The prevailing coronavirus disease-19 (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has presented some neurological manifestations including hyposmia, hypogeusia, headache, stroke, encephalitis, Guillain–Barre syndrome, and some neuropsychiatric disorders. Although several cell types in the brain express angiotensin-converting enzyme-2 (ACE2), the main SARS-CoV-2 receptor, and other related proteins, it remains unclear whether the observed neurological manifestations are attributed to virus invasion into the brain or just comorbidities caused by dysregulation of systemic factors. Here, we briefly review the neurological manifestations of SARS-CoV-2, summarize recent evidence for the potential neurotropism of SARS-CoV-2, and discuss the potential mechanisms of COVID-19-associated neurological diseases.

**Keywords:** SARS-CoV-2, ACE2, brain invasion, neurological manifestations

**Introduction**

In less than two decades, three coronavirus outbreaks prevailed to form major epidemics that mainly attack the respiratory system of patients, including severe acute respiratory syndrome (SARS) caused by SARS-coronavirus (SARS-CoV) in 2002–2003, Middle East respiratory syndrome (MERS) by MERS-CoV in 2012, and the ongoing coronavirus disease-19 (COVID-19). SARS affected a total of 8096 people and caused ~9.56% of deaths (De Wit et al., 2016), and MERS was responsible for 34.4% of deaths in 2494 total patients (Berger, 2020). As of May 10, 2021, COVID-19 has caused nearly 160 million cases and over 3.3 million deaths globally and it is becoming the most severe pandemic over the last century.

The most common symptoms of COVID-19 are fever, cough, fatigue, muscle pain, and shortness of breath (Garg et al., 2020; Grasselli et al., 2020; Guan et al., 2020; Huang et al., 2020a). Some reports showed that >36.4% of confirmed cases presented neurological manifestations, including dizziness, headache, hypogeusia, and hyposmia (Helms et al., 2020; Mao et al., 2020). Cerebrovascular diseases such as stroke have also been identified in some patients (Giustozzi et al., 2020; Oxley et al., 2020; Viguier et al., 2020). The neurological involvement is not specific for COVID-19, because similar neurological abnormalities are also observed following infections from other coronaviruses, such as SARS-CoV and MERS-CoV (Glass et al., 2004; Li et al., 2016; Eliul et al., 2020).

Like SARS-CoV, SARS-CoV-2 also uses protease-processed spike (S) protein to invade host cells through angiotensin-converting enzyme-2 (ACE2) (Li et al., 2003; Hoffmann et al., 2020; Walls et al., 2020). The cellular serine proteases transmembrane protease serine 2 (TMPRSS2) and furin are responsible for S protein priming and pre-activated cleavage, respectively, to facilitate the access to host cells (Hoffmann et al., 2020; Shang et al., 2020). In addition, other cellular receptors, such as Neurupillin-1 (NRP-1) and CD147, may mediate the virus entry into the host cell through ACE2-independent manner (Cantuti-Castelvetri et al., 2020; Daly et al., 2020; Zhou et al., 2020). Using pseudovirus system, it has been shown that SARS-CoV-2 entry and replication can be facilitated by the proprotein convertase furin, the cell surface protease TMPRSS2, and the lysosomal proteases cathepsins (Shang et al., 2020). The presence of a polybasic furin-type cleavage site in the SARS-CoV-2 S protein might explain why SARS-CoV-2 spreads much more rapidly than SARS-CoV (Coutard et al., 2020).

ACE2 protein was found to be expressed in neurons of the brain (Song et al., 2021), and NRP-1 expression was observed in the olfactory system (Kawakami et al., 1996), including neurons of the olfactory epithelium (Cantuti-Castelvetri et al., 2020). The expression of putative SARS-CoV-2 receptors in several neuronal cell types raised possibility of direct invasion of SARS-CoV-2 into the brain (Yang et al., 2020).
Table 1 Neurological and neuropsychiatric features of COVID-19 patients.

