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COVID-19 AND THE NERVOUS SYSTEM: PATHOGENESIS, MECHANISMS, AND OUTCOMES

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In the acute period of COVID-19, more than 1/3 patients develop neurological symptoms, 25% of which can be attributed to direct damage to the central nervous system. Most often, all these complications arise due to the penetration of the virus into the systemic circulation, its dissemination and damage to the vascular endothelium. All clinical manifestations associated with the penetration of COVID-19 into the nervous tissue can be divided into several groups:1) signs of damage to the central nervous system, including headache, impaired consciousness, encephalitis, cerebrovascular diseases, seizures and ataxia; 2) signs of damage to the peripheral nervous system, such as anosmia/hyposmia, dysgeusia, visual disturbances, neuralgia and Guillain-Barre syndrome; and 3) signs of damage to the musculoskeletal system, such as myopathy, myalgia and fatigue.

The aim of the review was to identify the main sources and mechanisms of nerve tissue damage in COVID-19 disease.

Literature search was conducted in the Web of Science, PubMed and Scopus databases. The search was carried out by the following keywords: «COVID-19», «nerve tissue», «endothelial dysfunction», «oxidative stress», «neuroinflammation». The literature search yielded 329 results, of which 234 articles.

As a result of the analysis of the articles, 2 main groups of studies were identified: descriptive and experimental. The pathogenesis of damage to the nervous system by the COVID-19 virus has two sources: by infecting nerve endings, such as olfactory sensory neurons, and retrograde penetration of the virus into the brain.

Key words: COVID-19; nerve tissue; endothelial dysfunction; oxidative stress; neuroinflammation

2019 witnessed the emergence of a new Serious Acute Respiratory Syndrome Virus (SARS), which causes the incidence of pneumonia in Wuhan. Pneumonia was noticeable because it did not respond to the standard treatment regimen [6]. The clinical symptoms of SARS are fever, dry cough, sore throat, pneumonia, severe shortness of breath (shortness of breath) and myalgia [1]. This symptom complex is caused by the SARS-CoV-2 virus and contributes to hypoxia, which can affect the brain and other organ systems. The World Health Organization has named this disease coronavirus - disease of 2019 (COVID-19). The SARS-CoV-2 virus shares genome-level sequence homology with other pathogenic β-coronaviruses, such as SARS-CoV, Middle East Respiratory Syndrome coronavirus (MERS-CoV) and human coronavirus OC43 (HCoV-OC43).

The virus enters human cells through a pathway controlled by the angiotensin converting enzyme receptor 2 (ACE2), primarily affecting the human respiratory tract [3, 32]. The main function of ACE 2 is to convert angiotensin II (Ang II) to Ang1-7. This peptide potentially has a vasodilating effect and suppresses the activity of the renin-angiotensin system. ACE2 also promotes SARS-CoV-2 endocytosis by binding to S-protein. Also, there is an evidence that ACE 2 has a dual role: as a pathway of virus penetration, and a means of protection against oxidative stress in case of lung damage. In contrast to ACE-2, ACE is responsible for the formation of angiotensin II by cleavage of angiotensin I, which subsequently binds to the angiotensin type 1 receptor and changes vascular tone, blood pressure, circulating fluid volume and electrolyte homeostasis.

So, SARS-CoV-2, binding to the ACE2 receptor, not only penetrates into cells, but can also reduce ACE2 activity, which is accompanied by an increase in ACE activity and may play an important role in the pathogenesis of the disease [2]. The expression of ACE2 is higher in the small intestine, heart, testicles, kidneys and thyroid gland and is average in the lungs, large intestine, bladder, liver, adrenal glands and minimal in bone marrow, spleen, blood and brain. The ACE 2 receptor is not found in microglia,

endothelial cells and pericytes of the human brain and is expressed in a limited amount in the hippocampus.

