American Journal of Medicine and Medical Sciences 2023, 13(6): 825-830
DOI: 10.5923/j.ajmms.20231306.11

Serum Level of Neurotropic Autoantibodies in COVID-19 Associated Ischemic Stroke Patients

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Abstract Since 2019, the whole world has been experiencing a pandemic of coronavirus infection. However, unlike previous outbreaks, COVID-19 has a high virulence and pathogenicity, and is also spreading around the world at lightning speed. In this connection, a pandemic was declared by the World Health Organization (WHO) on March 11, 2020. At the moment, there is an increase in the number of patients with COVID 19 around the world who develop coagulation disorders and a high prevalence of thromboembolic complications. Neurological syndromes caused by the production of antibodies to nervous tissue during COVID-19 coronavirus infection are a new area of modern clinical neurology, which is of great interest from theoretical and practical positions.

Keywords COVID-19, Ischemic stroke, Immune system

1. Introduction

Neurological syndromes caused by the production of antibodies to nervous tissue during COVID -19 coronavirus infection are a new area of modern clinical neurology, which is of great interest from theoretical and practical positions. Significantly affecting the immune system, COVID -19 causes autoimmune and metabolic changes that occur in the human body when an infection enters both in the acute and late (post-COVID) period [9,23,24,26].

One of the well-documented additional clinical manifestations of COVID-19 is acute cerebrovascular accident (ACV) [7,21]. Ischemic stroke (IS), secondary to severe COVID-19, is common and often fatal. Exploring the mechanisms by which SARS-CoV-2 induces AI has become a popular research topic. Even the first L. Mao et al. (2020) demonstrated that patients with severe COVID-19 were more likely to develop complications of IS, which were associated with higher mortality rates [23].

It is known that various functional states of the body are accompanied by shifts in the content of natural autoantibodies (e-AT), associated with changes in metabolic processes of key endogenous targets for the development of the disease or providing a physiological norm. Similar studies on the analysis of the content of n-AT were carried out in various neurological and psychiatric diseases: ischemic [2,11,15,16] and hemorrhagic stroke [29], epilepsy [14], schizophrenia and psychosis [10], dementia, Alzheimer's disease [5,6], chronic alcohol intoxication [1], neurodegenerative diseases [17,18], encephalitis [19], and others.

Significant variability of pathogenetic events that occur with COVID -19 determines the multiorganism of the lesion, in the development of which the immunopathogenic properties of SARS-CoV-2 can also play a certain role. Autoantibodies associated with a number of autoimmune diseases have been found in patients with COVID-19 [20,22,25,27]. Researchers have identified the presence of antinuclear antibodies (ANA), anticytoplasmic neutrophil antibodies (ANCA) and anti-antiphospholipid (APL) antibodies in patients with COVID-19. The results showed that 45% of patients were positive for at least one autoantibody, and patients with positive autoantibodies tended to have a worse prognosis and a significantly higher respiratory rate on admission. The positive rate for ANA was 33%, the positive rate for anticardiolipin antibodies (IgG and/or IgM) was 24%, and three patients were positive for antibodies against β2-glycoprotein-I (IgG and/or IgM) (9%). However, ANCA was negative in all patients [13,20,28].

Analysis of the content of n-ATs, which preserve all changes in the EB system in patients with COVID-19 associated IS, will allow solving the problem of diagnosing and treating neurological syndromes in COVID-19.

The purpose of the study: was to conduct a comparative analysis of the content of natural neurotropic autoantibodies in the blood serum of patients with COVID-19 associated IS in the course of the disease.

2. Materials and Methods

This study was carried out at the Department of Internal

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Received: May 25, 2023; Accepted: Jun. 22, 2023; Published: Jun. 26, 2023
Published online at http://journal.sapub.org/ajmms

Medicine, Nephrology and Hemodialysis of TashPMI in the period 2020-2022. The basis of the clinical study included the results of monitoring 150 patients in acute and early recovery periods of IS, of which 100 patients were with IS due to COVID-19 pneumonia (main group or group 1) and 50 patients with acute IS without symptoms and a positive test for COVID -19 (comparison group or group 2). Clinical studies were carried out in the departments of resuscitation and intensive care, neurology of the Specialized Multidisciplinary Infectious Diseases Hospitals Zangiota-1 and Zangiota-2, as well as the City Clinical Hospital No. 5 in Tashkent.

