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Headache and other Neurological Symptoms in the Structure of the New Clinical Picture Corona Virus Infection (Covid-19)

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ABSTRACT

The literature review provides information on the neurological manifestations of COVID-19. One of the initial neurological manifestations of a new coronavirus infection is a headache. It can be caused by developing meningitis or encephalitis, or it can be a manifestation of a systemic viral infection. The mechanisms of headache occurrence are related to the peculiarities of virus penetration into human body cells through interaction with the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 functions are closely related to nociception regulation. In addition to headache, patients with SARS-CoV-2 have severe weakness, myalgia, impaired sense of smell and taste, and may develop inflammatory demyelinating polyneuropathy. Taking into account the peculiarities of the occurrence of neurological manifestations in SARS-CoV-2, the role of N-acetylaspartate in restoring the functions of the nervous system after a viral infection is of interest.

KEYWORDS: COVID-19, nervous system, headache, syndrome Guillain–Barre, Kawasaki syndrome, N-Acetylaspartate.

Coronavirus infection COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020. A comprehensive review of the neurological disorders that accompany this disease found that SARS-CoV-2 infection affects the central nervous system(CNS), peripheral nervous system, and muscles [1]. The first manifestations of COVID-19 from the central nervous system usually include headache and decreased overall activity (weakness), which are considered initial evidence of potential neurological damage; anosmia, hyposmia, hypogeusia and dysgeusia are also common early symptoms of a new coronavirus infection. Cephalgia in coronavirus infection is the most common brain-wide symptom, and its etiology is variable. You can select the following options cephalgia in the context of the pandemic COVID-19: 1) cephalgia, caused by wearing of the means of virus protection, as due to physical discomfort, and the background of hypoxia during prolonged wearing of masks and respirators; 2) cephalgia, due to taking of drugs, and iatrogenic cephalgia; 3) cephalgia on the background astenodepressivnyh as forced restrictions and isolation, and also due to the anxiety-phobic disorders; 4) cephalgia, due to the direct impact of the virus SARS-CoV-2. According to the meta-analysis In 60 publications involving more than 3,500 patients, headache in COVID-19 was observed in 12% of cases (95% confidence interval 4-23%) [2]. In some publications of Chinese authors, the prevalence of headaches in patients with COVID-19 reached 34% [3]. However, in most studies, data on the nature and location of headache are not available. Of interest is a study that noted that in patients with COVID-19 with gastrointestinal manifestations, the frequency of headaches at the onset of the disease was higher than in patients without gastrointestinal disorders. The authors explain this feature by a higher level of fever and more pronounced electrolyte disturbances in patients with