As for the nervous system of the body, according to M. Heneka and co-authors, in the acute period of COVID-19, more than 1/3 of patients develop neurological symptoms, of which 25% can be attributed to direct damage to the central nervous system. Most often, all these complications arise due to the penetration of the virus into the systemic circulation, its dissemination and damage to the vascular endothelium [14, 19]. All clinical manifestations associated with the penetration of COVID-19 into the nervous tissue can be divided into several groups:1) Signs of damage to the central nervous system, including headache, impaired consciousness, encephalitis, cerebrovascular diseases, seizures and ataxia; 2) signs of damage to the peripheral nervous system, such as anosmia/hyposmia, dysgeusia, visual disturbances, neuralgia and Guillain-Barre syndrome; and 3) signs of damage to the musculoskeletal system, such as myopathy, myalgia and fatigue [34]. As other individual diseases that may manifest these symptoms are encephalitis and encephalopathy, strokes, and rarely encephalitis. A clear example of this is one of the postmortem studies, which showed that six patients in Germany had changes in encephalitis and meningitis with signs of perivascular and inflammatory changes in the brain stem associated with the loss of neurons [33]. Encephalitis, particularly, plays a significant role in SARS-CoV-2-mediated CNS damage, as does encephalomyelitis [25]. Interestingly, several studies have shown that activation of microglia and astrocytes is a key mediator of the neuroinflammatory response induced by SARS-CoV-2 infection. For example, Kanberg and co-authors investigated glial activation in patients with moderate to severe COVID-19 by measuring plasma biomarkers of CNS damage. It was also found that the light chain protein of neurofilaments was significantly elevated in patients with severe infection ($P < 0.001$), whereas glial fibrillar acid protein was elevated in both patients with severe infection and in patients with severe form ($P = 0.001$) and patients with moderate infection ($P = 0.03$). Another case report recorded an increase in the expression of glial fibrillar acidic protein in the white matter of a patient who died from COVID-19 [12].

Another example showing the involvement of microglia in neuroinflammation is an experimental study in mice. In which it was shown that microglia plays a key role in clearing debris and in initiating demyelination after infection with neurotropic coronavirus, but is not necessary at later stages of remyelination. It is a well-known fact that neurotropic coronaviruses, such as the HBV HIV strain, cause acute and chronic demyelinating encephalomyelitis. In this experimental study, it was shown that after infection with the neuroattenuated variant rJ2.2 of the JHMV virus, (referred to here as JHMV), mice develop mild acute encephalitis approximately 5-10 days after infection (DPI), in which 80-90% of mice survive. The surviving mice develop immuno-mediated demyelination and paresis/paralysis of the hind limbs as a result of virus clearance, starting from 7-8 dots per inch and reaching a peak at 12-14 dots per inch. These mice then begin to recover from demyelination and undergo remyelination as the antiviral immune response weakens. It is currently known that microglia are activated after infection with JHMV and play a critical role in the early immune response to the virus; if they are absent during the first on the 3rd day of infection, mice are uniformly susceptible to infection. But the question remains whether microglia plays a pathogenic or protective role in demyelinating encephalomyelitis [24].

Thus, the aim of the review was to identify the main sources and mechanisms of nerve tissue damage in COVID-19 disease.

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As a result of the analysis of the articles, 2 main groups of studies were identified: descriptive and experimental. The articles of the descriptive group discuss clinical signs, features of tissue demyelination, indicators of inflammation in the blood. In the experimental group of articles, data were presented to build a structured model for the study of the neuroinflammatory and demyelinating process.

Mechanisms of cellular homeostasis and plasticity of brain tissue in COVID-19 lesions. All the above studies prove the vulnerability of the nervous system to SARS-CoV-2, and that infection of the brain and peripheral nervous system can lead to dysfunction of other organs, and subsequently to multiple organ failure. The hypothalamus-pituitary-adrenocortical (HPA) axis is very sensitive in patients with COVID-19 to many humoral factors. The main activators of the HPA axis are IL-6, IL-1ß and TNF. This axis plays a key role in regulating the pro-inflammatory response and suppressing the immune response by releasing glucocorticoids. In case of damage to the blood-brain barrier (BBB) in patients with COVID-19, the HPA axis may be activated, which can lead to neutrophilia and

lymphopenia. It is known that reactive microglia and macrophages penetrating into the brain disrupt the mechanisms of cellular homeostasis and plasticity, such as the continued generation of myelin-forming oligodendrocytes, myelin plasticity and the generation of new neurons in the hippocampus. Local cytokine secretion by microglia contributes to at least part of this dysregulation. Elevated circulating cytokine levels/chemokine levels, especially CCL11, may also limit neurogenesis and contribute to cognitive impairment.

