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Relationship between clinical and neuro-immunological parameters in post-COVID patients

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Abstract

The coronavirus infection continues to circulate among the population, which may lead to an increase in the number of patients with post-COVID neurological consequences. By studying the profiles of neurotropic autoantibodies, it is possible to diagnose the pathological process that began in the nervous tissue at the earliest stages of its development in post-COVID patients, which makes it possible to justify personalized neurotropic therapy, as well as predict the degree of reversibility of neurological disorders depending on their causation by a neurodestructive process or neurodysfunction. A neurological and neuropsychological study was conducted on 77 patients (average age 37.4 ± 1.7 years; 41.6% men and 58.4% women) with a history of COVID-19 (in the period from 12 weeks to 12 months from the onset of the acute stage of COVID-19) and having long-term symptoms after COVID-19. Of these, serum levels of neurotropic autoantibodies were studied in 29 patients. It was found that female patients compared to males, as well as patients who had moderate acute COVID-19 compared to patients who had mild acute COVID-19, were relatively more likely to experience post-COVID neurological symptoms and more pronounced changes in neurotropic autoantibody profiles. Neuropsychological testing revealed cognitive impairment in half of patients with post-COVID syndrome, which positively correlated with the presence of abnormal changes in the level of autoantibodies to neurofilamentary factor (NF200), and a third of patients were diagnosed with pathological fatigue, which positively correlated with the presence of abnormal changes in the level of autoantibodies to myelin basic protein (MBP).

Keywords: Post-COVID syndrome; Long-term neurological manifestations of coronavirus infection; Neurotropic autoantibodies; Early diagnosis and prognosis of post-COVID neurological disorders

1. Introduction

According to WHO [1], approximately 6% of patients who have recovered from COVID-19 experience long-term symptoms, a complex of which is referred to as the "post-COVID-19 condition" ("post-COVID syndrome", "long COVID-19"). According to the WHO definition, the "post-COVID-19 condition" is a set of symptoms that develop during or after COVID-19, persist after 3 months from the onset of the acute stage, last for at least 2 months and are not explained by the presence of another disease. Patients who have recovered from COVID-19 often experience general weakness and fatigue, cognitive and psychoemotional disorders, headaches and dizziness, olfactory and taste disorders, muscle and joint pain, and autonomic disorders for several months [2, 3, 4, 5]. The development of neurodegenerative diseases is also discussed [6, 7].

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The exact pathophysiological mechanisms underlying the development of neurological long-term sequelae of SARS-CoV-2 infection have not been fully established [8]. SARS-CoV-2 can persist in the body and trigger low-intensity autoimmune reactions [9, 10], thereby maintaining chronic systemic low-grade inflammation, which is thought to clinically manifest as post-COVID syndrome [11, 12, 13, 14, 15]. Cytokines affect neurotransmission in the brain [16]. For example, proinflammatory cytokines can reduce serotonin synthesis by activating the enzyme indoleamine 2,3-dioxygenase, which breaks down tryptophan, an amino acid precursor of serotonin, to kynurenine [17]. Kynurenine metabolites (3-hydroxykynurenine and quinolinic acid) have a neurotoxic effect. Cytokines also reduce the synthesis of monoamines (such as dopamine, norepinephrine, and serotonin) by depleting tetrahydrobiopterin (a cofactor for monoamine hydroxylase enzymes) in the periphery for neopterin and nitric oxide production by macrophages during inflammation [18]. Cytokines can enhance the reuptake of synaptic serotonin and dopamine [19]. Proinflammatory cytokines can stimulate the release of glutamate by astrocytes [20], are also involved in the stimulation of N-methyl-D-aspartate (NMDA) receptors, and can attenuate signaling through GABA and acetylcholine [21].

Since the new coronavirus infection continues to circulate among the population as a seasonal ARI, this may lead to an increase in the number of patients with post-COVID neurological consequences, which can be observed even in patients who have had asymptomatic or mild COVID-19 [22], which requires a comprehensive study of this problem. Unfortunately, in most cases, widely used functional and neuroimaging research methods are unable to detect the pathological process at the earliest stages of its development, and mainly diagnose neurological complications that appear only after the loss of a significant part of the nervous tissue structures. But it turned out that by studying the profiles of neurotropic autoantibodies of the IgG class, it is possible to identify the pathological process that began in the nervous tissue at the earliest (preclinical) stages of its development [23, 24], which makes it possible to carry out justified preventive personalized neurotropic therapy. Also, based on individual changes in the profiles of neurotropic autoantibodies of the IgG class, it is possible to predict with great accuracy the expected neurological symptoms and the degree of their reversibility depending on whether the symptoms are caused by a neurodestructive process or neurodysfunction. In this regard, we studied the features of neurotropic autoantibody profiles in post-COVID patients and assessed the nature of the relationship between neurological symptoms and changes in neurotropic autoantibody profiles.

2. Material and methods

A total of 107 adult patients were examined, the main group consisted of 77 patients (mean age 37.4±1.7 years; 41.6% men and 58.4% women) with a history of COVID-19 (in the period from 12 weeks to 12 months from the onset of the acute stage of COVID-19) and with long-term symptoms after COVID-19 (post-COVID syndrome). The control group consisted of 30 healthy patients without a previous diagnosis of COVID-19 and not vaccinated against COVID-19 (seronegative). The main and control groups were comparable in age and gender. Informed consent was obtained from all individual participants included in the study.

