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PREDICTION OF LONG-TERM NEUROLOGICAL CONSEQUENCES OF CORONAVIRAL INFECTION USING NEUROTROPIC AUTOANTIBODIES

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ABSTRACT

Today, amid the ongoing COVID-19 pandemic, it has become clear that SARS-CoV-2 infection can have long-term consequences, even after asymptomatic or mild acute cases, raising concerns about the consequences of COVID-19. The terms “long-COVID-19”, “chronic COVID-19”, “post-COVID-19 syndrome” have appeared. Patients who have had COVID-19 often have fatigue, cognitive and psycho-emotional disorders, which are often referred to as "brain fog", and the possibility of developing neurodegenerative diseases is also discussed. The exact pathophysiological mechanisms of the development of the neurological long-term consequences of COVID-19 have not been established, but at the same time, numerous links are emerging between the post-COVID-19 syndrome, immunological changes, and neurotransmission dysfunction in the brain. Using method of immunochemical analysis ELI-Neuro-Test, developed by Professor A.B. Poletaev, we analyzed an individual profile of serum immunoreactivity, depending on changes in the relative content of IgG autoantibodies directed to 12 autogens of the nervous system. We identified in patients who underwent COVID-19 immunochemical signs of damage to the GABAergic (58.6%), opioid (37.9%), serotonergic (20.7%), cholinergic (13.8%) neurotransmitter systems, and also markers of axonal damage (20.7%), demyelination (10.3%) and reactive astrogliosis (24.1%). However, given the small sample size, further research is required.

Key words: COVID-19, nervous system, neurotropic autoantibodies, early diagnosis, ELI-Neuro-Test.

INTRODUCTION

At the end of 2019, the SARS-CoV-2 virus was discovered in China, which caused a new disease – COVID-19 and the second viral pandemic in human history. More than 420 million cases of the disease have been registered, the pandemic continues to grow, it is believed that the number of unreported cases of infection is several times higher. More than 35% of COVID-19 patients develop neurological symptoms [31], such as anosmia, ageusia, headaches, dizziness, cognitive decline, seizures, depression, as well as acute cerebrovascular disease, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, Guillain-Barre syndrome and etc. Neurological complications of COVID-19 are caused not only by cytokine storm, hypoxia, disorders in the hemostasis system, but can also be a direct result of the neurovirulent properties of SARS-CoV-2 [43].

Some scientists suggest that all viruses can reach the CNS under the right conditions depending on viral factors (mutations in specific virulence genes) and host factors (immunosuppression, age and comorbidities) [21]. To date, several studies provide direct evidence for SARS-CoV-2 neurotropism [13]. The receptor for the entry of SARS-CoV-2 into the host cell is ACE2 [17]. ACE2 is expressed in most areas of the brain [7]. RNA of SARS-CoV-2 was detected in brain dissection samples [35] and in the cerebrospinal fluid of patients with COVID-19 [46]. Immunological detection in preparations of brain organelles revealed the presence of the membrane (M) protein SARS-CoV-2 mainly in the soma of neurons, as well as in neurites [5]. Electron microscopy also demonstrated the presence of SARS-CoV-2 in neurons [42]. These facts point to the neuroinvasive properties of SARS-CoV-2.

It is known that some neurotropic viruses, such as the pathogens of measles, rubella, herpesviruses, retroviruses, can cause a disease of the nervous system several years after infection, and this list may be supplemented by SARS-CoV-2 in the future. So far, little is known about the long-term impact of COVID-19. Viruses with neuroinvasive properties activate the immune response in the brain and can cause long-term damage similar to those seen in some neurodegenerative diseases [47]. SARS-CoV-2 infection itself may be a factor contributing to the risk of developing neurological disorders throughout life [43]. In a pandemic, this poses the risk of a significant increase in patients with neurological disorders in the coming years.

