COVID-19 and central nervous system

Overwhelming evidence demonstrates that Coronavirus disease 2019 (COVID-19) infection is a systemic illness, often with involvement of the central nervous system.

With over 20,000 published articles on COVID and the brain in 2021, it is virtually impossible to present an unbiased comprehensive review of how SARS-Co-V2 impacts the nervous system [1].

Mechanisms

Multiple mechanisms may underlie the development of neurologic manifestations of illness, including hypoxia, systemic illness, hypercoagulability, endothelial dysfunction, general critical illness, inflammatory response, and neurotropism of the severe acute respiratory syndrome coronavirus 2 (SARS-Co-V2) virus. COVID-19 infection is associated with neurologic involvement in all stages; acute infection, subacute/post-infection, and growing evidence also suggests during a chronic phase, the post-acute sequalae of COVID-19 (PASC).

Around 40 % of patients with COVID-19 develop neurological symptoms and other brain dysfunction symptoms [2].

Despite many studies reporting respiratory infections as the primary manifestations of this illness, an increasing number of investigations have focused on the central nervous system (CNS) manifestations in COVID-19.

Nazari et al. aimed to evaluate the CNS presentations in COVID-19 patients in an attempt to identify the common CNS features and provide a better overview to tackle this new pandemic.

In this systematic review and meta-analysis, they searched PubMed, Web of Science, Ovid, EMBASE, Scopus, and Google Scholar. Included studies were publications that reported the CNS features between 1 January 2020 and 20 April 2020. The data of selected studies were screened and extracted independently by four reviewers. Extracted data analyzed by using STATA statistical software. The study protocol was registered with PROSPERO (CRD42020184456).

Of 2,353 retrieved studies, they selected 64 studies with 11,687 patients after screening. Most of the studies were conducted in China (58 studies). The most common CNS symptom of COVID-19 was headache (8.69%, 95%CI: 6.76%-10.82%), dizziness (5.94%, 95%CI: 3.66%-8.22%), and impaired consciousness (1.90%, 95%CI: 1.0%-2.79%).

A growing number of studies have reported COVID-19, CNS presentations as remarkable manifestations that happen. Hence, understanding the CNS characteristics of COVID-19 can help us for better diagnosis and ultimately prevention of worse outcomes [3].

Since cytokine storm has been known as a major mechanism followed by SARS-CoV-2, inflammasome may trigger an inflammatory form of lytic programmed cell death (pyroptosis) following SARS-CoV-2 infection and contribute to associated neurological complications.

Sepehrinezhad et al. reviewed and discussed the possible role of inflammasome and its consequence pyroptosis following coronavirus infections as potential mechanisms of neurotropism by SARS-CoV-2. Further studies, particularly postmortem analysis of brain samples obtained from COVID-19 patients, can shed light on the possible role of the inflammasome in neurotropism of SARS-CoV-2 [4)]

Evidence of the Distribution of ACE2 in the Human Brain

The brain has been reported to express ACE2 receptors that have been detected over glial cells and neurons, which makes them a potential target of COVID-19. Previous studies have shown the ability of SARSCoV to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium [5)].

It has been shown that similar to SARS-CoV, COVID-19 virus exploits the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry inside the cells. This finding raises the curiosity of investigating the expression of ACE2 in nervous tissue and determining the possible contribution of neurological tissue damage to the morbidity and mortality caused by COVID-19.

Most of the evidence of ACE2 expression in the brain comes from literature and mammalian tissue expression databases, [6)] which prompted Baig et al. to investigate the neurotropic effects of SARSCoV-2 and its contribution toward the morbidity and mortality of patients with COVID-19.

Baig et al. investigated the density of the expression levels of ACE2 in the CNS, the host-virus interaction and relate it to the pathogenesis and complications seen in the recent cases resulting from the COVID-19 outbreak. They also debated the need for a model for staging COVID-19 based on nervous tissue involvement [7)].

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In the SARS-CoV infections that were reported in the past, autopsy findings of the patients have shown strong evidence of the presence of SARS-CoV by electron microscopy, immunohistochemistry, and real-time reverse transcriptional [9)].

Patients with acute SARS-CoV illness have also demonstrated the presence of the virus in cerebrospinal fluid. The role of the blood-brain barrier in containing the virus and preventing it from gaining access to the neural tissues needs to be further explored in patients diagnosed with COVID-19. Recently, a study posted in medRxiv [10)] has reported neurological manifestations in COVID-19 in the current outbreak that involved 214 patients, of which 78 (36.4%) patients had neurologic manifestations, which affirms our rationale of the neurotropic potential in the COVID-19

virus. Also, a finding published on a patient who had loss of involuntary control over breathing [11] during the recent outbreak with several other patients suffering acute respiratory failure implores healthcare professionals and clinicians to segregate COVID-19 patients into neurologically affected cases and those who are devoid of neurological deficits.

The dissemination of COVID-19 in the systemic circulation or across the cribriform plate of the ethmoid bone during an early or later phase of the infection can lead to cerebral involvement as has been reported in the past for SARS-CoV affected patients. The presence of the COVID-19 virus in the general circulation understandably enables it to pass into the cerebral circulation where the sluggish movement of the blood within the microcirculation could be one of the factors that may facilitate the interaction of the COVID-19 virus spike protein with ACE2 expressed in the capillary endothelium. Subsequent budding of the viral particles from the capillary endothelium and damage to the endothelial lining can favor viral access to the brain. Once within the milieu of the neuronal tissues, its interaction with ACE2 receptors expressed in neurons2 can initiate a cycle of viral budding accompanied by neuronal damage without substantial inflammation as has been seen with cases of SARS-CoV3 in the past. It is important to mention here that, long before the proposed anticipated neuronal damages occur, the endothelial ruptures in cerebral capillaries accompanied by bleeding within the cerebral tissue can have fatal consequences in patients with COVID-19 infections. The movement of the COVID-19 virus to the brain via the cribriform plate close to the olfactory bulb can be an additional pathway that could enable the virus to reach and affect the brain. Additionally, the findings like an altered sense of smell or hyposmia in an uncomplicated early stage COVID19 patient should be investigated thoroughly for CNS involvement.

Continued studies needed to fully undertstand the long term consequences of COVID on the neurological system [12].

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