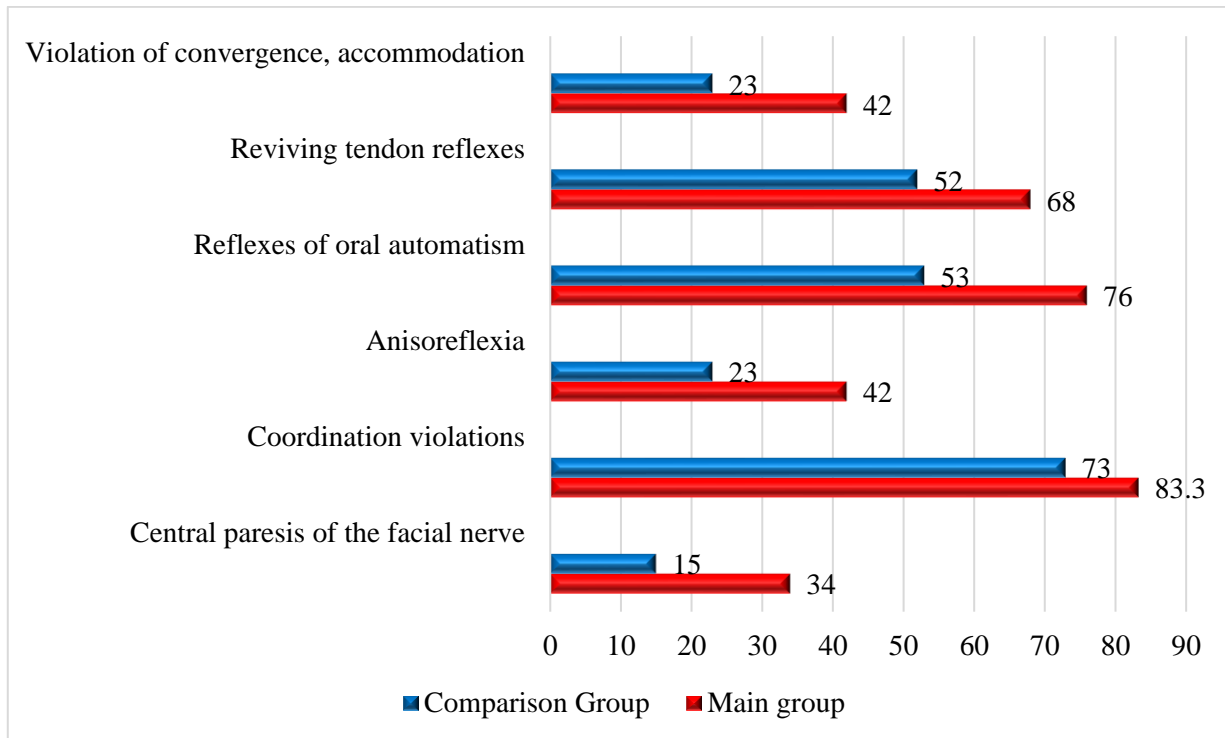


Fig. 2. Frequency of occurrence of disorders in the neurological status in patients with ChCI, depending on the presence of a history of covid infection

All the examined patients showed varying degrees of cognitive impairment. Thus, according to the MMSE scale, in patients of the main group, the

