A&L
ISSN 2709-0205
Vol 2 Issue 3 (2021)
https://doi.org/10.47855/jal9020-2021-4

Coronavirus disease 2019: neurological aspects.

Review and own research

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https://doi.org/10.47855/jal9020-2021-4-2

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Received: 05.11.2021; Accepted: 16.12.2021; Published: 22.12.2021

Abstract. The main neurological consequences of COVID-19 (depression, psycho-emotional disturbances, strokes, neurodegenerative disorders and others); major ways of coronavirus penetration into the nervous system as well as mechanisms of development of some neurological complications of COVID-19 are presented in the article. The preliminary results of the analysis of changes in the functional state of the central nervous system of 36 patients with dyscirculatory encephalopathy of atherosclerotic and hypertensive genesis of the 1-2 stages before and 3-4 months after COVID-19 have been presented. It was found that in patients who have had COVID-19, there were headaches, sleep disorders, general weakness, memory impairment, muscle and limbs pains. Reorganization of bioelectrical activity of the brain also appeared. The general structure of the EEG was characterized by an increased power in the range of slow rhythms against a background of decreasing power in the range of cortical rhythms. A tendency to a decrease of cerebral blood flow in the separate vessels of carotid and vertebrobasilar basins, as well as expressed suppression of the vascular endothelial function were also found. It is evident from the results of this study that inclusion of the drugs possessing a multimodal vasoactive and metabolic action is necessary.

Key words: coronavirus disease 2019, neurological complications, bioelectrical activity of the brain, cerebral blood flow, endothelial function.

In December 2019, numerous cases of pneumonia were recorded in Wuhan (China) and quickly spread to Europe, America and Asia. It was confirmed, that the outbreak was caused by a new coronavirus (CoV) [1]. In the case of new CoV, the symptoms resembling the symptoms of severe acute respiratory syndrome caused by coronavirus SARS-CoV 2003 were observed. The new virus was named SARS-CoV-2, and in February 2020 the World Health Organization (WHO) named the disease "coronavirus disease 2019" (COVID-19) [2]. In the mathematical forecast of the epidemiological situation of the spreading of "COVID-19" in different countries, which was conducted by the Coronavirus Research Center of Johns Hopkins University (USA) and Boston Consulting Group, it was found that there will be several peaks in 2020-2021 [3]. SARS-CoV-2 is a single-stranded enveloped RNA virus that can be transmitted from person to person [4,5]. SARS-CoV-2 is approximately 50% genetically identical to MERS-CoV and approximately 79% identical to SARS-CoV, to which it has a similar structure of the receptor-binding domain. Both viruses use the same receptor - angiotensin-converting enzyme 2 (ACE-2) [6,7,8]. ACE-2 is present on the cells of the respiratory tract, central nervous system (CNS), kidneys, heart, intestines [9]. According to publications, SARS-CoV-2 affects variety of organs and systems: immune system, lungs, cardiovascular, musculoskeletal, central and peripheral nervous systems, digestive system etc.

Since 2021, the questions of the possibility to develop chronic COVID-19 associated neurological pathology are discussed, the prevalence and manifestations of which will depend on a large number of factors (genetic determination, adaptive-compensatory reserve of the nervous system and, in particular,

its regulatory mechanisms, existing neurological pathology, comorbidities, conditions and constitutional features of the immune system).

Among neurological complications of COVID-19 of great importance and serious consequences are strokes, delirium, psycho-emotional disturbances, depression, neurodegenerative diseases and some other pathologies of central and peripheral nervous system.

Ways of getting SARS-CoV-2 into the CNS.

Analysis of the clinical and experimental studies suggests, that the coronavirus has neuroinvasive properties. It can reach neurons directly and non-directly crossing the blood-brain barrier (BBB) [9, 10]. At the current stage of the research the following ways of penetration of a coronavirus into CNS are considered:

1. The first way (direct) is SARS-CoV-2 invasion through the ethmoid plate and olfactory bulb into neurons and astrocytes of various brain structures – thalamus and brainstem, including cardiorespiratory center [11, 12].

2. The second way (non-direct) of the virus penetration into the CNS is cell invasion. Coronavirus infection of monocytes and macrophages happens, which penetrate through the blood brain barrier and mediate neuroinvasion. There is evidence that the inflammatory response may be altered by mediators, that are released from the sensory and parasympathetic neurons, and conversely, the inflammatory response may affect the release of the mediators [13]. The viruses can infect endothelial cells of the blood-brain barrier in the vascular plexuses of the brain ventricles (through the olfactory bulb and olfactory nerves) [14]. One of the possible transneural ways of penetration of pathological agents into the central nervous system is considered to be via vagus nerve, which innervate the structures of the airways [7, 15].

3. The third way of the neuroinvasion is through endothelial cells. SARS-CoV-2 interacts with two types of receptors - ACE2 (that are expressed in many tissues, including lungs, heart, kidneys, intestines) and CD209L [16, 17]. Infected cells can penetrate into the CNS [7].

Neurological complications of COVID-19.

Damages of the nervous system in COVID-19 can occur by various mechanisms, both due to the direct damages of its structures by the virus (virus-induced processes) and mediated, for example, because of inadequate immune mechanisms (excessive activation with cytokine storm, development of autoimmune processes) and/or influence of hypoxia (3).

As the COVID-19 pandemic progresses, the number of reports of the neurological manifestations of COVID-19 increases [18, 19, 20]. The clinical manifestations of COVID-19 that are associated with the central nervous system, include headache, dizziness, ataxia, convulsions [21, 22, 23].

In retrospective cohort study of 236379 six-month survivors of COVID-19, it was found that there were increased risks of developing intracranial hemorrhage or ischemic stroke, parkinsonism, dementia, Guillain-Barre syndrome, encephalitis, mood, anxiety or psychotic disorders and some other neurological pathologis [18].