The age of patients in group 1 (57 males) and (43 females) ranged from 41 to 89 years (mean age) 68.3±9.8 years in group 2 (27 males) and (23 females) - from 42 to 83 years (mean age 64.2±10.2 years).

The control group consisted of 16 people without stroke and COVID-19, aged 50 to 68 years (mean age 61.2±5.7 years) with stage 1 dyscirculatory encephalopathy, whose data were used to compare immunological parameters.

The criteria for inclusion in the study of patients of the main group were the first acute IS, the transferred coronavirus infection COVID -19 for up to 1 month; comparison groups: new acute IS, absence of clinical symptoms and a positive test for COVID -19, absence of COVID -19 infection before the onset of IS (included patients with IS before March 2020).

Criteria for exclusion of patients from the study: hemorrhagic stroke, late recovery period and consequences of ischemic stroke, recurrent stroke, presence of neurocognitive disorders before COVID-19 and stroke, neurodegenerative and extrapyramidal diseases, severe TBI, epilepsy, mental and oncological diseases, severe somatic diseases in the stage of decompensation.

All patients underwent a detailed clinical and neurological examination according to the classical method. The assessment of consciousness and the severity of its impairment was carried out using the Glasgow coma scale. The severity of neurological deficit and the severity of IS were assessed using the Stroke Severity Scale of the US National Institutes of Health (National Institutes of Health Stroke Scale - NIHSS). Assessment of the condition of patients was carried out once at the time of the initial examination in clinics on days 1-5, 14, 28 of the disease.

The formulation of the diagnosis of COVID -19 associated IS was carried out on the basis of the results of an epidemiological history, clinical and neurological examination and data from laboratory and instrumental studies in accordance with the criteria of the ICD-10 (U07.1 - U07.2), the National Guidelines for Neurology and generally accepted documents (European Stroke Organization (ESO) Executive committee; ESO Writing Committee, Guidelines for management of ischemic stroke and transient ischemic attack, 2008), Temporary Guidelines of the Ministry of Health of Russia, "Prevention, diagnosis and treatment of a new coronavirus infection COVID-19" [3,4]. To identify COVID-19 pneumonia, its complications, differential diagnosis with other lung diseases, as well as to determine the severity and dynamics of changes, to evaluate the effectiveness of the therapy, chest MSCT was performed. According to the examination standards, to clarify the nature of the pathological process and exclude hemorrhagic stroke, all patients underwent brain CT upon admission to the clinic.

The basic laboratory examination of inpatients included standard general clinical and biochemical blood tests, a detailed coagulogram, and a general urinalysis. According to the COVID -19 Diagnostic Protocols, the levels of C-reactive protein (CRP), procalcitonin, D-dimer, ferritin, fibrinogen, and triglycerides were also examined. The detection of class M and G immunoglobulins (IgM and IgG) using immunochemical methods was of primary importance for the etiological laboratory diagnosis of COVID-19. The main type of biomaterial for laboratory testing by PCR for SARS-CoV-2 RNA was the material obtained by taking a swab from the nasopharynx (from two nasal passages) and oropharynx. Swabs from the mucous membrane of the nasopharynx and oropharynx were collected in one tube for a higher concentration of the virus.

In blood serum samples of all observed patients with IS, as well as in blood samples of the control group (n = 16), a quantitative determination of serum immunoreactivity of neurotropic autoantibodies of the IgG class (natural neurotropic autoantibodies - e-AT1 and their functional counterweights - anti-idiotypic antibodies - AiAT2) was carried out, directed to nervous tissue proteins NF-200, GFAP, S-100, MBP.

Determination of the content of neurotropic autoantibodies (NAAT) was carried out using standard procedures for enzyme-linked immunosorbent assay ELI-N-Test and test kits of the same name produced by the Immunculus Medical Center (Russia) according to the method of A.B. Poletaev [11,12]. The level of serum content of n-AT to each of the neuroantigens was expressed in arbitrary units (arb. units): percentage deviations from the standard serum IR. AAT immunoreactivity values from 80 to 140 c.u., AT1/AIAT2 immunoreactivity index from 0.8 to 1.2 were taken as the norm [14]. "ELI-tests" can be detected when signs of blood are detected, detection is still on that detection of development. This test allows patients to assess the state of the central and peripheral nervous system by antibody markers. The study is especially significant when a person is at risk (hereditary predisposition) to severe pathologies of the nervous system, such diseases as stroke, amyotrophic lateral (lateral) sclerosis.

