Postcovid Syndrome – The New Reality

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The second year of the COVID-19 pandemic has demonstrated the need for detection and assessment of the long-term consequences SARS-CoV-2 infection, including adequate cognitive functioning. This review addresses our current understanding of the direct and indirect mechanisms of nervous system infection in COVID-19, paying special attention to cause-effect relationships between SARS-CoV-2 infection and long-term neuropsychological disorders. Understanding the pathogenesis of neurological impairments in COVID-19 is important for studies of the long-term sequelae of the disease and for identifying preventive and therapeutic possibilities in relation to brain damage. Further studies of nervous system lesions in COVID-19 are clearly needed to expand existing knowledge. Early initiation of therapeutic measures for emerging disorders will probably have decisive importance for improving quality of life for many COVID-19 survivors.

Keywords: COVID-19, long-term sequelae, cognitive disorders.

The pandemic caused by SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2) has impelled closer study of the long-term sequelae of this virus infection. The acute clinical manifestations of coronavirus disease 2019 (COVID-19) have already been quite well studied and consist of pulmonary and extrapulmonary lesions [1]. However, there is now increasing data on the long-term sequelae of COVID-19.

The term “postcovid syndrome” covers pathological symptoms and syndromes persisting and/or appearing more than four weeks after the acute course of COVID-19 and whose development is not associated with other causes. A temporal classification of postcovid syndrome has been proposed: 1) subacute COVID-19 symptoms, including disease symptoms at 4–12 weeks after acute COVID-19; 2) chronic, including disease symptoms lasting more than 12 weeks from the onset of COVID-19 and not associated with any other cause [2].

It is important to note that complaints can arise both in COVID-19 patients who have been hospitalized and in patients treated at home [3]. Published data indicate a risk of long-term sequelae affecting the respiratory, cardiovascular, and nervous systems, the mental domain, the musculoskeletal system, the skin, and the kidneys [4].

Thus, interdisciplinary cooperation is important for providing complex care to COVID-19 survivors. It should be noted that people with severe acute-phase COVID-19 and those requiring intensive care, the elderly, and those with chronic diseases (respiratory diseases, obesity, diabetes, cardiovascular diseases, chronic renal disease, oncological pathology) are at higher risk of developing postcovid syndrome.

A prospective multicenter cohort study including 327 hospitalized patients aged over 18 years showed that three months after discharge, more than half (55%) did not feel healthy, while most patients (93%) had persistence of various symptoms or onset of new symptoms. The most widespread stable symptoms were fatigue (83%), breathlessness (54%), sleep impairment (46%), and pain (headache, myalgia, arthralgia). The authors emphasized significant degradation of quality of life among the patients interviewed, which was linked with decreased activity, anxiety, depression, and various pain disorders [5].

Results from a study in Italy provided evidence of persistence of disease symptoms in 87.4% of patients after hospitalization with COVID-19 at 60 days follow-up. Fatigue...
(53.1%), breathlessness (43.4%), joint pain (27.3%), and chest pain (21.7%) were the most frequently encountered; 55% of patients had three or more symptoms. Decreased quality of life in this study was seen in 44.1% of patients [6].

Serious concern is raised by data showing that COVID-19 can lead to long-lasting persistence of symptoms even in people with mild courses of illness and treated as out-patients. Results from one of the largest studies addressing the sequelae of COVID-19 in 73,435 patients receiving out-patient treatment and 13,654 hospitalized patients at six months of follow-up after acute illness were published. The risk of death during the follow-up period after COVID-19 was increased even in nonhospitalized patients. There were increases in cognitive and mental disorders, chronic fatigue, sleep impairments, thromboembolic complications, and metabolic, respiratory, cardiovascular, and gastrointestinal disorders. In addition, there were significant increases in the use of analgesics, antidepressants, anxiolytics, antihypertensives, and hypoglycemics. It is important to note that the risk level increased with increases in the severity of COVID-19 in the acute phase and that those patients requiring intensive care had the highest risk of long-term sequelae [7].

**Neuropsychiatric Disorders after COVID-19.** A cohort study conducted by the Global Consortium Study of Neurological Dysfunction in COVID-19 and the European Academy of Neurology showed that neurological manifestations were seen in 82% of patients hospitalized with COVID-19 (n = 3744). The commonest complaints among patients were headache (37%) and anosmia or ageusia (26%), while the commonest neurological complications were acute encephalopathy (49%), coma (17%), and stroke (6%), which produced the highest hospital death rate. In addition, the study noted that the presence of pre-existing neurological disease was associated with an elevated risk of developing neurological complications in COVID-19. Nonetheless, the long-term perspective for recovery of health of even recovered patients remains uncertain [8].

