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Review

Role of retroelements in the development of COVID-19 neurological consequences

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Abstract: Retroelements play a key role in brain functioning in humans and other animals, since they represent dynamic regulatory elements controlling the expression of specific neuron types. The activity of retroelements in the brain is impaired under the influence of SARS-CoV-2, penetrating the blood-brain barrier. We propose a new concept, according to which the neurological complications of COVID-19 and their long-term effects are caused by modified expression of retroelements in neurons due to viral effect. This effect is implemented in several ways: a direct effect of the virus on the promoter regions of retroelement-encoding genes, virus interaction with miRNAs causing silencing of transposons, and an effect of the viral RNA on the products of retroelement transcription. Aging-related physiological activation of retroelements in the elderly is responsible for more severe course of COVID-19. The associations of multiple sclerosis, Parkinson's disease, Guillain-Barré syndrome, acute disseminated encephalomyelitis with coronavirus lesions also indicate the role of retroelements in such complications, because retroelements are involved in the mechanisms of the development of these diseases. According to meta-analyses, COVID-19-caused neurological complications ranged 36.4-73%. The neuropsychiatric consequences of COVID-19 are observed in patients over a long period after recovery, and their prevalence may exceed those during the acute phase of the disease. Even 12 months after recovery, unmotivated fatigue, headache, mental disorders, and neurocognitive impairment were observed in 82%, 60%, 26.2-45%, and 16.2-46.8% of patients, correspondingly. These manifestations are explained by the role of retroelements in the integration of SARS-CoV-2 into the human genome using their reverse transcriptase and endonuclease, which results in a long-term viral persistence. The research on the role of specific retroelements in these changes can become the basis for developing targeted therapy for neurological consequences of COVID-19 using miRNAs, since epigenetic changes in the functioning of the genome in neurons, affected by transposons, are reversible.

Keywords: COVID-19, SARS-CoV-2, brain, retroelements, transposons, microRNAs, neurological pathology.

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Introduction

Coronaviruses (CoVs) are viruses containing positive-sense single-stranded RNA. The sizes of their genomes vary from 27 to 32 kb, while a diameter of their particles ranges 100 to 160 nm. The *Coronaviridae* family includes four genera: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus*. The SARS-CoV-2, SARS-CoV and MERS-CoV viruses belong to the genus *Betacoronavirus* [1]. CoVs were always the leading cause of acute respiratory viral infections in human populations, as evidenced, in particular, by the results of seroepidemiologic studies in 1960s that established the presence of CoVs in the nasopharynx of patients in nearly half of catarrhal cases [2].

However, in December 2019, a novel coronavirus infection was detected in Wuhan, China, rapid spreading and causing high mortality. The study by WHO experts of the virus isolated from the patient's nasopharynx reported completed sequencing of the pathogen by January 12, 2020, which was specified as *'2019-nCoV'*. On February 11, 2020, the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses named the novel coronavirus SARS-CoV-2, and the disease caused by it – COVID-19 (Coronavirus Disease-2019) [3]. The infectious process caused by SARS-CoV-2 may affect the respiratory system, as well as the gastrointestinal tract. According to disease severity, four types of the clinical course of COVID-19 could be distinguished: mild, moderate, severe, and critical (such as acute respiratory distress syndrome – ARDS, acute heart or kidney failure, DIC syndrome, and shock) [1]. People over 60 years of age are more susceptible to SARS-CoV-2 infection, thereby developing more severe forms of the disease [4] and hyperactivity of immune responses [1].

The SARS-CoV-2 penetrates into the cells by interacting with angiotensin-converting enzyme 2 (ACE2), which serves as a receptor for the viral spike protein (S). Subsequently, SARS-CoV-2 uses the host serine protease *TMPRSS2* to trigger S protein, which is necessary for the fusion of viral and cell membranes with viral penetration into the cell [5]. Besides damage in the respiratory

and cardiovascular systems, along with gastrointestinal tract, we should mention an expressed pathogenic effect of SARS-CoV-2 on the brain with long-term effects of viral exposure, which constitutes a serious social problem. In this regard, it is important to determine the prevalence of neurological consequences of COVID-19, its persistence over time, mechanisms of development, and promising ways of their treatment. It should be pointed out that CoVs demonstrate tropism to CNS tissues, which is confirmed by the fact that the cases of brain infections caused by coronaviruses have been described in the literature. For instance, murine hepatitis virus (MHV), a strain of *Murine coronavirus* species belonging to *Coronaviridae* family, affects the central nervous system of animals with developing demyelination [6]. *Feline coronavirus* belonging to *Alphacoronavirus 1* species causes infectious peritonitis with brain damage, accompanied by developing inflammation, formation of infiltrates consisting of lymphocytes, neutrophils, macrophages, eosinophils, and by accumulation of IL-1ß, IL-6, IL-12, IL-18, and TNF-α [7]. In addition, the cases of detected HCV-OC43 in the brain of a patient who died from fatal human viral encephalitis [8], and in the cerebrospinal fluid of a patient with acute disseminated encephalomyelitis have been described [9].