In accordance with the results of a retrospective analysis of the clinical registration of COVID-19 in 214 patients, 36% of them had neurological disorders. Headaches and dizziness were noted in 12,1% of the patients. Unfortunately, the pathophysiological mechanisms of these manifestations have not been discussed. In a retrospective study of 221 patients with COVID-19, 5% have had developed acute ischemic stroke (IS) and 0,5% have had cerebral hemorrhage [24]. According to other clinical observations, IS was diagnosed in 2,5%. The development of IS in COVID-19 may be conditioned by the disorders of the blood coagulation, the sympathoadrenal system and mechanisms of autoregulation of cerebral blood flow. In most cases, stroke often occurs in one to three weeks after the onset of COVID-19 symptoms, although a smaller part of the patients had stroke as the first symptom. Recently, the development of IS was noted 1-2 months after COVID-19. In patients with a stroke hypercoagulation of blood is more expressed: they have the increased content of fibrinogen and D-dimer. COVID-19 causes endothelial dysfunction, which explains the main systemic manifestations of the disease, including

hypercoagulation and thrombotic complications [25, 13, 15]. The maladaptive activity of the renin-angiotensin system, which is caused by SARS-CoV-2, is also an important pathogenic mechanism of stroke. A number of publications report about the development of acute cerebrovascular pathology in patients with COVID-19, it is considered its clinical and paraclinical characteristics and features of progression. Strokes became more frequent at a young age. In accordance with the retrospective cohort study, ischemic stroke was diagnosed in 0,9% of the hospitalized patients diagnosed with COVID-19 during the March 2020 in the primary care system in New York. It's important, that 43,8% of them had a stroke during hospitalization, the rest of them had COVID-19 symptoms, and the stroke occurred later (3-4 months later). Cryptogenic stroke was significantly more common in the patients with COVID-19 than in the current and retrospective control groups (patients without COVID-19) [1].

The data of autopsy, that have been received recently, indicate direct endothelial invasion of SARS-CoV-2. Viral particles are detected by electron microscopy in the endothelium. These factors are the reason of the cerebrovascular complications, including stroke.

Chinese physicians had conducted a retrospective study of 113 patients with COVID-19 and identified hypoxic encephalopathy in 20 of them [26]. Acute necrotic encephalopathy in patients with COVID-19 was noted in 12% of cases. One of the reasons is the damage of the blood-brain barrier and consequently damage to the brain parenchyma [5].

The most characteristic lesions of the CNS in patients with COVID-19, which are determined during the neuroimaging, are symmetrical, multifocal lesions with the obligatory involvement of the visual cortex [14]. Other localizations that are often found in COVID-19 include the brainstem, white matter of the brain, and cerebellum [27, 17].

Using the method of Internet research with the help of surveys, the fact of chemosensory dysfunctions in COVID-19 (olfactory and taste disorders - in 16% and 17%, respectively) were established [28]. Anosmia and hyposmia have been noted in the acute period of COVID-19 in 76,24% of cases. Anosmia and dysgeusia are common early symptoms of COVID-19, occurring in more than 80% of the patients. These symptoms may be the initial manifestation of COVID-19 and sometimes they are the only clinical manifestations of COVID-19. In some patients with COVID-19 there is the development of Guillain-Barre syndrome and polyneuropathy [29, 30, 31].

In patients with COVID-19, the damage of skeletal muscles - myalgia is noted. Myalgia is one of the most common first symptoms of coronavirus disease. In the WHO report, based on an analysis of 56,000 patients with COVID-19 in China, it is noted that muscle pain was in 15% of cases, in other studies - in 36% of cases. This statistical variance may be explained because of different follow-up periods and severity of the disease. Features and severity of musculoskeletal disorders are associated with the degree of respiratory disorders, state of hemodynamics, dysfunction of the brain stem and damage of muscle cells themselves. The most typical at histopathological examination there was the focal necrosis of myofibrils. Based on these facts, the hypothesis of immune-mediated damage of muscle fibers was assumed [32].

In such a way, the lesions of the central and peripheral nervous system in COVID-19 infection are polymorphic in clinical symptoms and severity of clinical manifestations.

There is some data, that after the treatment of COVID-19 in the patient's brain can persist fragments of the virion (analogy with the herpes simplex virus). And if SARS-CoV-2 is really able to persist as inactive fragments for a long time, the disease will be able to recur in susceptible individuals in the case of unfavorable conditions [33]. Panis Mondolfi et al. (37) reported the presence of SARS-Cov-2 in neurons and capillary endothelial cells in the frontal part of the brain. During the electron microscopic examination of the sections of the frontal part there were revealed viral particles in the cytoplasm of neuronal bodies, outside of them and in small vesicles of endothelial cells. The obtained data have confirmed the neuroinvasiveness of SARS-CoV-2 and is the evidence of the role of endothelium of the capillary bed and hematogenous pathway in brain damage. This condition determines the relevance of longitudinal observations and the study of the distant neurological complications among the infected and cured patients.

Numerous studies of the bioelectrical activity of the brain occupy a special place in determining pathogenic mechanisms of action of COVID-19. The analysis of the bioelectrical activity of the brain in patients in the acute period of COVID-19 was performed in a number of clinics [34, 35]. In the group of 380 patients, for 36% have been stated an abnormal background activity and a general slowdown in the frequency of the main rhythms of the electroencephalogram (EEG). The part of patients with epileptiform discharges was 20,3%. However, the frequency of seizures and status epilepticus according to the EEG data was 2,05% and 0,80%, respectively [35].

Based on the analysis of data of bioelectrical activity of the brain in patients with COVID-19, three main types of EEG changes were identified. In the first type, diffuse changes were absent. The dominance of alpha rhythm in the occipital regions is reduced (68%). The second type was characterized by generalized periodic discharges and lateralized discharges (12%). At the third type of EEG changes the focal and generalized changes, epileptiform discharges (10%) were observed. EEG frontal patterns predominated, which some researchers have suggested to use as a biomarker of encephalopathy in COVID-19 [36].

Results of our own study.

The purposes of the study were to analyze post-COVID changes in the functional state of the central nervous system (electrogenesis, blood flow, endothelial stutus).

36% patients with dyscirculatory encephalopathy (DEP) of atherosclerotic and hypertensive genesis of 1-2 stages before and 3-4 months after COVID-19 were included into this study. The average age of the patients was 63,1 ± 2,4 years. In 2019-2020, the patients underwent a comprehensive clinical and neurological examination, electroencephalography (18-channel electroencephalograph Nihon Kohden, Japan), duplex scanning of the vessels of the neck and head on Toshiba Aplio 300 (Japan), laser Doppler flowmetry (Transonic Inc., USA) with functional test (reactive hyperemia) [37].

The subjective status of patients was characterized by presence of complaints on recurrent headaches (52,8%), sleep disturbances (41,7%), general weakness (77,8%), memory impairment (50,0%), pains in muscles and limbs (27,8%) - see Fig. 1.