| Neurological symptoms       | Etiology/pathophysiology                                                                 | References                                                                 |
|-----------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Cerebrovascular disease     | Neuroimaging, viral presence in CSF, inflammatory factors                                 | Poyiadji et al. (2020); Mao et al. (2020); Pleasure et al. (2020); Jin et al. (2020); Eliui et al. (2020) |
| Ischemic strokes            |                                                                                          |                                                                            |
| Brain hemorrhage            |                                                                                          |                                                                            |
| Thrombocytopenia            |                                                                                          |                                                                            |
| CNS neurological disease    | Neuroimaging, viral presence in CSF, CNS infection, spine imaging                         | Helms et al. (2020); Poyiadji et al. (2020); Mao et al. (2020); Duong et al. (2020); Asadi-Pooya and Simani (2020) |
| Encephalopathy             |                                                                                          |                                                                            |
| Encephalitis                |                                                                                          |                                                                            |
| Myelitis                    |                                                                                          |                                                                            |
| PNS neurological disease    | PNS infection, nerve demyelination, neuromuscular junction, immune dysregulation           | Sedaghat and Karimi (2020); (Zhao et al., 2020a)                           |
| Guillain–Barre              |                                                                                                                                               |
| Myalgia                     |                                                                                                                                               |
| Paralysis                   |                                                                                                                                               |
| Sensory impairment          | Olfactory viral invasion, CNS autoimmunity                                                | Poyiadji et al. (2020); Naijar et al. (2020); Mao et al. (2020); Sohal and Mansur (2020) |
| Hypogeusia                  |                                                                                                                                               |
| Hyposmia                    |                                                                                                                                               |
| Anosmia                     |                                                                                                                                               |
| Ageusia                     |                                                                                                                                               |
| Seizure                     | Neuroimaging, viral presence in CSF                                                       | Mao et al. (2020); Poyiadji et al. (2020); Duong et al. (2020); Sohal and Mansur (2020) |
| Neuropsychiatric disorder   | Not reported                                                                              | Mao et al. (2020); Rogers et al. (2020); Varatharaj et al. (2020)         |
| Depression                  |                                                                                                                                               |
| Anxiety                     |                                                                                                                                               |
| Confusion                   |                                                                                                                                               |
| Agitation                   |                                                                                                                                               |
| Delirium                    |                                                                                                                                               |

COVID-19-associated neurological manifestations

Accumulating case reports have shown that COVID-19 patients exhibit a wide range of neurological manifestations of either the central nervous system (CNS) or the peripheral nervous system (PNS), in isolation or together with other features (Ellul et al., 2020; Iademola et al., 2020; Table 1). For example, a retrospective study from Wuhan, China, reported that 53 of 214 COVID-19 patients (~25%) had CNS symptoms, including 28 with headache, 36 with dizziness, and 16 with consciousness impairment (Mao et al., 2020). Notably, only ~50% of those with CNS symptoms (27/53) showed severe respiratory problem. In another study carried out in France for 58 COVID-19 patients, 49 (84%) had neurological complications, including 40 with encephalopathy (Helms et al., 2020), which was defined based on alterations in mental status, such as confusion, agitation, disorientation, or delirium. The alterations in mental status were most likely caused by systemic disorder, rather than encephalitis resulted from direct SARS-CoV-2 infection, because only a few cases showed modest amount of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) (Huang et al., 2020b; Morighichi et al., 2020).

In addition to encephalopathy, cerebrovascular manifestations are also seen in some of COVID-19 patients. Ischemic stroke has been reported in 1%–6% COVID-19 patients (Klok et al., 2020; Mao et al., 2020; Merkler et al., 2020; Yaghi et al., 2020), and notably, the rates are several folds higher than that in patients with common influenza (Merkler et al., 2020). The COVID-19-associated endothelial dysfunction might be related with increased susceptibility to cerebrovascular disease (Klok et al., 2020).

Compared to influenza patients, much higher ratio of COVID-19 patients reported olfactory dysfunction or gustatory disorders (Ellul et al., 2020). In a multicenter European study of 417 COVID-19 patients, 85.6% reported decreased sense of smell, and 79.6% reported a complete loss of taste (Lechien et al., 2020). Although anosmia and ageusia are emerging as common symptoms of COVID-19, it remains unclear whether these abnormalities were caused by direct invasion of olfactory nerve or just because of coronavirus, which can occur in many other respiratory viral infections.

Systemic inflammation and dysregulated immune responses elicited after acute phase of viral infection are known to cause CNS or PNS neurological complications. Up to now, only rare cases of post-infectious CNS inflammations, typically encephalomyelitis and myelitis, were reported (Zanin et al., 2020; Zhao et al., 2020b; Zhang et al., 2021). More cases of Guillain–Barre syndrome resulted from immune attack on PNS were reported in COVID-19 patients, with evidence of axonal demyelination and consequent symptoms of muscle weakness, ataxia, or areflexia (Dinkin et al., 2020; Gutiérrez-Ortiz et al., 2020; Marta-Enguita et al., 2020; Toscano et al., 2020). Interestingly, a recent study showed that all the brain regions with SARS-CoV-2 signals had minimal lymphocyte or leukocyte infiltration, suggesting that SARS-CoV-2 may not elicit strong post-infectious immune response (Song et al., 2021). This feature is distinct from other neurotropic viruses like ZIKV, rabies virus, and herpes virus. In line with this notion, SARS-CoV-2-infected brain organoids exhibited little change in the pathways related with defense response to virus, cellular response to type I interferon, and innate immune response, which were observed in ZIKV-infected organoids (Song et al., 2021).
Neurotropic characteristics of SARS-CoV-2

Of the seven types of coronaviruses that infect humans, at least two strains have been shown to be able to enter and persist in the brain, including SARS-CoV (Arbour et al., 2000; Gu et al., 2005). The high similarity of SARS-CoV-2 in its nucleotide sequence to SARS-CoV, in particular the receptor-binding domain, indicates that it may also invade the host cells through ACE2 (Lu et al., 2020; Wang et al., 2020a). In support of this conclusion, intranasal infection of mice expressing human ACE2 with SARS-CoV-2 caused high viral loads in the lung, trachea, and brain (Sun et al., 2020).