The results obtained were recorded in individual patient registration cards and then entered into the electronic database of the Microsoft Excel 2010 program. The generally accepted methods of variation statistics were used. The results are presented as M (mean) ± m (error) and μ (mean) ± (standard deviation). After confirming the normality of the data distribution, the analysis of quantitative indicators was carried out using Student's t -test. Differences were considered statistically significant at a significance level of at least 95% ($p<0.05$). The degree of connection

between the obtained indicators was determined by the regression equation, taking into account the strength of the connection and its direction by calculating the correlation coefficient (r) according to Pearson.

3. Results and Discussion

The consciousness of patients with COVID-19 associated IS was clear in 62 (%) patients (mean Glasgow score), deafened in 31 (%) patients (mean Glasgow score), soporous in 5 (%) patients (mean Glasgow score). 2 (%) patients were in a coma (mean score on the Glasgow scale) (Table 1).

Table 1. Disturbances of consciousness in the examined patients

Consciousness	Covid-19 + II (n=100)		II (n=50)		P
	abs.	%	abs.	%	
Clear	62	62,00	46	92,00	<0,001
Stun	31	31,00	3	6,00	<0,001
Sopor	5	5,00	1	2,00	<0,001
Coma	2	2,00	0	0,00	<0,001

Note: P - significance of values between groups

Among patients with COVID-19 pneumonia, mild IS was observed in 29 (%) patients (average NIHSS score), moderate IS in 25 (%) patients (average NIHSS score), and severe IS in 46 (%) patients (mean NIHSS score) (Table 2).

Table 3 presents comparative data on the measurement of neurotropic n-Abs in the bloodstream of examined individuals with COVID-19 associated IS, including the control group and the IS group. Analysis of blood serum samples in the listed groups was carried out in accordance with the terms of blood collection of patients (5th, 14th and 28th day).

When studying the characteristics of serum immunoreactivity of the patients we observed, we used a test system represented by four proteins directly related to the functions of nerve cells: NF -200 protein, GFAP protein (astrocyte intermediate filament protein), S-100 protein (calcium-dependent regulator of many cellular functions, metabolic processes in the nervous tissue, in particular, the neurotrophic factor of serotonergic neurons, apoptosis regulator) and myelin basic protein (MBP).

The NF-200 protein is a specific axonal protein. The growth of nAb accompanies the processes of degeneration of nerve fibers (including in diabetic neuropathy) [12]. The analysis of the results of immunological monitoring made it possible to establish a significant increase in the level of n-AT to the NF-200 protein in all examined patients of groups 1 and 2 (132.9±4.1 vs. 121.56±2.8 c.u., respectively) in 1.8 and 1.6 times, respectively, compared with the parameters obtained for persons in the control group (72.88±6.83 units) ($p < 0.001$) (Table 3). At the same time, there was a tendency to a higher increase in n-AT in patients of group 1 by 1.09 times ($p<0.05$) from the values of group 2, which may indicate pronounced degenerative changes in axons in IS against the background of COVID-19 (Fig. 1).

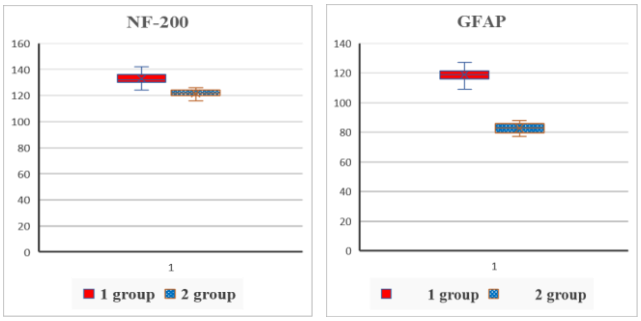

Figure 1. Comparative content of autoantibodies to NF-200 and GFAP in the blood serum of the examined patients (conventional units)

Table 2. Distribution of patients depending on the severity of stroke

Stroke severity	Covid-19 + II (n=100)		II (n=50)		P
	abs.	scale score NIHSS	abs.	scale score NIHSS	
Mild stroke	29	5-15	17	5-15	0,001
Moderate stroke	25	16-20	14	16-20	>0,05
Severe stroke	46	21-42	19	21-42	<0,05

Note: P is the significance of values between groups.

