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Neurological impacts of COVID-19

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COVID-19 is a pandemic respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has infected more than 72 million people and claimed 1.6 million lives worldwide (15 Dec 2020). Recent studies suggest a neurotropic element of COVID-19 infections, as 36.4% (78/214) of patients exhibit neurological abnormalities, including headache, acute ischemic stroke, epilepsy, encephalitis, encephalopathy, ataxia, anosmia, ageusia, and acute disseminated encephalomyelitis [1,2] in addition to or in the absence of systemic and respiratory symptoms. SARS-CoV-2 invades human cells via the Angiotensin-Converting Enzyme 2 (ACE2) receptor and can replicate in neuronal cells *in vitro* [3,4] the viral uptake is further facilitated by a priming protease TMPRSS2. ACE2 is a cardio-cerebrovascular protection factor that regulates blood pressure and anti-atherosclerosis mechanisms [5]. Given that the SARS-CoV-2 spike protein binds to ACE2 expressed in the vascular endothelium, the virus may enter the Central Nervous System (CNS) by a hematogenous route. In addition, ACE2 is expressed in both neurons and glia in the brain, particularly in the brainstem and regions that regulate cardiovascular function. Thus, blockage of ACE2 by spike protein could lead to dysregulation of blood pressure and cerebrovascular function, astrogliosis, and microglia activation. SARS-CoV-2 may spread towards the CNS through neuronal dissemination, where the virus travels from peripheral nerves with retrograde or anterograde neuronal transport proteins. The olfactory nerve functions as a gateway to the CNS in that it communicates with the nasal epithelium and the olfactory bulb. SARS-CoV-2 binds to ACE2 receptors on sustentacular cells of the olfactory epithelium and potentially impairs the sense of smell in COVID-19 patients [6]. Alternatively, SARS-CoV-2 may enter the CNS through other trans-synaptic contacts, such as the trigeminal nerve, which possesses nociceptive neurons in the nasal cavity, or the sensory fibers of the vagus nerve, which stems from the brainstem and innervates the respiratory tract. Certain neuronal damages may exacerbate or lead to cardio-respiratory failure. An important aspect of SARS-CoV-2 infection is that it triggers a cytokine storm with a massive release of pro-inflammatory signals and subsequent leakage of the blood brain barrier (BBB). The increased BBB permeability by destabilizing the tight junctions could further facilitate viral transmigration into the CNS. However, SARS-CoV-2 is largely undetected in the cerebrospinal fluid from patients with confirmed COVID-19 and neurological conditions [7,8], which hints at a role of immune responses in neurological manifestations. Consistently, interleukin (IL)-6, an important member of the cytokine storm, positively correlates with the severity of COVID-19 symptoms [9]. Persistent neuroinflammation severely disturbs brain homeostasis, causes neuronal death, and may contribute to cognitive impairment as observed in COVID-19 patients. In theory, SARS-CoV-2 may also induce antibody production through molecular mimicry to human proteins, leading to an enhanced autoimmune response [10]. Close examinations of SARS-CoV-2 viral involvement in the nervous system will have wide implications on treatment as well as prediction of long-term effects on neurology. If a large number of patients have active viruses in their CNS, treatment should be designed to achieve better CNS penetrance and neuroinflammatory regulation.

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