All these facts indicate that even patients who have had COVID-19 in a mild form have subsequent manifestations of cognitive deficits. Colloquially known as «COVID-fog», the COVID-related cognitive impairment syndrome is characterized by impaired attention, concentration, information processing speed, memory and executive functions. Together with increased indicators of anxiety, depression, sleep disorders and fatigue, this cognitive impairment syndrome contributes significantly to the incidence of 'prolonged COVID' and in many cases does not allow people to return to their previous level of professional activity [25].

Pathogenesis of the lesion in COVID-19. At the same time, an increased level of cytokines in patients with COVID-19 leads to an immune reaction in vascular endothelial cells, which jeopardizes the body's defenses against SARSCoV-2 virus in various organs [35]. So, in the lungs, inflammation causes hypoxia in damaged tissues due to an inflammatory reaction, and hypoxia itself already creates a situation for the production of more inflammatory cytokines by immune cells in the same place. This may be due to the expression of hypoxia-induced factor 1a (HIF-1a), a critical factor that is activated under hypoxia conditions. HIF-1 is a conservative heterodimeric transcription factor that is regulated by oxygen availability and concentration. From all this, it can be concluded that the expression of HIF-1a in the focus of inflammation is regulated as a response to inflammation-hypoxia. Macrophages and neutrophils, as important phagocytic cells existing in tissues, play a crucial role in the innate immune response against various pathogens, such as viruses. At normal concentration and oxygen saturation, they express low levels of HIF-1a, but on the other hand, when oxygen demand and/or its supply is interrupted, the expression of HIF-1a begins to increase. The transcriptional activity of HIF-1a includes an increase in cell survival, as well as stimulation of the expression of angiogenic factors such as VEGF, as well as pro-inflammatory cytokines (for example, interleukin 1 β or IL-1β, IL-6, IL-12 and tumor necrosis factor-α) at the site of inflammation caused by infection. This increase in the levels of pro-inflammatory cytokines, as well as previous levels, can lead to deterioration and/or initiation of a cytokine storm, which is a serious risk factor for the severity of the disease [7].

As for endothelial dysfunction, its markers are proteases, cell adhesion molecules, glycocalyx components, clotting factors such as tissue factor, sE-selectin, endothelin-1, endogenous nitrites, nitrates, total nitrates, arginase and plasminogen activator inhibitor type 1. In addition, according to some data, it was recorded that increased release of integrins and selectins during inflammation was associated with higher activation of the endothelium [21]. Also, endothelial dysfunction can lead to a decrease in the expression of vasodilating and antithrombotic molecules (for example, nitric oxide (NO). In the case of patients with COVID-19, this manifests itself in the form of pulmonary vasculopathy, microangiopathy, thrombosis and alveolar-capillary occlusion [15]. It is noteworthy that micro- and macrovascular thrombosis are present in both1 venous and arterial circulation, and that venous thrombotic phenomena (for example, pulmonary embolism) are associated with elevated D-dimer levels in patients with COVID-19. According to one of the studies, 31% of cases of thrombotic complications were reported in patients in the intensive care unit with infections caused by COVID-19 [4]. Other sources give examples of the level of thrombotic complications that led to a fatal outcome, so abnormal coagulation parameters were determined, including significantly higher levels of D-dimer and fibrin breakdown products, longer prothrombin time and activated partial thromboplastin time in non-survivors with COVID-19 [17]. While there is an information, demonstrating that patients with pulmonary embolism had higher levels of D-dimer levels than those who do not have them [31]. According to pathoanatomic autopsies, it was found that thrombotic microangiopathy in small vessels and capillaries of the lungs contributed to death in patients with severe COVID-19 [18].