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gastrointestinal manifestations [4]. In another study conducted in the Netherlands, in order to detect early symptoms of coronavirus infection, 803 employees of a medical clinic who experienced symptoms possibly caused by COVID-19 were interviewed, followed by laboratory tests to detect infection. 90 employees were diagnosed with coronavirus infection. In the infected group, along with symptoms such as anosmia, myalgia, eye pain, general malaise, severe fatigue and fever, one of the earliest symptoms was also headache, which was observed in 71.1% of patients, while in the group with an unconfirmed diagnosis, headache occurred in 41.5% of patients [5]. Headache in COVID-19 can be a manifestation of viral meningitis or encephalitis. According to the International Classification of Headaches of the 3rd revision (ICGB-3), headache associated with viral meningitis or encephalitis is usually accompanied by stiffness of the muscles of the back of the neck, fever and can be combined, depending on the severity of the infection, with neurological symptoms and changes in mental state [6]. According to this classification, the occurrence of headache associated with viral meningitis or encephalitis can be caused by various viral agents, which is usually confirmed by the study of cerebrospinal fluid (CSF) by polymerase chain reaction (PCR): enteroviruses (in most cases), arbovirus, poliovirus, echovirus, virus are detected Coxsackievirus, herpes simplex virus, chickenpox virus, adenovirus, mumps virus, etc. However, a number of studies have found that the sensitivity of PCR in CSF is reduced by more than half if the test is performed 1 week after the onset of symptoms, and false negative results can be obtained. If the results of PCR performed after 1 weekare negative, the diagnosis can be made based on the changed ratio of the number of antibodies in the CSF/blood. As with intracranial bacterial infection, viral infection is difficult to distinguish between involvement of the meninges exclusively and isolated involvement of brain matter. Nevertheless, it is important to make such a distinction, since these two conditions differ prognostically, with an increased risk of more serious consequences if the substance is affected ва the brain. For this reason, separate diagnostic criteria are given for headache classified as viral meningitis and for headache classified as viral encephalitis [6]. To date, the literature contains separate publications describing the clinical picture of encephalitis and meningitis in patients with COVID-19, and in most cases this type of course of viral infection is accompanied by pronounced cerebral, meningeal and focal symptoms, specific changes are detected according to magnetic resonance imaging [7]. It is possible to confirm the diagnosis of aseptic (viral) meningitis and encephalitis caused by SARS-CoV-2 in patients with COVID-19 by CSF testing, but often it does not give positive results [8]. Acute necrotizing encephalopathy is also described in the literature, which is a rare complication of influenza and other viral infections, but apparently a more frequent complication of COVID-19 [1]. Acute encephalopathy in viral infection can develop not directly due to viral invasion, but due to indirect brain damage during an inflammatory immune response. This is due to a sharp increase in the blood content of a number of pro-inflammatory cytokines hyper cytokinemia, or cytokine storm). Hyper cytokinemia triggers uncontrolled inflammation that leads to tissue damage, including the central nervous system, the destruction of the blood-brain barrier without direct viral invasion or para-infectious demyelination. Most authors are inclined to believe that headache in COVID-19 can also be a manifestation of a systemic viral infection. Usually, headache in systemic infections is a non-specific symptom, since fever, general malaise, etc. mainly prevail. However, some infections, especially the flu, as well as coronavirus infection, are characterized by headache as a significant symptom along with fever and other manifestations of the disease. Definition of this type of headache according to

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ICGB-3: headache caused and occurring in combination with other symptoms and/or clinical signs of systemic viral infection in the absence of meningitis or encephalitis. Diagnostic criteria for headache associated with a systemic viral infection are given below. A. Headache of any duration that meets the criterion of S. B. Both criteria are listed below: 1) a systemic viral infection has been diagnosed; 2) There are no signs of meningitis or encephalitis. c. A causal relationship confirmed by at least two of the following facts: 1) the headache developed in временна temporaryой connection with the onset of systemic viral infection; 2) the headache significantly increased simultaneously with the exacerbation of systemic viral infection; 3) the headache significantly decreased or disappeared simultaneously with the improvement of the condition or resolution of systemic viral infection; 4) the headache has one or both of the following characteristics: a) diffuse character; b) moderate or strong intensity.

The headache could not be better explained by another ICGB-3 diagnosis. In an infectious disease, headache usually co-exists with fever and may depend on it, but cephalgia can also occur in the absence of an increase in body temperature or precede its increase. Such variability of clinical symptoms in systemic infection may indicate that various mechanisms are involved in the occurrence of headache, and not just an increase in body temperature due to exogenous and endogenous pyrogens. The mechanisms that cause headache include both the direct effect of the pathogen on cellular structures and the triggering of pathological processes caused by the release of immune in flammatory mediators [6]. Most publications do not provide detailed descriptions of the characteristics of headache in COVID-19. Single articles are the following features cephalgia an infection caused by SARS-CoV-2: headaches appear suddenly or gradually grew, was bilateral, and had a moderate or high intensity, could be throbbing or pressing was reinforced when the head tilts, localized predominantly in the temporal-parietal or frontal regions and in the periorbital region and the projection of the paranasal sinuses. Many patients reported pain resistance to conventional analgesics or a high frequency of headache relapses during the active phase of COVID-19. In some patients, the high intensity of headache against the background of other symptoms of infection served as a reason for contacting a doctor and could cause suicidal thoughts. Most of these patients did not have a history of migraines or tension headaches or other neurological disorders. Patients who suffered from migraines prior to the development of COVID-19 described a different, different type of headache from migraines with an infectious lesion, but justas with migraines, they noted the presence of pronounced symptoms of phonophobia and photophobia [9]. The literature presents several possible factors that influence the occurrence of headache in COVID-19 and are associated with direct exposure to SARS-CoV-2. Before proceeding with their consideration, it is necessary to understand how the virus enters the human body and what it leads to. It has been established that the virus enters human cells using the transmembrane metalloproteinase receptor-angiotensin-converting enzyme 2. The ACE2 protein is expressed in most tissues, but mainly on the membranes of type II, small intestinal enterocytes, arterial and venous endothelial cells, and smooth muscle cells of various organs. In addition, matrix RNA for ACE2 was found in cells of the cerebral cortex, striatum, hypothalamus, and brainstem [10]. Thus, the presence of the ACE2 receptor on brain neurons and glia makes these cells susceptible to infection with the SARS-CoV-2 virus. The angiotensin-converting enzyme (ACE) itself is an extracellular circulating enzyme that catalyzes the cleavage of angiotensin I decapeptide to angiotensin II octapeptide (Ang II). Both forms of angiotensin play a crucial role in the renin-angiotensin system, which regulates