The diagnosis of previous COVID-19 was established on the basis of a positive laboratory test for SARS-CoV-2 (from a swab from the nasopharynx and oropharynx) and / or based on signs of viral pneumonia based on the results of computed tomography (CT). The severity of COVID-19 was determined based on the percentage of lung damage according to CT results: CT-1 (up to 25%), CT-2 (up to 50%), CT-3 (up to 75%), CT-4 (75% or more). 45.4% of patients in the main group had mild acute COVID-19 and 48.1% of patients had moderate COVID-19.

To ensure the reliability of the study results, additional exclusion criteria were met: a) patients with neurological complications of COVID-19 such as acute cerebrovascular accidents, acute encephalitis and encephalomyelitis, acute demyelinating processes, the onset of neurodegenerative diseases, convulsive syndrome; b) the presence of neurological and mental disorders before COVID-19; c) the presence of a previous diagnosis of chronic or a current diagnosis of acute and chronic somatic and endocrine diseases; d) the presence of shortness of breath at the time of examination; d) treatment with corticosteroids, antihistamines, hypnotics at the time of the study.

The clinical examination was conducted according to the generally accepted methodology. During the examination, all patients had their complaints and medical history collected in detail, a retrospective analysis of the course of the acute period of COVID-19 and the characteristics of the post-COVID period was conducted, and the neurological and general somatic status was assessed. A neuropsychological examination was conducted using the SAGE (Self-Administered Gerocognitive Exam) test to identify cognitive impairment, the HADS (Hospital Anxiety and Depression Scale) to determine depression and anxiety, and the FAS (Fatigue Assessment Scale) to assess fatigue.

Serum levels of neurotropic autoantibodies were studied in 29 patients (mean age 38.2±2.7 years, men 48.3%, women 51.7%) from the main group. Neurotropic autoantibody profiles of 30 serum samples of practically healthy adults

studied in the pre-pandemic period were used as a control group for immunochemical analysis. The immunochemical method was used to simultaneously determine the serum content of 12 types of neurotropic autoantibodies of the IgG class directed to the following autogenes of the nervous system: neurofilamentary factor (NF200), glial fibrillary acidic protein (GFAP), protein S100, myelin basic protein (MBP), voltage-gated calcium channel protein (VGCC), N-cholinergic receptors, glutamate receptors, GABA receptors, dopamine receptors, serotonin receptors, opiate μ-receptors and β-endorphin. The results were assessed after recalculating the absolute values of optical density relative to the average individual reactivity of the immune system of each patient in order to prevent false-negative responses due to immunosuppression. Correlation analysis was performed with the calculation of the contingency coefficient – φ for dichotomous variables.

3. Results and discussion

Post-COVID patients from the main group most often complained of general weakness and fatigue (in 64.9% of cases), headaches (in 41.6% of cases), decreased mood and anxiety (in 32.5% and 18.2% of cases, respectively), attention deficit and memory loss (in 31.2% of cases), olfactory and taste disorders (in 28.6% and 10.4% of cases, respectively), muscle pain (in 23.4% of cases), sleep disturbances (unrefreshing sleep, daytime sleepiness, and others, in 22.1% of cases), a crawling sensation in the limbs (in 19.5% of cases), dizziness (in 19.5% of cases) occurring in a standing position (Table 1).

Table 1 Frequency of complaints among patients in different periods of time with respect to COVID-19

No	Patient complaints	Main group (post-COVID patients)			Control group
		Before COVID-19	During acute COVID-19	At the time of examination in the post-COVID period	
1	Headaches	28.6%	85.7%	41.6%	13.3%
2	Dizziness	13%	41.6%	19.5%	3.3%
3	Olfactory impairment	2.6%	76.6%	28.6%	0%
4	Taste disturbance	0%	57.1%	10.4%	0%
5	Muscle pain	13%	74%	23.4%	0%
6	Decreased memory	2.6%	24.7%	31.2%	0%
7	Difficulty concentrating	3.9%	37.7%	31.2%	0%
8	Sleep disturbance	6.5%	31.2%	22.1%	3.3%
9	Decreased mood	6.5%	40.3%	32.5%	6.7%
10	Anxiety	3.9%	32.5%	18.2%	3.3%
11	Noise in the ears	6.5%	15.6%	11.7%	0%
12	Hearing loss	5.2%	14.3%	9.1%	0%
13	Hot flashes	3.9%	24.7%	3.9%	3.3%
14	A crawling sensation in the limbs	5.2%	28.6%	19.5%	0%
15	Fever	3.9%	79.2%	1.3%	0%
16	Deterioration of well-being when standing	13%	41.6%	19.5%	0%
17	General weakness and rapid fatigue	6.5%	81.8%	64.9%	3.3%

When collecting complaints from post-COVID patients, we specified the time of their occurrence, the presence or absence of certain complaints in the pre-pandemic period and during the acute COVID-19 period, in order to determine

the frequency of first-time cases and to track the dynamics of symptom development. Figure 1 more clearly demonstrates the frequency of symptoms in different periods relative to the transferred COVID-19.