A scientific novelty of our review includes investigating the mechanism of developing neurological consequences of COVID-19, associated with pathological activation of retroelements (REs) affected by SARS-CoV-2. This effect is caused by a key role of REs in regulating the differentiation and functioning of brain neurons throughout human ontogenesis [10, 11]. In addition, the role of REs in the regulation of gene expression is due to *cis* and *trans* effects, as well as to the formation of microRNAs [12] and long noncoding RNAs (lncRNAs) [13, 14] from their transcripts, which play an important role in the functioning of the central nervous system [15, 16] and its pathology [17].

The role of REs activation [18], which results in interferon overproduction and age-related aseptic inflammation in the organism [19], explains higher sensitivity of older individuals to SARS-CoV-2 infection, accompanied by manifestation of more severe forms of the disease [4] and hyperactivity of immune reactions [1]. REs play an important role in the immune system functioning due to activation of image-recognizing TLR, NLRP3, and RLR receptors [20] and control of C4A class III major histocompatibility complex [21]. Besides, many genes of the immune system have evolved from REs [22].

Brain impairments, accompanying COVID-19, are caused by the role of REs in regulating expression of specific genes essential for neuronal differentiation and functioning [23, 24]. The evolutionary origin of multiple genes involved in the functioning of human and animal neurons from REs has been reported. These examples include *Zcchc16, ARC, Mart4, Sirh11* [22], *PEG 10* genes (forms viral-like capsid structures with its own mRNA loaded into extracellular vesicles of neuronal branches) [25], and *IEG* (encodes ARC protein interacting with synaptic proteins [26] and promotes formation of dendrite spikes in hippocampal neurons) [27]. Consequently, pathological activation of REs caused by SARS-CoV-2 explains the mechanism of long-term development of neurological pathology in COVID-19 patients, which represents a significant factor of severe symptoms and increased mortality in COVID-19 [28, 29].

The role of REs in manifesting COVID-19 complications is supported by the data on their direct activation by SARS-CoV-2. Based on the analysis of ChIP-Seq data, SARS-CoV-2 promotes the expression of certain Res that are involved in the transcriptional regulation of immune response genes. The experiment conducted on human cell lines demonstrated that SARS-CoV-2 infection resulted in increased levels of 52 different HERV and 40 LINE1 REs [30]. The transcriptome of bronchoalveolar lavage and peripheral blood monocytes obtained from COVID-19 patients was also characterized by a significant increase in the level of HERV transcripts, compared with healthy individuals [31]. The study involving 17 COVID-19 patients demonstrated an enhanced expression of HERV-W REs, compared with the control group. At the same time, HERV-W concentration directly correlated with production of differentiation markers of T-lymphocytes and IL-6, IL-17, TNF-α, CCL2, and CXCL6 cytokines, as well as with COVID-19 severity [32]. The obtained data were supported experimentally: an introduction of the SARS-CoV-2 spike protein into the leukocyte culture caused activation of the expression of the HERV-W envelope protein [33].

LINE1 RE activation, initiated by SARS-CoV-2, reduces endothelial cell proliferation and migration via regulating the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and Tie-2 (protein kinase receptor) [34]. Therefore, one of the mechanisms of endothelial dysfunction, caused by SARS-CoV-2, may be the activation of REs caused by the virus [30-32].

The cause of prolonged neurological effects of SARS-CoV-2, related to the activation of REs, is a phylogenetic relationship between the virus and REs. In evolution, transposons have originated from exogenous viruses and, hence, they possess common nucleotide sequences in their genome. It was observed that products of HERV expression were initiating translation on the ribosome, changing the structure of open reading frames (ORFs) in SARS-CoV-2 virus in various cells, which affected the severity of infection [35]. Reverse transcriptase and RE endonuclease can be used as mediators for the integration of SARS-CoV-2 into the human genome [36], which also constitutes a factor of long-lasting pathological viral effects on the human body, including the development of neurological symptoms. This finding was confirmed by detected integration of positive-stranded RNA-containing bornaviruses (similar to SARS-CoV-2) into the host genomes via REs with the development of lethal neurological diseases [37].