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blood pressure. And Ang II is involved in the pathogenesis of a number of cardiovascular diseases, vasoconstriction, inflammatory reactions and oxidative stress through exposure to the angiotensin receptor (AT1R). A special form of the enzyme, ACE2, is a membrane protein, an exopeptidase thatcatalyzes the conversion of Ang I in Ang-(1-9) and Ang II in Ang-(1-7). The heptapeptide Ang- (1-7) counteracts the ACE/Ang II/AT1 (AT1R) receptor axis and has opposite Ang II functions, including cardiovascular protection, vasodilation, antioxidant stress, tissue protection, and antinociception. Thus, ACE2 not only stops the action of Ang II, but also generates a peptide that has the opposite effect on the Ang II/AT1R axis. Binding of SARS-CoV-2 to the ACE2 receptor reduces its functional capabilities, leads to an imbalance in the regulation of Ang II/AT1R, and the development of acute respiratory distress syndrome, pulmonary edema, and myocarditis [11]. Thus, the first factor leading to головныхheadaches in COVID-19 may be the direct introduction of the virus into the endings of the trigeminal nerve in the nasal cavity and their direct damage. Although the presence of transmembrane ACE2 as a necessary component for virus binding in the peripheral endings of the trigeminal nerve has not yet been proven, ACE2 expression has been detected in other cranial nerves associated with smell and taste [12,20]. The mechanism of viral penetration into these structures determines direct damage to neurons and the occurrence of symptoms such as anosmia and dysgeusia, even in the early phase of the infectious process in COVID-19 [13]. As already mentioned, ACE is closely related to the nociceptive system through the chemical reactions in which it participa. For example, dysregulation of the ACE2/Ang-(1-7)/MasR (mitochondrial assembly receptor) axis has been found to be involved in the pathogenesis of diseases such as stroke, Alzheimer's disease, and Parkinson's disease, as well as in the occurrence of pain [14, 15]. The production of Ang II locally in rat and human spinal ganglia neurons and its co-localization with substance P and CGRP (calcitonin-gene-bound peptide) may indicate the involvement of Ang II in the regulation of nociception [16]. The presence of the angiotensin system in the trigeminal ganglia of humans and rats further supports this theory [17]. In addition, Ang II has been shown to increase the level of CGRP circulating in the blood, which is a key neuropeptide in migraine that provokes headaches, and its antagonists are effective in treating migraines [18]. The next mechanism leading to headache may be vascular factor-through the involvement of endothelial cells with high expression of ACE2, which play an important role in the activation of the trigemino vascular system. It is known that ACE2 is expressed in large quantities on respiratory epithelial cells, as well as on epithelial cells of the gastrointestinal tract, endothelial cells and heart tissues. It was found that the SARS-CoV-2 virus is detected in endothelial cells along with the detection of diffuse endothelial inflammation [19]. In addition, the role of the vascular factor is a tendency to increased thrombosis detected in patients with COVID-19, especially in severe cases of the disease and multiple organ failure. insufficiency [20]. It is known that viral infections can contribute to endothelial cell dysfunction, which leads to excessive accumulation of thrombin and disruption of fibrinolysis processes [2]. Hypercoagulation in patients with COVID-19 is one of the leading factors in the development of cerebral circulatory disorders in both the arterial and venous bed [20]. Violations of blood supply at the level of the microcirculatory bed (microthrombosis) can also lead to damage and irritation of sensitive nerve endings and the appearance of pain. Unbalanced vasoconstriction, oxidative stress, and free radical formation due to the virus ' effect on transmembrane ACE2 functions can trigger the development of vasculopathy. Inflammation leads to irritation of the perivascular fibers of the trigeminal nerve located both

