COVID-19: Cellular and Molecular Mechanisms of Brain Damage

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Abstract—The most common clinical manifestation of COVID-19 is bilateral pneumonia, a diffuse, alveolar injury with severe microangiopathy. Systemic infection is accompanied by an increase in circulating chemokines and interleukins in the blood, which penetrate the blood–brain barrier (BBB) and enter the brain. Clinical materials indicate lesions of the brain and peripheral nervous system, as well as neurodegenerative and mental disorders. Due to violations of the cerebral endothelium system and changes in the balance of ACE2-coupled cytochemical processes, coagulopathy develops, leading to microthrombosis and vascular occlusion. The concept of SARS-CoV-2 “neurotropism” is discussed as a rationale for the penetration by the virus into the brain. Infection can occur as axonal transport through the bulbar zone and the olfactory area of the cerebral cortex. Even more common is the “hematogenous pathway” of viral transfection, which includes damage to the vascular endothelium and a violation of the protective role of the BBB. Another concept that explains the mechanism of brain damage relates to the phenomenon of neuroinflammation. Astrocytes and microglia are considered potential targets of the SARS-CoV-2 coronavirus. The dissonance of the biochemical processes of the axis ACE2/ACE and changes in the functions of angiotensin peptides leads to the activation of astroglia with the development of neurodestructive processes in COVID-19.

Keywords: COVID-19 pandemic, cytokine stress, blood-brain barrier, coronavirus neurotropism, angiotensin-converting enzyme 2, neuroinflammation, neurodegenerative pathology

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INTRODUCTION

The development of events associated with the COVID-19 pandemic led to a large-scale analysis of the pathogenesis of the disease, a complex set of negative processes. The outbreak is caused by a variant of the SARS-CoV group of coronaviruses. The International Taxonomy Committee has officially named the new pathogen SARS-CoV-2. The World Health Organization has defined the disease as pandemic COVID-19 (Mao et al., 2020).

Clinical studies have established that acute lung injury with an inverted response of the immune systems is diagnosed as a characteristic manifestation of the pathogenesis of COVID-19. The “cytokine storm” initially caused by a viral attack demonstrates the symptomatology of a proinflammatory etiology with the phenomena of hemodynamic instability, dysfunction of many organs of the body, and neurological dissonance.

INITIAL CONCEPTS OF THE PATHOGENESIS OF COVID-19. GENERAL CLINICAL SIGNS

The fundamental position that determines the specificity and scale of COVID-19 infection is the coincidence of chemical structures, due to which the SARS-CoV-2 coronaviruses have an exceptional ability to bind to a special protein designated “angiotensin-converting enzyme” (ACE2), or angiotensin-converting enzyme of the second type (ACE2). The level of binding of SARS-CoV-2 to ACE2 is 10–20 times higher than its affinity for the previous viral strain, SARS-CoV. The new virus, due to its special spine structure, uses ACE2 as a “Trojan horse” to enter the host cell (Tai et al., 2020). This circumstance, on the one hand, distinguishes the initial stages of a complex disease, and, on the other hand, it determines the target orientation in the development of specific vaccines as virus blockers and limits the consequences.

The binding to ACE2 and the transfer of the process to the endosome trigger viral replication in the cells of the pulmonary alveolar epithelium and vascular endothelium. Due to its very high pathogenic affinity, the SARS-CoV-2 coronavirus disrupts the natural reactions of cytoimmune and hematovascular control. Since ACE2 is expressed in many human organs, alveolar epithelial cells of the lungs are the primary target of coronavirus. Pathochemical analysis also established the localization of the ACE2 enzyme in humans in the endothelium of arterial and venous vessels and in the arteries of smooth muscles of almost all organs. ACE2 molecules were found in the mucous membrane of the nose, mouth, stomach, intestines,
etc. as the first stage of viral invasion (Hamming et al., 2004). This information about the spread of ACE2 indicates the possibility of a large pathogenic spread of infection and various manifestations of COVID-19, including severe pneumonia, multiple organ disorders, and neurological disorders.