Table 3. Parameters of natural neurotropic autoantibodies (M ± m) in the blood serum of examined patients with IS (arb. units)

Values e-AT	Covid-19+ II (n=50)	II (n=30)	Control (n=16)	P
NF-200	132.9 ± 4.1	121.56 ± 2.8 _	72, 88±6, 83	< 0.00 1
GFAP	118.9 ± 3.9	82.7 ± 3.42	57.88 ± 5.49	< 0.00 1
S - 100	129.5 ± 10.2	122.8 ± 4.9	77.47 ± 7.32	< 0.00 1
MBP	97.3 ± 4.5	85, 56±3, 4	58, 76±5,36	< 0.00 1

Note: P - significance of values in relation to the control group.

The astroglial protein GFAP is the main structural component of the intermediate filaments of astrocytes. Changes in its expression are observed in various pathological processes involving brain glia (gliosis as a consequence of ischemic lesions, a consequence of hemorrhages, trauma, toxic effects, etc.) [2,8,12]. The level of GFAP protein immunoreactivity and the number of GFAP-positive cells is a marker of neuronal loss in different molecular layers of the hippocampus up to the dentate gyrus, indicating a close relationship between neuronal and glial dysfunction [11]. In all patients with IS, there was a significant increase in the level of nAbs to the GFAP protein, in contrast to the control group (57.88±5.49 c.u.) by 2 and 1.1 times, respectively, in groups 1 and 2 ($p < 0.001$) (Table 3). The largest increase in n-AT was observed in group 1 (118.9±3.9 units) by 1.4 times in comparison with the indicators of group 2 (82.7±3.42 units) ($p<0 .05$) (Fig. 1). An increase in GFAP levels is a sensitive marker of brain damage, the extent of which has been associated with stroke severity and the development of COVID -19 pneumonia. The growth of antibodies to GFAP accompanies abnormally active proliferation of astroglial cells (gliosis), which may be the outcome of a previous infarction (damage) of the brain and inflammatory processes in the central nervous system.

The S-100 protein, a neurospecific isoform of the S-100 protein, is a $Ca2^{+}$-binding protein and a trophic factor for serotonergic neurons. It is synthesized by glia and has a predominant localization in the cytoplasm of astrocytes. There is evidence that the functions of S-100 are associated with the regulation of the permeability of ion channels (stimulates an increase in the level of intracellular calcium in neurons), as well as with the mechanisms of learning, memory, emotional and motivational reactions, i.e. integrative activity of the brain [8,10,11]. In addition, since S-100 proteins in the extracellular sector exhibit the properties of cytokines and interact with RAGE receptors, which are expressed in the nervous system not only by neurons, microglia and astrocytes, but also by cells of the vascular wall, it can be assumed that the vascular network is also involved in the inflammatory response [18]. Patients with COVID -19 associated IS significantly differed in the individual serum level of nAbs to the S-100 protein (129.5±10.2 c.u.) with a tendency to increase their content by 1.05 and 1.6 times compared with group 2 (122.8±4.9 c.u.) and control (77.47±7.32) ($p < 0.001$) (Table 3). At the same time, the level of nAbs to S-100 in group 2 was 1.5 times higher than the control values ($p < 0.05$) (Fig. 2).

Myelin basic protein (MBP) is a protein in the myelin sheaths of nerve fibers. MBP is the main target of pathological autoimmune processes accompanying demyelinating diseases of the nervous system. The growth of antibodies to it is typical for neuritis (radiculoneuritis). MBP ensures fast conduction of a nerve impulse along the axons that it surrounds [20,29]. We have revealed the greatest scatter of immunoreactivity in terms of the level of n-Abs to MBP. Thus, the largest significant ($p < 0.001$) increase in n-AT titer to MBP was observed in group 1 (97.3 ± 4.5 units) by 1.6 times in comparison with the control (58.76 ± 5.36 units) and 1.14 times compared with group 2 (85.56±3.4 units) (Table 3). In group 2, an increase in the level of nAbs to MBP by 1.4 times was registered in comparison with the control ($p<0.001$) (Fig. 2).