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outside the cranial cavity (in the nasal and oral cavities, paranasal sinuses, surface vessels of the head) and inside the cranial cavity (vessels of the dura mater). There is no clear evidence yet for vasculo pathycaused by SARS-CoV-2, but a similar pattern of headache occurs in diseases such as giant cell arteritis (GCA). The causes of HCA are still not fully understood, but the viral etiology of the disease is assumed, for example, the role of influenza, chickenpox, and hepatitis viruses. There is also a hereditary (genetic) predisposition (family cases of the disease are described): The role of certain polymorphisms of the HLA (human leukocyte antigen system) B14, B8, and A10 genes involved in the functioning of the endothelium, innate immune system, cytokines, and cytokine receptors has been established [10]. Another factor that determines the development of headache is the following: exposure to the SARS-CoV-2 virus leads to the release of pro-inflammatory mediators and cytokines, which trigger irritation of the perivascular nerve endings of the trigeminal nerve. It is well known that various inflammatory mediators, such as interleukin-1b (IL-1b), NF-kb (nuclear factor kb), PGE2 (prostaglandin E2) and NO (nitric oxide), play an important role in the activation trigemino vascular system and increase the sensitivity of nociceptive receptors to the mediators of pain, which are histamine and bradykinin [7, 8]. Recently, it was found that patients with a more severe course of COVID-19 and patients treated in the intensive care unit had higher levels of various inflammatory factors and mediators (IL-2, IL-7, IL-10, GCSF (granulocyte colony-stimulating factor factor), IP-10 (interferon-gamma-induced protein 10), MCP1 (monocyte chemotactic protein 1), MIP1A (macrophage inflammatory protein 1a), and TNF-a (tumor necrosis factor a)) in blood plasma than in patients with a milder course of the disease [9]. In turn, in a study conducted among patients with COVID-19 in Wuhan, it was noted that patients with severe disease were more likely to complain of intense headache (17%) than patients with a milder course of it (10%) [13]. Thus, it can be assumed that the severity of inflammation and hypoxia, which correlates with the severity of the disease, also plays an important role in the intensity of headache. There is a possibility that COVID-19 as a trigger for headaches can cause the occurrence of a chronic pain disorder, such as a daily persistent headache. Therefore, careful monitoring of patients who have had COVID-19 is important. A relatively common neurological symptom of SARS-CoV-2 infection is also increased fatigue and weakness. Thus, according to observations of Chinese doctors in Wuhan, complaints of general weakness were presented by 26 to 51% of patients with COVID-19, and complaints of myalgia-36% [19]. Many patients who have had the disease in severe and moderate form, even after full recovery, continue to complain of increased fatigue and reduced overall physical endurance, symptoms of vegetative disorders. Such symptoms can be considered as manifestations of fatigue syndrome after a viral disease or benign myalgic encephalomyelitis (chronic fatigue syndrome). By definition, benign myalgic encephalomyelitis is a long-term debilitating disease characterized by.

This condition is characterized by severe and disabling fatigue (which does not have an adequate clinical explanation), which persists for at least 6 months and is not relieved by rest, accompanied by malaise after physical exertion and sleep disorders [10]. This condition is assumed to be a complex, polysystemic neuroimmune disease [1]. It seems that long-term follow-up follow-ups of patients who have had COVID-19 are required, which would allow such a diagnosis to be accurately established. It should be noted that severe fatigue, along with a decrease in muscle strength, can also be a symptom of another neurological complication of a new coronavirus infection-the syndrome Guillain–Barre [2, 3]. In addition, the literature describes the development of Miller Fischer syndrome in patients with COVID-

