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NEUROLOGICAL MANIFESTATIONS AND COMPLICATIONS IN PATIENTS WITH CORONAVIRUS INFECTION

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Tayanch so'zlar: insult, COVID-19 nevrologik asoratlari, o'tkir mielit, Giyyen-Barre sindromi, ensefalit, COVID-19.
Ключевые слова: инсульт, неврологические осложнения COVID-19, острый миелит, синдром Гийена-Барре, энцефалит, COVID-19.

It is becoming clear that the neurological complications of COVID-19 are very common, but in some cases it is difficult to establish a causal relationship. For example, stroke may occur for reasons unrelated to coronavirus infection, while Guillain-Barré syndrome and meningoencephalitis are likely to be parainfectious. Only long-term epidemiological studies in large groups of patients allow to clarify some of these issues. This study helps to understand better the mechanisms of development of complications and develop schemes for their treatment and subsequent rehabilitation. The article presents the mechanisms of penetration of the coronavirus into the nervous system and systematizes the neurological manifestations and complications of COVID-19, which were described in the first 18 months of the pandemic. Particular attention is paid to the complications of COVID-19 in the central and peripheral nervous system, the most interesting clinical examples are given. Summing up the analysis of the literature, we can say that the clinical picture of neurological diseases and syndromes caused by coronavirus infection corresponds to the usual ideas. We also considered the assumption that SARS-CoV-2 can persist in the central nervous system for a long time in the form of inactive fragments, which means that it can recur in predisposed individuals when appropriate conditions arise. This assumption raises concerns regarding to long-term neurological complications in infected and cured patients.

KORONAVIRUS INFEKTSIYASI BILAN KASALLANGAN BEMORLARDA NEVROLOGIK ASORATLARNING NAMOYON BO'LISHI

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COVID-19 ning nevrologik asoratlari juda keng tarqalganligi aniq bo'lib bormoqda, ammo ba'zi hollarda sabab-oqibat munosabatlarini o'rnatish qiyin. Masalan, insult koronavirus infektsiyasiga bog'liq bo'lmagan sabablarga ko'ra yuzaga kelishi mumkin, Giyyen-Barre sindromi va meningoensefalit esa parainfeksion bo'lishi mumkin. Bemorlarning katta guruhlarida faqat uzoq muddatli epidemiologik tadqiqotlar ushbu masalalarning ba'zilariga aniqlik kiritishi mumkin. Bu asoratlarni rivojlanish mexanizmlarini yaxshiroq tushunishga yordam beradi va ularni davolash va keyinchalik reabilitatsiya qilish sxemalarini ishlab chiqadi. Maqolada koronavirusning asab tizimiga kirib borish mexanizmlari ko'rsatilgan va pandemiyaning dastlabki 18 oyida tasvirlangan COVID-19 ning nevrologik ko'rinishlari va asoratlari tizimlashtirilgan. COVID-19 ning markaziy va periferik asab tizimidagi asoratlariga alohida e'tibor qaratiladi, eng qiziqarli klinik misollar keltiriladi. Adabiyotlar tahlilini sarhisob qilsak, shuni aytishimiz mumkinki, nevrologik kasalliklar va koronavirus infeksiyasi keltirib chiqaradigan sindromlarning klinik ko'rinishi odatiy fikrlarga mos keladi. Shuningdek, biz SARS-CoV-2 uzoq vaqt davomida markaziy asab tizimida faol bo'lmagan bo'laklar ko'rinishida saqlanishi mumkin degan taxminni ko'rib chiqdik, ya'ni tegishli sharoitlar paydo bo'lganda u moyil odamlarda takrorlanishi mumkin. Ushbu taxmin infektsiyalangan va davolangan bemorlarda uzoq muddatli nevrologik asoratlar bilan bog'liq xavotirlarni keltirib chiqaradi.

НЕВРОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ И ОСЛОЖНЕНИЯ У БОЛЬНЫХ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ

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Становится ясно, что неврологические осложнения COVID-19 встречаются очень часто, но в ряде случаев установить причинно-следственную связь сложно. Например, инсульт может возникнуть по причинам, не связанным с коронавирусной инфекцией, тогда как синдром Гийена-Барре и менингоэнцефалит, скорее всего, будут носить параинфекционный характер. Только многолетние эпидемиологические исследования на больших группах больных смогут внести ясность в некоторые из этих вопросов. Это поможет лучше понять механизмы развития осложнений и разработать схемы их лечения и последующей реабилитации. В статье представлены механизмы проникновения коронавируса в нервную систему и систематизированы неврологические проявления и осложнения COVID-19, которые были описаны в первые 18 месяцев пандемии. Особое внимание уделено осложнениям COVID-19 на центральную и периферическую нервную систему, приведены наиболее интересные клинические примеры. Подводя итог анализу литературы, можно сказать, что клиническая картина неврологических заболеваний и синдромов, вызванных коронавирусной инфекцией, соответствует обычным представлениям. Мы также рассмотрели предположение, что SARS-CoV-2 может длительное время сохраняться в ЦНС в виде неактивных фрагментов, а значит, может рецидивировать у предрасположенных лиц при возникновении соответствующих условий. Это предположение вызывает обеспокоенность в отношении долгосрочных неврологических осложнений у инфицированных и вылеченных пациентов.

List of abbreviations: IVIG - intravenous immunoglobulin, BBB - blood-brain barrier, IS - ischemic stroke, CT - computed tomography, MRI - magnetic resonance imaging, CO - chest organs, CVA - acute cerebrovascular accident, PCR - polymerase chain reaction, GBS — Guillain-Barré syndrome, CNS — central nervous system, ENMG — electroneuromyography.

Introduction. At the end of 2019, an outbreak of a new coronavirus infection occurred in the city of Wuhan (People's Republic of China). On February 11, 2020, the International Committee on the Taxonomy of Viruses assigned the official name SARS-CoV-2 to the infectious agent [1]. Currently, despite the number of infected and successfully treated patients around the world, there is very little information about the epidemiology, clinical features, prevention and treatment of this disease. To date, Temporary guidelines for the prevention, diagnosis and treatment of coronavirus infection have been created, which are based on data published by experts from WHO, the Chinese, American and European Centers for Disease Control in materials on the treatment and prevention of this infection [1].

Coronaviruses (Coronaviridae) are a large family of RNA viruses that can infect humans and animals. The entrance gate of the pathogen is the epithelium of the upper respiratory tract and the epitheliocytes of the stomach and intestines. The initial stage of infection is the penetration of SARS-CoV-2 into target cells that have receptors for angiotensin-converting enzyme type II (ACE2). ACE2 receptors are present on the cells of the respiratory tract, kidneys, esophagus, bladder, ileum, heart, and central nervous system (CNS). The infection is transmitted by airborne droplets (the leading route of transmission), airborne dust and contact routes. It is known that at room temperature SARS-CoV-2 is able to remain viable on various environmental objects for 3 days. The main source of infection is a sick person, including those in the incubation (from 2 to 14 days, on average 5–7 days) period of the disease [1]. The diagnosis is established on the basis of epidemiological history, clinical examination and laboratory results. Specific laboratory diagnostics include the detection of SARS-CoV-2 RNA by polymerase chain reaction (PCR) [1]. Clinical variants and manifestations of COVID-19 include acute respiratory viral infection, pneumonia without respiratory failure, pneumonia with acute respiratory failure, sepsis, septic (toxic) shock. Possible complications: acute heart failure, acute renal failure, septic shock, hemorrhagic syndrome against the background of a decrease in blood platelets, multiple organ failure (impaired functions of many organs and systems) [1]. At the same time, the described complications appear during the course of the disease, and there are no data on long-term complications.

