Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Letter to the Editor: "What Are the Long-Term Neurological and Neuropsychiatric Consequences of COVID-19?"

Letter:

The severe acute respiratory disease caused by SARS-CoV-2 is called COVID-19, and its scale has never been seen since the 1918 influenza pandemic. It is likely to overtake the Spanish flu as the largest and most severe pandemic. Although the respiratory disease is the most common and important manifestation, there is increasing evidence that hospitalized COVID-19 patients often involve the nervous system.

Because the cerebrovascular system can concert with the endothelium's ability to sense circulating interferon type I signals, therefore, it usually exhibits a strong antiviral ability. SARS-CoV-2 may invade the central nervous system (CNS) through infection of the olfactory nerve or vascular endothelium, or the migration of infected leukocyte through the blood-brain barrier. Once the virus enters the CNS, it gradually spreads along neurotransmission or hematogenous pathways.

Before 2020, 6 coronaviruses were reported to infect humans; all of them can lead to respiratory illness. Among them, SARS-CoV and MERS-CoV have caused a large-scale epidemic. All of these coronaviruses have been reported to be related to CNS and/or peripheral nervous system occasional symptoms. Considering that the sequence similarity between SARS-CoV-2 and SARS-CoV is as high as 85%,[1] it is not surprising that COVID-19 has neurological symptoms. Although the currently available clinical data are preliminary and incomplete, the neurological manifestations of COVID-19 have shown some difference from other viruses; they are more common and disabling than SARS-CoV and MERS-CoV.

There has been a reported case of meningitis associated with SARS-CoV-2 that the specific SARS-CoV-2 RNA was not detected in the nasopharyngeal swab but was detected in a cerebrospinal fluid.[2] Considering that the sensitivity of the test kit is not 100%, patients with neurological and/or neuropsychiatric symptoms as well as patients who have recently been exposed to COVID-19, even the nucleic acid test is negative, clinicians should not trust unexpected negative results. The combination of repeated swab tests and CT scans may help patients who are clinically highly suspected of COVID-19 infection but have negative nucleic acid screening. Some patients with more severe infection had neurologic manifestations, including acute cerebrovascular diseases and impaired consciousness.

The main receptors for SARS-CoV-2 docking are angiotensin-converting enzyme-2, basigin, and neuropilin-1. Among them, angiotensin-converting enzyme-2 has been observed in human cerebral blood vessels and expressed in pericytes and smooth muscle cells of the vascular wall. At the same time, noncanonical SARS-CoV-2 receptors exist in several brain cell types, which makes the CNS vulnerable to SARS-CoV-2.

SARS-CoV-2 induces IL-1 family members by activating the inflammatory protein complex of NOD-like receptor protein 3 inflammasome. The NOD-like receptor protein 3 inflammasome assembles inside of microglia on activation, increasing tau hyperphosphorylation and aggregation by regulating tau kinases and phosphatases, resulting in neurodegeneration and cognitive decline, which may lead to Alzheimer's disease.[3]

Approximately 5% (2087 of 44,672) of severely ill patients with COVID-19 infection show rapid progressive respiratory failure and develop acute respiratory distress syndrome.[4] Acute respiratory distress syndrome can lead to serious long-term brain-related diseases, manifested as neurocognitive impairment, depression, anxiety, and decreased quality of life.

It is now generally believed that the SARS-CoV-2 virus will trigger a disproportionate immune response, leading to systemic damage, especially in obese patients. Because obesity itself is a chronic multiorgan inflammatory disease, this systemic damage is more obvious in obese patients. Chronic damage to system organs can lead to chronic hypoxia, hormonal imbalance, anaerobic metabolism, and accumulation of toxic metabolites. These toxic metabolites cause nerve swelling and brain edema to further cause brain damage.

After SARS-CoV-2 virus infection triggers an immune response, immune cells accumulate in visceral adipose tissue and together with paracrine adipocytes release a wide range of biologically active cytokines, causing local, pulmonary, and systemic inflammation. In severe patients, there is an extreme immune response, and the body has a cytokine storm. Inflammation and cytokine elevation is linked to subsequent hippocampal atrophy and cognitive impairment. Increased inflammation and cytokines are related to hippocampal atrophy and cognitive impairment.[5]

The glial fibrillary acidic protein and neurofilament light chain are the markers of astrocytic and neuronal injury. Patients with COVID-19 have a high plasma level of glial fibrillary acidic protein and neurofilament light chain, which indicates astrocytic and neuronal injury.[6] Some people speculate that SARS-CoV-2 infection may cause changes in the composition of intestinal microbes and participate in the pathogenesis of neuropsychiatric symptoms through the intestinal brain axis.

Study analysis of the link between respiratory virus infections and neurological and psychiatric sequelae indicated that respiratory virus infections are associated with neurological and psychiatric sequelae, including Parkinsonism, dementia, depression, post-traumatic stress disorder, memory impairment, sleep disorder, and anxiety.

The neurological symptoms of COVID-19 may be due to a combination of nonspecific complications of systemic diseases, direct viral infection, and inflammation of the nervous system and vasculature. On the basis of these characteristics of COVID-19, especially among survivors of severe illness, we must pay attention to the neurological and neuropsychiatric consequences that may occur in the long term.

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