The differences in manifestation frequency of neurological symptoms, accompanying COVID-19 [38], may be attributed to population specificity of RE distribution in human genomes. Indeed, a comparative analysis of HERV-K distribution in human genomes demonstrated a presence of 12 insertions that were polymorphic in different populations [39]. The study of polymorphic insertions of REs at 16,192 loci in 2,504 individuals from 26 populations revealed specific differences in insertions, depending on the place of residence [40]. Distributions of REs in genomes, specific for different populations, were also reported in the study of 14,384 insertions in 1,511 individuals from 15 populations [41].

Telomeres represent another link between the development of long-term neurological consequences of COVID-19 and activation of REs. The analysis of published data demonstrated that individuals with shorter telomeres developed severe forms of COVID-19. This observation could explain more severe course of infection in older patients [42], since telomere shortening is

characteristic of ageing [43]. The latter, according to published sources, is caused by age-related derepression of REs, regulating telomere functioning [10]. Another evidence is provided by their phylogenetic relationship, since telomeres [44] and telomerase [45] have evolved from REs.

The role of coronaviruses and retroelements in developing specific neurological pathology

It should be noted that prior to the COVID-19 pandemic, several scientific publications reported the association of neurological diseases with seropositivity of patients to CoVs. Even in 1980s, CoVs were identified *post mortem* in the brain of patients with multiple sclerosis (MS). An assumption about the role of CoVs in the development of this disease was made, since antibodies to CoVs were detected at higher concentrations in MS patients, compared with control subjects [46]. Subsequently, coronaviral RNA polarizable continuum model, PCM-229E, was detected in the cerebrospinal fluid in 4 out of 11 MS patients (negative results were reported in patients with another neurological pathology and in healthy controls) [47]. In another study, HCV-OC43 RNA was detected in the cerebrospinal fluid in 10 patients vs. HCV-229E in 7 MS patients [48]. The participation of CoVs in the development of Parkinson's disease is also likely, since antibodies to CoVs were found in the cerebrospinal fluid of these patients, as opposed to patients with other neurological diseases [49]. The above data are consistent with the effect of coronaviruses on REs, since an association of activation of LINE-1 elements with Parkinson's disease [50], as well as with endogenous retroviruses and MS [51], was found.

Additionally, CoVs were detected in cerebrospinal fluid in children with acute disseminated encephalomyelitis. In murine experiments, CoV was confirmed to cause a chronic demyelinating state similar to MS. The ability of CoV to infect human nerve cells has been proven *in vitro* [9]. After infection with MERS-CoV, the development of a severe neurological syndrome was noted, which was manifested by a change in consciousness from confusion to coma, ataxia, and focal motor insufficiency. Using MRI of patient brain, bilateral hyperintense lesions were identified on T2-weighted images in the white matter, subcortical regions, basal ganglia, and corpus callosum [52]. Murine experiments revealed that SARS-CoV penetrated through olfactory epithelium into the brain, thereby resulting in neuronal death. The accompanying neuronal infection was the main cause of animal death, especially with the development of encephalitis in the region of cardiorespiratory center [53]. The mechanism of encephalomyelitis development in coronavirus infections may be attributed to activation of REs, since an increased HERV expression was identified in patients with myalgic encephalomyelitis (chronic fatigue syndrome) [54].

The study of 369 patients reported the presence of mental illnesses in 40% of patients and chronic fatigue in 40.3% of patients within 41.3 months after SARS infection [55]. A comparative analysis of neurological manifestations, related to coronaviral infection caused by different types of CoVs in humans, demonstrated that CNS damage was more frequent in COVID-19 (71% vs. 64% in SARS and 60% in MERS cases), whereas the frequency of encephalitis in COVID-19 was less pronounced (14% vs. 18% in SARS and 40% in MERS cases) [56]. Since a probable role of other CoVs in the development of specific neurological diseases has been identified, similar properties may be attributed to SARS-CoV-2. The meta-analysis conducted in 2021, based on 136,746 COVID-19 patients, demonstrated that the frequency of Guillain-Barré syndrome was 0.15%, which was significantly higher than in the general population [57].

It should be noted that published data also described a case of developing Guillain-Barré syndrome as a consequence of MERS infection [58]. Since clinical manifestations of Guillain-Barré syndrome include a polyradiculopathy, associated with dysimmune processes [59], it can be assumed that pathological immune changes are the most important cause of neurological impairment in patients after COVID-19 recovery. At the same time, according to a meta-analysis of data collected on 103,874 COVID-19 patients, the presence of Parkinson's disease was significantly associated with an unfavorable outcome of infection and mortality in hospitalized patients, especially in the elderly [60]. A similar association was determined in the meta-analysis of 46,391 patients with dementia [61]. This indicates the presence of common pathogenetic mechanisms of a specific neurological pathology caused by the impact of SARS-CoV-2 on the brain. The mediators of these changes are virus-activated RE, which affects epigenetic factors, involved in immune pathological processes and neuronal functioning in the CNS [50]. Since REs are the sources of specific non-coding RNAs (ncRNAs), which include small ncRNAs (microRNAs are the best known of them) [12] and lncRNAs [13, 14], the activation of REs mediates ncRNAs. Indeed, the largest amount of ncRNA is transcribed in the brain, which is consistent with a high phenotypic diversity of neurons, since ncRNAs regulate the expression of protein-encoding genes. For instance, 849 of 1,328 known lncRNAs are actively expressed in the murine central nervous system. At the same time, they are related to the genes functioning in the brain [62].