How does SARS-CoV-2 enter the CNS? The latest data on the study of SARS-Cov-2 neurovirulence, presented in an article by Pakistani scientists, indicate that the virus penetrates only into cells that have ACE2 receptors on the membrane [2]. In order to determine the expression of ACE2 in the nervous tissue, a search was carried out in databases of human proteins [3]. The findings prompted researchers to begin studying the neurotropic effects of SARSCoV-2 and their contribution to mortality in infected patients. Data from clinical and animal studies have shown that coronavirus can cross the blood-brain barrier (BBB) and exhibit neuroinvasive properties [4–5]. The exact mechanisms of entry into the CNS are not yet fully understood, but four routes of transmission are now proposed. The first of these is the olfactory nerves. Intranasal inoculation of MERS-CoV mice causes brain damage involving the thalamus and brainstem [6]. In addition, it has been reported that the mortality rate of mice increased when infected with SARS-CoV via intranasal inoculation, which may be associated with the death of brainstem neurons [7]. The second way the virus enters the CNS is cellular invasion. In this case, coronavirus-infected monocytes and macrophages penetrate the BBB and mediate neuroinvasion [8]. At the same time, in vitro studies have shown that the affected monocytes and macrophages can be a reservoir for the virus and contribute to its spread to other tissues [9]. BBB endothelial cells are the third possible pathway for neuroinvasion; they are capable of expressing two types of receptors, ACE2 and CD209L [10], interacting with which SARSCoV-2 can enter the CNS. The fourth possible way for the virus to enter the nervous system is transsynaptic transmission through peripheral nerves [11].

Neurological Complications of COVID-19. It is now known that many patients with neurological diseases are at increased risk of infection and severe course of COVID-19. Thus, according to Italian colleagues, in-hospital mortality rates in patients with neurological diseases and COVID-19 were significantly higher than in similar patients without COVID-19 [12]. At the same time, initially neurologically healthy patients with coronavirus infection may show neurological symptoms during the course of the disease. A recently published retrospective study from Wuhan

showed that in a sample of 216 patients with confirmed COVID-19, 37 % had neurological manifestations [13]. All the lesions of the nervous system caused by COVID-19 encountered in practice can be divided into 3 groups: 1) CNS manifestations [headache and dizziness, acute cerebrovascular accident (CVA), encephalopathy, encephalitis, acute myelitis]; 2) damage to the peripheral nervous system [anosmia, Guillain-Barré syndrome (GBS)]; 3) damage to skeletal muscles.

Headache and dizziness. Headaches and dizziness are nonspecific symptoms of many diseases. They have been reported as concomitant symptoms associated with COVID-19 disease in many publications, while their occurrence against the background of coronavirus infection ranges from 4 to 13.1 % [14-16]. However, the exact mechanism and pathophysiology of their occurrence has not been discussed in detail in any of the presented works.