It is clear that the clinical symptoms of damage to organs and systems may not appear immediately after the start of the pathological process, since the body has enormous compensatory capabilities. Even biochemical changes in the blood, although ahead of clinical manifestation, appear after the loss of a significant number of cells in organs and tissues. It is appropriate to pose the question, is there a method that can reveal with great accuracy an increased risk of developing neurological disorders after the pathological process has started, but even before changes appear in the indications of traditionally used methods for early diagnosis of a developing neurological disease?

Our cells of organs and tissues are constantly, but at different rates, renewed, as well as the nervous system. This is not only about neurogenesis, the rate of which is incomparably slow relative to the rate of cell division in other organs. The brain not only of a child, but also of an adult is surprisingly constantly changing its structure, which is called neuroplasticity [14]. This process is based on the formation of new neural networks, new synapses (synaptogenesis) appear in the process of assimilating new information [39]; the connection between neurons is strengthened, which are activated during frequently repeated actions; and synapses that have not been used for a long time are lost (partial apoptosis of a neuron - its processes).

What happens to the remnants of dead organ cells, to the destroyed processes of neurons? They are phagocytosed [8]. But the set of phagocyte receptors is not provided for recognizing the entire variety of protein structures to be utilized. And here a very interesting point is observed - specific autoantibodies are attached to the protein components of the destroyed structures - a special label is put on the protein to be cleared in a peculiar way, through which the phagocyte unmistakably identifies and phagocytes the required object. Therefore, it is not surprising that normally all people have a large set of autoantibodies [30], corresponding to the set of proteins of the body, which was named by Professor A.B. Poletaev "Immunculus" [34], like the well-known homunculus of Penfield to neurologists. Although traditionally autoantibodies are associated with autoimmune diseases, they are present in minimal amounts in all healthy individuals [27]. As stated by the immunologist P. Matzinger [28], the main function of the immune system is precisely the recognition of harmful antigens (in our case, harmful decay products of cellular structures), regardless of infectious or non-infectious nature, and exogenous or endogenous origin. There is a whole spectrum of serum antibodies autoreactivity: from congenital poly-reactive IgM, which cleanse tissues of post-apoptotic debris [11] mainly arising from the constant renewal of tissue and cell structures, to conditionally pathological IgGs, which act as an adaptive mechanism for the selective purification of pathology-specific debris [30]. When, under the influence of various etiological factors, the process of cell destruction is accelerated, the immune system begins to produce more IgG autoantibodies so that the clearance process proceeds at an appropriate rate. This is a very important point, since it is the increase in the levels of specific IgG autoantibodies that is the very early and sensitive marker indicating the start of the pathological process long before the appearance of biochemical preclinical shifts. Disease-induced changes in IgG autoantibody profiles can be identified and used as diagnostic biomarkers of diseases with a high degree of sensitivity and specificity [15, 29]. Since many diseases exhibit cell and tissue-specific damage, identification of characteristic disease-induced changes in autoantibody profiles can be used as a successful diagnosis for a wide range of diseases [30].

Patients after COVID-19 have been noted to have fatigue, cognitive and psycho-emotional disorders, and the development of neurodegenerative diseases is also discussed. The mechanism for the development of long-term symptoms has not been definitively established. Our goal was to study the involvement of different neurotransmitter systems in the pathological process in patients who underwent COVID-19 using neurotropic autoantibodies. We believe that this will help to better understand the pathogenesis of post-COVID syndromes, as well as change the traditional attitude towards neurotropic antibodies as exclusively pathogenic agents.