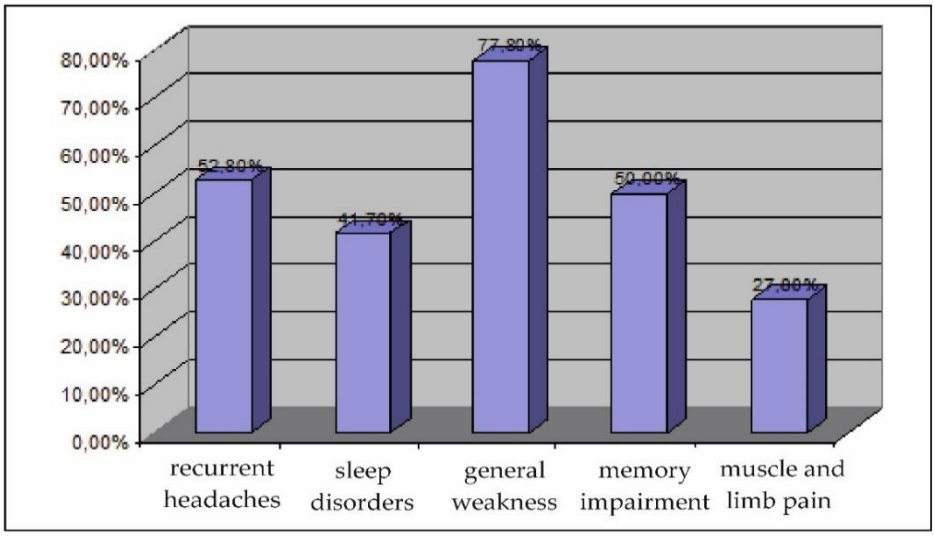


Figure 1. Characteristics and frequency of the complaints in DEP patients after COVID-19 (there were no such complaints before COVID-19).

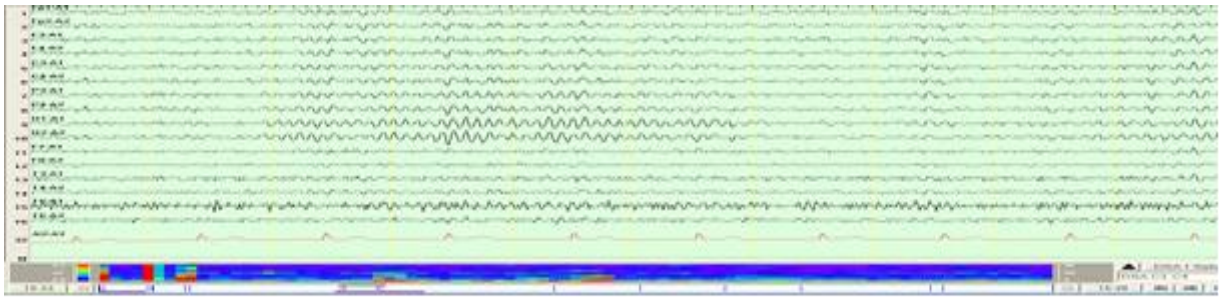
In 33,3% of patients who previously had normal blood pressure, there was increase to 150/100 mm Hg.

Bioelectric activity of the brain.

A comparative analysis of the structure of the bioelectrical activity of the brain of studied patients with DEP before and after coronavirus disease 2019 showed that 85% of patients have had changes in the frequency-amplitude of the electroencephalogram (EEG).

In fig. 2, 3, 4 EEG patterns before (A) and after (B) COVID-19 are shown, as well as quantitative characteristics of the power of the main EEG rhythms and the average frequency of the alpha rhythm before (C) and after (D) COVID-19.

A



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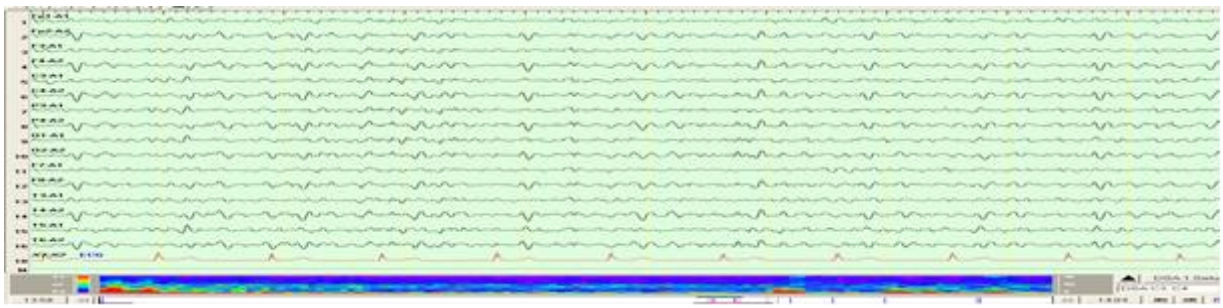

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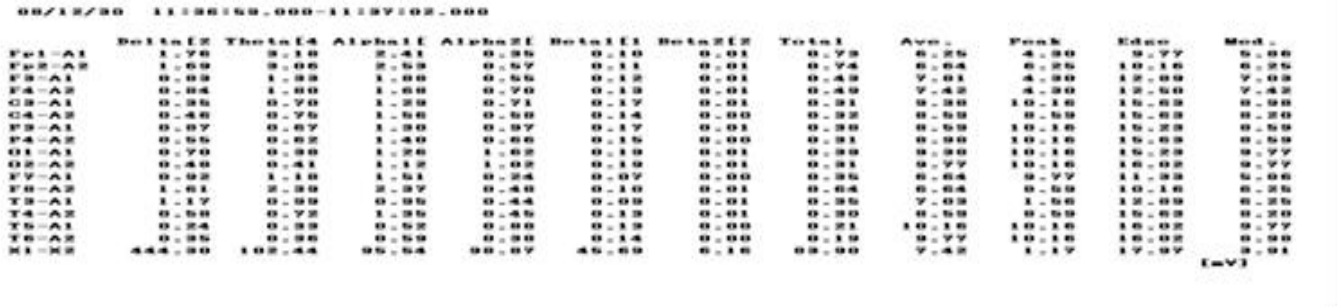
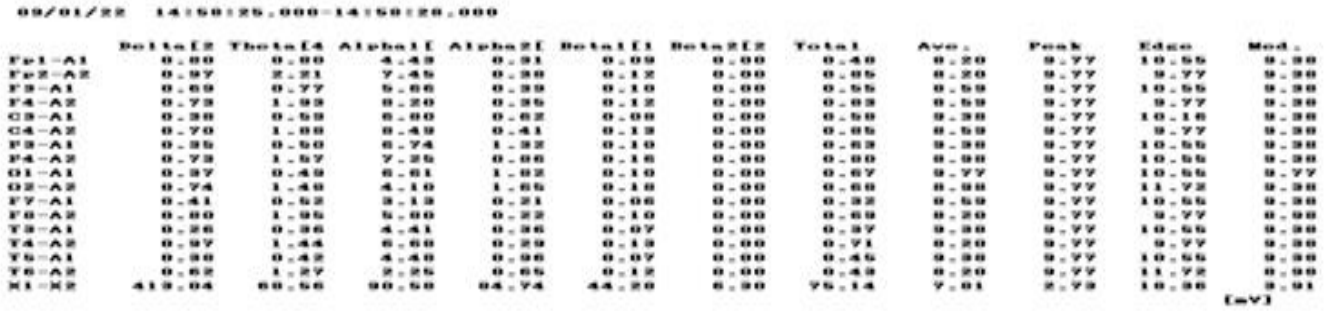


