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# Neurological Complications of COVID-19 in the Elderly

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SARS-CoV-2 virus is a β-coronavirus and produces a severe viral pneumonia which can be complicated by acute respiratory distress syndrome and multiorgan failure. As knowledge of the new coronavirus infection (COVID-19) increases, it has become known that SARS-CoV-2 has pronounced neurotropism, producing a wide spectrum of neurological complications. This article addresses the characteristics of the neurological complications of COVID-19 in elderly people.

**Keywords:** COVID-19, coronavirus, SARS-CoV-2, neurological complications, encephalopathy, neurodegenerative diseases.

Coronaviruses are a family of RNA-containing viruses and have been known for more than 50 years. They include the pathogens of acute respiratory syndromes such as SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (COVID-19). An outbreak of SARS-CoV-1 occurred in 2002 and studies of the new virus in subsequent years showed that the virus had tropism not only for the lungs, but also for nervous tissue [1]. Results from studies of autopsy specimens in 2005 identified the coronavirus in the brain and demonstrated neuron death, glial hyperplasia, and local edema [2]. It was suggested that the virus penetrates into the brain mainly via the olfactory nerve [1]. Patients with SARS-CoV-1 experience headache, vertigo, ataxia, hypogeusia, hyposmia, stroke, myopathy, and epileptic seizures. These neurological complications were seen in 36.7% of patients with COVID-19 [3, 4]. Elderly and old people are more susceptible to COVID-19 than young people. Various pain syndromes (headache, myalgia) are associated with COVID-19, along with anosmia, dysgeusia, meningitis, encephalitis, epileptic seizures, cerebrovascular diseases, and encephalopathy. In addition, chronic COVID-19 can develop (postcovid syndrome), as well as decompensation of neurodegenerative diseases on the background of infection.

The aim of the present work was to analyze the characteristics of the neurological complications of COVID-19 in the elderly.

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**Pathogenesis of COVID-19.** SARS-CoV-2 spike protein has resemblance to angiotensin-converting enzyme 2 (ACE2) and uses its receptors to penetrate into cells. ACE2 receptors are present in many human tissues, for example, the membranes of pneumocytes, small intestinal enterocytes, arterial and venous endothelial cells, nerve and glial cells, and also smooth muscle cells in most organs [5].

The direct action of the virus on ACE2 receptors on vascular endothelial cell membranes provokes the development of an inflammatory response and leads to increases in inflammatory cytokine concentrations. COVID-19 patients show increases in the quantities of proinflammatory cytokines (tumor necrosis factor, interferon-γ, interleukin (IL)-1, IL-2, IL-6, and IL-8) and anti-inflammatory cytokines (IL-4 and IL-10) [6, 7]. The inflammatory cascade in turn damages vessel walls and increases prothrombotic factor production [8].

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Studies have indicated that 58% of patients with COVID-19 have antiphospholipid antibodies, 64% have lupus anticoagulant, and 9–10% have anticardiolipin anti-