Methods

The method of immunochemical analysis ELI-Neuro-Test (registered in 2009 in the Russian Federation), developed by Professor A.B. Poletaev, makes it possible, long before the appearance of neurological symptoms, to predict diseases of the central nervous system with a high probability. According to the instructions, the ELI-Neuro-Test kit is used for the semi-quantitative determination of IgG autoantibodies that interact with antigens of neurons (NF200), glial cells (GFAP), nerve fibers (MBP) and neurotransmitter receptors by enzyme-linked immunosorbent assay. Using this method, an individual profile of serum immunoreactivity is analyzed, depending on changes in the relative content of IgG autoantibodies directed to 12 autogens of the nervous system: neurofilament factor (NF200), glial fibrillar acidic protein (GFAP), myelin basic protein (MBP), voltage-gated calcium channels (VGCC), calcium binding protein S100β, N-cholinergic receptors, glutamate receptors, dopamine receptors, serotonin receptors, GABA receptors, μ-opiate receptors, and β-endorphin. Such a multiparametric analysis eliminates the influence of the general reactivity of the immune system on the results of the study (this prevents false-negative results against the background of general immunosuppression and false-positive results against the background of general hyperactivation of the immune system).

It is known that the basis of the functioning of the nervous system is the synaptic transmission of the nerve impulse. The structural components that make up the synapse have specific proteins. The presynaptic part is usually the terminal section of the axon. Axon-specific protein is phosphorylated neurofilament H (pNF-H/NF200), axon-covering myelin sheaths (oligodendrocytes) specific protein is myelin total protein (MBP), and voltage-gated calcium channels (VGCC) are specific for axon terminal thickenings. Specific proteins for postsynaptic membranes (to a lesser extent for presynaptic ones) are receptors for various neurotransmitters. In addition, synapses are enveloped by processes of astrocytes, which are involved in the regulation of their activity [1]. Characteristic proteins for astrocytes are the S100 protein and glial fibrillary acidic protein (GFAP). Thus, the set of autogens of the ELI-Neuro-Test panel makes it possible to comprehensively assess the state of neurotransmitter systems.

We examined blood serum samples from 29 apparently healthy adult patients (14 males and 15 females, aged 21 to 71 years) with a history of COVID-19 (confirmed by PCR with a nasopharyngeal swab test or serum testing for anti-SARS-CoV-2 antibodies) mild (17 patients) and moderate (12 patients) severity. At the same time, in order to minimize the effect of hypercytokinemia on the results of research, we selected persons who recovered from COVID-19 at least 2 months ago before the time of blood sampling. During acute infection, patients with COVID-19 experienced respiratory symptoms, fever, and non-specific nervous system symptoms (headache, dizziness, anosmia, ageusia). Patients with neurological complications of COVID-19, such as acute cerebrovascular accidents, acute encephalitis and encephalomyelitis, acute demyelinating processes, onset of neurodegenerative diseases, and convulsive syndrome, were excluded. At the time of the study, some patients complained of recurrent headaches, hyposmia, fatigue, and difficulty concentrating. Additional inclusion criteria were: a) the absence of neurological and psychiatric disorders prior to COVID-19, b) the absence of a previous diagnosis of chronic or current diagnosis of acute and chronic somatic and endocrine diseases that could potentially affect the nervous system, c) the absence of dyspnoea at the time of examination, d) no treatment with corticosteroids, antihistamines, antihypertensives, diuretics, hypnotic drugs at the time of study.

We determined the serum content of autoantibodies to 12 antigens of the nervous system using the ELI-Neuro-Test method on an enzyme immunoassay analyzer using the test kits of the same name manufactured by the Medical Research Center "Immunculus" (Moscow, Russian Federation). In the ELI-Neuro-Test kit, there is a mandatory control serum, which is used in parallel for each reaction setting (the kit contains panels designed to simultaneously determine the serum levels of autoantibodies of 3 patients and control serum). The calculation of the results obtained was carried out using an appropriate computer program developed by the staff of the Medical Research Center "Immunculus".

Results and discussion

In our study, all serum samples showed a decrease in individual mean immunoreactivity (immunosuppression state), against which the absolute concentrations of all neurotropic autoantibodies were lower than in control serum, which did not allow the use of absolute values for interpretation. Therefore, the results of the study reflect deviations in the immunoreactivity of autoantibodies of each specificity, expressed as a percentage of the individual average level of serum immunoreactivity of the subject. The level of activity of the patient's immune system is taken as zero. In the normal state of organs and systems, there are only small dynamic fluctuations in serum concentrations of organ-specific autoantibodies ranging from -15% to + 10% around the individual average serum immunoreactivity.