	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	1.76	3.18	2.41	0.35	0.10	0.01	0.73	6.25	4.30	9.77	5.86
Fp2-A2	1.69	3.06	2.53	0.57	0.11	0.01	0.74	6.64	6.25	10.16	6.25
F3-A1	0.83	1.83	1.88	0.55	0.12	0.01	0.43	7.81	4.30	12.89	7.03
F4-A2	0.84	1.80	1.88	0.70	0.13	0.01	0.49	7.42	4.30	12.50	7.42
C3-A1	0.35	0.70	1.20	0.71	0.17	0.01	0.31	9.38	10.16	15.63	9.38
C4-A2	0.46	0.75	1.56	0.58	0.14	0.00	0.32	8.59	8.59	15.63	8.20
P3-A1	0.07	0.07	1.80	0.97	0.17	0.01	0.38	8.59	10.16	15.23	8.59
P4-A2	0.05	0.02	1.40	0.66	0.15	0.00	0.31	8.98	10.16	15.63	8.59
O1-A1	0.70	0.38	1.20	1.02	0.19	0.01	0.38	8.98	10.16	15.23	8.97
O2-A2	0.48	0.41	1.18	1.02	0.19	0.01	0.31	9.77	10.16	15.62	8.97
F7-A1	0.92	1.18	1.51	0.24	0.07	0.00	0.35	6.64	9.77	11.33	5.86
F8-A2	1.61	2.88	2.37	0.48	0.10	0.01	0.64	6.64	8.59	10.16	6.25
T3-A1	1.17	0.89	0.95	0.44	0.09	0.01	0.35	7.03	1.56	12.89	6.25
T4-A2	0.58	0.72	1.35	0.45	0.13	0.01	0.30	8.59	8.59	15.63	8.20
T5-A1	0.24	0.33	0.52	0.88	0.13	0.00	0.21	10.16	10.16	16.02	8.97
T6-A2	0.35	0.38	0.59	0.30	0.14	0.00	0.19	9.77	10.16	16.02	8.98
X1-X2	444.80	102.44	95.54	98.87	45.89	6.16	88.98	7.42	1.17	17.97	9.01

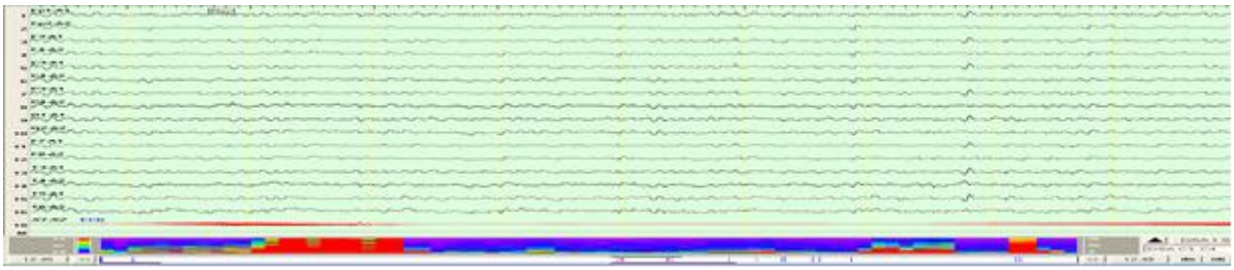
D



	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	0.80	0.80	4.43	0.31	0.09	0.00	0.48	8.20	8.77	10.55	8.98
Fp2-A2	0.97	2.21	7.45	0.38	0.12	0.00	0.85	8.20	8.77	8.77	8.98
F3-A1	0.60	0.77	5.86	0.39	0.10	0.00	0.55	8.59	8.77	10.55	8.98
F4-A2	0.73	1.93	8.20	0.35	0.12	0.00	0.83	8.59	8.77	8.77	8.98
C3-A1	0.38	0.58	6.80	0.62	0.08	0.00	0.58	8.38	8.77	10.16	8.98
C4-A2	0.70	1.88	8.48	0.41	0.13	0.00	0.85	8.59	8.77	8.77	8.98
P3-A1	0.35	0.50	6.74	1.32	0.10	0.00	0.53	8.38	8.77	10.55	8.98
P4-A2	0.73	1.57	7.35	0.86	0.16	0.00	0.80	8.98	8.77	10.55	8.98
O1-A1	0.37	0.48	6.81	1.82	0.10	0.00	0.67	8.77	8.77	10.55	8.77
O2-A2	0.74	1.48	4.10	1.85	0.18	0.00	0.88	8.98	8.77	11.72	8.98
F7-A1	0.41	0.52	3.13	0.21	0.06	0.00	0.32	8.59	8.77	10.55	8.98
F8-A2	0.80	1.95	5.80	0.22	0.10	0.00	0.88	8.20	8.77	8.77	8.98
T3-A1	0.26	0.36	4.41	0.36	0.07	0.00	0.37	8.38	8.77	10.55	8.98
T4-A2	0.97	1.44	6.80	0.28	0.13	0.00	0.71	8.20	8.77	8.77	8.98
T5-A1	0.30	0.42	4.48	0.98	0.07	0.00	0.45	8.38	8.77	10.55	8.98
T6-A2	0.62	1.27	2.25	0.65	0.12	0.00	0.43	8.20	8.77	11.72	8.98
X1-X2	419.04	88.56	90.58	84.74	44.20	6.80	75.14	7.81	2.73	18.36	9.01

Figure 2. Fragments of the EEG of the male patient K., 62 years, A - before COVID-19, B - 3 months after COVID-19. Quantitative characteristics of the power of the main EEG rhythms and the average frequency of the alpha-rhythm of the same patient K., 62 years, C - before COVID- 19, D - 3 months after COVID-19.
After COVID-19, changes in the bioelectrical activity of the brain of the patient K. are characterized by a general disorganization and leveling of the regional representation of the basic EEG rhythms. There is an asymmetry of power in the range of slow rhythms, especially in the range of theta-rhythm due to a decreased power predominantly in the right hemisphere.