One characteristic feature of the pathogenesis of COVID-19 is a cytokine storm with elevated levels of interleukin-6 (IL-6), IL-1β, tumor necrosis factor-alpha (TNF-α), chemokine ligand 2 (CCL2), and granulocyte macrophage colony stimulating factor (GM-CSF). Immunological distress leading to cytokine storm syndrome and acute respiratory syndrome is common in COVID-19 patients. Cytokines provoking cellular inflammation, including tumor necrosis factor TNF, interferon-gamma IFNγ, interleukins IL-1, IL-6, IL-18, etc., are secreted in large quantities, forming a field of stochastic dissonance (Kempuraj et al., 2020).

Typical clinical manifestations of COVID-19 are bilateral pneumonia with severe microangiopathy. Hypercoagulable syndrome, which develops in some patients, can affect the heart, brain, kidneys, and other organs, in addition to the lungs. The development of vascular endothelial dysfunction is accompanied by intracellular diffusion, coagulopathy, and thrombosis (Tang et al., 2020).

**ENDOTHELIAL DYSFUNCTION AS A TARGET OF SYSTEMIC DAMAGE IN COVID-19. STORM-2 CONCEPT**

The variety of manifestations of coronavirus disease suggests a complex of dissonances of pathophysiological processes in the body. The main cellular target of SARS-CoV-2 is ACE2, a natural factor in hemovascular regulation. The coronavirus blocks the activity of the enzyme, disrupting the balance of cytoimmune and hemovascular control. Under normal physiological conditions, this regulatory mission is carried out by a complex of related proteins, ACE and ACE2, which control the synthesis and activity of the physiologically active peptides angiotensins and bradykinin. The specific acceptance of the ACE2 enzyme by the coronavirus leads to dissonance in the hemovascular control and multiple disturbances in the hemostatic system. In the first publications on ACE2, this protein is already considered the primary link in pathologies caused by viral strains of SARS (Hamming et al., 2004; Kuba et al., 2005).

The second aspect of the problem relates to the role of the endothelium, the cells lining the endovascular surface. Since the main site of localization of the ACE and ACE2 enzymes, which regulate the hemovascular homeostasis system, is the vascular endothelium, its disturbance turns out to be the main site of dissonance. Violation of the renin–angiotensin enzymatic “axis” due to ACE2 blockage and an increase in negative ACE activity leads to the implementation of prooxidative and proinflammatory processes on the “bridgehead” of the vascular endothelium.

Based on this and the clinical materials of COVID-19, the concept of STORM-2 was formulated. Its essence refers to the manifestation of multiple disorders when cellular inflammation caused by the SARS-CoV-2 coronavirus develops into multiple organ dysfunction (Gomazkov, 2021). In the acute course of the disease, problems were recorded in the work of the heart, brain, kidneys, endocrine system, etc.; they were expressed as disorders of microhemodynamics, coagulopathy, and disseminated microthrombosis.

**COVID AND NERVOUS SYSTEM LESIONS**

The evidence of neurological complications in COVID-19 indicates the presence of lesions of the brain and peripheral nervous system, their localization, and associated mental disorders. The first clinical publications described neurological excesses detected in one third of patients infected with the virus SARS-CoV-2 (Mao et al., 2020). In 2020–2021 the number of articles in the journals of the PubMed database on neurological complications in COVID-19 exceeded 2500. There is growing evidence that SARS-CoV-2 is the cause of neuroinvasion from the periphery to the brain (Li et al., 2020a, 2020b).

Overall, the rates of such disorders included:

- lesions of the central nervous system (CNS), e.g., vestibulopathy, headache, changes in consciousness, ataxia, convulsions, cerebrovascular accidents;
- lesions of the peripheral nervous system, e.g., smell, taste, vision, pain reactions;
- lesions of the musculoskeletal system, e.g., pain symptoms, discomfort of physical activity; and
- deep cerebrovascular disorders, e.g., ischemic stroke, thrombosis of the venous sinus of the brain, hemorrhage.