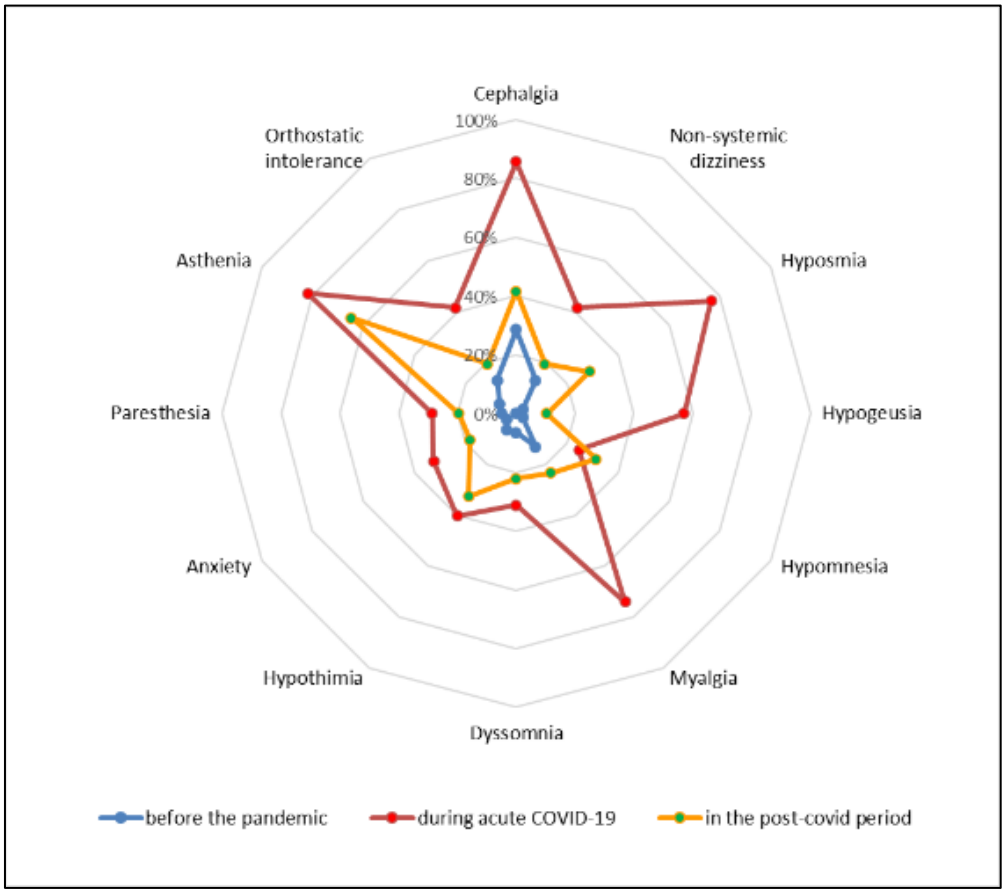

Figure 1 Frequency of symptoms in patients of the main group at different periods relative to the previous COVID-19

It is evident that cognitive decline is characterized by negative dynamics, which indicates that forgetfulness, problems with concentration, and slowing down of mental activity in COVID-19 are not just transient manifestations of the nervous system during a feverish state, but are rather associated with the provocation of the process of neuroinflammation, which continues its long-term and subsequently independent of peripheral inflammation development in the post-COVID period, disrupting neurotransmission and causing degenerative changes in the brain.

The frequencies of complaints of patients in the main group, depending on the severity of COVID-19, differed somewhat (Fig. 2). In patients who had acute COVID-19 of moderate severity, symptoms such as myalgia, memory loss and depressive mood were observed approximately twice as often in the post-COVID period compared to patients who had mild COVID-19, while symptoms associated with the direct neuropathic effect of the SARS-CoV-2 virus (hyposmia, hypogeusia) did not differ significantly in frequency among these patients.