A



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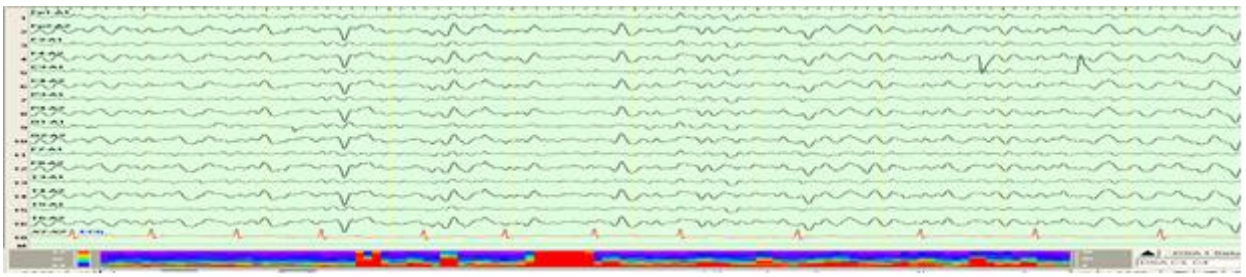

C

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	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	0.19	0.28	0.31	0.20	0.03	0.00	0.10	0.00	0.00	10.94	0.00
Fp2-A2	0.37	0.13	0.31	0.10	0.03	0.00	0.00	7.81	1.17	10.00	7.81
F3-A1	0.10	0.35	0.42	0.07	0.05	0.00	0.12	0.00	0.00	10.45	0.00
F4-A2	0.31	0.17	0.17	0.17	0.03	0.00	0.00	0.00	1.17	10.00	7.81
C3-A1	0.10	0.00	0.33	0.23	0.05	0.00	0.11	0.00	0.00	10.45	0.00
C4-A2	0.25	0.00	0.25	0.10	0.05	0.00	0.10	0.00	0.10	14.06	7.81
P3-A1	0.10	0.20	0.40	0.07	0.05	0.00	0.11	0.00	0.00	10.00	0.00
P4-A2	0.20	0.25	0.20	0.01	0.05	0.00	0.11	0.00	7.82	10.07	7.81
O1-A1	0.25	0.25	0.40	0.20	0.05	0.00	0.10	0.00	0.00	14.45	0.00
O2-A2	0.20	0.25	0.01	0.10	0.00	0.00	0.11	0.00	7.82	10.07	0.00
F7-A1	0.00	0.10	0.23	0.10	0.03	0.00	0.07	0.00	0.00	10.03	0.00
F8-A2	0.20	0.14	0.10	0.14	0.04	0.00	0.00	7.81	1.95	14.84	7.42
T3-A1	0.10	0.24	0.40	0.20	0.05	0.00	0.10	0.00	0.00	10.94	0.00
T4-A2	0.00	0.20	0.20	0.01	0.00	0.01	0.10	7.03	1.95	10.07	5.47
T5-A1	0.00	0.24	0.06	0.20	0.10	0.01	0.06	0.00	1.17	10.28	7.42
T6-A2	0.07	0.25	0.17	0.10	0.00	0.01	0.10	0.00	1.17	10.45	4.69
X1-X2	0.00	0.01	0.10	0.07	0.03	0.01	0.25	0.01	1.17	0.00	1.56

[mV]

D

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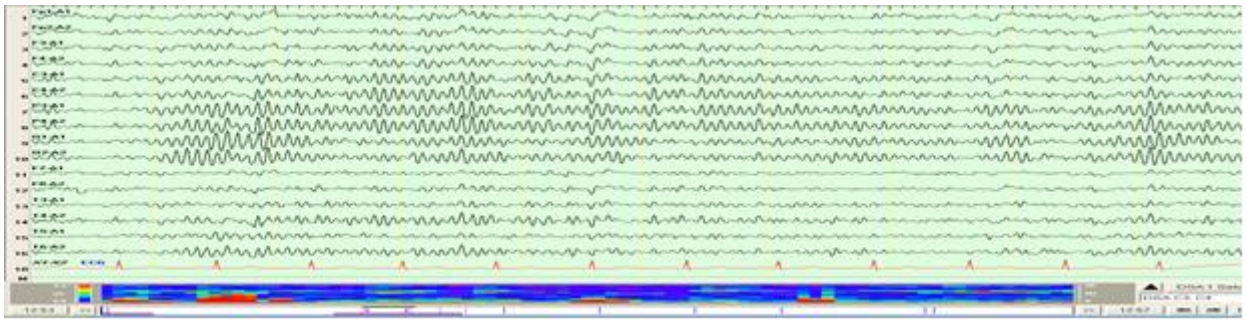
	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	0.53	0.47	1.09	0.19	0.05	0.00	0.20	7.42	8.59	10.94	7.81
Fp2-A2	3.97	4.95	2.05	1.10	0.07	0.01	1.18	5.86	4.30	9.77	5.08
F3-A1	0.53	0.40	0.86	0.15	0.05	0.00	0.18	7.42	8.59	12.50	7.42
F4-A2	3.57	4.76	1.82	0.92	0.06	0.00	1.09	5.47	4.30	9.38	5.08
C3-A1	0.50	0.42	0.75	0.17	0.05	0.00	0.18	7.03	1.17	12.11	7.42
C4-A2	3.36	3.42	1.20	0.76	0.06	0.00	0.86	5.47	4.30	9.77	4.69
P3-A1	0.47	0.41	0.53	0.19	0.04	0.00	0.15	7.42	2.73	12.50	7.03
P4-A2	3.25	3.56	1.16	0.96	0.05	0.00	0.88	5.47	4.30	9.77	4.69
O1-A1	0.96	0.66	0.60	0.33	0.05	0.00	0.25	6.64	2.73	12.11	5.47
O2-A2	3.34	3.73	1.03	1.02	0.05	0.00	0.91	5.47	4.30	9.77	4.69
F7-A1	0.72	0.39	0.80	0.17	0.04	0.00	0.19	6.64	1.17	10.94	5.86
F8-A2	4.15	4.06	1.75	0.91	0.06	0.00	1.05	5.47	4.30	9.77	4.69
T3-A1	0.48	0.40	0.53	0.11	0.04	0.00	0.15	7.03	1.56	12.89	5.86
T4-A2	4.05	4.08	1.62	1.05	0.06	0.00	1.05	5.47	4.30	9.77	4.69
T5-A1	0.57	0.40	0.47	0.12	0.04	0.00	0.15	6.64	2.73	11.72	5.47
T6-A2	3.61	4.16	1.40	1.17	0.07	0.00	1.02	5.47	4.30	10.16	5.08
X1-X2	228.05	257.61	265.14	295.93	167.33	11.80	150.75	11.33	4.30	19.14	10.94