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19 [4, 5]. Syndromes Guillain–Barre and Miller Fischer are variants of inflammatory demyelinating polyneuro pathyassociated with damage and / or progressive degeneration of nerve fibers. Demyelinating polyneuropathy is believed to be based on an autoimmune process that occurs as a result of a previous infection or as a result of the use of an anti-influenza vaccine. The most common infectious agents associated with Miller Fischer syndrome are Staphylococcus aureus, human immunodeficiency virus, Campylobacter jejuni, Haemophilus influenzae, and Epstein-barr virus–Barr, varicella varicella zoster virus, Coxiella burnetii, Streptococcus pyogenes, Mycoplasma pneumoniae [6, 7]. Thus, SARS-CoV-2 has a tropism to the nervous tissue and, like other types of coronavirus, can trigger autoimmune demyelinating processes, as well as cause the development of other disorders of the central nervous system. The main feature of the course of COVID-19 in children older than 1 year is its easier course in comparison with adults. According to a published review of the literature on COVID-19 in children and including 280 cases, the main symptoms were cough (49%), fever (47%), sore throat (36%), vomiting/diarrhea (17%), rhinorrhea (9%). Pneumonia was detected in 60% of patients, but in most cases it was mild. Only 4% of patients required hospitalization in the intensive care unit. The authors suggest that this course of infection is associated with a number of possible reasons: ACE2 receptors in children differ from those in adults (e.g., low binding capacity due to their immaturity); children are often exposed to other respiratory viruses such as respiratory syncytial virus, influenza viruses A and b, which increase the level of antibodies in the serum and can provide cross protection; regenerative ability of the lungs in children is higher than in adults; in children less likely to develop cytokine storm. Due to mild symptoms or an asymptomatic course, COVID-19 infection in children may not be diagnosed at all [8]. In other publications, the authors note the predominance of gastrointestinal symptoms in children (vomiting, diarrhea, bloating) or symptoms associated with upper respiratory tract damage (nasal congestion, less often sore throat, rhinorrhea and cough), in combination with a slight increase in body temperature or without it [9]. When analyzing symptoms in 291 children with a confirmed diagnosis of COVID-19, the following signs of nervous system involvement were identified: headache – in 28% of cases, myalgia – in 23%, nausea and vomiting – in 11% [4]. In another study conducted among 133 children and young adults (mean age 9.6 years) infected with COVID-19 but who did not have indications for hospitalization, headache was detected in 18% of patients, myalgia – in 16%, loss/deterioration of taste and/or smell – in 10% [12]. It should be noted that younger children are less likely to indicate the occurrence of anosmia or dysgeusia as a symptom of the disease, perhaps not being able to explain their feelings. In addition to these symptoms, children experience increased fatigue (weakness) and dizziness [20]. At the early stages of monitoring the manifestations of COVID-19, it was indicated that the new coronavirus affects mainly the elderly and elderly, much less often young adults, and only casuistic cases were observed in children. However, against the background of the spread of the pandemic, there were an increasing number of pediatric cases, including severe and fatal outcomes. The most severe manifestation of COVID-19 in children is multisystem inflammatory syndrome, which also includes clinical signs of Kawasaki disease and toxic shock syndrome [14]. Clinical signs include fever for ≥24 hours, severe multisystem inflammatory response with elevated levels of inflammatory markers. Children may develop multiple organ failure affecting the gastrointestinal tract, cardiovascular system, central nervous system, kidneys, and other organs and systems, in addition to severe lung damage. In some children, a severe