In parallel with endothelial dysfunction, the pathogenesis is aggravated by oxidative stress (OxS) caused by endocrine and cardiovascular molecules, such as angiotensin-II, which leads to a violation of the redox balance of cells. OxS leads to the loss of biochemical properties of macromolecules that allow the development of lipoperoxidation (for example, malondialdehyde (MDA), protein carbonylation (for example, products of extended protein oxidation), glucose oxidation products (for example, methylglyoxal (MGO), a precursor of products of extended glycation) and DNA oxidation (for example, 8-oxoguanine). OxS biomarkers are associated, particularly, with dysfunction of the cardiovascular and respiratory systems [10, 11, 20]. As for the nervous system, it is noteworthy that

there were no signs of infiltration of lymphocytes or leukocytes in areas of the human brain infected with SARS CoV-2.

As a result, it has been suggested that, although the virus is neurotropic, it does not cause an immune response, as is the case with other neurotropic viruses, such as Zika, rabies, herpes. Infected neurons derived from organoids created a local hypoxic environment. A similar condition occurring in the brain can affect vascular networks and lead to ischemic infarction, which causes further infection of the tissue [29]. Thus, according to the author of Spence, hemorrhagic stroke was lower in patients with COVID-19 compared to ischemic stroke. Ischemic stroke in patients with COVID-19 can be caused by hypercoagulation, vasculitis and cardiomyopathy. Hemorrhagic stroke can be caused by rupture of the cranial vessel endothelial cells that express the ACE2 receptor. It is believed that cytokine storm can also damage blood vessels and cause hemorrhagic stroke [31].

To conclude, the pathogenesis of damage to the nervous system by the COVID-19 virus has two sources: by infecting nerve endings, such as olfactory sensory neurons, and retrograde penetration of the virus into the brain. It is also believed that cytokine storm and viral sepsis can indirectly disrupt the BBB and cause coagulopathies leading to endothelial dysfunction and brain damage and stroke. Other sources have tried to identify common biomarkers for stroke and COVID-19. So, in one of the studies, patients with respiratory insufficiency were evaluated, and it was found that these patients had elevated levels of matrix metalloproteinase-9 (MMP-9) in blood serum. It is known that matrix metalloproteinases (MMPs) are a pathological sign of many neurodegenerative diseases and increase regulation in both stroke and COVID-19. The source of this MMP-9 is probably neutrophils and macrophages of the lung [23]. Other MP, the level of which was increased in the blood serum of patients with COVID-19, are MP-3 (stromelizin-1), MMP-8. Based on this, it has been suggested that MMPS and SARS-CoV-2 are mainly based on respiratory and pulmonary stress [27, 16, 28, 13, 26]. Other studies have also shown that MMPs can cleave the soluble Fas ligand (fasl), releasing it into the extracellular medium. Moreover, the researchers demonstrated that neutrophils induce apoptosis in epithelial cells of the lungs using sFasL [22]. The Fas system, which includes both membrane-bound (MFAs and mFasL) and soluble (sFas and sFasL) forms, plays an important role in apoptosis and immune regulatory reactions [8]. Thus, sFasL inhibits the interaction between Fas and FasL on the cell surface and blocks programmed cell death [5, 19]. Consequently, sFasL may be a dysfunctional agent among immunoregulatory reactions against COVID-19 and may contribute to the maintenance of harmful inflammatory processes that are involved in the activation and survival of neutrophils by suppressing Fas. Determining the role of sFasL and Mps as therapeutic targets in the fight against excessive inflammatory immune response in severe COVID-19 requires further study of neutrophils, sFasL and MMPs in COVID-19 [34].

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L. Takenova – Collection and analysis of material, writing and editing.