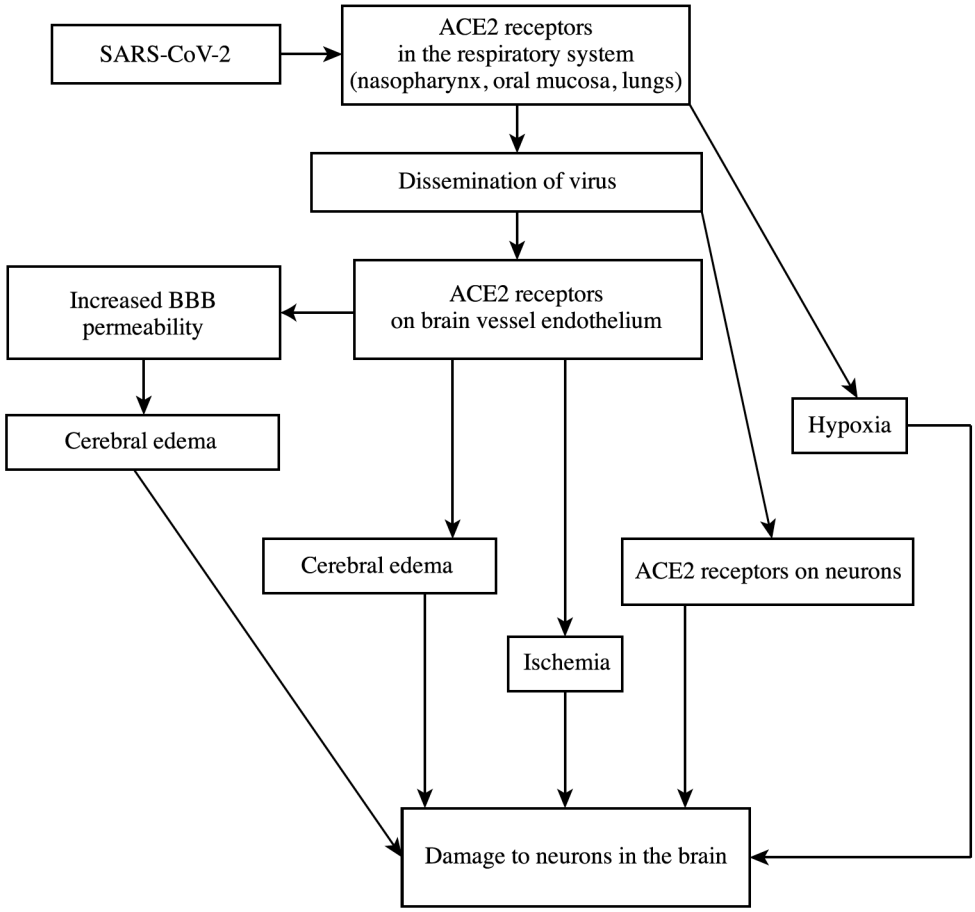


Fig. 1. Main mechanisms of damage to neurons in the brain.

bodies. It has been suggested that patients develop antiphospholipid syndrome leading to hypercoagulation and thromboses [9, 10].

Thus, SARS-CoV-2, acting on ACE2 receptors, induces the following: production of inflammatory cytokines, vessel wall damage, impairments to the blood clotting system, increases in the permeability of the blood:brain barrier (BBB), and dysregulation of the renin-angiotensin system (RAS), which can lead to arterial hypertension, blood pressure (BP) variability, and impaired electrolyte balance.

It has been noted that the virus can have a direct action on brain tissue in COVID-19 patients. ACE2 receptors, which SARS-CoV-2 uses to enter cells, are present on neuron and glial cell surfaces [11]. Two possible pathways for entry of the virus into the brain have been considered: retrograde axonal transport from peripheral olfactory neurons and across the BBB, which becomes permeable because of vascular endothelial damage and the development of an inflammatory response [7, 12, 13]. Having entered the CNS, the virus can also infect astrocytes and glial cells, provoking release of inflammation mediators and reactive oxygen species, inducing a cascade of neuroinflammatory processes in the brain [14].

In COVID-19, cerebral hypoxia can develop on the background of respiratory and/or cardiovascular failure, and also as a result of neuroinvasion with damage to the vasomotor and respiratory centers [14].

The main mechanisms of neuron damage in the brain are shown in Fig. 1.

**Neurological Complications in the Acute Phase of COVID-19.** *Acute cerebrovascular accident (ACVA).* One of the most severe complications of COVID-19 is ACVA, which is often encountered in elderly people. Data from the World Stroke Organization indicate that the risk of developing ischemic stroke (IS) in patients with COVID-19 ranges from 2.8% to 8.7% in the first days after onset of respiratory symptoms, at a mean seven days after onset of COVID-19 symptoms [4, 15]. In addition, mortality from stroke among patients with COVID-19 is 5–6 times greater than among patients without COVID-19 [8, 16].

Risk factors for more severe course and death in COVID-19 are male sex, age >65 years, smoking, obesity, arterial hypertension, diabetes mellitus, and cardiovascular disease [17]. These risk factors for stroke and severe course of acute respiratory syndrome are clearly the same. Elderly patients more often have cerebrovascular impairments, which more often lead to lethal outcomes.