Human lncRNAs share a similar expression model with neurogenesis genes via regulating their expression. The examples include *9930014A18Rik, C230034O21Rik, 2610307P16Rik, Gm14207, Gm17566, Gm16758, MIAT*, and *RMST* [63]. Several lncRNAs (BC1) are used for post-transcriptional regulation of specific genes in neuronal dendrites in the brain [64]. The role of specific microRNAs in the development and functioning of the human brain has also been proven. For instance, miR-137 (regulates the expression of the *Mib1* and *Ezh2* genes), miR-34a (affects the *synaptotagmin-1, syntaxin-1A,* and *TAp73* genes), miR-221 and miR-222 are involved in control of neuronal differentiation. The formation of dendrite spikes is controlled by miR-21 due to the silencing of the *SPRY2* gene; of axonal regeneration, by miR-431 (suppresses the expression of the *Kremen-1* gene); of axonal development, by miR-9 (causes repression of microtubule-associated MAP1B protein); and of axonal growth, by miR-17-92 and miR-431 (affect *PTEN* gene) [65]. Since epigenetic changes in the expression of protein-coding genes and REs, associated with ncRNAs, are reversible, it is promising to determine the pathological activation of specific ECs in the brain of patients after recovery from COVID-19 in order to use miRNAs for their targeted action. The obtained data could also become the basis for preventing brain damage caused by changed expression of REs due to SARS-CoV-2 infection.

The effect of retroelements on neurological impairment caused by COVID-19

Hypomethylation, which was significantly associated with ischemic stroke in the study of 280 individuals [66], reflects a

pathological activation of REs. Accordingly, an increased risk of stroke in COVID-19 patients would also indicate a stimulating effect of SARS-CoV-2 on REs expression as a factor of developing disease complications. Indeed, the study of 214 COVID-19 patients in Wuhan demonstrated that, along with specific manifestations of the disease, 36.4% of patients had neurological complications, which, in turn, affected disease severity. For instance, 5.7% of patients with severe COVID-19 developed an ischemic stroke. At the same time, the frequency of this complication was only 0.8% in the general sample of patients [67]. In France, neurological symptoms (impairment of the corticospinal tract) were found in 14% of 58 hospitalized patients with COVID-19 on admission to the intensive care unit (ICU) and in 67% after withdrawal of muscle relaxants and sedation [68]. Neurological impairments, accompanying COVID-19, include smell abnormalities (dysosmia and anosmia), which are observed in 85.6% of patients, and taste disorders (in 88%). It is worth noting that in 11% of cases, anosmia occurs prior to other clinical manifestations of the infection [69].

The study of 730 patients recovered after COVID-19 in China, revealed that 96.2% of them were diagnosed with symptoms of severe post-traumatic stress [70]. A meta-analysis based on 3,868 patients revealed the development of delirium in 27% of COVID-19 patients [71]. It should be noted that brain damage in COVID-19 is a factor of elevated mortality in patients. Hence, according to a meta-analysis based on the results of 10 original studies involving 1,296 patients, who were treated via extracorporeal membrane oxygenation (ECMO), a mortality rate was 36% in the general group, whereas it achieved 92% in patients with neurological symptoms [29]. In another study, based on the data from 20 publications, the development of delirium was more frequent in elderly patients and significantly correlated with a higher risk of adverse COVID-19 outcomes [28]. It should be noted that older people had accelerated neurodegenerative processes after COVID-19 recovery [72]. This finding could be explained by an increased pathological activation of REs occurring in the brain during ageing [17].