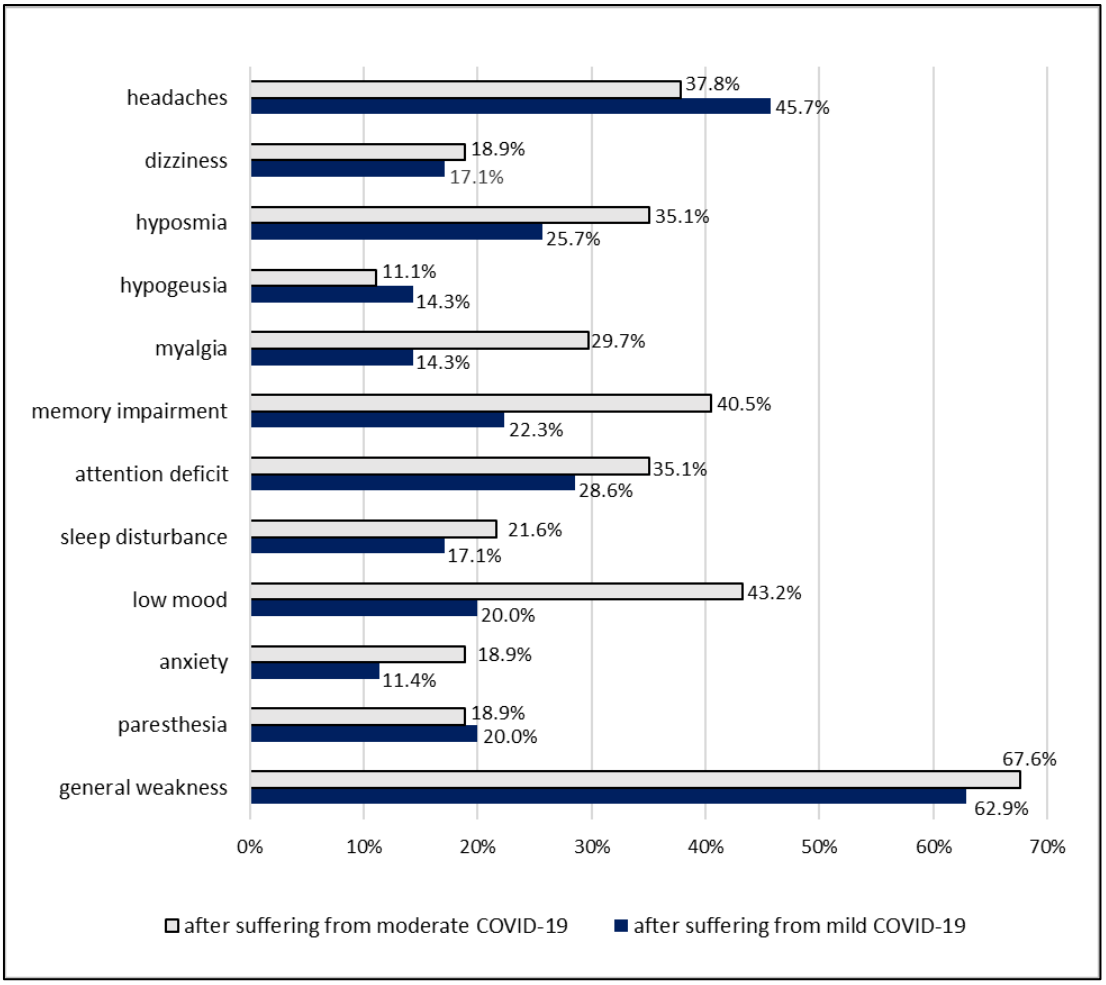

Figure 2 Frequency of occurrence of individual symptoms in the post-COVID period depending on the severity of COVID-19

Among men and women in the group of post-COVID patients, the frequencies of some complaints differed significantly (Fig. 3). Women, compared to men, complained relatively more often of symptoms associated with dysfunction of capacitive vessels, such as headaches, non-systemic dizziness, orthostatic intolerance. This may be due to the initially weaker tone of the venous system in women due to the influence of female sex hormones, and thus, superimposed on this background, systemic venous dysfunction caused by post-COVID systemic sluggish inflammation manifests itself more clearly in women.