In line with frequently observed loss of smell in COVID-19 patients, ACE2 and TMPRSS2 that mediates proteolytic processing of the S protein were observed in the olfactory epithelium, but not olfactory neurons, in both murine and human samples (Bilinska et al., 2020; Brann et al., 2020). Varied expression of ACE2 was observed in human neurons in a subtype- and region-specific manner, and high expression of ACE2 and TMPRSS2 was observed in pericytes, endothelial cells, or choroid plexus cells (He et al., 2020; Jacob et al., 2020; Ramani et al., 2020; Chen et al., 2021; Song et al., 2021).

Other evidence supporting the neurotropism of SARS-CoV-2 came from in vitro cellular or organoid models. In a cultured human brain organoid model, SARS-CoV-2 exhibited neuroinvasive ability in an ACE2-dependent manner, leading to neuronal death (Song et al., 2021). Several independent studies using brain organoids have also shown neurotropism of SARS-CoV-2 in their brain organoid systems (Ramani et al., 2020; Yang et al., 2020; Zhang et al., 2020). However, the results for targeted cell types were inconsistent among different studies. Some studies showed that SARS-CoV-2 preferably targets mature neurons (Ramani et al., 2020; Song et al., 2021), whereas other studies state that SARS-CoV-2 cannot target neuronal cell types (Pellegrini et al., 2020) or only has minimal neuronal infection ability (Jacob et al., 2020). Interestingly, in the brain organoids of hippocampal-like regions, SARS-CoV-2 signals were found to be enriched in choroid plexus epithelia-like cells and SARS-CoV-2 entry can lead to damages for the integrity of choroid plexus epithelium (Jacob et al., 2020; Pellegrini et al., 2020), suggesting that barrier disruption might facilitate SARS-CoV-2 invasion into the brain.

It is worth noting that SARS-CoV-2-positive neurons in human brain organoids exhibit mis-localization of axonal protein Tau to the cell soma and aberrant Tau phosphorylation, a phenomenon often seen in tauopathy-related neurodegeneration diseases (Ramani et al., 2020). In accordance with positive association between the ApoE4, a strong genetic risk factor for Alzheimer disease, and severe COVID-19 (Kuo et al., 2020), the ApoE4/4 neurons, astrocytes, or brain organoids exhibit increased rate of SARS-CoV-2 infection (Wang et al., 2021). These results indicate that particular attention should be paid to the potential long-term effects of SARS-CoV-2 infection on different patient populations, in particular the neurological and neuropsychological morbidities.

In histological analyses of the deceased individuals with COVID-19, SARS-CoV-2 RNA and protein were found in epithelial tissues of the olfactory mucosa and defined CNS regions receiving olfactory neuronal projections (Meinhardt et al., 2021). Notably, the SARS-CoV-2 S protein was observed in cortical neurons of ischemic regions in brains of some cases of post-mortem COVID-19 patients, who were diagnosed with severe encephalopathy and multiple ischemic infarcts (Song et al., 2021). These studies have provided direct evidence supporting neurotropism of SARS-CoV-2 in COVID-19 patients and substantiated the findings obtained in human brain organoids.

Possible mechanisms of neurological manifestations

Viral entry to the brain via the olfactory bulb is a possible route given frequent anosmia in COVID-19 patients (Figure 1). In support of this possibility, the brain has been shown to be one of the major organs in hACE2 transgenic mice after intranasal infection with either SARS-CoV or SARS-CoV-2 (Tseng et al., 2007; Netland et al., 2008; Sun et al., 2020). Notably, magnetic resonance imaging analysis in a COVID-19 patient with anosmia showed a transient hyperintensity in the olfactory cortex, as well as a subtle hyperintensity in the olfactory bulb suggestive of viral infection (Politi et al., 2020). The presence of SARS-CoV-2 RNA and protein in the olfactory mucosa, its neuronal projections, and several CNS regions has provided direct evidence supporting the olfactory route of CNS entry by SARS-CoV-2 (Meinhardt et al., 2021). The presence of SARS-CoV-2 in defined neuroanatomical areas receiving olfactory tract projections, including the primary respiratory and cardiovascular control center, raises the possibility of axonal transport and/or trans-synaptic spread of virus (Meinhardt et al., 2021; Zubair et al., 2020). The trans-synaptic spread of virus has been demonstrated for several other types of coronaviruses, such as HCoV-OC43 (Dubé et al., 2018).