The meta-analysis, conducted in 2021, based on the data collected on 2,533 hospitalized COVID-19 patients from different countries reported the development of neurological symptoms in 73% of cases. The main manifestations were headache (1.8-20.4%), myalgia (1.8-32.4%) and impaired consciousness (1.8-21.3%). Nonspecific encephalopathy developed in 13-40% of patients with neurological complications. In addition, acute demyelinating encephalomyelitis, acute necrotizing encephalopathy, generalized myoclonus, Bickerstaff brainstem encephalitis, limbic and mixed encephalitis, acute transverse myelitis, cerebral venous sinus thrombosis, hemorrhagic stroke, posterior reversible encephalopathy syndrome, and myoclonus were characteristic of the post COVID-19 condition [56]. The role of RE activation caused by SARS-CoV-2 is probable in the development of listed complications, since an enhanced RE expression results in inflammatory processes in the brain [73]. Peripheral nervous system damage was detected in 24% of COVID-19 patients [56]. In children, the development of neurological symptoms was observed less frequently. According to the meta-analysis based on the data from COVID-19 children, headache, myalgia and weakness were detected in 16.7% of cases, while more severe manifestations, such as encephalopathy, seizures, and meningeal signs in total were detected in just 1% of children [74].

A meta-analysis conducted in 2020 demonstrated accurate data on the prevalence of neurological manifestations in COVID-19 in adult patients: dysgeusia in 38.5%, dysosmia in 35.8%, myalgia in 19.3%, headache in 14.7%, dizziness in 6.1%, syncopes in 1.8%, ischemic stroke in 2.1%, hemorrhagic stroke in 0.4%, and cerebral venous sinus thrombosis in 0.3% [75]. According to another meta-analysis, anosmia occurred in 43.1% of COVID-19 patients, weakness was characteristic of 40%, fatigue was detected in 37.8%, dysgeusia was observed in 37.2%, myalgia took place in 25.1%, depression was noted in 23%, headache was complained for by 20.7%, anxiety was felt by 15.9%, and mental disorder was experienced by 8.2% of post COVID-19 patients [76].

It should be noted that the frequency of neurological manifestations accompanying COVID-19 slightly differs from country to country. For instance, the study of 514,459 SARS-CoV-2 infected patients, using six national digital surveillance platforms, revealed the development of anosmia and ageusia in 43% of COVID-19 patients in the USA, in 29% in the UK, and in 14% in Israel, which was significantly higher, compared with individuals with negative PCR tests [38]. These differences could be probably caused by specificity of RE distribution in the genomes of different populations, which affected their activation in response to SARS-CoV-2 in brain neurons with the development of complications [39-41]. According to instrumental research, intracranial hypertension was observed in 65% of COVID-19 patients, and leptomeningeal enhancement contrast on brain MRI was seen in 27% [77]. A meta-analysis of the EEG results of COVID-19 patients demonstrated an abnormal background activity and general deceleration in joint proportions in the majority of the patients (96.1%), along with the presence of epileptiform discharges in 20.3% of cases [78]. Due to high prevalence of neurological complications of COVID-19, it is necessary to determine their possible effects, the long-term consequences of the altered functioning of the brain, and the mechanisms of their development for possible correction.

Long-term neurological consequences of COVID-19

An activating effect of SARS-CoV-2 on REs [30-33] causes serious changes in brain functioning, which could persist for a long period after recovery. This is evidenced by the data of multiple original studies analyzed in the conducted meta-analyses. For example, the data on 47,910 individuals demonstrated that 14-110 days after COVID-19 recovery, 58% of them were diagnosed with unmotivated fatigue, 44% with headache, and 27% with an impaired attention [79]. A meta-analysis based on 15,244 hospitalized patients and 9,011 COVID-19 outpatients confirmed the presence of ageusia in 15-20% and anosmia in 10-20% of individuals 30 to 90 days after their recovery [80]. The development of reliable encephalitis as COVID-19 complication was determined in 0.215% of patients on average 14.5 days after the diagnosis (the study of 129,008 individuals infected by SARS-CoV-2). A mortality rate in these patients was 13.4%, while characteristic laboratory indicators included elevated serum inflammation and pleocytosis of cerebrospinal fluid [81].

According to the meta-analysis conducted in 2022, based on data from 11,324 COVID-19 patients, fatigue was observed in 37% of those, confusion in 32%, memory issues in 27%, impaired attention in 22%, myalgia in 18%, anosmia in 12%, dysgeusia in 11%, and headache in 10% of cases three months after infection. Neuropsychiatric abnormalities included an impaired sleep in 31%

of patients, anxiety in 23% of those, and depression in 12% of individuals [82]. A study of 215 patients with COVID-19 showed that four months after diagnosis, the incidence of persistent neurological deficits depended on the severity of COVID-19: 13.5% in those requiring intensive care, and only 1.2% in those who did not require hospitalization to the intensive care unit [83]. In a study of 2113 patients with COVID-19, 112 of whom were hospitalized, neurological symptoms persisted three months after infection, even after a mild and asymptomatic course of the disease. The most frequent complications (87%) were fatigue, anosmia, headaches, dizziness, and muscle pain [84]. One of the large-scale original studies that analyzed the consequences of 1,733 COVID-19 patients, reported the presence of unmotivated weakness in 63%, sleep disorders in 26%, and anxiety or depression in 23% of patients six months after their discharge from the Wuhan hospital [85].