IS develops most frequently in COVID-19 – shown by studies to occur in 90.3% of cases [8]. IS has uncertain caus-

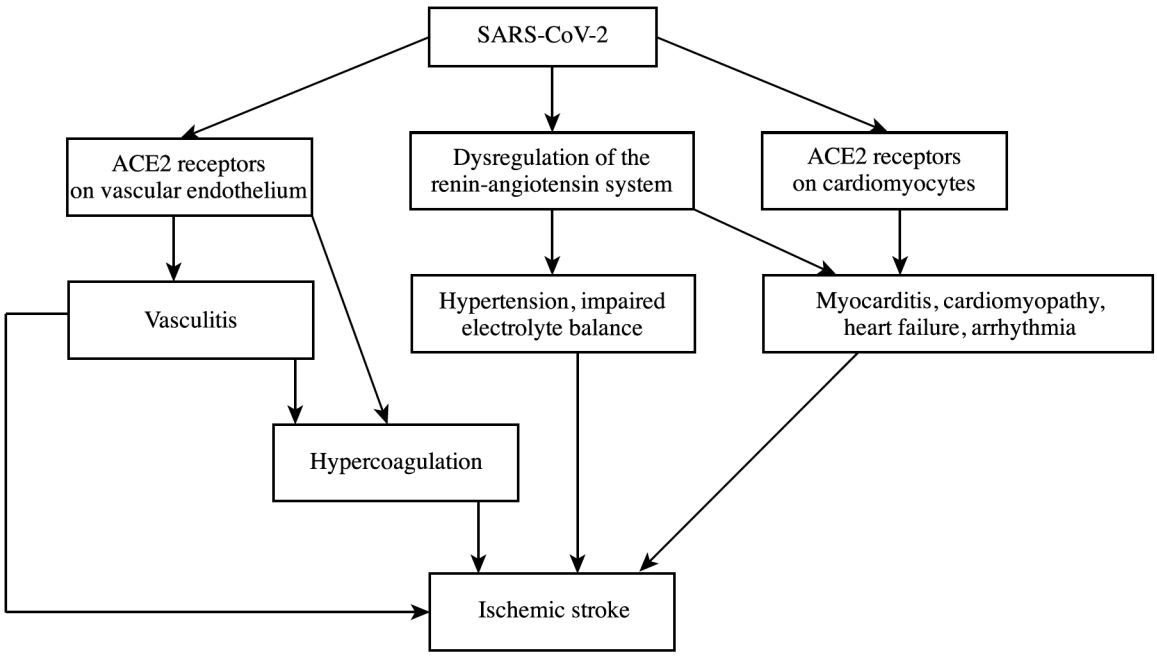


Fig. 2. Main mechanisms of development of ischemic stroke.

es in 65–70% of cases [18, 19], while IS is due to cardioembolism in 9.9–22% of cases [19, 20]. Stroke in COVID-19 is particularly characterized by damage to the large vessels. The probability of large vessel damage in COVID-19 is 2.4 times greater than in patients without COVID-19 [20, 21].

IS on the background of COVID-19 mostly affects the frontal and temporal-parietal areas, which may be linked with the greater area of these structures [8, 20, 22]. Multifocal strokes are seen in 10–28% of cases [8, 20].

The main pathogenetic mechanisms of development of IS in COVID-19 may be vasculitis induced by an immune response to damaged vascular endothelium, hypercoagulopathy, and cardioembolism.

Heart damage and clinically significant arrhythmia are seen in about 10% of patients hospitalized with COVID-19 and 20–40% of patients requiring intensive care for coronavirus infection [23]. ACE2 receptors are found in the largest numbers on the membranes of cardiomyocytes and smooth muscle cell membranes in hart vessels [24]. Direct damage to the myocardium by SARS-CoV-2 occurs with development of viral myocarditis; damage is promoted by an immune response consisting of activation of IL-6 with development of a cytokine storm [25]. Impairments to regulation of the RAS lead to electrolyte imbalance, which also affects heart function [24]. Patients develop myocarditis, cardiomyopathies, heart failure, and arrhythmia. Changes in heart functioning are aggravated by hypercoagulation with thrombus formation, which can increase the risk of developing cardioembolic stroke [26].

The main mechanisms for the development of IS in COVID-19 are presented in Fig. 2.

The treatment of IS on the background of COVID-19 can use surgical revascularization methods. There are as yet no data indicating that the presence of COVID-19 adversely affects recanalization success [27].

Low molecular weight anticoagulants are indicated for prevention of thrombosis in patients with ACVA in COVID-19, particularly in patients in the intensive care unit and patients with cardioembolism [26]. Use of anticoagulants decreases the risk of death in patients with high D-dimer levels [28]. Studies indicate that patients with IS and COVID-19 receiving anticoagulant therapy have mortality two times lower than in those not receiving prophylactic doses of anticoagulants [29]. However, careful evaluation of the risks and benefits of using anticoagulants must be made, as disordered and unevidenced use can lead to the development of hemorrhagic complications [11]. Intravenous administration of Alteplase can also increase the risk of hemorrhagic transformation in COVID-19. Thus, in a study reported by Ntaios et al. [22], of 174 patients with IS on the background of COVID-19, hemorrhagic transformation occurred in 12%, of whom 20% had received thrombolytic therapy.