In our study, 25 (86.2%) of 29 blood serum samples had a pathological profile of neurotropic autoantibodies (Table 1).

Table 1

Individual profiles of immunoreactivity based on serum levels of neurotropic autoantibodies in persons who have had an infection SARS-CoV-2.

Patients (age in years, gender)	anti-NF200	anti-GFAP	anti-S100β	anti-MBP	anti-VGCC	anti-N-Cholinergic receptors	anti-Glutamate receptors	anti-GABA receptors	anti-Dopamine receptors	anti-Serotonin receptors	anti-Opiate receptors	anti-β-endorphin	Number of rejected indicators
№1 (44, f)	-8%	28%	3%	-6%	-5%	-2%	-4%	6%	-9%	-1%	-5%	0	1
№2 (32, m)	1%	22%	-6%	-4%	-2%	0	-3%	11%	-8%	-7%	-5%	3%	2
№3 (59, m)	6%	3%	18%	-4%	-13%	1%	0	11%	-8%	-7%	-5%	4%	2
№4 (31, f)	-14%	-10%	-8%	19%	-11%	-4%	28%	5%	-7%	-1%	-8%	7%	2
№5 (33, m)	-10%	-1%	3%	-5%	-6%	-5%	6%	7%	2%	0	-3%	13%	1
№6 (39, m)	-5%	9%	1%	-4%	-7%	8%	0	0	-5%	4%	2%	-2%	0
№7 (69, m)	-8%	13%	7%	-8%	-6%	8%	4%	-1%	-6%	3%	-4%	-6%	1
№8 (31, f)	-11%	-6%	-1%	-1%	-4%	11%	3%	5%	-6%	5%	-4%	10%	2
№9 (57, f)	-26%	-16%	-4%	-2%	-5%	12%	4%	23%	4%	7%	0	3%	4
№10 (38, m)	-13%	0	-4%	-8%	-3%	9%	-2%	17%	1%	4%	-1%	5%	1
№11 (35, m)	-7%	1%	-3%	-1%	0	-3%	3%	12%	1%	2%	2%	-1%	1
№12 (31, m)	-12%	3%	-1%	-18%	-12%	8%	0	14%	-7%	5%	6%	15%	3
№13 (21, m)	-9%	-3%	-2%	-4%	-1%	1%	9%	6%	6%	3%	-1%	1%	0
№14 (30, f)	-9%	-3%	2%	0	-1%	1%	2%	5%	1%	6%	-1%	0	0
№15 (21, f)	-25%	-23%	-7%	-10%	-4%	-5%	2%	29%	3%	10%	17%	10%	6
№16 (22, f)	-8%	-2%	-7%	-11%	-3%	4%	3%	11%	2%	12%	-3%	4%	2
№17 (22, f)	-16%	-6%	6%	-16%	-4%	1%	-2%	31%	0	4%	-3%	10%	4
№18 (27, f)	-17%	-9%	-3%	-8%	-12%	18%	3%	17%	-4%	10%	-2%	13%	5
№19 (37, f)	-7%	8%	-1%	-8%	-5%	11%	1%	3%	-5%	9%	-3%	-3%	1
№20 (42, f)	-11%	8%	1%	-7%	1%	1%	-2%	15%	-1%	0	-5%	-4%	1
№21 (59, f)	-12%	-5%	-2%	-7%	-2%	1%	-2%	13%	0	12%	1%	2%	2
№22 (28, m)	-7%	5%	-2%	-6%	-3%	6%	-2%	13%	-3%	0	-3%	5%	1
№23 (71, f)	-12%	-4%	-2%	-11%	26%	1%	-15%	16%	-10%	-1%	2%	12%	3
№24 (21, m)	9%	-3%	-1%	-9%	-14%	-7%	-6%	4%	0	6%	-3%	20%	1
№25 (40, m)	-10%	8%	0	-8%	-10%	1%	4%	9%	-3%	6%	4%	0	0
№26 (48, m)	-14%	4%	-8%	-4%	-9%	3%	-5%	10%	-1%	5%	1%	16%	2
№27 (36, f)	-13%	-3%	-6%	1%	-4%	-2%	-1%	9%	2%	12%	4%	0	1
№28 (57, f)	-28%	-19%	-11%	-8%	-11%	6%	13%	28%	2%	9%	11%	9%	5
№29 (28, m)	-40%	-20%	-6%	-5%	-5%	-1%	9%	28%	13%	11%	3%	17%	6
Number of cases is higher than the individual norm		3 (10,34%)	1 (3,45%)	1 (3,45%)	1 (3,45%)	4 (13,80%)	2 (6,90%)	17 (58,62%)	1 (3,45%)	6 (20,69%)	2 (6,90%)	10 (34,48%)	48
Number of cases is below the individual norm	6 (20,69%)	4 (13,80%)		2 (6,90%)									12
Total number of cases of deviations from the individual norm	6 (20,69%)	7 (24,14%)	1 (3,45%)	3 (10,34%)	1 (3,45%)	4 (13,80%)	2 (6,90%)	17 (58,62%)	1 (3,45%)	6 (20,69%)	2 (6,90%) 11 serum samples (37,93%)	10 (34,48%)	