The changes in neuropsychiatric functions are observed even a year after COVID-19 recovery. For instance, the Netherlands study of 452 patients demonstrated that 12 months after COVID-19 treatment at the intensive care unit, mental disorders were detected in 26.2% of examined patients, while cognitive impairment in 16.2% [86]. In a similar study of 171 patients hospitalized for COVID-19 treatment in Spain, 46.8% demonstrated neurocognitive impairments and 45% experienced mental disorders within a year after the treatment [87]. Besides, in a study of 156 patients from the USA, fatigue was diagnosed in 82% of patients, brain fog in 67%, and headache in 60% of COVID-19 patients on day 351 after SARS-CoV-2 infection [88]. Thus, neurological complications of COVID-19 persist for a long period after recovery in a significant part of patients, which represents a serious socioeconomic problem. To resolve it, it is necessary to determine the mechanisms of developing long-term effects of SARS-CoV-2 on the brain and peripheral nervous system. Identification of primary mechanisms of the viral effect could become the basis for diagnostic methods aimed at early detection of the nervous system impairment, and for the development of methods of treating neurological consequences. As has been already mentioned, the cause of long-term neurological consequences of COVID-19 includes activation of REs influenced by the virus [30-33], and REs have a regulatory effect on specific genes in neurons. The SARS-CoV-2 integration into the human genome via reverse transcriptase and RE endonuclease is also important [36], and has also been observed in other positive-stranded RNA viruses [37]. In this regard, it remains promising to study the role of ERs and microRNAs in these processes, which are also associated with vascular and immune disorders.

Vascular and immune factors of developing COVID-19 neurological complications

REs are important mediators of emerging vascular changes, which have a regulatory effect on the expression of angiogenic VEGF (vascular endothelial growth factor) and Tie-2 (protein kinase receptor) factors [34]. SARS-CoV-2 promotes production of plasma coagulation factor VIII, D-dimer and von Willebrand factor. At the same time, patients with severe forms of COVID-19 had hypercoagulation features, such as an increased fibrin formation, reduced fibrinolysis, and greater strength of blood clots [89]. Also, SARS-CoV-2 causes platelet hyperreactivity, which results in resistant hypercoagulation [90]. An additional factor includes inflammation-related enhanced blood viscosity [91]. The REs, which stimulate interferon production in the brain, are the mediators of developing inflammatory reactions caused by the virus [19].

SARS-CoV-2 is a direct cause of the development of acute ischemic strokes, as evidenced by the results of *post mortem* histological examination of the brain of passed away COVID-19 patients. The elevated levels of immune reactivity to the SARS-Cov-2 spike protein were identified in the thromboembolic regions [92]. An important role in these processes belongs to REs, activation of which is associated with stroke in humans [66]. Coagulation condition, accompanying COVID-19, especially in severe cases, may resemble the DIC syndrome. However, several distinctive parameters of this infection exist, since high D-dimer levels are not accompanied by thrombocytopenia, while prothrombin and partial thromboplastin, along with antithrombin levels, remain relatively normal, compared with the DIC syndrome [93].

Since neurological disorders more frequently manifest themselves in patients with severe course of COVID-19 [67, 68], immunopathological responses constitute a likely factor of their development, characteristic in these patients. Indeed, compared with moderate COVID-19 cases, severe course patients are more likely to demonstrate lymphopenia, enhanced levels of CRP, D-dimer, interleukins (IL)-2R, -6, -10, and tumor necrosis factor alpha (TNF-α). The absolute number of CD4+ and CD8+ T-lymphocytes declines in nearly all patients, especially noticeable in severe infection [94]. The key factor in CNS inflammation caused by SARS-CoV-2 is the activation of astrocytes and microglia [95], which are the main sources of cytokines in the inflamed CNS, including interferon and interleukins involved in the development of a cytokine storm in the brain [96]. The consequences of such responses are microgliosis and the formation of microglial nodules in the CNS, which may affect the development of long-term, often irreversible, neurological consequences of COVID-19 [97]. It is worth noting that REs mediate immunopathological changes in this disease because SARS-CoV-2 has an activating effect on REs, which plays an important role in the regulation of the immune system functioning [20-22].