Pathogens like viruses can enter the blood and circulate to cerebrovascular after crossing the blood–brain barrier (BBB), following viremia or through infected immune cells (Bohmwald et al., 2018). Of note, remarkable percentage of the blood specimen, varying from 1% to 22%, derived from COVID-19 patients, displayed SARS-CoV-2 RNAemia suggestive of viremia (Huang et al., 2020a; Peng et al., 2020; Wang et al., 2020b). The lack of detailed clinical information of patients limits the correlation of viremia with prognosis or disease course. The BBB formed by tight junctions consisted of endothelial cells together with surrounding pericytes and astrocytes plays a crucial role in maintaining the homeostasis of the brain and prevents pathogen invasion into the brain. Virions in the blood can directly attach to endothelial and pericytes through viral entry receptors for SARS-CoV-2, leading to alterations of the tight junction. High expression of ACE2 and TMPRSS2 in pericytes and endothelial cells supports this possibility (He et al., 2020; Chen et al., 2021). The transcytosis transport across the endothelia and pericytes by endocytic vesicles is an alternative pathway, as that done by other neuroinvasive respiratory
viruses (Suen et al., 2014; Bohmwald et al., 2018). The presence of SARS-CoV-2 S protein in cerebral and leptomeningeal endothelial cells also supports the possible route of viral entry along CNS endothelia (Meinhardt et al., 2021).

Dysregulated immune response like cytokine storm is a common phenomenon in many severe COVID-19 patients (Mehta et al., 2020). High levels of inflammatory cytokines saturate in the blood can cause breakdown of the BBB (Poyiadji et al., 2020; Quirch et al., 2020), which may facilitate virion entry into the brain (Figure 1). Furthermore, cytokines may cause damage to the CNS by facilitating the formation of thrombosis, leading to cerebrovascular diseases (Hoffmann et al., 2020; Figure 1). It has been suggested that the infected immune cells can cross the BBB via the paracellular route (Suen et al., 2014; Bohmwald et al., 2018). Indeed, a report demonstrated that circulating monocytes, B lymphocytes, and CD4+ T lymphocytes are the main cell types frequently detected with positive signals for SARS-CoV-2 (Pontelli et al., 2020). Interestingly, immune cells with SARS-CoV-2 settled down in the lung of COVID-19 patients (Pontelli et al., 2020), implying the 'Trojan Horse' invasion mechanism—injected immune cell may mediate viral invasion into organs, including the brain. This entry strategy has been suggested to be used by immunodeficiency virus (HIV-1) (Albright et al., 2003; Spindler and Hsu, 2012) and another coronavirus HCoV-229E (Desforges et al., 2007). Further studies are needed to confirm whether SARS-CoV-2 entry into the brain is also via this route.

**Conclusion and perspective of future study**

In addition to the potential direct cytolytic effect, SARS-CoV-2 can also lead to brain dysfunction and neuronal damage through indirect systemic effects such as secondary inflammatory response (Van den Pol, 2006). In the absence of direct viral invasion, the neurotoxicity of the cytokine storm itself may cause damage to the CNS, such as acute necrotizing encephalopathy (Ouattara et al., 2011). Besides, cytokines may also cause brain damage by activating the thrombotic pathway (Hoffmann et al., 2020), which may lead to ischemic stroke.

Although many reports demonstrated that SARS-CoV-2 could cause nervous system diseases, the underlying mechanism is not clear. The effects of SARS-CoV-2 on the CNS most likely involve the direct entry of viruses into neurons, which causes neuronal cell death, and indirect pathway through the cytokine storm and thrombosis (Figure 1). In addition, SARS-CoV-2 may invade the CNS through axonal transport and trans-synaptic transfer via the olfactory nerve and through infection of pericytes or endothelial cells that make up BBB or leukocytes that
pass through BBB (Zubair et al., 2020; Alquisiras-Burgos et al., 2021; Figure 1). These possibilities can be thoroughly verified using animal models such as hACE2 transgenic mice, which can be used to resemble the systemic effects of the disease.

Besides ACE2, other receptors and accessory proteins have been shown to facilitate SARS-CoV-2 entry into the cell. What factors mediate the interaction of SARS-CoV-2 with human brain remains to be studied systematically. Their expression and subcellular localization in human cell types, including various neurons, glia, and vascular cells, would be essential information. Furthermore, CNS control of systemic functions, such as autonomic pathways that control breathing, would help to disentangle neurological and systematic complications. Given the ongoing trends of COVID-19 pandemic, the long-term neurological and psychiatric sequelae of SARS-CoV-2 infection need serious consideration and follow-up tracking studies.

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