As noted above, SARS-CoV-2 has direct injurious actions on brain vessels, provoking wall rupture and hemorrhagic complications [30]. Furthermore, increases in BP on the background of dysregulation of the RAS induced by viral invasion can also contribute to the development of hemorrhages.

The development of hemorrhagic stroke in COVID-19 patients almost doubles the risk of lethal outcome [31]. Studies have indicated that hemorrhagic complications are typical of younger patients [11]. More than half of pa-

tients with COVID-19 show subarachnoid hemorrhages, while intracerebral hemorrhages are seen in about a third of patients [31].

BP variability on the background of RAS dysfunction and damage to cerebral vessel walls, as well as the increased BBB permeability on the background of COVID-19, can lead to the development of posterior reversible encephalopathy syndrome (PRES) with a hemorrhagic component [32]. Patients form vasogenic edema in the parietal-occipital area, producing transient visual and cognitive impairments (CI) and convulsive seizures [33].

The fact that there has been a significant increase in the level of anxiety and stress in the population during the pandemic cannot be ignored. Social isolation, constant anxiety for their health and the health of relatives, and changes in the usual mode of life are inevitably reflected in catecholamine levels. Excessive adrenergic stimulation leading to marked vasospasm and impaired microcirculation represent another possible cause provoking the development of ACVA during the COVID-19 pandemic [34].

*Encephalopathy*. Encephalopathy usually refers to multifocal or diffuse brain dysfunction. The main signs of encephalopathy are degradation of cognitive functions (CF). These and other impairments to CF, from mild reductions in memory and attention to severe impairments, are seen in 43–66.8% of patients hospitalized with COVID-19 [35]. In addition, encephalopathy may be apparent as patients complaining of pain, impaired sensation, and loss of balance.

About 50% of patients hospitalized with hyperthermia of over 39°C and decreased oxygen saturation had signs of encephalopathy such as ataxia, dimmed consciousness, and impaired CF. On the background of normalization of status, signs of encephalopathy generally regressed [4].

Acute encephalopathy is usually apparent in other ways and the condition is characterized by signs such as dimming of consciousness, which can reach the level of coma. Changes typical of encephalopathy such as disorientation, agitation, and increased sleepiness are rarely encountered in patients with mild COVID-19 (no more than 5%), though they are frequent among elderly patients with acute respiratory distress syndrome [36, 37]. Some 84.3% of patients in intensive care units with COVID-19 are patients with delirium, encephalopathy, and/or other neurological impairments. These patients have a worse prognosis and often require intubation; the duration of intensive care stays is greater in these patients than in those without neurological complications [38].

Factors influencing the development of encephalopathy in elderly patients with COVID-19 are the presence of vascular risk factors, hypodynamia, diabetes mellitus, metabolic syndrome, etc.; cerebral hypoxia on the background of respiratory and cardiovascular failure in COVID-19; other metabolic impairments on the background of multiorgan failure (affecting the kidneys and liver); multiple foci of cerebral ischemia of the background of vasculitis, coagulopathy, and hypertension typical of severe COVID-19; the duration of medication-induced sedation and high doses of sedative drugs, especially in intubated patients; cerebral edema as a result of elevated BBB permeability; release of inflammatory mediators such as tumor necrosis factor and IL-6 on the background of COVID-19 can induce activation of the microglia, leading to neuron death and encephalopathy; direct damage to cerebral neurons by SARS-CoV-2. Studies indicate that 72% of patients with history of CI reached the level of dementia in the six months following COVID-19, while patients with dementia accounted for 16% of all those dying on the background of COVID-19 [39, 40].

The development of IS on the background of COVID-19 is an important predisposing factor for the development of CI and dementia after recovery from COVID-19. In almost 20% of patients with dementia after COVID-19, CI arose on the background of thromboembolism of the large cerebral arteries. However, the main contribution to the development of severe CI after COVID-19 is made by small vessel pathology in the brain. Thus, about 80% of cases of vascular dementia are linked with small brain vessel pathology. This is confirmed by neuroimaging: 50% of patients with dementia showed changes in the white matter due to damage to small cerebral arteries. Neuroimaging data confirmed the occurrence of microstructural brain damage three months after regression of the main symptoms of COVID-19 [41]. Some 20–40% of patients admitted to intensive care units for treatment for COVID-19 displayed persistence of reductions in CI after recovery [42].