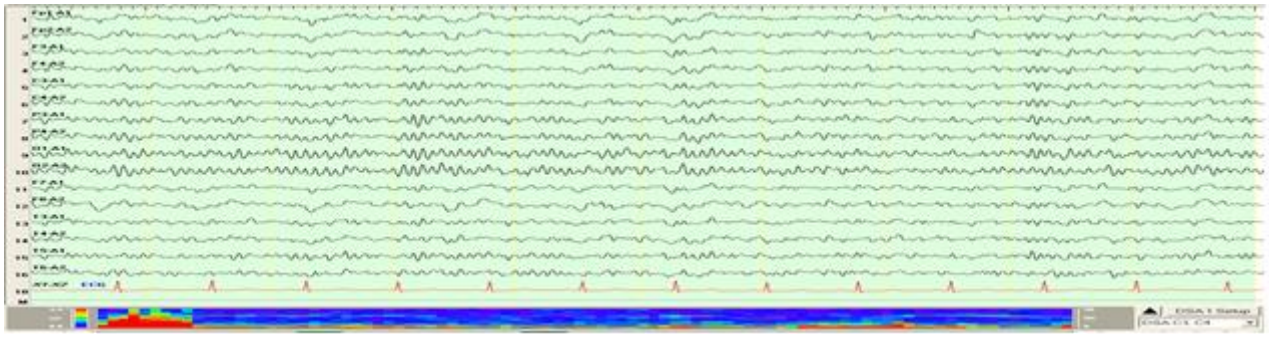
[mV]

Figure 3. Fragments of the EEG of the female patient N., 63 years, A - before COVID-19, B - 3 months after COVID-19. Quantitative characteristics of power of the main rhythms of EEG and average frequency of an alpha- rhythm of the same patient N., C – before COVID-19, D - in 3 months after COVID-19.
The patient after COVID-19 had a statistically significant increase of power e of delta- and theta-rhythm in the right hemisphere.

A



B



C

08/09/21 12:54:32.000-12:54:35.000

	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	2.14	0.87	0.77	0.45	0.54	0.27	0.77	10.94	2.73	22.66	8.98
Fp2-A2	1.75	0.70	0.71	0.49	0.48	0.20	0.65	10.94	2.73	21.88	9.38
F3-A1	2.13	0.85	0.74	0.52	0.49	0.24	0.75	10.94	2.73	22.27	8.59
F4-A2	1.58	0.70	0.70	0.54	0.50	0.22	0.63	11.72	2.73	22.66	10.16
C3-A1	2.00	0.86	0.69	1.05	0.60	0.25	0.81	11.33	2.73	21.88	10.16
C4-A2	1.68	0.69	0.66	1.13	0.71	0.21	0.76	11.72	12.89	21.09	12.11
P3-A1	2.00	0.85	0.63	2.02	0.82	0.27	1.03	11.72	12.89	20.70	12.11
P4-A2	1.70	0.71	0.68	2.03	0.88	0.21	0.99	11.72	12.89	19.92	12.50
O1-A1	2.06	0.80	0.60	1.66	0.70	0.20	0.93	10.94	12.89	19.92	10.94
O2-A2	1.55	0.64	0.46	2.04	0.78	0.19	0.94	11.72	12.89	19.92	12.11
F7-A1	2.13	0.76	0.49	0.35	0.33	0.16	0.68	9.77	2.73	21.09	6.64
F8-A2	1.60	0.62	0.58	0.43	0.38	0.16	0.57	10.55	2.34	21.88	8.98
T3-A1	2.03	0.77	0.49	0.62	0.42	0.20	0.70	10.55	2.73	21.48	8.59
T4-A2	1.68	0.66	0.58	1.24	0.68	0.20	0.77	11.72	12.89	20.31	12.11
T5-A1	1.97	0.74	0.39	0.56	0.37	0.15	0.66	9.77	2.73	20.70	7.42
T6-A2	1.56	0.62	0.49	1.26	0.58	0.15	0.72	11.33	12.89	19.53	11.33
X1-X2	17.10	13.07	12.78	12.97	10.17	6.12	10.70	13.67	7.81	23.83	12.50
											[uV]

D

08/12/22 16:41:20.000-16:41:23.000

	Delta[2	Theta[4	Alpha1[	Alpha2[	Beta1[1	Beta2[2	Total	Ave.	Peak	Edge	Med.
Fp1-A1	0.48	0.33	0.40	0.29	0.10	0.01	0.17	8.98	9.38	16.80	8.20
Fp2-A2	0.45	0.32	0.40	0.39	0.11	0.00	0.17	8.98	3.13	16.80	8.20
F3-A1	0.65	0.31	0.45	0.18	0.11	0.01	0.17	8.20	1.56	16.02	6.25
F4-A2	0.36	0.40	0.39	0.45	0.15	0.00	0.19	9.77	10.55	17.58	9.38
C3-A1	0.82	0.42	0.41	0.20	0.13	0.01	0.22	7.81	1.56	16.02	5.86
C4-A2	0.52	0.50	0.24	0.55	0.10	0.01	0.23	9.38	10.55	17.58	8.98
P3-A1	0.80	0.48	0.52	0.39	0.21	0.01	0.27	8.98	1.56	17.19	8.20
P4-A2	0.79	0.50	0.28	0.77	0.22	0.01	0.29	9.38	1.17	17.19	9.77
O1-A1	1.16	0.67	0.63	1.09	0.22	0.02	0.40	8.98	12.50	16.80	8.98
O2-A2	0.85	0.54	0.38	1.03	0.27	0.01	0.35	9.77	12.50	17.19	10.16
F7-A1	0.54	0.35	0.34	0.19	0.07	0.00	0.15	7.42	3.91	14.45	5.86
F8-A2	0.61	0.39	0.48	0.34	0.10	0.00	0.19	8.20	2.73	16.41	7.03
T3-A1	0.62	0.35	0.30	0.18	0.11	0.01	0.16	7.81	1.56	16.02	5.86
T4-A2	0.98	0.42	0.51	0.40	0.14	0.01	0.25	7.81	1.56	16.02	6.64
T5-A1	0.55	0.35	0.39	0.28	0.21	0.01	0.21	9.77	1.56	18.36	8.98
T6-A2	0.45	0.40	0.32	0.29	0.15	0.01	0.19	8.98	6.25	16.80	7.81
X1-X2	292.78	240.62	302.59	190.78	141.60	11.68	138.84	10.94	6.64	19.92	9.38
											[uV]