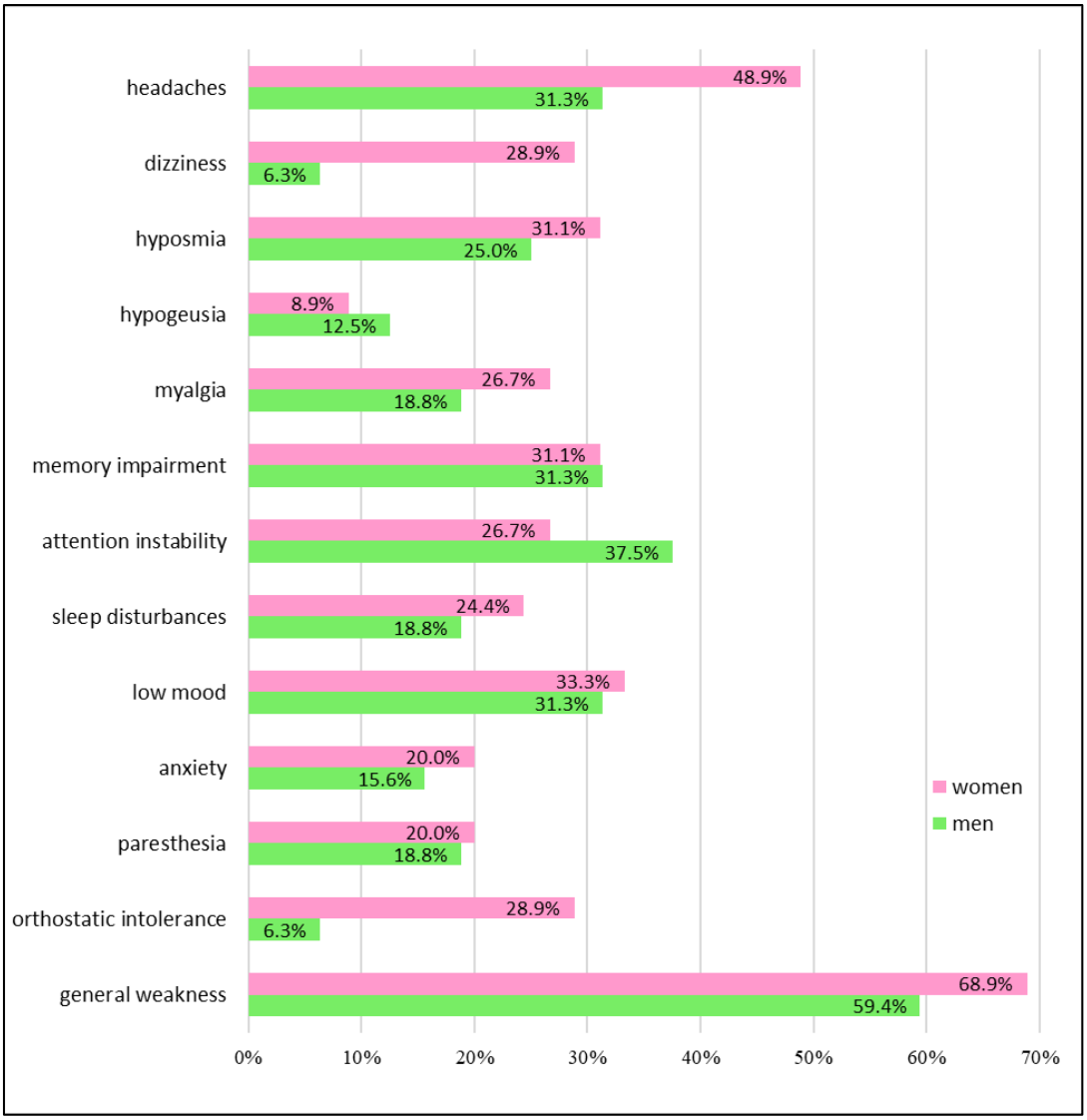

Figure 3 Frequencies of some complaints of post-COVID patients depending on gender

The frequencies of symptoms detected during neurological examination of post-COVID patients are presented in Figure 4. The neurostatus of patients is generally characterized by cranial nerve neuropathy, symmetrical moderate decrease in the inhibitory effect of the central motor neuron on the motor neurons of the spinal cord, mild dysfunction of the coordination system, and autonomic dysregulation. In this context, except for cranial nerve neuropathy, all other identified neurological symptoms are nonspecific and their occurrence can be explained by a systemic subclinical inflammatory background and associated dysfunction of capacitive vessels.