Impairments to CF in the form of slowing of psychomotor reactions and feelings of "brain fog" and "torpidity" can arise in the context of the chronic phase of COVID-19.

In addition, considering the characteristics of the pathogenesis of SARS-CoV-2, it has been suggested that the virus can provoke the development of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, which are accompanied by CI and dementia [34].

*Meningitis and encephalitis*. Results from studies using the polymerase chain reaction (PCR) to detect SARS-CoV-2 RNA in cerebrospinal fluid (CSF) are contradictory, with negative findings in most studies. However, there are some studies confirming the presence of viral RNA in the CSF in patients with COVID-19 and clinical meningitis and encephalitis [44, 45]. In some studies, the CSF of patients with COVID-19 was found to contain antibodies to SARS-CoV-2. In addition, a number of studies have noted increases in CSF IL-6 levels in COVID-19 patients [46].

Studies of SARS-CoV-1 autopsy material revealed signs of demyelination, along with viral proteins and antigens in the brain. Considering that the pathogenesis of coronaviruses is very similar, it can be suggested that SARS-CoV-2 may also have direct actions on neurons and glial cells in the brain [47].

Cases of encephalitis in coronavirus infection using neuroimaging for confirmation, along with histological

investigations after neurosurgical procedures, have been described. The temporal lobe was the most affected, while the thalamus and hippocampus could also be involved [36]. In addition, studies of autopsy specimens revealed SARS-CoV-2 in 53% of COVID-19 patients (21 cases) [48].

Most authors suggest that the most likely cause of the development of meningitis and encephalitis in COVID-19 is associated with activation of the microglia and increases in the formation of inflammatory mediators in the brain and development of a cytokine response, and not with direct neuron damage by SARS-CoV-2 [48, 49].

*Pain syndromes*. Headaches and muscle pains are often encountered in acute respiratory viral infections, especially in elderly patients [50]. These are linked mainly with increases in body temperature and production of pyrogens, as well as the direct action of the virus and activation of various inflammatory mediators [51].

Headaches are encountered in 1.7–33.9% of COVID-19 patients [52]. The following mechanisms of development of headache in COVID-19 patients have been considered [53, 54]:

– cerebral hypoxia due to viral damage to lung tissue can lead to cerebral vasodilation, meningeal edema, and consequent headache;

– given the presence of large quantities of ACE2 receptors in the brain, virus may have a direct action on nervous tissue;

– furthermore, responses to virus infection can include increases in inflammatory cytokine release;

– impairments to the functioning of the RAS on the background of coronavirus infection can lead to BP variability;

– increased permeability of the BBB with development of cerebral edema;

– coagulopathy typical of coronavirus infection with formation of ischemic foci.

About 38% of patients continue to experience headaches six weeks after coronavirus infection [42].

Myalgia is one of the commonest complications of COVID-19 and studies have shown that muscle pain is encountered in 35–50% of COVID-19 patients. In elderly patients, muscle pain is reminiscent of the symptoms of polymyalgia rheumatica.

Myalgia in COVID-19 is associated with direct damage to muscle tissue by the virus (musculoskeletal cells have ACE2 receptors), the development of a cytokine immune response to viral invasion, and muscle ischemia and hypoxia on the background of COVID-19 [54, 55]. Patients with myalgia and COVID-19 show increased levels of creatine kinase and lactate dehydrogenase, whose levels provide assessment of the severity of rhabdomyolysis [54].

Studies have indicated that myalgia arising on the background of COVID-19 can afflict patients weeks and even months after recovery [42].

*Impaired smell and taste*. Studies have indicated that impairments to olfaction are seen in an average of 41% of COVID-19 patients; the prevalence in reports from different authors varies from 3.2% to 98.3%, while impairments to taste are encountered in 38% of patients [56]. Impairments to taste and smell are noted to be more typical of young women, at the early stages of illness, in mild and moderate infections; in elderly patients, impairments to smell are found more rarely.