Structural changes in the brain were confirmed with imaging techniques that demonstrated morphophysiological abnormalities. According to magnetic resonance imaging (MRI) 2–4 weeks after the onset of primary symptoms, 60% of patients showed signs of acute ischemic infarction, deep vein thrombosis, multiple microbleeds, and perfusion disorders (Chougar et al., 2020). Subcortical microbleeds and edematous nonspecific deep changes in the white matter of the brain were established (Coolen et al., 2020). Hemorrhagic lesions were detected in the thalamus, medial temporal lobes, and visual hillocks (Poyiadji et al., 2020). Cytochemical analysis indicated reactive astrogliosis, the appearance of glial fibrillar acidic protein, and the presence of destruction markers, light chain proteins of neurofilaments and intra-axonal lesions (Kanberg et al., 2020).
It was noted that, when the endothelium is damaged and the control of thrombogenesis is impaired, the pathology of small vessels is formed by the type of inflammatory angiopathy (vasculitis). The development of ischemia primarily affects the small perforating vessels that provide blood supply to the limbic zones of the brain (Sokolova and Fedin, 2020). Neuropathological damage can be caused by multifocal cerebral ischemia or thrombogenesis in violation of the BBB. Changes in the protective role of the BBB included edema, inflammatory endothelial injury, systemic vasculitis, and necrosis of brain cells.

There has been a relationship between the severity of COVID-19 and the frequency of neurological manifestations, which include cerebrovascular accidents, acute necrotizing encephalopathy, and Guillain–Barré syndrome. Factors potentially complicating the development of neurological pathologies in COVID-19 include arterial hypertension, diabetes mellitus, and chronic heart and respiratory diseases. Special attention should be paid to the control of progressive neurological diseases against the background of cerebral circulation disorders (Gusev et al., 2020). In the long term, neuropsychiatric disorders are noted: depression, psychosis, hallucinations, etc. (Troyer et al., 2020; Szczesniak et al., 2021). Pathological examination of patients with changes in mental status revealed fragments of the SARS-CoV-2 virus in the neurons of the frontal lobes of the brain (Paniz-Mondolfi et al., 2020).

Figure 1 (Aghagoli et al., 2020) summarizes the main targets of brain damage in COVID-19.

- The cytokine storm, which is caused by the primary action of the SARS-CoV-2 virus, disrupts the protective function of the BBB, which leads to penetration of the brain by agents.
- Due to disturbances in the endothelium and changes in the balance of the biochemical axis of angiotensin peptides enzymes (ACE2/ACE), coagulopathy develops, which leads to microthrombosis and vascular occlusion.
- The complex of these processes contributes to neuronal damage as a result of astroglial cellular neuroinflammation.

**Fig. 1.** Coronavirus SARS-CoV-2: the main targets and staging mechanisms of brain damage (adapted from: Aghagoli et al., 2020).

**PENETRATION OF THE BRAIN BY THE SARS-COV-2 VIRUS**

Neurotropism, as a biological concept, is considered as a common feature of viral pathology, as evidenced by a comparative analysis of the SARS-CoV family of coronaviruses. Neuroinvasive agents directly damage structures of the brain and peripheral nervous system as a result of altered host immune responses...
et al. demonstrated the presence of fragments SARS-CoV-2 in cerebrospinal fluid against the background of meningoencephalitis manifestations of the pathogenesis of COVID-19 (Moriguchi et al., 2020).

Previous model studies have shown that viral replication in endothelial cells results in the degradation of contact proteins, which leads to disruption of the BBB defense system (Verma et al., 2009; Lega et al., 2019). SARS-CoV caused cellular stress associated with increased cytotoxic effects and degeneration through the mechanisms of apoptosis (Desforges et al., 2014). These preclinical data are associated with COVID-19, since the presence of SARS-CoV-2 virus particles in the microvascular endothelium of the frontal lobe of the brain was found in the pathological examination (Paniz-Mondolfi et al., 2020). The defeat of endothelial cells is associated with the expression of adhesion molecules (VCAM and ICAM): the introduction of the virus induces matrix metalloproteinases, which contribute to the destruction of subcellular contacts. Endothelial cell death disrupts the microenvironment of the brain parenchyma, making the coronavirus available to other sites (Alquisiras-Burgos et al., 2021).