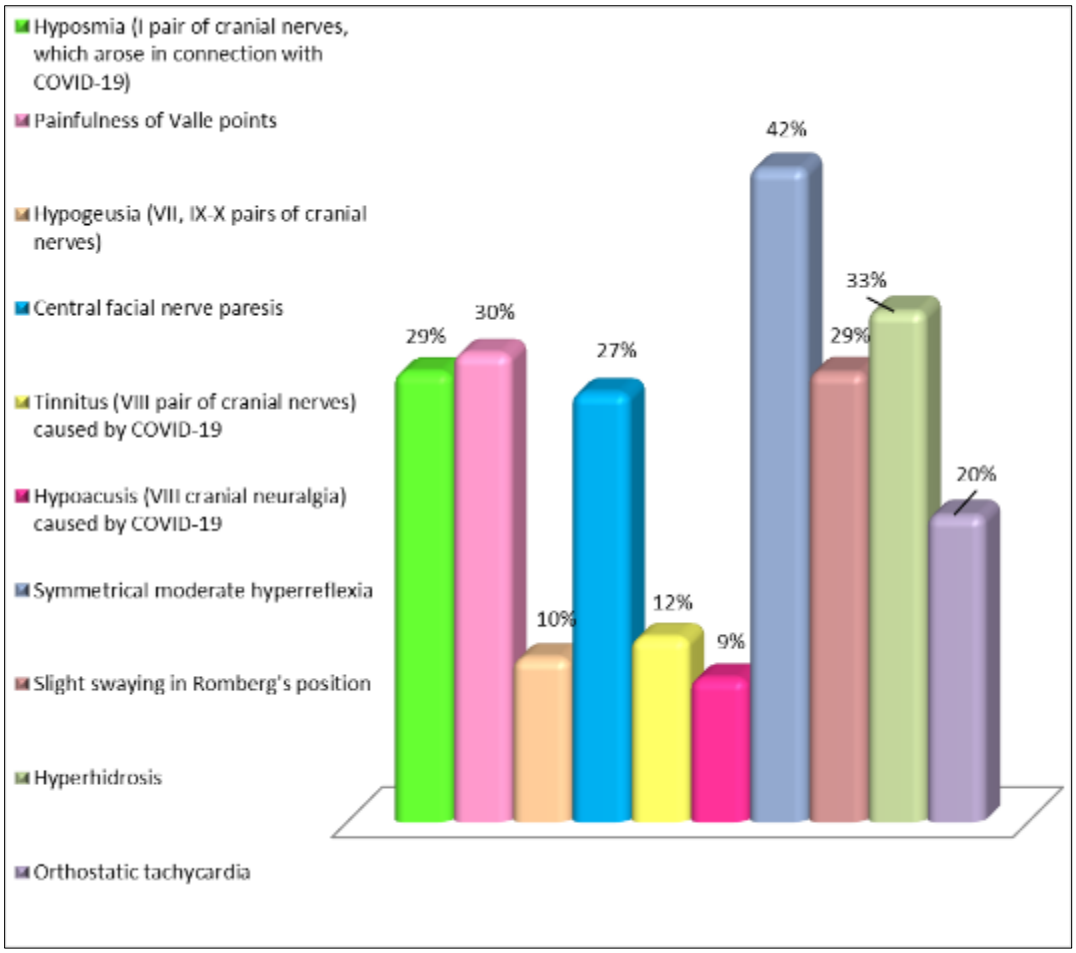

Figure 4 Neurological status of post-COVID patients

The results of the neuropsychological examination using the SAGE (Self-Administered Gerocognitive Exam) test to identify cognitive impairment, the HADS (Hospital Anxiety and Depression Scale) to determine depression and anxiety, and the FAS (Fatigue Assessment Scale) to assess fatigue are presented in Table 2.

Table 2 Neuropsychological characteristics of post-COVID patients

Frequency of occurrence of disorders	**Cognitive impairment (based on the SAGE test)**		**Psychoemotional disorders (on the scale HADS)**		**Increased fatigue (according to the FAS scale)**
	Mild memory or thinking impairments	**More severe memory or thinking condition**	**Anxiety**	**Depression**	
Among all patients in the main group	26%	23.4%	13%	11.7%	35.1%
	49.4%				
Particularly among men	21.9%	18.8%	12.5%	6.3%	34.4%
	40.7%				
Among women	28.9%	26.7%	13.3%	15.6%	35.6%
	55.6%				
	28.6%	17.1%	8.6%	8.6%	25.7%

<table>
<tr><td>Among patients who had mild cases of COVID-19</td><td colspan="2">45.7%</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Among patients who have had moderate COVID-19</td><td>27%</td><td>27%</td><td rowspan="2">13.5%</td><td rowspan="2">13.5%</td><td rowspan="2">45.9%</td></tr>
<tr><td colspan="2">54%</td></tr>
</table>

Among women in the post-COVID period, the incidence of depression was more than 2 times higher than among male patients. According to the FAS scale, the incidence of pathological fatigue in the post-COVID period was almost 2 times higher among patients who had moderate acute COVID-19 compared to patients who had a mild acute stage of the disease, which indicates the pathogenetic role of systemic inflammation in the development of pathological fatigue in the post-COVID period.

According to the results of the immunochemical study, only 4 (13.8%) of the 29 samples of post-COVID patients' blood serum had normal profiles of neurotropic autoantibodies. The majority of the samples studied - 25 (86.2%) showed pathological profiles of neurotropic autoantibodies (Table 3). Of the 25 blood serum samples with pathological profiles of neurotropic autoantibodies, 12 samples (41.4%) showed signs of a pathological process of a neurodysfunctional nature and 13 samples (44.8%) indicated the presence of an active neurodestructive process.

Table 3 Results of immunochemical analysis

Nature of neurotropic autoantibody profiles:	**Main group, n=29**	**Control, n=30**
Normal	13.8%	93.3%
Pathological, in particular signs of:	86.2%	6.7%
- changes in the gabaergic system	58.62%	6.7%
- Changes in the opiate system (anti-β-endorphin, anti-μ-opiate receptors)	37.93%	3.3%
- astrocytic gliosis (anti-GFAP)	24.14%	0
- axonopathies (anti-NF200)	20.69%	0
- Changes in the serotonergic system	20.69%	0
- Changes in the cholinergic system	13.8%	0
- anti-myelin process (anti-MBP)	10.34%	0
- changes in the NMDA receptor system, the glutamatergic system	6.9%	0
- changes in the neuromuscular junction system (anti-VGCC)	3.45%	0
- Changes in the dopaminergic system	3.45%	0
- changes in emotional status regulation associated with HPV infection (anti-S100)	3.45%	0

Among patients who had a mild acute stage of COVID-19 (n=13), the frequency of normal profiles of neurotropic autoantibodies was 23.1%, and the frequency of abnormally altered profiles was 76.9%, of which, according to the nature of the pathological process, immunograms in 46.2% of cases reflected a neurodysfunctional process and in 30.8% of cases indicated the presence of a neurodestructive process, on average, each patient had 1.46 abnormally altered types of autoantibodies. Among patients who had undergone the acute stage of moderate COVID-19 (n=15), the frequency of normal profiles of neurotropic autoantibodies was only 6.7%, and the frequency of abnormally altered profiles was 93.3%, among which, according to the nature of the pathological process, immunograms in 40% of cases showed signs of a neurodysfunctional process and in 53.3% of cases demonstrated signs of an active neurodestructive process, and on average, the number of abnormally altered varieties of neurotropic autoantibodies per patient was 2.67. The frequencies of occurrence of pathological shifts in the entire spectrum of serum levels of neurotropic autoantibodies depending on the severity of the acute stage of COVID-19 are presented in Fig. 5.