Impairments to taste and smell are quite often found in viral infections, usually being associated with edema of the mucous membranes of the nasal passages and abundant excretions interfering with the flow of air to receptors. This may be one of the numerous mechanisms of anosmia in COVID-19. However, many authors have suggested that obstruction of the nasal passages is not the only cause of development of anosmia in COVID-19. The respiratory system has a high concentration of the ACE2 receptors used by SARS-CoV-2 to enter cells [57]. It has been suggested that SARS-CoV-2 penetrates into the olfactory neuroepithelium of the nasal cavity, damaging it, and then reaches the olfactory bulb via the nerve [58]. Decreases in the volume and structural changes in the olfactory bulb have been confirmed by MRI brain scans in patients with anosmia in COVID-19, the severity of changes correlating with the severity of anosmia [59]. It is interesting that many patients note distortion of olfaction (cacosmia), which also points more to olfactory bulb damage than obstruction of the nasal cavity in COVID-19.

Degradation of the sense of taste can occur secondary to impaired olfactory function. In addition, the high concentration of ACE2 receptors on the mucosal surface of the oral cavity and direct viral damage to the mucosa may cause dysgeusia [58].

Impairments to smell and taste persist in every tenth COVID-19 patient for six months after regression of the other symptoms of the disease [42].

*Epileptic seizures*. Epileptic seizures quite rarely arise in COVID-19 – studies indicate that this occurs in 0.08–0.7% of cases [7, 60]. In most cases, epileptic seizures arose on the background of viral encephalitis and encephalopathy on the background of COVID-19 [61]. The causes of seizures include the following [62]: formation of large quantities of proinflammatory cytokines in the brain on the background of infection, inducing nerve cell apoptosis and death; increased BBB permeability and migration of proteins such as albumin, leading to impairments to the osmotic balance in the CNS and cerebral edema; ACVA (ischemic and/or hemorrhagic) can develop on the background of coagulopathy, vasculitis, and hypertension); the cerebral hypoxia typical of patients with severe lung damage in COVID-19 may be among the causes of epilepsy; impaired regulation of the RAS leading to electrolyte imbalance may also be a trigger for the development of epileptic seizures.

**The Chronic Phase of COVID-19 (postcovid syndrome).** Elderly patients with COVID-19 come up against the development of so-called postcovid syndrome, whose

neurological complications can include muscle weakness, chronic fatigue syndrome (CFS), chronic pain syndromes; CI, "brain fog," "torpidity;" depressive and anxiety disorders, post-traumatic stress disorder, and sleep impairment.

One of the key components in the pathogenesis of coronavirus infection is activation of oxidative stress due to increased concentrations of reactive oxygen species (peroxides, free radicals). Oxidative stress results in impairment to mitochondrial functioning [63, 64].

The mitochondria of skeletal muscles are the most sensitive to the actions of free radicals. Increases in the concentrations of reactive nitrogen and oxygen species with age are believed to lead to impaired mitochondrial functioning, wile impairments to their operation lead to the development of apoptosis and sarcopenia in elderly people. A similar situation evidently occurs in patients with COVID-19. Increases in the free radical concentrations impair mitochondrial function with subsequent decreases in adenosine triphosphate (ATP) synthesis, leading to muscle weakness due to reductions in strength and muscle mass [65].

Coronavirus inducing severe acute respiratory syndrome (SARS) was found to be able to provoke the development of CFS. Thus, for example, after the SARS epidemic in 2003, 54% of patients experiencing the coronavirus infection complained of general and muscle weakness and fatigue six months after illness, this reaching 60% by 12 months [66]. Surprisingly, symptoms of chronic fatigue persisted in 27.1–40.3% of subjects at four years [67]. Furthermore, symptoms of CFS were seen to persist for more than a year in half the patients experiencing MERS (Middle East Respiratory Syndrome, caused by a member of the coronavirus family, of which there a an epidemic in 2012) [68].

It has now been noted that 69% of patients hospitalized with COVID-19 complain of feelings of constant fatigue [69] and that many patients also experience symptoms of CFS after recovery, though as yet there are no statistical data on the occurrence of the syndrome in patients who have had COVID-19.

Damage to glial cells by SARS-CoV-2 leads to the production of inflammatory mediators, which may in turn lead to peripheral and central sensitization. Patients with COVID-19 can display reductions in the pain sensitivity threshold, allodynia, and hyperalgesia, with formation of chronic pain syndromes in different locations.

The inflammatory cascade, activation of oxidative stress, and mitochondrial dysfunction on the background of viral infection lead to impairments to the operation of the autonomic nervous system in the form of elevated sympathetic nervous system activity and decreased parasympathetic nervous system activity, including vagal nerve activity, which can be apparent as orthostatic hypotension, impairments to heart rate variability, impairments to sweating, digestion, and urination [63, 70]. In addition, dysregulation of the RAS on the background of coronavirus infection may lead to BP lability.