Thus, the following sequence of events is considered a mechanism of BBB damage during the invasion of SARS-CoV-2: (1) the virus binds to the ACE2 protein on the membrane of endothelial cells, which leads to massive cell infection; (2) fixation of the virus affects the contact of intercellular adhesion molecules, inducing matrix metalloproteinases, which contribute to the destruction of endothelial structures; (3) the death of endothelial cells determines the availability of the SARS-CoV-2 virus to other parts of the brain.

NEUROINFLAMMATION AS A LEADING CELLULAR MECHANISM OF LESIONS IN COVID-19

In previous studies of viruses of the SARS-CoV group, it was found that disruption of the BBB integrity during a respiratory attack may be due to a cytotoxic mechanism with the induction of apoptosis (Desforges et al., 2014). The BBB plays the role of a regulatory mediator between the CNS and the brain's immune system. The process of neuroinflammation, during which the dissonance of defense mechanisms develops, is considered to be a generalizing cause of the lesion (Erickson et al., 2012). In a study of acute respiratory syndrome caused by previous strains of the SARS coronavirus, it was found that monokines induced by IFNγ are expressed in the brain mesenchyme in gliocytes with infiltration of monocyte/macrophages and T-lymphocytes (Xu et al., 2005).

Neuroinflammation. Dual Principle of Brain Regulation

Initially, attention should be focused on the role of astroglial cells in the large arsenal of regulatory processes in the “normal” brain. Modern data consider...
Microglial cells are involved in remodeling (in fact, “ordering”) of the neural environment, participating in the elimination of “worn out” structures (debris of cells, synapses, organelles, etc.) and contributing to the development and survival of neurons. Astrocytes are responsible for the formation of synapses as key components of neurotransmitter function. It was noted that transforming growth factor TGF-β plays a signaling role in the astrocyte-induced synaptogenesis of cortical cells (Diniz et al., 2012). The data on the regulation of higher mental functions by astrocytes, including memory and social behavior, have been summarized (Gomazkov, 2019).

At the same time, most of the literature associates astroglial cells with the concept of “neuroinflammation,” which is traditionally understood as participation in negative (pathogenic) processes (Bentivoglio et al., 2011). Reactive glial cells have a dual phenotype of neurotoxic or neuroprotective nature, depending on the infectious stimuli, pathophysiological state, and patient age (Peñky et al., 2016). Acute neuroinflammation develops as a systemic process of overexpression of immunodefense molecules, endothelial-cell dysfunction, and damage to brain structures (Matias et al., 2019).

In laboratory studies, primary neurological disorders in COVID-19 are described as “cytokine release syndrome” (Moore and June, 2020). Neuroinflammatory reactions develop as a consequence of an inverted immune response with the participation of cytokines IL-1β, IL-6, TNF-α, chemokines CCL2, CCL5, CXCL1, secondary signaling messengers (NO), and reactive oxygen species. Many of these inflammatory mediators are produced by reactive astroglia cells (Norden et al., 2016).

Stating the dual principle of neuroinflammation, Di Sabato et al. (Di Sabato et al., 2016) share adaptive (protective, physiological) and maladaptive (negative) processes of neuroinflammation, which is figuratively defined as “the devil is in the details.” Proapoptotic pathways leading to the formation of reactive oxygen species and the elimination of cellular structures are mediated by the inclusion of signaling molecules synthesized by astroglia. One of them, the nuclear transcription factor NF-kB, regulates the activity of inflammatory molecules associated with neurodegenerative diseases (Shabab et al., 2017).