Figure 4. Fragments of the EEG of the female patient L., 56 years old, A - before COVID-19, B - 4 months after COVID-19. Quantitative characteristic of the power of the main EEG rhythms and average frequency of the alpha-rhythm: C- before COVID-19, D - 4 months after COVID-19.

In the case of the patient L., COVID-19 caused changes in regional representation of the basic rhythms of EEG and decrease of the power in the range of alpha-2-rhythm and frequency of alpha-rhythm.

In Fig. 5 are general directions of the changes in the power of main EEG rhythms and frequency of the alpha-rhythm in the DEP patients after COVID-19.

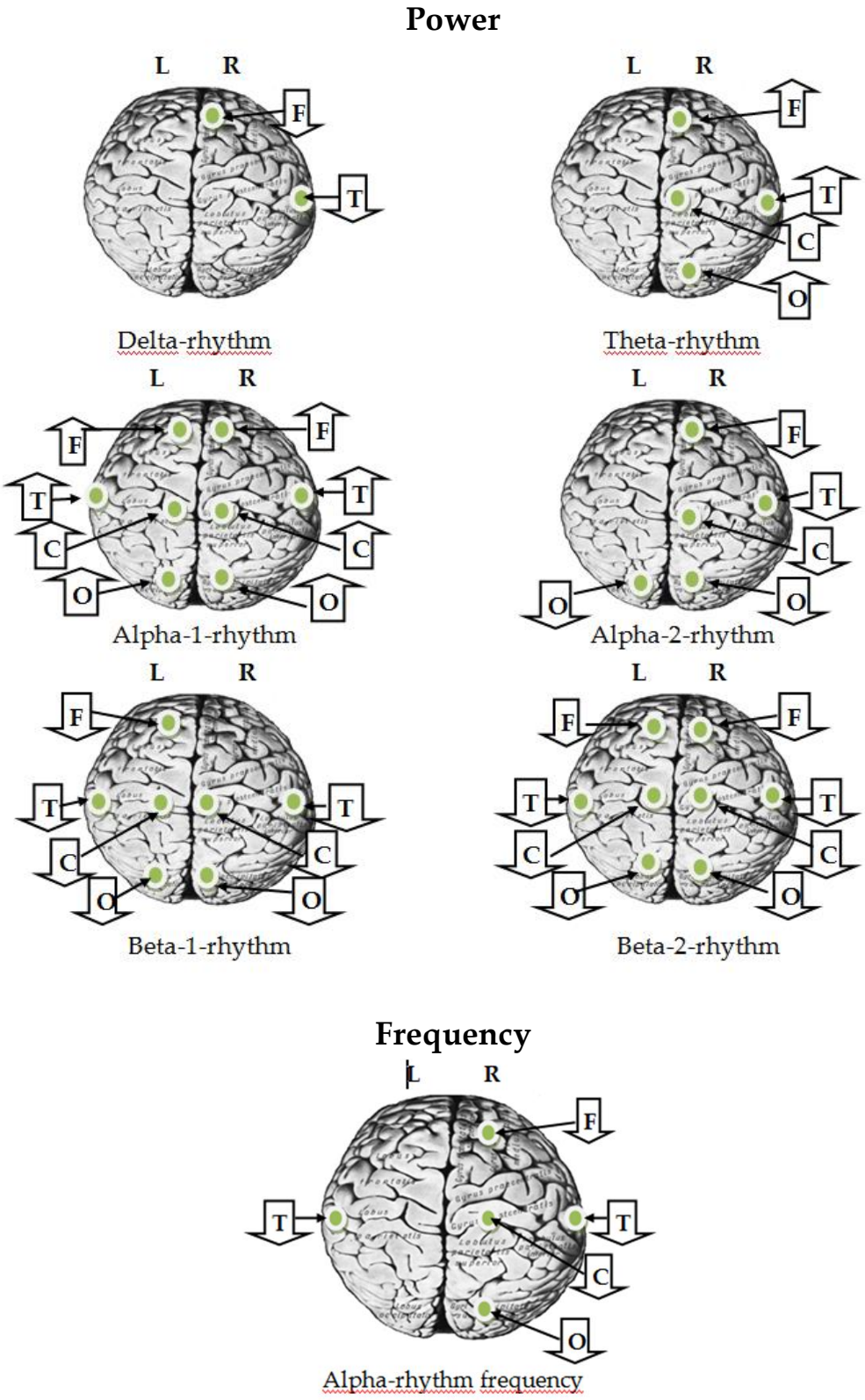


Figure 5. Direction of statistically significant changes in the average indicators of the power of main EEG rhythms and the frequency of the alpha- rhythm in 3-4 months after COVID-19 in DEP patients.
Brain lobes: F – frontal, T – temporal, C – central, O – occipital)

A special attention in the post-COVID EEG was paid to the reduction of the frequency of the alpha-rhythm, which is the biological timer of the brain [38]. In patients after COVID-19 there was a statistically significant decrease in the frequency of alpha-rhythm in the right hemisphere in all areas, while in the left hemisphere - in the temporal one (Tab. 1). There was a redistribution of the power in the range of alpha-rhythm: the power increases in the range of alpha-1-rhythm against the background of a decrease in the range of alpha-2-rhythm. In both hemispheres there was a decrease of the power of cortical rhythms (beta-1 and beta-2-rhythm). EEG changes after COVID-19 were characterized by an increase of the power in the theta-rhythm range in the right hemisphere.