overall score was - 21.4 ± 0.49 ; in the comparison group - 26.46 ± 0.15

1-table: Indicators of cognitive functions of patients on the MMSE scale

No	MMSE scale	Main group (n=60)	Comparison Group (n=50)	Control group (n=20)	P, OG to GS	P, OG to KG	P, GS to KG
1.	Landmark	$3,75 \pm 0,13$	$4,56 \pm 0,09$	$4,96 \pm 0,09$	$<0,05$	$<0,05$	$<0,01$
	Time (date)	$3,73 \pm 0,13$	$4,44 \pm 0,09$	$4,86 \pm 0,10$	$<0,05$	$<0,05$	$<0,01$
2.	Place	$3,73 \pm 0,13$	$4,44 \pm 0,09$	$4,86 \pm 0,10$	$<0,05$	$<0,05$	$<0,01$
	Perception	$1,85 \pm 0,08$	$2,46 \pm 0,08$	$3,85 \pm 0,11$	$<0,01$	$<0,001$	$<0,05$
3.	Attention and account	$3,35 \pm 0,14$	$3,84 \pm 0,10$	$4,85 \pm 0,11$	$<0,01$	$<0,01$	$<0,01$
4.	Memory	$1,55 \pm 0,09$	$2,32 \pm 0,07$	$3,85 \pm 0,11$	$<0,01$	$<0,01$	$<0,01$
5.	Speech, reading and writing. Name 2 items	$1,61 \pm 0,07$	$1,96 \pm 0,03$	$1,96 \pm 0,03$	$<0,05$	$<0,05$	$<0,05$
	Repeat the phrase	$0,96 \pm 0,03$	$0,96 \pm 0,02$	$1,00 \pm 0,00$	$<0,05$	$<0,05$	i/e
	Execution of a 3-stage command	$2,07 \pm 0,1$	$2,08 \pm 0,14$	$2,95 \pm 0,01$	i/e	$<0,05$	$<0,05$
	Reading	$0,87 \pm 0,04$	$1,0 \pm 0,00$	$1,00 \pm 0,01$	$<0,05$	$<0,05$	i/e
	Write an offer	$0,6 \pm 0,07$	$0,96 \pm 0,02$	$1,00 \pm 0,01$	$<0,01$	$<0,01$	i/e
	Draw a picture	$0,93 \pm 0,03$	$0,98 \pm 0,02$	$1,00 \pm 0,01$	$<0,05$	$<0,05$	i/e
	Total score	$21,4 \pm 0,49$	$26,46 \pm 0,15$	$29,2 \pm 0,13$	$<0,05$	$<0,01$	$<0,05$

According to a full analysis of the results of the MMSE and Moca scales, patients who had a history of COVID-19 had lower scores compared to the comparison group on all lines, except for the item "name items". In particular, when checking visual-constructive and performing ability, 2.9 ± 0.17 points out of the maximum 5 points were revealed in the main group, and 3.47 ± 0.22 points ($p < 0.05$) in the comparison group. In the paragraph on attention, in terms of forward and reverse pronouncing of figures from the maximum 2 points in two groups, respectively, 0.9 ± 0.03 and 1.8 ± 0.02 points (from the maximum 2 points). At the point of response to the letter A in a row of letters from the maximum 1 point, respectively, 0.43 ± 0.02 and 0.97 ± 0.01 ($p < 0.05$); when subtracting 7 from the number 100 in

two groups, the results are 2.1 ± 0.08 points and 2.92 ± 0.04 points ($p < 0.05$), respectively. At the point of repetition of sentences, which is speech activity, out of the maximum 2 points in the main group 1.1 ± 0.06 points and in the comparison group 1.3 ± 0.04 points ($p < 0.05$) and at the point of rapid enumeration of words beginning with a certain letter in the groups 0.73 ± 0.05 points and 0.8 ± 0.04 points (maximum 1 point) ($p > 0.05$). In the process of delayed word reproduction, 3.81 ± 0.11 points and 4.22 ± 0.15 points were determined, respectively ($p < 0.05$). The maximum score for this activity is 5. In the question of orientation, representatives of the main group scored 4.9 ± 0.12 points, and patients of the comparison group - 5.6 ± 0.14 points ($p < 0.05$).

2-table: Montreal Scale for the Assessment of Cognitive Functions

Indicator	Main Group	Comparison Group	p
Visual-constructive/executive skills (5 points)	2,9±0,17	3,47±0,22	<0,05
Title (3 points)	3,0±0	3,0±0	>0,05
Attention			
Repetition of numbers in forward and reverse order (2 points)	0,9±0,03	1,8±0,02	<0,05
Reaction (1 point)	0,43±0,02	0,97±0,01	<0,05
Serial subtraction of 7 out of 100 (3 points)	2,1±0,08	2,92±0,04	<0,05
Speech:			
Repetition of sentences (2 points)	1,1±0,06	1,3±0,04	<0,05
Fluency of speech (1 point)	0,73±0,05	0,8±0,04	>0,05
Abstraction (2 points)	1,4±0,03	1,4±0,02	>0,05
Delayed playback (5 points)	3,81±0,11	4,22±0,15	<0,05
Orientation (6 points)	4,9±0,12	5,6±0,14	<0,05
Total score	21,27±0,54	25,48±0,21	<0,05