One of the commonest neurological disorders in COVID-19 is “cognitive COVID” a term designating impairment to cognitive functions during the acute phase of COVID-19 and/or after infection. These may appear in the form of impairments to consciousness, encephalopathy, delirium, etc. during the acute phase of COVID-19, as well as cognitive dysfunction on long-term follow-up of recovered patients. Impairments to attention and executive functions are typical signs of cognitive COVID [9–12].

It should be recognized that such symptoms as, for example, weakness, pain, and numbness are reported more frequently, as it is easier for patients to be aware of them. However, cognitive dysfunction may remain unnoticed, especially if mild. Despite the fact that cognitive deficit can last several weeks, the development of long-term disorders can lead to disability [13].

The results of a retrospective cohort study using data obtained from the TriNetX electronic medical records network demonstrated significant increases in neurological and psychiatric morbidity after COVID-19. Among 236,379 surviving patients, almost 33.6% received neurological or psychiatric diagnoses over the following six months. Anxiety disorders were seen in 17.4%, sleep disorders in 5.4%, peripheral neuropathy in 2.9%, ischemic stroke in 2.1%, dementia in 0.67%, and hemorrhagic stroke in 0.56%. It was also shown that patients with severe COVID-19 who had received intensive care had the highest risk of neuropsychiatric sequelae [14].

A study reported by Jaywant et al. found that neuropsychological testing of patients with severe acute-phase COVID-19 at a mean 40 days after discharge revealed cognitive deficit in 81%. Mild cognitive impairments were encountered more frequently than moderate or severe cognitive impairments. Changes mainly affected attention and executive functions, while the frequency of cognitive impairments was not associated with the presence of cardiovascular and metabolic diseases or the duration of mechanical pulmonary ventilation [15].

Data on cognitive dysfunction after COVID-19 in patients with mild and moderate-severe illness without complications are a particular cause for concern. Almost 80% of young patients (mean age 42 years) were shown by the results of a cognitive status screening study using a modified telephone interview to have mild cognitive impairments (mean duration of follow-up 85 days). Patients reported attention deficit, short-term memory disorders, word-finding difficulty, fatigue, and mood swings. Study results showed that cognitive impairments may be a common complication of COVID-19 in young people regardless of the clinical course of illness [16, 17].

Along with high levels of morbidity and mortality, COVID-19 has psychosocial effects. Large-scale fear of COVID-19, “coronaphobia,” and quarantine with self-isolation give rise to a multitude of mental disorders in the community, which can lead to cognitive sequelae in the long-term perspective [18].

Among the stress-inducing factors of the pandemic, the long-term potential threat to life, quarantine with self-isolation, the lack of persistent immunity, limited access to medical services, etc., are of particular importance.

Increases in the numbers of cases diagnosed with depressive, anxiety, and anxious-phobic, panic, anxious-depressive disorders, and post-traumatic stress disorder (PTSD) have been noted on the background of the ongoing pandemic. Patients who have had COVID-19, despite convalescence, the frequencies of depressive and anxiety disorders decreased insignificantly and was 14.9–30.4% immediately after discharge and 17.23% at six months [19].

In addition, prophylactic measures based on isolation during the COVID-19 pandemic had adverse influences on cognitive and mental health and everyday functional activity in patients with cognitive impairments throughout the world [20, 21]. This is associated with restriction to social contacts,
increases in feelings of loneliness and sadness, the development of aggravation of anxiety and depressive disorders and sleep impairments, and reductions in physical activity. Depression, social isolation, and lack of physical activity are known to be factors modifying the risk of dementia [22]. Thus, chronic stress as a consequence of the pandemic can in turn promote the development of or accelerate decline in cognitive functions in the longer term [23, 24].

Studies in Argentina demonstrated significant adverse effects of quarantine for COVID-19 on the health of patients with dementia. After eight weeks of self-isolation, elevated anxiety was noted in 43% of patients, sleeplessness in 28%, depression in 29%, and gait disturbance in 41%. It should be noted that anxiety, depression, and sleeplessness in patients with mild dementia were more prevalent than in a group of patients with severe dementia [21].

Another study showed that quarantine induces deterioration of mental state in almost 60% of patients with dementia and, as a result, the need for corrective therapy in a third of these cases. Irritability, apathy, agitation, and sleep disorders were the most frequent symptoms whose increases or appearance were reported by the patients [25].

**Mechanisms of Nervous System Changes in COVID-19.** Penetration of SARS-CoV-2 into host cells requires binding to receptors by means of a viral protein termed spike protein. SARS-CoV-2 binds to ACE2 receptors (angiotensin-converting enzyme 2, ACE2) on target cells. Despite the relatively low level of ACE2 expression in the human brain, there is evidence that neurons are the target for SARS-CoV-2. This is presumptively associated with the fact that even the basal level of ACE2 expression is sufficient for penetration of virus into neurons. In addition, there is a high probability that there are other neuron-specific factors for binding of virus with nervous system cells [26].