The results of previous experimental studies indicate that neurovirulence SARS-CoV correlates with the ability to induce proinflammatory cytokine sig-

nals. Viruses with different neurovirulence provoke the activation of cytokines IL-12, p40, tumor necrosis factor TNF-α, etc., both in astrocytes and microglia of the brain and spinal cord (Li et al., 2004). Upon the controlled activation of microglia and Toll-like pathogen recognition receptors, astrocytes are transformed into proinflammatory and pro-neurodegenerative brain cells (Rosciészewski et al., 2018).

### Astrocytes and Mechanisms of Neurodegeneration in COVID-19

Astrocytes and microglia are considered potential targets of SARS-CoV-2 (Vargas and Geraldo, 2020). The complex of clinical materials suggests that activated microglia during a peripheral cytokine storm may be involved in the neurological manifestations of the disease. Analysis of severe cases of COVID-19 found that systemic infection is accompanied by an increase in chemokines and interleukins circulating in the blood, which, penetrating the BBB, enter the brain. The function of immune and glial cells is critical in the determination of neurological damage and disease outcome (Tremblay et al., 2020). The acute neuroinflammatory response involves the activation of resident tissue macrophages in the CNS and the subsequent release of cytokines and chemokines associated with activation of oxidative stress and delayed neuronal damage. The selective use of therapeutic agents with indirect anti-inflammatory and antiviral effects is noteworthy (Putilina and Grishin, 2020).

Plasma biochemical analysis of severe and moderate COVID-19 patients showed an increase in damage biomarkers such as glial fibrillar acidic protein (GFAP) and neurofilament light chain protein (NFL), which is indicative of astrocyte activation and neuronal damage (Kanberg et al., 2020). With extreme activation of glial cells, neuronal damage can be related to both local synaptic elimination and apoptotic destruction of the neurons themselves. These phenomena lead to an imbalance of synaptic processes in the brain (Garber et al., 2019).

This line of reasoning led to the conclusion that the reactive phenotype of microglia may be the leading cause of neurodegenerative disorders in the pathology of COVID-19. Proinflammatory priming (“anticipation”) of microglia in SARS-CoV-2 infection enhances the symptoms of the patient’s previous diseases.

### Dissonance of the Angiotensin System and Neuroinflammation

The presentation of the renin–angiotensin system is a separate topic in the analysis of the pathogenesis of COVID-19. A complex of biochemical processes, starting with the catalytic function of the ACE2 enzyme and the interaction of angiotensin fragments with receptors, determine the control of microhemo-
dynamics, blood transfusion, neuroinflammation, oxidative stress, and apoptosis (Kangussu et al., 2020). The role of the renin–angiotensin system as a link in signal regulation (hemodynamic disorders, reactions to stressful and neurotoxic influences, and special forms of social behavior) was presented in our book (Gomazkov, 1993).

The main cellular target of SARS-CoV-2 aggression is the angiotensin-converting enzyme of the second type (ACE2), a natural biochemical factor of vascular regulation. Violation of the conjugated relationship of the ACE2/ACE enzyme systems under the influence of coronavirus aggression plays a significant role in the pathogenesis of COVID-19. The biochemical role of ACE2 and ACE is in the hydrolysis of fragments of “large” angiotensin I (ANG1–10): the combination of ACE2 → ANG (1–7) → MasR receptor functionally opposes the ACE axis → ANG (1–8) → AT1R receptor. The peptide ANG (1–7), binding to MasR, potentiates a complex of defense reactions (Fig. 2). MasR receptors are localized in many structures of the brain, including the hippocampus, amygdala, thalamic nucleus, and cortex (Regenhardt et al., 2014).