Elderly COVID-19 patients often present complaints of forgetfulness, distractibility, and decreased concentration of attention. Patients complain of the feeling of "brain fog" or "torpidity," with slowed thinking, difficulty in trying to concentrate on things, and the need to make efforts to remember things.

The causes of "brain fog" are unknown, though it is believed that these complications can occur as a result of dysfunction of the autonomic nervous system [70]. A correlation between impairment to heart rate variability and psychomotor reaction speed has been noted. Impairments to both the cognitive domain and the regulation of the autonomic nervous system can occur simultaneously on the background of neuroinflammatory processes [71].

Brain MR spectroscopy data in patients complaining of "torpidity" and "brain fog" revealed increases in brain temperature by 0.28–0.5°C as compared with the control group independently of body temperature, as well as an increase in the levels of inflammatory markers in the brain. It is of note that increases in brain temperature and lactate levels were noted in the same areas of the brain: the insula, thalamus, and cerebellum. Lactate is the product of cellular anaerobic metabolism and is not seen in large quantities in the brain in healthy people, though its concentration increases on the background of systemic inflammation. In aerobic glycolysis, ATP is synthesized in significantly smaller quantities, resulting in the appearance of an energy deficit possibly leading to mental fatigue [72].

Rasouli et al. [73] conducted a study of the cognitive domain in patients complaining of "brain fog" and "torpidity" on the background of CFS arising after neurotropic virus infection, for example, herpesviruses (Epstein–Barr virus, cytomegalovirus, human herpesvirus type 6). The study indicated that the leading symptom of impairment in the cognitive domain is slowing of psychomotor reaction speed, with lesser impairment to attention and memory. The study noted that subjective complaints of impaired CF did not correspond to objective results from neuropsychological tests. It is of note that the severity of complaints of memory and attention degradation correlated with the severity of fatigue, pain, and the presence of concomitant depression. It was suggested that a possible cause of the lack of correlation between the objective data and subjective feelings might be that the neuropsychological tests had insufficient sensitivity [73].

Depression, anxiety disorders, post-traumatic stress disorder, and sleep impairments are encountered in 30–40% of COVID-19 patients [42]. Elderly people's fear of the unknown disease and concern for own and relatives' health, hospitalization, and severe illness cannot fail to be reflected in psychoemotional state. Long-lasting chronic stress in conditions of social isolation and restrictions may also lead to the onset and exacerbation of anxiety and depressive disorders on the background of COVID-19.

Apart from the stress factor, it has been suggested that impairment to normal RAS functioning on the background

of coronavirus infection can induce subclinical systemic neuroinflammation leading to the development of depressive disorders [74].

Systemic neuroinflammation arising on the background of COVID-19 can accelerate the development of neurodegenerative diseases in elderly people. There is some similarity between the possible development of the neurodegenerative process after COVID-19 and the development of multiple sclerosis, one of whose etiological factors is preceding infections which appear to trigger the neurodegenerative process.

It is interesting that a study was published in 1992 in which patients with Parkinson's disease were found to have elevated levels of antibodies to coronavirus infection in the CSF and proposed that coronaviruses can induce degenerative disease [75].

*Neurodegenerative diseases*. Elderly age is one of the most important risk factors both for severe COVID-19 and the development of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. SARS-CoV-2 may be a trigger for the development of neurodegenerative diseases in patients with predispositions to them. These include people of elderly age (mainly men) with concomitant cardiovascular and metabolic diseases such as atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, or impaired glucose tolerance. These are risk factors for the development of severe COVID-19 and neurodegenerative diseases.

As already noted, the ACE2 receptors used by SARS-CoV-2 for entering cells are present on neuron and glial cell surfaces [11]. High ACE2 receptor concentrations in the brain are also seen in the olfactory bulb, substantia nigra, and the middle temporal and posterior cingulate gyri [12]. Attention is drawn to the fact that the brain areas most subject to the actions of SARS-CoV-2 are the areas involved in the neurodegenerative process in diseases such as Parkinson's disease and Alzheimer's disease. Several authors have suggested that some neurotropic viruses can increase the risk of developing Parkinson's disease, for example, hepatitis C and herpes zoster viruses. This list may in future be supplemented with SARS-CoV-2.