A receptor for penetration of SARS-CoV-2 into host cells termed neuropilin-1 (NRP1) was identified; this is widely distributed in human tissues, with predominant expression in vascular endothelial and smooth muscle cells in the retina, the epithelia of the respiratory and gastrointestinal tracts, and nervous system cells [27].

The neuroinvasive potential of SARS-CoV-2 can be explained in terms of the expression of these receptors in parts of the brain such as the cingulate gyrus, motor cortex, substantia nigra, ventricles, olfactory bulb, middle temporal gyrus, and brainstem nuclei. These zones are known to have an active blood supply, which promotes the neurotropic spread of SARS-CoV-2 [28, 29]. Histological studies of patients dying from COVID-19 showed that these areas of the brain contained diffuse petechial hemorrhages, lymphocyte and macrophage infiltration, neuron death, and axon degeneration [29-31]. Furthermore, abnormalities in the distribution of tau protein have been described, along with hyperphosphorylation in SARS-CoV-2-infected neurons, occurring in combination with obvious signs of neuron death, which is evidence of the potential neurotoxic action of SARS-CoV-2 [26].

It has been suggested that SARS-CoV-2 undergoes latent persistence in the CNS in patients who have had COVID-19, increasing the risk of long-term sequelae [32]. Studies of 60 patients (mean age 44.1 ± 16 years) hospitalized with COVID-19 using three-dimensional T1-weighted neuroimaging three months after the outbreak revealed microstructural changes predominantly in the olfactory cortex, hippocampus, insula, Heschl’s gyrus, and cingulate gyrus. These data point to potential long-term neurological sequelae in patients with severe forms of COVID-19 [33].

One hypothesis explaining the formation of the long-term sequelae of COVID-19 is that of the development of persistent brainstem dysfunction due to the high levels of expression of ACE2 receptors and NRP1 [34, 35].

However, ever more data are becoming available showing that neurological disorders in COVID-19 patients are more linked with secondary mechanisms of CNS damage. The immunological mechanisms of neurological complications are linked with high levels of proinflammatory cytokines, which may be the main causes of damage to nervous tissue. SARS-CoV-2 is believed to be able to infect macrophages, glial cells, and astrocytes in the CNS [36]. Studies of cytokines in plasma samples from patients with confirmed COVID-19 showed that levels were significantly higher than normal. Very high levels of C-reactive protein (CRP), interleukins 1 and 6, and tumor necrosis factor-α (TNF-α) were seen [37].

Data have been obtained on a possible connection between cognitive disorders after COVID-19 and impairments to the balance of pro- and anti-inflammatory cytokines in the CNS. One study demonstrated a correlation between slowed psychomotor reactions and difficulties maintaining attention with CRP levels in COVID-19 patients [11]. Psychological stress associated with the COVID-19 pandemic also influences the cytokine system, leading to depression and deterioration of cognitive functions [36].

Inflammatory cytokines, including interleukins and TNF-α, have been shown to be able to lead to damage to the blood:brain barrier (BBB), such that cytokines can activate a microglial inflammatory reaction. Furthermore, data have been obtained showing that SARS-CoV-2 produces endothelial damage and increases vascular permeability, which may explain the impairments to the BBB [12]. In turn, impairments to the functioning of neurovascular units play a key role in the development and progression of cognitive dysfunction [38].

Dementia and COVID-19 have many risk factors, most of which are linked with hyperactivation of the renin–angiotensin system, cerebrovascular dysfunction, and neuroinflammation. These common mechanisms may also explain the high morbidity and mortality of COVID-19 patients with dementia [39].

Acute respiratory distress syndrome (ARDS), which has been the focus of extensive attention during the pandemic, can also lead to long-term cognitive impairments [40].
The prevalence of cognitive dysfunction after ARDS is ≈80% [41, 42]. Three months after hospitalization, about 40% of patients with ARDS have persistent mild cognitive deficit, while 26% have moderate deficit [43].

Inflammatory processes, hypoxia, dysregulation of the hypothalamo-hypophyseal-adrenocortical axis, coagulopathy, and organ failure may in turn contribute to the development of cognitive deficit [44].

The mechanisms of damage to the nervous system are believed to be able to produce significant increases in the risk of long-term delayed neurological impairments in patients surviving COVID-19 [29, 39]. Representatives of more than 30 countries under the technical direction of the World Health Organization formed an international interdisciplinary consortium for collecting and evaluating the short-term and long-term CNS sequelae of SARS-CoV-2 [45]. Long-term neuropsychiatric monitoring is important for determining the degree and extent of neurological and psychiatric sequelae of COVID-19.