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inflammatory reaction in combination with cytopenia, coagulopathy, and hyper ferritinemia is similar to macrophage activation syndrome or toxic shock. Other patients have mucocutaneous symptoms that are characteristic of Kawasaki syndrome. In some cases, dilatation of the coronary artery and even the formation of giant coronary aneurysms may develop [5]. Kawasaki syndrome was first identified by a Japanese doctor Tomisaku Kawasaki in 1961, a boy aged 4 years and 3 months was hospitalized with an unusual combination of symptoms: fever, hemorrhagic rash and peeling on the skin, inflamed eyes, swollen lymph nodes on the neck and a bright red ("strawberry") tongue. A clinical case was described in a Japanese journal in 1967, and an English-language publication was published in 1974 [9]. Kawasaki syndrome is a systemic necrotizing vasculitis. The main symptoms are fever of 38-40°C, bright red hemorrhagic rash on the hands and feet, conjunctivitis, bright crimson tongue with hemorrhagic rashes, cracked and red lips and oral mucosa, ulcerative gingivitis, enlarged lymph nodes. Complications include damage to the cardiovascular system (up to a heart attack), lungs (pneumonitis, pleurisy), gastrointestinal tract (ulcerative-necrotic enterocolitis with diarrhea, cholecystitis, pancreatitis), urinary system (nephritis, urethritis) and nervous system (aseptic meningitis, increased neuro-reflex excitability). Kawasaki syndrome affects mainly children from 1.5 to 5 years of age, and boys are more likely to get sick than girls. Kawasaki syndrome was considered a rare, almost casuistic disease in children until the Italian province of From February 18 to April 20, 2020, 10 children with signs of this syndrome were not taken to the hospital, while 8 out of 10 tested positive for coronavirus. Subsequently, Italian doctors found a 30-fold increase in the number of patients with Kawasaki syndrome against the background of the COVID-19 pandemic [6]. Cases of Kawasaki syndrome in COVID-19 have been reported in the United Kingdom, Spain, Switzerland, France, and India [4]. It should be noted that children with various chronic diseases, including diseases of the nervous system (cerebral palsy, epilepsy, consequences of traumatic brain and spinal injuries), had a more severe course of COVID-19 infection. Physiological mechanisms of restoration of damaged functions underlie such a phenomenon as neuroplasticity, when the nervous system after suffering damage is able to adapt to the conditions that have arisen and restore its functional viability as much as possible. The recovery process is genetically determined, involving a large number of biochemical substrates that regulate the optimal interaction of all cellular structures of the nervous tissue, as well as optimize the metabolic processes necessary for full recovery. One of these biochemical substrates is (NAA), which is a derivative of aspartic acid, which is synthesized in the mitochondria of neurons from aspartate and acetyl coenzyme A (acetyl-CoA) using aspartate-N-acetyltransferase. N-acetylaspartate is also a precursor.

The main neurotransmitter is N –acetylaspartyl glutamate [15]. In terms of brain concentration, NAA is on the 2nd place, second only to glutamate. In the central nervous system, NAA is localized in neurons, occurs in the optic nerves, and is most concentrated in the gray matter of the brain, and its intracellular concentration is higher than extracellular. It was found that it is one of the main regulators of osmotic processes in the brain. N-acetylaspartate is considered as a signaling molecule in the neuron-glia interaction system. It is believed that NAA is synthesized in neurons, and the enzyme that cleaves it is found only in oligodendrocytes. Therefore, the release of NAA signals oligodendrocytes to release aspartoacylase II. It should be noted that acetate and aspartateformed during the NAA degradation reaction are not used in its resynthesis, which may be the basis for the inability to quickly compensate for NAA deficiency in the case of pathological conditions. N-

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cetylaspartate is involved in the synthesis of brain lipids, can serve as a source of aspartate, acyl groups in the synthesis of myelin. It passes from neurons to oligodendrocytes as a key metabolite for myelin synthesis [16]. The appearance of the ability to determine the NAA concentration by magnetic resonance spectroscopy (MRS) has significantly increased the interest of researchers in NAA as a marker of CNS damage [17]. Subsequent studies led to the discovery of a link between NAA catabolism and myelin lipid metabolism, as well as to the establishment of a reversible decrease in NAA levels in the brain in various CNS injuries (hypoxia, multiple sclerosis, etc.). A decrease in the level of NAA in brain tissues indicates damage to the nervous tissue or a violation of the function of neurons [18]. It was found that in the case of ischemic stroke, there is a clear decrease in the NAA concentration in the area of damage, with a slow gradual recovery in the case of a small amount of changes [19]. A correlation was determined between the degree of NAA reduction in the frontal lobe cortex and the severity of cognitive disorders in patients with multiple sclerosis [10]. In Alzheimer's disease, a direct correlation was found between a decrease in hippocampal volume and a decrease in NAA content, which increased the reliability of diagnosis to 90% [11]. Several studies using MRI in individuals with traumatic brain injury have demonstrated a decrease in the level of NAA in the area of injury, as well as its normalization with clinical improvement [12]. Interesting data were obtained in another study, which noted that lower NAA concentrations in brain regions involved in pain perception and modulation correlate with greater severity of neuropathic pain symptoms in patients who have suffered a traumatic brain injury [21].