* The level of activity of the patient's immune system is taken as zero. Deviations ≥10% or <(- 15%) may indicate an emerging or existing change in the respective structures.

The neurotropic properties of coronaviruses allow them to elude the host's immune response and reach a latency period. This makes them a potent contributor to acute and late neurological effects [22]. SARS-CoV-2 can be dormant in the neurons of patients recovering from the acute effects of COVID-19, which increases the risk of long-term effects, causing demyelination and neurodegeneration [25]. Kumar et al. suggest that in the medium to long-term, an influx of patients with mental and cognitive problems who were otherwise healthy before contracting COVID-19 is expected. Early detection and prevention of neuropsychiatric and cognitive problems should be a long-term goal of health services and governments around the world, as this can be presented as next wave of a pandemic [22].

Although the exact mechanisms responsible for the long-term complications of SARS-CoV-2 infection remain unknown, there are a number of pathophysiological mechanisms that may explain the neurological long-term consequences of COVID-19, some of the proposed mechanisms include direct viral lesion, systemic inflammation, and cerebrovascular changes [9]. Of particular interest are data showing that neuronal cells express specific molecules that may act as immune receptors to modulate the innate immune response in the brain [4]. Since these molecules also play an important role in neuroplasticity and the organization of neural networks and synapses, such autonomous activation of neuronal cells using innate receptors during viral infections may compromise neuroplasticity and provoke subsequent neuronal dysfunction [47]. Also, neuroimmunological mechanisms may be involved in the development of long-term consequences of coronavirus infection, such as fatigue, impaired concentration, attention and memory, mood changes and sleep disturbances [41]. For example, autoantibodies targeting neurotransmitter receptors have the potential to cause depression-like symptoms [48]. Depression is often associated with various neurodegenerative disorders [12]. Depression correlates with decreased neurogenesis in adults [18]. Numerous clinical reports underscore the frequency of olfactory impairments in patients suffering from major depressive disorders [40]. Anosmia is associated with impaired neurogenesis [36]. New neurons formed in the subventricular zone in adulthood migrate to the olfactory bulb, where they finally differentiate into GABAergic inhibitory interneurons that contribute to olfactory function [24]. GABAergic transmission regulates neurogenesis in adults [33]. GABAergic deficiency linked to depression [26], along with serotonergic and dopaminergic neurotransmission disorders [10]. Adult hippocampal neurogenesis has been implicated in cognitive processes [2]. Several studies have identified the involvement of GABA in learning and memory [16, 20, 37]. Cortical GABAergic activity decreases in post-COVID-19 patients with cognitive disturbances and fatigue [45]. Fatigue is a dominant complaint in “long COVID” [38]. Fatigue is considered as neuroimmune exhaustion [6]. Thus, there are numerous links between clinical symptoms, dysfunction of neurotransmitter systems and immunological disorders. Many scientists consider IgG autoantibodies to be potentially pathogenic, although there is a need to clarify causal relationships. For example, Vargas et al. demonstrated the importance of autoreactive IgG antibodies in the nervous system. Anti-myelin IgG contribute to the removal of tissue debris after damage to peripheral nerves, and in their absence, axonal regeneration is hampered [44].