As noted above, it has been suggested that the entry portal for SARS-CoV-2 may be the olfactory nerve. Considering the occurrence of gastrointestinal symptoms in COVID-19 patients, these being associated with damage to intestinal enterocytes, the enteric nervous system and vagus nerve may also be pathways for penetration of the virus into the CNS. Furthermore, the early symptoms of Parkinson's disease, appearing long before diagnosis, are anosmia and impaired gastrointestinal tract function (constipation) [78].

Having entered the CNS, SARS-CoV-2 damages neurons in the brain, entering cells using ACE2 receptors. Neuron damage can activate the microglia and SARS-CoV-2 can also damage glial cells directly.

Microglia are brain immune cells which support normal homeostasis in the CNS. These cells take part in eliminating both damaged neurons and their components and defective or excessive proteins in the brain [79]. Activation of the microglia can lead to neuroinflammatory changes in the brain, while impairment of the operation of microglial cells leads to proteinopathy. The neuroinflammatory process and excessive accumulation of protein complexes are important trigger mechanisms for the development of the neurodegenerative process. The result of microglial activation is release of cytokines (IL-1, IL-6, tumor necrosis factor), as well as reactive oxygen species, high concentrations of which lead to the development of oxidative stress, which also leads to neurodegeneration [80].

A number of studies have noted that impairments to RAS play an important role in the development of neurodegenerative diseases [81]. Thus, interacting with ACE2 receptors, the coronavirus can provoke increases in the angiotensin II concentration, which in turn can lead to vasoconstriction. In addition, excessive angiotensin II, acting on AT1 receptors, leads to the development of inflammation, oxidative stress, and neurodegeneration.

Considering that neurodegenerative disease develops decades before the appearance of clinical symptoms and diagnosis, it can be suggested that COVID-19 produces sharp decompensation in patients in whom the neurodegenerative process is already developing.

It remains unknown what effect the coronavirus pandemic will have on the population 10–15 years into the future or whether the pandemic infection will induce neurodegenerative diseases in a couple of decades' time.

At present, given the neurotropicity of SARS-CoV-2, an important task is to seek drugs for treating patients in the acute phase of COVID-19 and preventing the sequelae of infection. One such drug may be Cerebrolysin – the only peptidergic drug with proven neurotrophic action supporting neuroregeneration and neuroplasticity [82]. Cerebrolysin has complex actions, affecting various components of the pathogenesis of SARS-CoV-2. Cerebrolysin decreases neuroinflammation and suppresses the cytokine storm; it also decreases the permeability of the BBB for foreign agents [83, 84]. In addition, Cerebrolysin improves the oxygen transport function of the blood, has neuroprotective actions, and protects brain cells from damage by suppressing excitotoxicity and decreasing apoptosis [85, 86]. By activating neurogenesis and neuroplasticity, Cerebrolysin produces neural recovery [87]. Studies have noted that Cerebrolysin decreases pathological protein production and reduces the extent of amyloid deposition, and stimulates neurogenesis in the subgranular zone of the dentate gyrus of the hippocampus in an experimental model of Alzheimer's disease [88].

Cerebrolysin is most effective in the treatment of stroke on the background of COVID-19 and in addressing the sequelae of cerebrovascular impairments. Studies have shown that Cerebrolysin decreases mortality and accelerates neurological recovery of patients after stroke, and also promotes recovery of the functional activity of neurons in patients after stroke, as demonstrated by functional MRI

brain scans [89, 90]. Thus, Cerebrolysin improves motor and cognitive functions, as well as psychoemotional state in poststroke patients, thus supporting their functional independence and decreasing disability [91].

Studies have noted that Cerebrolysin at a dose of 20 ml/day improves cognitive status and slows the progression of cognitive impairments in patients with dementia [92]. Given that the new coronavirus infection can provoke the development of neurodegenerative processes in the brain, Cerebrolysin should be prescribed to elderly patients with COVID-19.

Furthermore, Cerebrolysin is effective in the treatment and prevention of so-called postcovid syndrome in the elderly, decreasing fatigue and the severity of asthenic disorders [93].

**Conclusions.** Thus, Cerebrolysin can be regarded as a drug of choice for the medication-based treatment of the acute and chronic phases of COVID-19, especially in the elderly, considering its pathogenic and clinical efficacy, as well as its optimum efficacy and safety profile.

The authors declare no conflict of interest.

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