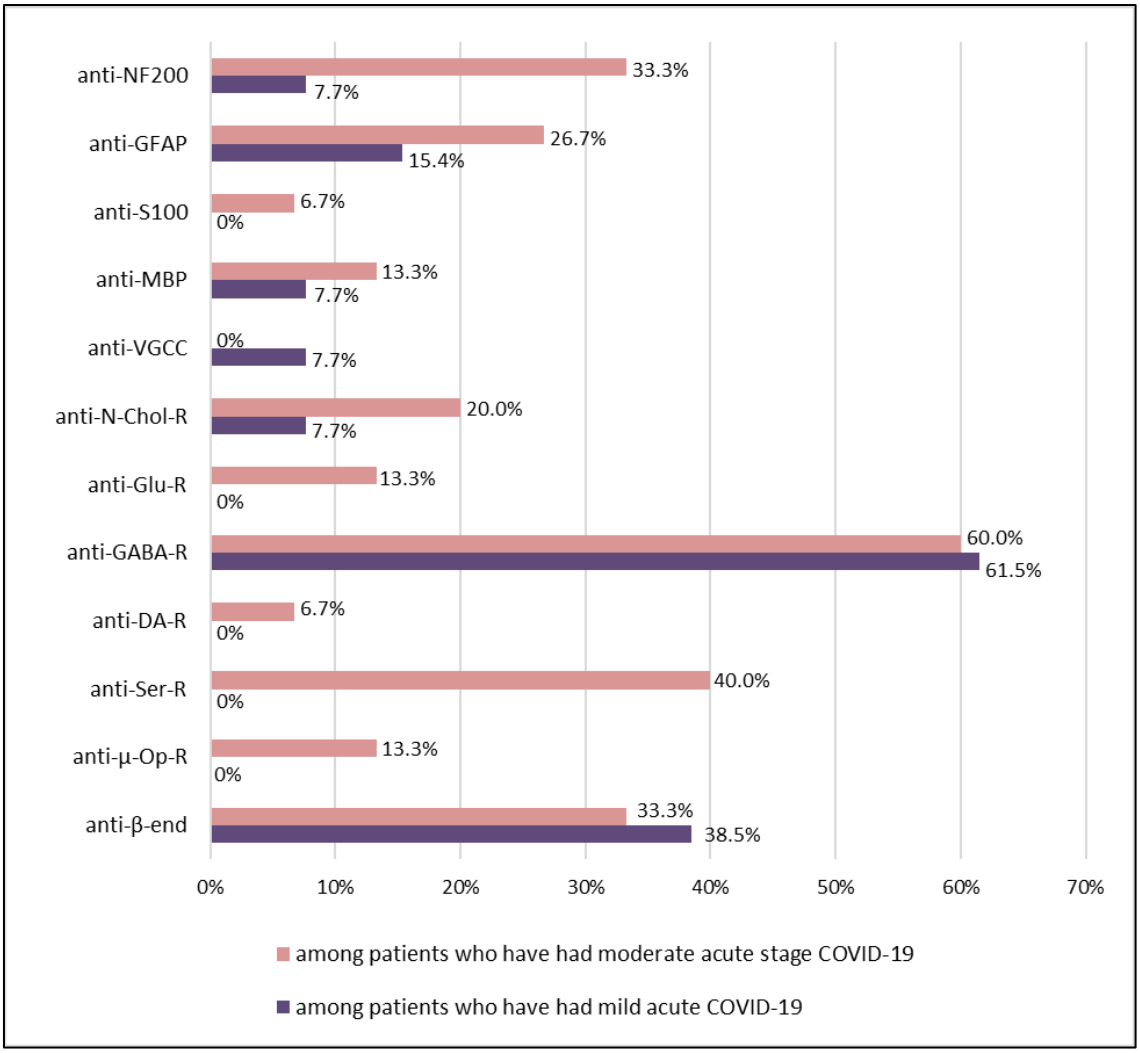

Figure 5 Frequency of occurrence of abnormal changes in the entire spectrum of neurotropic autoantibodies in the post-COVID period depending on the severity of the acute stage of COVID-19

14 (93.3%) of the examined female blood serum samples and 11 (78.6%) of the male blood serum samples showed pathological profiles of neurotropic autoantibodies. Each examined male patient had, on average, 1.5±0.43 pathological shifts in the content of neurotropic autoantibodies, and in the examined women, on average, 2.6±0.48 of 12 indicators were pathologically altered. Also, among women, a relatively increased immunoreactivity to the following autoantigens of the nervous system was significantly more common: NF200, serotonin receptors and N-cholinergic receptors (Fig. 6).