The most informative pathological processes in the body can be reflected in changes in the ratio between different autoantibodies. According to the instructions of the ELI-Neuro-Test, which is intended for the simultaneous quantitative assessment of changes in the content of 12 neurotropic autoantibodies IgG, it can be used as an indicator of existing or emerging disorders in the nervous system. A steady rise in the production of specific autoantibodies IgG reflects the activation of the processes of apoptosis of specialized cells or the decay of subcellular structures. These immunological changes are the earliest sign of beginning pathological processes, which can reach the stage of characteristic clinical disorders only after a few months or even years.

In our small study, we identified in patients who underwent COVID-19 immunochemical signs of damage to the GABAergic (58.6%), opioid (37.9%), serotonergic (20.7%), cholinergic (13.8%) neurotransmitter systems, and also markers of axonal damage (20.7%), demyelination (10.3%) and reactive astrogliosis (24.1%). In general, this does not contradict the results of previous studies. According to other authors, the onset of cognitive symptoms after COVID-19 may indicate an underlying neurodegenerative process [22]; SARS-CoV-2 infection causes reactive astrogliosis in the central nervous system [23]; an increase in plasma GFAP levels may indicate damage to the central nervous system in patients with COVID-19 [19]; in COVID-19, cases of demyelinating Guillain-Barre syndrome have been reported [3, 32]; Versace et al. revealed a general decrease in cortical GABAergic and, to a lesser extent, cholinergic activity in post-COVID-19 patients using transcranial magnetic stimulation [45].

At the same time, the results of our study have some limitations, in particular, a small sample size reduces the reliability of our results; secondly, subclinical pathological processes reflected in changes in immunoreactivity profiles in reality, under certain circumstances, may not reach the stage of clinical manifestation; thirdly, most neurotransmitter systems have several receptor subtypes, sometimes with opposite effects, which is not taken into account in our method, this causes difficulties in interpreting the results obtained. But in general, we consider Professor Poletaev's approach to diagnosing neurological diseases to be very promising and interesting.

Thus, changes in neurotropic autoantibodies reflect the pathological intensification of apoptosis of neurons and glial cells and their subcellular structures, which is the very first stage in the formation of neurological diseases, far ahead of the appearance of any other signs of damage to the nervous system. In our opinion, this will also help to capture the moment when functional disorders develop into structural changes, as well as to critically reconsider the blurred line between "functional disorders" and "morphofunctional disorders". The study of individual profiles of immunoreactivity according to the serum level of neurotropic IgG autoantibodies in patients who have undergone COVID-19 makes it possible to identify the onset of subclinical changes and predict the neurological long-term consequences of coronavirus infection, which, according to the results of our study, will mainly affect GABAergic, opioid, serotonergic and cholinergic neurotransmitter systems. Also, the use of this approach makes it possible to understand in more detail the violations of which neurotransmitter systems are associated with the existing clinical symptoms of long-COVID, which, in our opinion, provides an opportunity to select a more targeted treatment, but this requires further research.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ELI-Neuro-Test, enzyme-linked immuno-neuro-test; IgG, immunoglobulin G; IgM, immunoglobulin M; NF200, neurofilament factor; GFAP, glial fibrillar acidic protein; MBP, myelin basic protein; VGCC, voltage-gated calcium channels; S100β, calcium binding protein; GABA, γ-aminobutyric acid; CNS, central nervous system; PCR, polymerase chain reaction.

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