Direct effect of COVID-19 on the brain

The ACE2 expression in neurons and glial cells [98], along with the presence of viral antigens with antibodies to them [99] and SARS-CoV-2 RNA in the cerebrospinal fluid of COVID-19 patients [100], constitute the evidence of SARS-CoV-2 direct effect on CNS tissue. Antibodies to the virus in the cerebrospinal fluid were detected in 77% of infected subjects [101]. Besides, the clinical study of 193 COVID-19 patients revealed that a positive PCR test for SARS-CoV-2 in the cerebrospinal fluid significantly correlated with intracranial hypertension (10% versus 0% of patients with normal intracranial pressure) and leptomeningeal enhancement on contrast MRI of the brain (25% versus 5%) [77]. A detailed examination of 33 COVID-19 patients via electron microscopy of biopsies from the nasal mucosa and nasopharynx revealed that SARS-CoV-2 penetrated into the brain through the olfactory mucosa along olfactory sensitive nerve fibers. The virus is characterized by tropism to neurons, thereby affecting the most sensitive neuroanatomic regions, such as respiratory and cardiovascular centers in the medulla oblongata [92]. In addition, brain regions responsible for memory, learning, and emotional responses represent preferred regions of viral reproduction,

where various types of impairment (inflammatory, neurotransmissive and neurogenetic) occur [102].

Activated macrophages, inducing TLR4/MyD88 signaling pathways followed by developing the inflammatory process (encephalitis), are detected directly in the brain tissues of COVID-19 patients. As a result, an enhanced expression of cytokines, including CC chemokine ligand 2 (CCL2), interleukins (IL-6 and IL-18) and soluble intercellular adhesion molecule-1 (sICAM-1), is detected in the cerebrospinal fluid of affected patients [92]. A significant increase in inflammatory indicators, e.g., ferritin, D-dimer, IL-6 and IL-10, is observed in such COVID-19 complication as stroke [101]. Clinical data on SARS-CoV-2 penetration into the brain and a direct pathogenic effect on neurons were experimentally confirmed. It was demonstrated that the virus actively penetrates neuronal stem cells, where it successfully reproduces [103].

A severe impairment of the lung tissue plays an important role in diminished functioning of hypoxia-sensitive neurons, since it is accompanied by a reduced oxygen content in arterial blood. This causes axonal damage and necrosis of neurons, which is detected by histological examination of brain tissues obtained from deceased COVID-19 patients [92]. Indeed, patients with severe COVID-19 (with observed severe hypoxemia) were characterized by more frequent occurrence of neurological deficiency [86, 104]. A significant correlation between the development of long-term brain lesions and degree of hypoxia in COVID-19 patients was revealed [105], involving the development of hypoxic encephalopathy. The latter is determined by instrumental methods. Accordingly, MRI examination of 749 SARS-CoV-2 infected patients with neurological deficiency demonstrated that changes in the intensity of cerebral cortex signals were observed in 37% of them [106].

A link between SARS-CoV-2 and microRNAs

Since ncRNAs play an important role in regulating the expression of genes required for normal functioning of neurons, a modified activity of specific ncRNAs, caused by the virus, could be among the possible mechanisms of the SARS-CoV-2 direct effect on the brain. These processes are influenced by REs, which were the sources of microRNAs in evolution [12], and, hence, they contain complementary nucleotide sequences in their structure. Accordingly, one of likely ways of SARS-CoV-2 effect is its interaction with specific microRNAs, regulating REs at the post-transcriptional level. Indeed, elevated levels of 35 different microRNAs and reduced levels of 38 microRNAs were detected in the blood serum of COVID-19 patients, compared with healthy controls. They target genes encoding peptidases, protein kinases, and the functioning of the ubiquitin system [107]. The expression of specific miRNAs also turned out to be different depending on the severity of the course of COVID-19, which indicates their involvement in the pathogenesis of the disease. Higher levels of miR-15b-5p and miR-486-3p, miR-486-5p, and lower levels of miR-181a-2-3p, miR-31-5p and miR-99a-5p were found only in severe COVID-19 cases vs. the control. No changes were detected in mild to moderate severity cases. The researchers concluded that miR-146a-5p, miR-21-5p, miR-142-3p and miR-15b-5p involved in the mechanisms of infection could be used for targeted COVID-19 therapy [108]. The greatest potential belongs to miR-200 that is essential for the virus penetration into cells. This microRNA suppresses the expression of the *ACE2* gene by attaching to the 3'-untranslated region of its mRNA [109]. In addition, miR-98-5p, which targets the mRNA of the *TMPRSS2* gene expressed by endothelial cells and is compulsory for the fusion of viral and cell membranes, is of great importance [110].