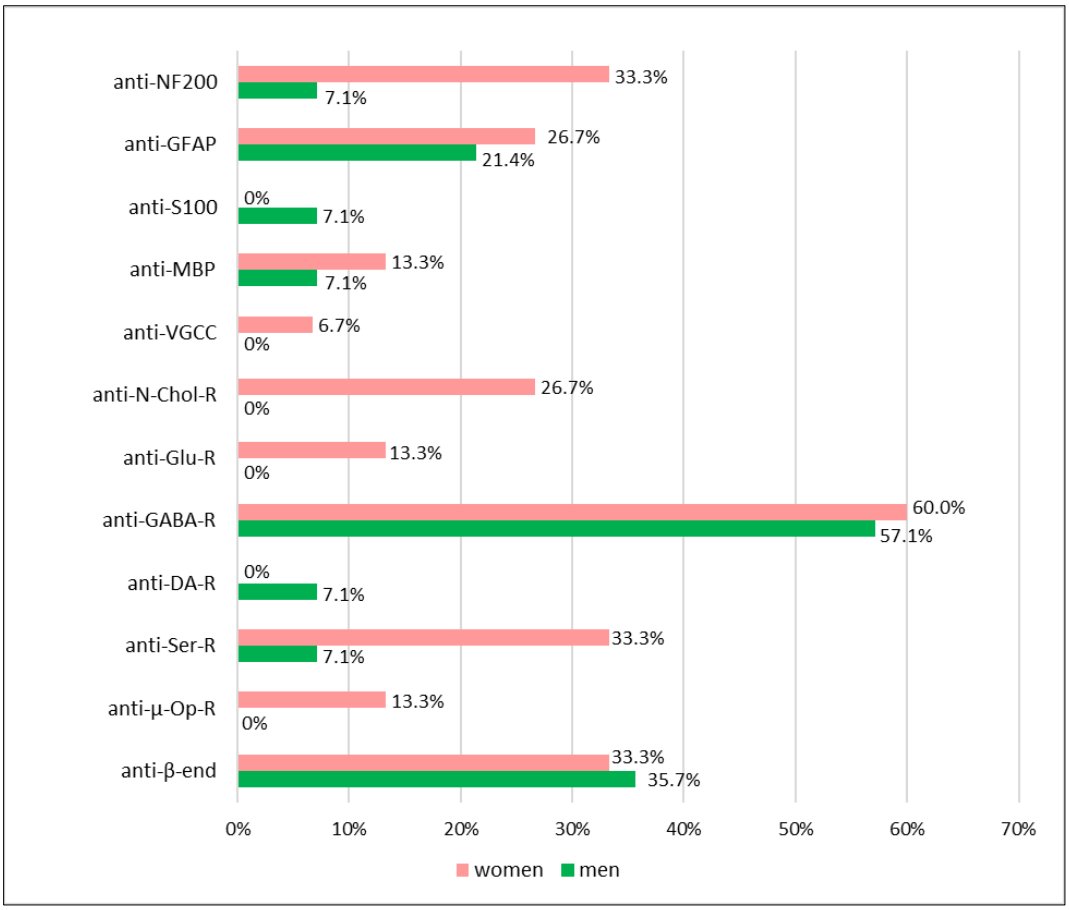

Figure 6 Frequency of occurrence of abnormal changes in serum levels of neurotropic autoantibodies in post-COVID patients depending on gender

Among 29 patients in whom serum levels of neurotropic autoantibodies were analyzed, cognitive impairment according to the SAGE test results was detected in 48.3% of cases (14 patients). Among these 14 patients with cognitive impairment, changes in serum autoantibody profiles were noted: anti-NF200 in 6 patients, anti-GFAP in 4 patients, anti-MBP in 2 patients, anti-VGCC in 1 patient, anti-N-cholinergic receptors in 3 patients, anti-glutamate receptors in 2 patients, anti-GABA receptors in 10 patients, anti-dopamine receptors in 1 patient, anti-serotonin receptors in 4 patients, anti-μ-opiate receptors in 2 patients and anti-β-endorphin in 8 patients.

Reliable ($p \leq 0.05$) correlation relationships were found between the following indicators: 1) $\varphi=0.53$ between the presence of cognitive disorders (according to the results of the SAGE test) and the presence of abnormal changes in the level of autoantibodies to NF200; 2) $\varphi=0.44$ between the presence of depression (according to the results of the HADS scale test) and the presence of abnormal changes in the level of autoantibodies to serotonin receptors; 3) $\varphi=0.43$ between the presence of pathological fatigue (according to the results of the FAS scale study) and the presence of abnormal changes in the level of autoantibodies to MBP.

4. Conclusion

Thus, in post-COVID patients, clinical and neurological examination reveals symptoms associated with the neuropathic effect of the SARS-CoV-2 virus and nonspecific symptoms associated with the general inflammatory background. In female patients compared to men, as well as among patients who have had moderate acute COVID-19 compared to patients who have had mild acute COVID-19, post-COVID neurological symptoms and more pronounced changes in neurotropic autoantibody profiles are relatively more common. In half of the patients (49.4%) with post-COVID syndrome, the SAGE test reveals cognitive impairment, which positively correlates with the presence of abnormal changes in the level of autoantibodies to NF200 ($\varphi = 0.53$), and in a third of patients (35.1%), according to the FAS scale, pathological fatigue is determined, which positively correlates with the presence of abnormal changes in the level of autoantibodies to MBP ($\varphi = 0.43$). This connection with the neurodestructive process to some extent explains the

relative persistence of symptoms such as cognitive impairment (mainly decreased short-term memory and attention deficit) and pathological fatigue in post-COVID patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interests

Statement of ethical approval

The presented results are part of the results of a study registered in BULLETIN, Supreme attestation commission at the Cabinet of Ministers of the Republic of Uzbekistan, 2021/2, p.173, B2021.2.PhD/Tib1846. www.oak.uz

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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