Table 1.

Characteristics of the frequency of alpha-rhythm in patients before (A) and 3-4 months after COVID-19 (B)

Brain lobe	Hemisphere	Alpha-rhythm frequency (M ± m)	
		A	B
Frontal (F)	**Left**	9.04 ± 0.38	9.02 ± 0.40
	Right	9.63 ± 0.28	9.10 ± 0.19*
Temporal (T)	**Left**	10.12 ± 0.26	9.63 ± 0.22*
	Right	9.60 ± 0.19	9.14 ± 0.41*
Central (C)	**Left**	9.06 ± 0.29	9.00 ± 0.32
	Right	10.05 ± 0.31	9.61 ± 0.28*
Occipital (O)	**Left**	9.67 ± 0.26	9.44 ± 0.41
	Right	9.87 ± 0.20	9.30 ± 0.51*

Note: *$p<0.05$

Among major causes of changes in electrogenesis of the brain are disorders in metabolism and blood supply to the brain due to COVID-19.

Cerebral blood flow.

There were changes of cerebral blood circulation in patients after coronavirus disease 2019. In 66.7% of patients, COVID-19 caused a decrease in cerebral blood flow in vessels of the carotid and vertebrobasilar basins, and in 40.0% of patients there was an appearance of venous dyscirculation. Decreased linear systolic blood flow velocity (LSBV) is observed in the right and left internal carotid arteries (ICA), right and left middle cerebral arteries (MCA), in the left posterior cerebral artery (PCA) and basilar artery (BA). These changes in LSBV are clearly seen in Fig. 6.

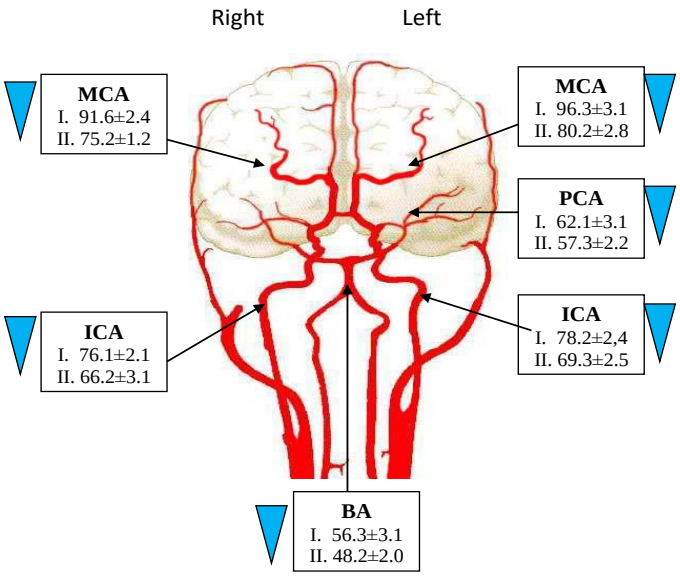


Figure 6. Changes in blood flow in extra- and intracranial vessels of the brain in DEP patients after COVID-19: I - before, II - after COVID-19 (differences are statistically significant).

Changes in cerebral blood flow are due to impact of COVID-19 onto intra- and extracerebral regulation and cardiovascular functions.

Considering the fact, that one of the targets of SARS-CoV-2 is the endothelium of vessels, the analysis of the functional state of the endothelium at the level of the microcirculatory vascular basin in the area of the volar surface of the left forearm in patients before and 3-4 months after COVID-19 was performed. In patients after COVID-19 there was a significant decrease in endothelial function ($p < 0,05$) (Fig. 7).

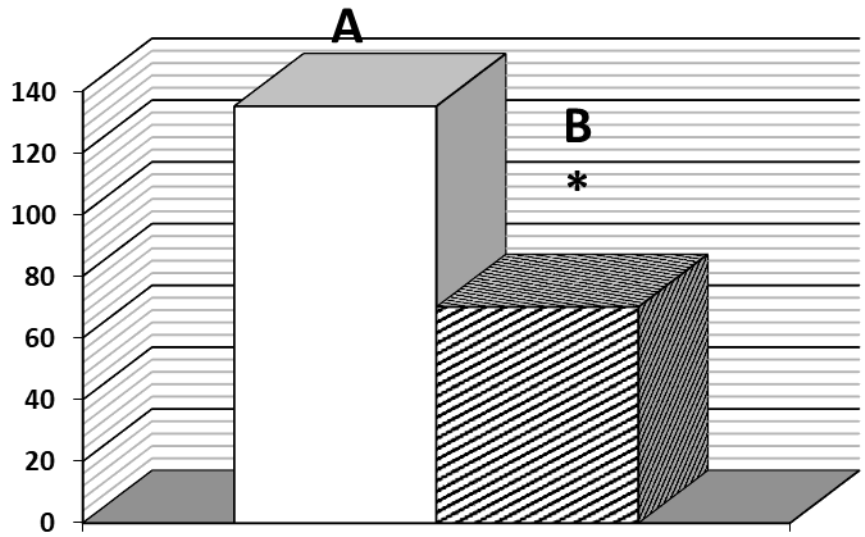


Figure 7. Post-compressional blood flow in vessels of the microcirculatory basin in the area of the volar surface of the left forearm in persons before (A) and 3-4 months after COVID-19 (B). Baseline level taken as 100%.
Note: *$p<0.05$

Such changes after COVID-19 can be explained by damaging effect of SARS-CoV-2 on the vascular endothelium and its metabolism.

Conclusions.

There exist direct and non-direct ways of SARS-CoV-2 penetration into the central nervous system.

Among neurological complications of COVID-19 of great importance and serious consequences are strokes, delirium, psycho-emotional disturbances, depression, neurodegenerative diseases, other disorders in central and peripheral nervous system functioning.

In our study in DEP patients 3-4 months after coronavirus disease 2019, there was seen a reorganization of the bioelectrical activity of the brain. In the overall EEG structure, there was an increase of specific power of slow rhythms against the background of a decrease of the power in the range of cortical rhythms.

A decrease of cerebral blood flow in separate vessels of carotid and vertebrobasilar basins as well as sharp deterioration of a functional state of endothelium at the microcirculatory level were also found.

Further long-term follow-up of patients after COVID-19 will allow to formulate more clearly and in details the mechanisms of post-COVID syndromes development and to propose ways of treating these patients.

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