Acute cerebrovascular accident

Nomadays, several papers have been published describing the development of stroke in patients with COVID-19: 9 descriptions of clinical observations [5 single cases, 4 publications describe case series (from 2 to 6)] [17–25] and 2 observational studies describing the incidence stroke in SARSCoV-2 positive patients. In a retrospective study conducted by colleagues from China, out of 221 patients, 11 (5 %) developed acute ischemic stroke (IS), 1 (0.5 %) had cerebral venous sinus thrombosis, and 1 (0.5 %) — hemorrhage in the brain [26]. In another prospective study of 288 patients, 9 (2.5 %) were diagnosed with IS [27]. In 9 published clinical cases, a total of 21 patients were described, of which 16 men and 5 women; the average age was 59.8 years (men — 63.1; women — 49.8). Most strokes (19) were ischemic, although three patients had hemorrhagic transformation of IS and 2 -hemorrhagic strokes. From 19 patients with IS, 8 were diagnosed with multiple infarcts. In 13 patients with IS, a thrombus was detected during imaging: 6 in the middle cerebral artery, 2 in the posterior cerebral artery, 3 in the vertebral arteries, and 1 in the internal carotid artery. Of the remaining number of cases, 4 were manifested by occlusion of large vessels, but the presence of a thrombus in them was not confirmed; the remaining 2 were represented by lacunar infarcts. From 19 observed patients with IS, 4 patients died, 6 continued treatment in the intensive care unit, 3 were transferred to the rehabilitation department, 5 patients recovered quickly; in one case the fate of the patient is unknown. Interestingly, 14 cases had significantly elevated D-dimer levels (≥ 1000 μg/L), of which 9 patients had variable anticardiolipin antibody test results [18, 21, 25]. Colleagues from Iran reported a case of intracranial bleeding in a 79-year-old man who tested positive for COVID-19 [24]. He was admitted urgently with a history of fever and cough and a Glasgow Coma Scale score of 7. Analysis of the secret from the nasopharynx by PCR was positive for COVID-19, computed tomography of the chest organs (CT scan of the chest) showed a ground glass pattern. CT of the brain revealed massive bleeding in the right hemisphere with expansion of the intraventricular space. The described patient was not hypertensive, had never taken anticoagulant drugs, and his blood pressure at the time of admission was normal for his age group. According to the authors, the blockage of ACE2 receptors could lead to disruption of the sympathoadrenal system and disruption of the mechanism of autoregulation of cerebral blood flow, which led to bleeding. French researchers described three cases of IS detected during neuroimaging performed for encephalopathy, and none of the patients had focal neurological symptoms [28]. The authors suggested that the symptoms were masked by the presence of encephalopathy, but this only highlights the importance of neuroimaging in evaluating such cases.

Encephalopathy. More recently, colleagues from the United States described a clinical case of a 74-year-old patient with a history of atrial fibrillation, cardioembolic subtype IS, Parkinson's disease, and chronic obstructive pulmonary disease, who was brought to the emergency department with fever and cough [29]. Primary diagnostics did not reveal any serious deviations in his health, and the patient was discharged home. Later, he returned to the hospital with worsening symptoms, including headache, altered mental status, fever, and cough. Diagnostic tests for COVID-19 were positive. Chest X-ray findings were suggestive of pneumonia, while brain CT scan was unremarkable except for signs of long-standing CVA. The patient soon developed severe respiratory problems and was transferred to the intensive care unit and intubated. The patient's condition at admission was interpreted by the authors as a manifestation of hypoxic encephalopathy. Chinese colleagues in their retrospective study of the clinical characteristics of 113 patients with COVID-19 revealed hypoxic encephalopathy in 20 patients [30]. Mao et al. in their article reported the occurrence of headache and hypoxic encephalopathy in 40 % of patients in their

study, but the details and diagnostic criteria used were not described [13]. At the end of March 2020, Poyiadji et al. reported the first case of COVID-19-associated acute hemorrhagic necrotizing encephalopathy (ANE) [31]. A middle-aged patient presented to the hospital with a 3-day history of cough, fever, and mental status changes. PCR for COVID-19 was positive, non-contrast CT scans of the brain showed a symmetrical decrease in signal intensity in the medial regions of the thalamus, while the CT angiogram and CT venogram were normal. The brain MRI of this patient showed hemorrhagic lesions in the medial thalamus, middle temporal lobes, and subinsular areas. As a therapy, the patient received intravenous immunoglobulin (IVIG), but the outcome of the treatment was not reflected in the publication. Acute necrotizing encephalopathy is known to be a rare complication of viral infections such as influenza. The mechanism of its occurrence is explained by a cytokine storm, which leads to a violation of the integrity of the BBB and damage to the brain parenchyma.