In case of metabolic stress, acetyl-CoA can lead to a decrease in NAA synthesis and an increase in NAA hydrolysis to produce acetate for myelin repair [14]. If the initial injury is not too severe or is not compounded by further metabolic stress, such as hypoxia or hypoperfusion, mitochondrial function and NAA levels can recover within a few weeks or months, while maintaining a population of neurons. If the injury is more severe, then there is a possibility of irreversible physical and metabolic damage to neurons, which leads to a significant decrease in the neuron population and, consequently, to the lack of NAA recovery according to MRC data [5]. These data prove the important role of NAA in restoring CNS functions after disorders of various origins. Of great interest is the study of NAA in infectious lesions of the central nervous system, including new coronavirus infection. In the Russian literature, there are publications on the use of potassium N-acety laminosuccinate (the drug Cogitum) in patients with asthenoneurotic disorders who have suffered bacterial meningitis or concussion of the brain. 24 patients were examined: Group 1 included 14 patients with bacterial meningitis (mean age 9.9 ± 1.7 years), group 2-10 patients with concussion (mean age 10.4 ± 2.4 years). All patients received potassium N-acetylaminosuccinate for 8weeks (Cogitum) 500 mg/day. Group 1 was dominated by complaints of diffuse headache, decreased mood, and tearfulness. The headache was worse with mental and / or physical exertion. Among other complaints, increased fatigue (64.2%), decreased ability to concentrate and remember (64.2%), emotional lability (57.1%), attention instability (57.1%), sleep disorders (35.7%), and a combination of them were more often noted. Group 2 patients had memory impairment (70%), attention instability (60%), increased fatigue (60%), headache (40%), irritability (30%). Positive results of potassium N-acetylaminosuccinate application (Cogitum) were noted by the end of week 6 in most patients and consisted in improving the ability to memorize educational material, increasing concentration, improving short-and long-term memory, and improving school performance in general. Usually,

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recovery dynamics in such categories of patients without the inclusion of the drug is longer and takes up to 4-6 months. In the patients observed in the study, there was a significant increase in the accuracy and speed of performing the Bourdon test ($p < 0.01$), an improvement in memorization of the testLuria (r Only 2 patients of the 1st group and 1 patient of the 2nd group did not achieve a pronounced clinical effect on the background of a long course of therapy. Among the side effects, a small number of patients showed increased irritability, emotional lability, and complaints of difficulty falling asleep [6]. A review article by A.V. Goryunova etal. describes the positive experience of using potassium N-acetyl aminosuccinate носукцината(Cogitum) in children with the consequences of traumatic brain injury, delayed speech development, hyperkinetic disorder and in the complex therapy of schizotypal disorders. Its effect on cognitive deficits and asthenia was evaluated. The neurotrophic effect of potassium N-acetylaminosuccinate was noted (Cogitum), which specifically affects cognitive and asthenic disorders in these diseases [7]. Considering the positive therapeutic effect of potassium N-acetylaminosuccinate (Cogitum) in asthenic disorders caused by previous neuroinfections, as well as the role of NAA as a metabolite for myelin synthesis in restoring interneuronal interaction, it seems appropriate to continue the study of the clinical effectiveness of potassium N-acetylaminosuccinate (Cogitum) in patients who have had SARS-CoV-2, as a drug that enhances recovery processes in the nervous system and has a positive effect on cognitive functions. In conclusion, it should be noted that the neurological manifestations of the new coronavirus infection are not fully understood and require careful analysis. It is not known whether they will be of a short-term nature or may transform into chronic diseases. It is also not clear how quickly it is possible to restore the damaged brain substance, what consequences the human immune system may have after a new viral infection. It is necessary to carry out dynamic monitoring of recovered patients and take into account information about the previous COVID-19 infection when interviewing patients with neurological pathology.

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