It can be stated that suppression of the ACE2 protein by the coronavirus leads to a leveling of the protective functions of the competing system and the development of neuroinflammatory responses (Gheblawi et al., 2020). Astrocytes that respond to proinflammatory mediators become factors in a reduction of antioxidant activity, which is also associated with ANH (1–7) and MasR receptors (Gallagher et al., 2006). From the standpoint of pharmacotherapy, maintaining the activity of the ACE2 → ANG (1–7) → MasR axis or blocking the ACE → ANG (1–8) → AT1R axis plays a protective role in brain damage. The use of a nonpeptide agonist of receptors and enhancement of the MasR signal as a protective mechanism may be promising (Santos and Ferreira, 2006).

Summarizing these results, it is possible to build a sequence of processes of pathogenesis and brain damage in COVID-19. (1) Damage to endothelial cells and impairment of the protective functions of the BBB leads to the transduction of proinflammatory signals from the periphery into the brain parenchyma with activation of the inflammatory response of microglia and astrocytes. (2) Astrocytes are the main actors in the neuroinflammation system, since viral blockade (acceptance) of the ACE2 enzyme is followed by stimulation of the release of proinflammatory cytokines by microglia. (3) The dissonance of the biochemical processes of the ACE/ACE2 complex and changes in the ratio of angiotensin peptides provoke the activity of astroglia components and neuroinflammation, which leads to neurodestructive complications in COVID-19.

Fig. 2. The renin–angiotensin axis ACE2/ACE and the balance of protective (antioxidant) and proinflammatory processes in the vascular endothelium. The aggressive interaction of the coronavirus with the ACE2 enzyme levels eliminates the protective mission and stimulates the hyperproduction of ANH (1–8), which leads to disturbances in vascular homeostasis.
CONCLUSIONS

Data from previous experimental work with various strains of SARS coronaviruses, as well as clinical materials from the COVID-19 pandemic, provide information on the mechanisms of its effect on the CNS. The following provisions characterize the specificity of neurodestructive processes can be distinguished.

(1) Information on SARS-CoV-2 neurotropicity is presented in a new position as a justification of viral transfection and the provocation of neurological disorders of various origins. Virus “ingrowth” into capillary cells facilitates its penetration of brain structures (Cardona et al., 2020).

(2) The “hematogenous pathway” of infection, which is associated with the massive impact of the cytokine storm on the endothelium, can affect cells of the brain microvessels that form the blood-brain barrier. The presence of the SARS-CoV-2 virus in the microvasculature suggests contact with ACE2 in the endothelium of various systems, including cerebral microhemodynamics.

(3) Activation of the neuroinflammatory response and the inclusion of reactive astroglia cells is considered a complex of cytobiochemical processes balancing on the “defense–damage” line. Acute neuroinflammation develops as a process of overexpression of immunodefense molecules, the activation of endothelial cells, and damage to brain structures. The syndrome of astrocyte expression serves as a prolog for the activation of the mechanism of prooxidative and proapoptotic effects affecting brain structures.

(4) Due to the violation of the cerebral endothelium and changes in the balance of ACE2-conjugated systems, coagulopathy and thrombosis of the cerebral vessels develop. The complex of these processes leads to neuronal damage as a result of activated neuroinflammation and the pathogenetic influence of astrogial mechanisms for the activation of apoptosis and necrosis.

(5) Based on an analysis of this information, a stepwise mechanism of damage to neurocytochemical, immunological, and organ systems was found and woven into the picture of neurological and mental complications.

These materials provide the rationale for the systemic application of therapeutic approaches:

- The need for a generalized prevention of coronavirus invasion with scopic vaccines and chemical ligands that inhibit the SARS-CoV-2 coronavirus;
- Limitation of immune dissonance, the cytokine storm, as a factor of generalization and progression of the disease;
- Restoration of the balance of biochemical systems of ACE2/ACE, which is disturbed by the influence of coronavirus, with the rehabilitation of anti-inflammatory, antithrombotic, and antihypertensive mechanisms;
- The use of specialized therapy for the affected organs (heart, brain, endocrine system, etc.) to maintain functions;
- Control of “delayed” manifestations of neurodestructive and mental manifestations of the disease, with allowance for the personalized characteristics of the patient.

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COMPLIANCE WITH ETHICAL STANDARDS

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