Encephalitis and meningoencephalitis. We analyzed 8 publications describing clinical cases of encephalitis and meningoencephalitis in patients with COVID-19; 7 of them contain descriptions of single cases [29, 31–36] and 1 article analyzes a paired case [37]. Among 9 described patients, there were 5 females and 3 males, one did not specify gender; the age group was 55.5 years. Clinical manifestations were mainly limited to fever. Meningeal symptoms were noted in 3 cases, headache in 4; 3 more patients had episodes of epileptic seizures. In 7 cases, CSF PCR was performed for SARS-CoV-2 — 2 results were positive [32, 35], 5 were negative [29, 33–34, 37]; the authors of 2 clinical descriptions noted that CSF analysis was not available at their institution [31, 31]. Most of the patients were treated with broad-spectrum antibiotics and antivirals, with the described paired case recovering spontaneously within 4 days [37]. The most interesting clinical case we considered was the first confirmed case of COVID-19-associated viral encephalitis in Japan [35]. A 24-year-old man got to the hospital with a fever followed by an epileptic seizure and loss of consciousness. In the neurological status, neck stiffness was revealed; The patient underwent CT scan, which did not reveal any pathology. CT scan revealed pneumonia. The PCR analysis of the nasopharyngeal swab was negative, but the PCR result of the cerebrospinal fluid was positive for COVID-19. The patient underwent MRI brain — diffusion-weighted images (DWI) showed signal hyperintensity along the wall of the right lateral ventricle; FLAIR mode revealed signal hyperintensity in the right middle temporal lobe and hippocampus. The authors concluded that imaging findings are indicative of right lateral ventriculitis and encephalitis associated with COVID-19 [35].

Acute myelitis. Kang Zhao et al. in their publication reported acute myelitis in a 66-year-old man from Wuhan, who at the time of admission to the hospital had fever and body pain [38], and also developed acute flaccid lower paraparesis with impaired sensitivity from the Th10 level and fecal incontinence and urine. CT scan of the chest confirmed SARS, the PCR result of the secret from the nasopharynx was positive for COVID-19. The patient received empirical therapy with IVIG, glucocorticosteroids, and antiviral therapy. During treatment, neurological symptoms partially regressed, and the patient was referred for further rehabilitation.According to the authors, acute myelitis was caused by a cytokine storm and a hyperactive inflammatory response, as evidenced by high levels of serum ferritin, C-reactive protein, and interleukin-6. The disadvantages of diagnostics in this case were the inability to perform PCR of cerebrospinal fluid for coronavirus and MRI of the spinal cord due to the epidemic in Wuhan.

Anosmia and chemosensory dysfunction. Scientists from the United States, using the methodology of Internet research using surveys, established the fact of chemosensory dysfunction (impaired sense of smell) in 59 COVID-19-positive and 203 COVID-19-negative patients [39]. They showed that the percentage of loss of taste and smell was higher in the COVID-19 positive group compared to the negative group (anosmia/smell impairment: 68 vs 16 %, loss of taste: 71 vs 17 %). It is indicated that the majority of patients in this study were outpatients and did not require hospitalization. The authors suggested that it is likely that SARS-CoV-2 spreads transnasally in outpatients, in contrast to critically ill patients, in whom the spread of the virus is most likely pulmonary [39]. Bagheri et al. (Iran) reported the results of a large study including 10,069 patients using an online questionnaire [40]. All participants in the study had complaints of decreased sense of smell recently within the last 4 weeks after the start of the COVID-19 outbreak in Iran. Anosmia and hyposmia were reported by 48.23 % of respondents, and 83.38% of respondents also com-

plained of a decrease in taste sensations. In 76.24 % of cases, the onset of anosmia and hyposmia was acute. The interviewed patients also named other clinical symptoms that preceded the violation of smell: cold symptoms (75.5 %), headaches (48.6 %), nasal congestion (43.7 %) and fever (37.3 %).