The SARS-CoV-2 virus can also capture the host microRNA, which allows modulating biological processes in the cell. Twenty-eight human microRNAs interacting with the SARS-CoV-2 genome have been predicted. They target 800 genes including those involved in immune response. These microRNAs are also important potential targets for the development of effective COVID-19 therapy [5]. In 2022, the results of a study of microRNAs in the blood plasma in 96 COVID-19 patients were published, characterized by a significant differential expression of 200 microRNAs, 75 of which were specific for mild and asymptomatic infection. The patients with severe COVID-19 demonstrated an enhanced expression level of 137 microRNAs, compared with the moderate disease severity patients [111]. Furthermore, microRNAs highly specific for COVID-19 have been identified; They could be used as biomarkers of this infection. They include miR-155 (90% sensitivity and 100% specificity), an expression level of which directly correlates with COVID-19 severity and mortality [112]. Similar properties were reported for miR-320b and miR-483-5p [113]. The study of microRNAs, specific for the development of targeted COVID-19 therapy, is promising: it was suggested to use miR-1307-3p and miR-3613-5p, suppressing SARS-CoV-2 reproduction due to interaction with 3'-untranslated regions of their genes [114].

It should be noted that 29 potential miRNA precursors were identified in the SARS-CoV-2 genome, mature miRNAs of which target 1,367 different human genes involved in transcription, metabolism, defense systems, and WNT and EGFR signaling pathways [115]. In another study, 45 candidate viral pre-microRNAs were identified, 15 of which were transcribed from the opposite strand of the genome. Seventy-three human genes have been identified as targets of these microRNAs, some of which were activated under the influence of the virus via the interaction of their promoter regions with viral microRNAs. For instance, miR-147-5p, miR-198-3p, and miR-66-3p stimulate *CXCL16*/*RRB2*, *ADAR*, and TNFa encoding gene, correspondingly [5]. In addition, five short sequences, each 24-27 nucleotides in length, identical to specific regions of the human DNA (Human Identical Sequences – HIS) have also been identified in SARS-CoV-2 genome. It is assumed that HIS could directly interact with the host genome and result in the activation of enhancers of certain genes, such as *HAS2* (hyaluronan synthase 2), which may explain high levels of hyaluronate in blood plasma of COVID-19 patients [116]. The expression of COV2-miR-O7a.1 and COV2-miR-O7a.2 viral microRNAs, transcribed from ORF7a and processed by *DROSHA* in humans, was established in human cell lines and in the samples of nasopharyngeal smears of SARS-CoV-2-infected patients via reverse transcription PCR [117].

Conclusions

REs are environment-sensitive components of the human genome responding to viral infection with pathological overexpression, which triggers the development of long-term neurological complications in COVID-19. This is due to both the direct activating effect of SARS-CoV-2 on REs and the indirect effect of microRNAs, which are promising tools for targeted action on RE-induced epigenetic changes in brain neurons in the course

of COVID-19. The role of REs in the development of neurological complications of COVID-19 is confirmed by the following findings. 1) RE activation under SARS-CoV-2 was revealed [30-33], while REs are key regulators of the expression of specific neuronal genes [23, 24]. Accordingly, pathological translocations of REs could result in impaired functioning of the central nervous system. 2) COVID-19 is accompanied by immunopathological processes involved in developing neurological pathology during and after the infection [94-96]. At the same time, COVID-19 is characterized by a pathological activation of REs, involved in the development of immunopathological reactions [20-22]. 3) It has been proven that RE derepression, which causes many pathological states including neurodegenerative diseases, is age-dependent [118]. This may explain more severe course of COVID-19 with the development of neurological symptoms in the elderly, since the virus strengthens the pathological effect of REs on brain functioning. 4) The role of REs in SARS-CoV-2 integration into the human genome was described [36]. Since virus penetration into the brain during infection has been proven [77, 99-101], such changes could cause pathological gene expression in neurons and the development of long-term neurological pathology. 5) REs are the most important sources of microRNAs [12] and human lncRNAs [13, 14] that play a key role in regulating gene expression in the brain and are involved in COVID-19 pathogenesis. 6) The described association of telomere shortening with more severe course of COVID-19 [42] may be attributed to a greater degree of RE dysregulation, since REs control telomeres functioning in the genome, while telomeres [44] and telomerase evolved from REs [45]. Coronaviruses can cause Parkinson's disease [49] and MS [46-48], which mediate activation of REs under the viral influence, since the association of activation of LINE1 elements with Parkinson's disease [50] and of endogenous retroviruses with MS were reported [51]. Since REs demonstrate reversible epigenetic changes in gene expression in the brain with the participation of ncRNAs, a promising direction in the development of COVID-19 therapy is the use of microRNAs for targeted therapy [108-110, 114] as biomarkers of the type and severity of CNS disorders caused by SARS-CoV-2 [112].

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Conflict of interest

The authors declare no conflicts of interest.

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