Further in-depth research into nervous system damage in COVID-19 is undoubtedly required, and this will significantly supplement existing data. Understanding of the pathogenesis of neurological impairments in COVID-19 is important for studies of the long-term sequelae of the disease and identifying prophylactic and therapeutic potentials in relation to brain damage.

**Potential for Treatment of the Neurological Manifestations of Postcovid Syndrome.** Patients who have had COVID-19 need to be monitored carefully. Early detection and treatment of neuropsychological impairments after COVID-19 may decrease the risk of further progression. Individual cognitive and psychological rehabilitation is as important as pharmacological methods [46].

In selecting drugs it is extremely important for the drug to have a multimodal mechanism of action, to be effective, and to have a good safety profile without producing undesirable drug interactions. One possible pathogenetic approach to the treatment of neurological manifestations/complications of COVID-19 consists of using the Russian formulation Cortexin, which has been employed in neurological practice for more than 20 years. This multicomponent formulation with an optimally balanced composition of amino acids and ribonucleic acids, has specific actions on the brain. Cortexin also contains a set of trace elements important for cell viability. When given i.m., the low molecular weight peptides in Cortexin cross the BBB. In the context of the overall characteristics, the protective actions of Cortexin activate repair processes, accelerate normalization of brain functions after stress, restore cognitive processes, and improve learning and memory. According to the patient information leaflet, Cortexin is indicated as part of complex therapy in the acute and recovery periods of stroke, in encephalopathies of different origins, in different types of meningitis and encephalitis, in cognitive dysfunction, and in asthenic states. Thus, use of Cortexin in COVID-19 is grounded both in the acute period of developing neurological complications and when they persist or develop in the long term.

The complex list of components present in Cortexin is a set of ligands (expressing agents) which, on binding their cognate targets, (receptors in neural structures, the active centers of signal kinase enzymes), promote normalization of biochemical processes. Due to its unique set of active substances, Cortexin acts on a variety of membrane and cellular “targets,” thus correcting several components of the pathological process in the brain [47].

Cortexin has been shown to produce effective and tissue-specific inhibition of caspase-8 activity in the brain. As proteases of the caspase family perform one of the key functions in neuron death in neurodegeneration, inhibition of caspase-8 can be regarded as a potentially possible mechanism of the neuroprotective action of the drug in vivo [48].

The peptides in Cortexin have direct and indirect neurotrophic actions on cells. The main mechanisms of this influence are based on changes in the operation of genes regulating the synthesis of intrinsic neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neuron growth factor (NGF). Cortexin was shown to have an effect on the survival of cultured neurons in conditions of peroxide or glutamate intoxication [49, 50]. Furthermore, Cortexin, by acting on ionotropic and metabotropic glutamate receptors, prevents excitotoxicity and optimizes excitation/inhibition processes and synaptic plasticity [51].

Results from animal studies showed that the formulation has antioxidant and anti-inflammatory actions. In the rat brain, the formulation restored the ratio of the pro- and antioxidant systems, particularly in the neocortex, though a systemic effect was also observed. In addition, a significant anti-inflammatory effect has been seen in Cortexin. Courses of the formulation significantly reduce blood IL-1β levels in animals [52].

Recent studies identified three neurospecific proteins operating as molecular targets for Cortexin peptides, interactions with which probably mediate its neuroprotective effects: tubulin β5, creatine kinase type B, and protein 14-3-3 α/β, as well as the cytoskeleton protein actin. Creatine kinase is a key enzyme in energy metabolism in the brain, which is impaired in various cerebral pathologies. Neuron-specific protein 14-3-3 is a signal transduction factor (“molecular switch”), particularly modulating neuron death. Cytoskeleton proteins (tubulin and actin) also support the normal functioning and integrity of neurons and other brain cells; impairments to their structure are accompanied by cell death [53].

Thus, Cortexin, having universal actions on the key mechanisms of the pathogenesis of cerebral pathologies, may minimize the actions of COVID-19 on the nervous system and improve patients’ quality of life in the long term.

**Conclusions.** The scale and severity of the ongoing COVID-19 pandemic has no analogs in current society, and the possible sequelae of the disease may be just as serious.
There is no doubt that the diagnosis and correction of the neuropsychiatric sequelae of COVID-19 require an interdisciplinary approach. In addition, there is an acute need for early detection of impairments for prompt prescription of therapeutic and rehabilitation measures, which will probably have decisive importance in improving the quality of life of many COVID-19 survivors.

The authors declare no conflict of interest.

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