Guillain-Barré syndrome. We reviewed 8 clinical descriptions of GBS occurring during or after COVID-19 [41-48]. These observations describe 13 patients (10 males, 3 females, mean age 58.9 years), 11 of them were positive for SARS-CoV-2 by PCR of nasopharyngeal secretions. In 11 cases, the clinical picture was presented by progressive flaccid tetraparesis, of which 5 developed bilateral weakness of facial muscles, and 7 patients required tracheal intubation. Another 2 cases were represented by the classic variant of the Miller Fisher syndrome [48]. Lumbar puncture was performed in 11 patients; cytosis was normal or slightly elevated (up to 9/μl in 5 cases), protein was normal in 3 cases, and >45 mg/dl in the remaining 8 cases (range 48–193 mg/dl). It is noteworthy that 8 patients underwent CSF PCR for SARS-CoV-2, and the result was negative. Electroneuromyography (ENMG) was performed in 10 patients: demyelinating changes were detected in 6 cases, and axonal GBS was detected in 4 cases. Testing for antiganglioside antibodies was performed in only 4 cases; three of these were negative, while a patient with Miller Fisher syndrome was anti-GD1b positive but anti-GQ1b negative [48]. To demonstrate the clinical picture of GBS as a complication of COVID-19, we present a description of 2 clinical cases from the above. Iranian colleagues describe a 61-year-old man with a long history of type II diabetes [45]. In the anamnesis of the disease - cough, fever and episodic dyspnea; 2 weeks after the appearance of these complaints, the patient developed acute tetraparesis and bilateral weakness of the facial muscles. The patient underwent ENMG, the results of which determined acute motor-sensory axonal neuropathy. IVIG was treated with subsequent good recovery. The authors suggested that GBS be considered a neurological complication of COVID-19, since the main route of infection with coronavirus infection is airborne, and most patients with GBS describe a respiratory infection before the development of the disease. The induction of SARS-CoV-2 antibodies to specific gangliosideshas been proposed as a mechanism for the development of this complication. The second patient is described by Virani et al. (USA) [43] — a 54-year-old man with a history of diarrhea that preceded an acute attack of muscle weakness. In the clinical picture at the time of admission: rapidly progressive ascending paralysis, leading to difficulty breathing; areflexia. The test result for COVID-19 was positive. MRI of the spinal cord revealed no pathology. She was treated with IVIG and antimalarial drugs. The patient responded well to treatment and was discharged for treatment at a rehabilitation center.

Skeletal muscle damage. Mao et al. (China) in their publication reported damage to skeletal muscles in 23 patients with COVID-19 [13]. The diagnosis was made in patients with myalgia and elevated serum creatine kinase (> 200 U/L). The authors suggested that a possible mechanism for the development of this syndrome was an infection-mediated immune response, which caused an increase in the content of pro-inflammatory cytokines in the serum, which led to massive damage to skeletal muscles. However, specific diagnostic procedures such as ENMG or histological characterization of muscle biopsies were not performed, so it is not possible to say whether these patients had critically ill myopathy or neuropathy in addition to skeletal muscle damage.

Conclusion:

Thus, three main groups of neurological complications associated with COVID-19 can be distinguished into the symptoms from the central and peripheral nervous system and damage to skeletal muscles. At the same time, it is quite difficult to establish a causal relationship between coronavirus infection and the complication that has arisen, however, in most of the examples considered, one can talk about one or another complication as a consequence of COVID-19. It can be said confidently that the clinical picture of neurological diseases and syndromes caused by coronavirus infection corresponds to our usual ideas, in contrast to the results of neuroimaging and laboratory methods of additional examination. Of course, additional studies on large groups of patients are needed to finally understand the mechanisms of complications, the degree of their connection with COVID-19 and the development of schemes for their treatment and subsequent rehabilitation. There is also evidence that HCoVOC43 RNA (a type of human coronavirus) is found in the CNS of infected mice that have had acute viral encephalitis for at least a year. Consequently, we can conclude that after the cure of COVID-19, virion fragments can be preserved in the patient's GM

(an analogy with the herpes simplex virus) [49]. If SARS-CoV-2 is indeed able to persist as inactive fragments for a long time, the disease could recur in susceptible individuals when the right conditions arise. This assumption raises concerns regarding long-term neurological complications in infected and cured patients.

The authors declare no conflict of interest.

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