D. Klyuev – concept, design and review.

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COVID-19 И НЕРВНАЯ СИСТЕМА: ПАТОГЕНЕЗ, МЕХАНИЗМЫ И ПОСЛЕДСТВИЯ

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В острый период COVID-19 более чем у 1/3 пациентов развиваются неврологические симптомы, 25% из которых можно отнести к прямому поражению центральной нервной системы. Чаще всего все эти осложнения возникают из-за проникновения вируса в системный кровоток, его диссеминации и повреждения сосудистого эндотелия. Все клинические проявления, связанные с проникновением COVID-19 в нервную ткань, можно разделить на несколько групп: 1) признаки поражения центральной нервной системы, включая головную боль, нарушение сознания, энцефалит, цереброваскулярные заболевания, судороги и атаксию; 2) признаки поражения периферической нервной системы, такие как как аносмия/гипосмия, дисгевзия, нарушения зрения, невралгия и синдром Гийена-Барре; 3) признаки повреждения опорно-двигательного аппарата, такие как миопатия, миалгия и утомляемость.

Основной целью обзора литературы было выявление основных источников и механизмов повреждения нервной ткани при COVID-19.

Поиск литературы проводился в базах данных Web of Science, PubMed, Scopus. Поиск осуществлялся по ключевым словам: «COVID-19», «нервная ткань», «эндотелиальная дисфункция», «окислительный стресс», «нейровоспаление». Поиск литературы дал 329 результатов, из которых 234 статьи.

В результате анализа статей были выделены 2 основные группы исследований: описательные и экспериментальные.

Патогенез повреждения нервной системы вирусом COVID-19 имеет два источника: путем заражения нервных окончаний, таких как обонятельные сенсорные нейроны, и ретроградного проникновения вируса в головной мозг.

Ключевые слова: COVID-19; нервная ткань; эндотелиальная дисфункция; окислительный стресс; нейровоспаление

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COVID-19 ЖӘНЕ ЖҮЙКЕ ЖҮЙЕСІ: ПАТОГЕНЕЗІ, МЕХАНИЗМДЕРІ ЖӘНЕ САЛДАРЫ

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Жедел COVID-19 кезеңінде пациенттердің 1/3 бөлігінен астамы неврологиялық белгілерді дамытады, олардың 25% - центральной орталық жүйке жүйесінің тікелей зақымдануына жатқызуға болады. Көбінесе бұл асқынулардың барлығы вирустың жүйелік қанға енуінен, оның таралуынан және тамырлы эндотелийдің зақымдануынан туындайды. COVID-19 жүйке тініне енуіне байланысты барлық клиникалық көріністерді бірнеше топқа бөлуге болады: 1) орталық жүйке жүйесінің зақымдану белгілері, соның ішінде бас ауруы, сананың бұзылуы, энцефалит, цереброваскулярлық аурулар, құрысулар және атаксия; 2) перифериялық жүйке жүйесінің зақымдану белгілері сияқты аносмия/гипосмия, дисгеузия, көру қабілетінің бұзылуы, невралгия және Гильен-Барре синдромы; және 3) миопатия, миалгия және шаршау сияқты тірек-қимыл аппаратының зақымдану белгілері.

Шолудың негізгі мақсаты-COVID-19 ауруындағы жүйке тінінің зақымдануының негізгі көздері мен механизмдерін анықтау.

Әдебиеттерді іздеу Web of Science, PubMed, Scopus дерекқорларында жүргізілді. Іздеу «COVID-19», «жүйке тіндері», «эндотелий дисфункциясы», «тотығу стрессі», «нейроинфламация» кілт сөздері бойынша жүргізілді. Әдебиеттерді іздеу 329 нәтиже берді, оның 234-і мақалалар.

Мақалаларды талдау нәтижесінде зерттеудің 2 негізгі тобы анықталды: сипаттамалық және эксперименттік.

COVID-19 вирусының жүйке жүйесінің зақымдануының патогенезінің екі көзі бар: иіс сезу нейрондары сияқты жүйке ұштарын жұқтыру және вирустың миға ретроградтық енуі.

Кілт сөздер: Covid-19; жүйке тіндері; эндотелий дисфункциясы; тотығу стрессі; нейроинфламация