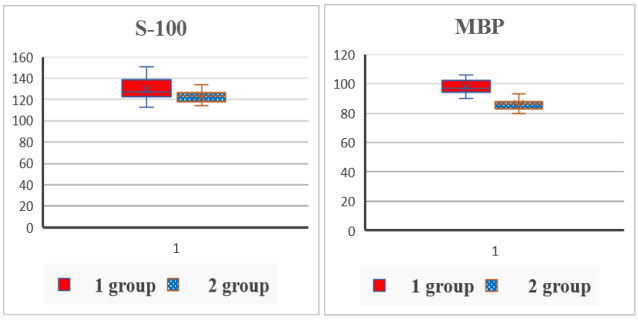

Figure 2. Comparative content of autoantibodies to S-100 and MBP proteins in the blood serum of the examined patients (conventional units)

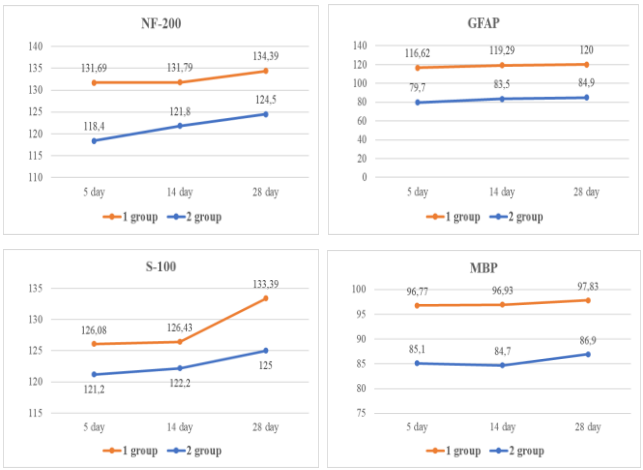

Figure 3. Analysis of blood serum samples in patients (on 5-th,14-th and 28-th day)

The study of the level of n-AT in patients with COVID -19 associated IS in the dynamics of the disease showed the greatest increase in the level of n-AT on the 28th day to the protein S-100 (increased by 1.1 times compared with 5 and 14 days and the values of group 2), NF-200 (increased by 1.1 times in comparison with 5 days and values of group 2) and MBP (increased by 1.1 times in comparison with 5 days and values of group 2). The levels of nAbs to other neurotransmitters did not have significant differences in the dynamics of stroke, although they significantly exceeded the values of group 2 and control (Fig. 3). Thus, an increase in the level of nAbs to the S-100 protein in dynamics can cause a spectrum of neuropsychic manifestations of COVID-19 from reversible activation to the formation of a glial scar, which is confirmed by some studies [24], with the preservation of the inflammatory response in the vascular network. An increase in nAbs to the NF-200 protein in dynamics may indicate the progression of degenerative changes in axons in IS against the background of COVID-19. MBP, being the main target of autoimmune disorders, can cause the progression of demyelinating processes in the nervous system. This is expressed by a longer preservation of

motor, sensory and speech disorders in this group of patients.

4. Conclusions

1. The study of the level of n-AT in patients with COVID -19 associated IS in the dynamics of the disease showed the greatest increase in the level of n-AT on day 28 to protein S-100, NF-200 and MBP, which may well explain the variety of symptoms of COVID-19 and long-term consequences coronavirus infection (post-covid syndromes) in patients with acute cerebrovascular accidents.
2. In patients with COVID-19 associated ischemic stroke, there were differences in the content of natural neurotropic autoantibodies in blood serum compared to patients with IS without COVID-19. In patients with IS against the background of COVID-19 pneumonia, a more enhanced production of serum autoantibodies to neuroproteins was revealed, which accompanied a worse course of IS and can be considered as a predictor of an unfavorable outcome of the disease.
3. The evidence obtained for the participation of natural neurotropic antibodies expands the current understanding of the dysregulatory mechanisms of neuroimmune interactions in COVID-19 and may further form the basis for the development of additional immunotherapy for this disease.

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