When assessing cognitive activity on the Montreal scale, the results of the main group averaged 21.27 ± 0.54 points versus 25.48 ± 0.21 points ($p < 0.05$) in the comparison group. According to these data, it was found that in the representatives of the main group, a decrease in memory and attention leads to a significant deterioration in the quality of life and, as a result, can pose a threat to health, family and society. According to the results of the analysis of the verification of cognitive functions by the MoCA test, only 11.7% (7) of patients in the main group had cognitive functions within the normal range ($MoCA \geq 26$) and the remaining 88.3% (53 patients) showed a decrease in cognitive functions of varying degrees ($MoCA \leq 25$). In the comparison group, 50% (25) of patients had reduced cognitive function ($MoCA \leq 25$), and the remaining 50% (25) did not have cognitive deficits ($MoCA \geq 26$).

In the study of neurobiomarkers of cognitive dysfunction, the level of autoantibodies to GFAP was determined higher than normal (% of autoantibodies, -20 to +10). In group 1, the GFAP level was $56.3 \pm 1.44\%$ ($r > 0.05$), in group 2 - $58.73 \pm 1.0\%$. Given that its normal limit is from -20 to +10, the result recorded in the groups, the recorded results were above the specified limit.

In the course of our study, the titer of autoantibodies to the S-100 protein was tested in all observed patients by enzyme immunoassay. According to this, a direct relationship was found between COVID-19 infection and S-100 protein, that is, 44.85 ± 1.03 points in the main group and 32.53 ± 1.52 points in the comparison group ($p < 0.05$). An increase in the titer of autoantibodies to the S-100 protein indicates a significant lesion of the brain substance.

3-table, Indicators of neurobiomarkers in patients

Indicator	Main Group	Comparison Group	p
AT to GFAP	45,71±0,59	58,68±1,4	>0,05
AT to S100	32,53±1,52	44,85±1,03	>0,05
AT to serotonin receptors	19,80±0,31	25,85±1,23	>0,05
AT to dopamine receptors	16,33±0,34	21,53±0,92	>0,05

The number of antibodies to serotonin receptors in the blood was recorded at a high level in patients of both groups (the normal range of autoantibodies, in % percentages, from -20 to +10). Its number was $19.80 \pm 0.31\%$ in representatives of the main group with a diagnosis of CHEM. In the comparison group, it was $25.85 \pm 1.23\%$. There was no significant statistical difference between the groups ($p > 0.05$).

In comparison with other neurobiomarkers, antibodies to dopamine receptors were detected in the blood in smaller quantities. However, its level slightly exceeded the normative indicators (the normative limit of autoantibodies, in % percentages, from -20 to +10). In particular, among the groups it was $16.33 \pm 0.34\%$ in the representatives of the 1st group, and in the 2nd its value was $21.53 \pm 0.92\%$ ($p > 0.05$), which is slightly higher than in the 1st group.

Conclusions. According to the results of the assessment of the clinical and neurological characteristics of patients diagnosed with CHEM, the

symptoms of asthenia, anxiety, panic and insomnia prevailed in the patients of the main group, while in comparison with them, coordination disorders and pathological reflexes were added to these symptoms. To assess the cognitive function of patients, the MMSE test and the MoHS scale were used in representatives of both groups, the cognitive functions of patients in the main group were 25.74 ± 0.19 points, and in the comparison group - 21.27 ± 0.27 points ($p < 0.05$). It was found that the number of all neurobiomarkers in the examined patients significantly exceeds normal values, and the GFAP AT and S100 AT indicators are recorded at a higher level than AT to serotonin receptors and AT to dopamine receptors.

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