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Acute and long-term SARS-CoV-2 infection and neurodegeneration processes—*circulus vitiosus*

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The global pandemic of COVID-19 caused by SARS-CoV-2 has had a devastating impact. Although many survived the acute effects of the pandemic, a significant number of survivors, including those with only mild symptoms, are now experiencing a prolonged and debilitating post-viral syndrome known as LC/PASC (long COVID/post-acute sequelae of SARS-CoV-2). Typical symptoms of LC/PASC include fatigue, breathlessness, chest pain, impaired cognition, difficulty sleeping, fever and gastrointestinal symptoms. Anxiety and depression can also last for weeks to months and range from mild to disabling. The association between neuropsychiatric symptoms and SARS-CoV-2 infection raises questions about the possible routes of SARS-CoV-2 entry to the central nervous system (CNS) and long-term effects of the virus on the CNS, their molecular basis, and the potential risk of neuronal damage associated with the subsequent development of neurodegenerative diseases.

KEYWORDS

SARS-CoV-2, long COVID symptoms, neurotropism, neurodegeneration, CNS

Introduction

As of 31 December 2023, there are more than 773 million reported cases and 7 million deaths worldwide caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) (World Health Organization, 2024). While the symptoms of infection are mainly respiratory complications, the neurological manifestations of COVID-19 have been increasingly recognized. Many patients present with mild neurological symptoms such as dizziness, headache, and smell or taste impairment, however a small percentage of patients may develop severe neurological disease, including myopathy, cerebrovascular disease, seizures, movement disorders, encephalitis, Guillain-Barré syndrome, optic neuritis, meningitis, acute transverse myelitis and coma, as well as altered mental status (Mao et al., 2020; Ray et al., 2021; Varatharaj et al., 2020; Whittaker et al., 2020). Moreover, imaging data shows reduction in grey matter thickness and global brain size after SARS-CoV-2 infection (Douaud et al., 2022). In this mini review article, we discussed the possible routes of SARS-CoV-2 entry to

the central nervous system (CNS) and the consequences of neuroinvasion based on the emerging evidence.

Neurotropism and neuropathologies caused by SARS-CoV-2

SARS-CoV-2's neurotropism is a controversial topic. *In vitro* study using cells and organoids derived from human pluripotent stem cells (hPSC) showed SARS-CoV-2's tropism for choroid plexus epithelial cells, limited neuronal infection and the inability of axonal trafficking of the virus (Jacob et al., 2020; Luczo et al., 2024). However, hPSC-derived dopaminergic neurons, but not cortical neurons, were shown to be susceptible and permissive to the virus (Yang et al., 2020; 2024). In contrast, in a study done by Kettunen et al. (2023), hPSC-derived cortical neurons were infected by SARS-CoV-2. Moreover, hPSC-derived astrocytes were not infected or rarely showed signs of infection (Jacob et al., 2020; Kettunen et al., 2023). Contradicting results were published by Crunfli et al. (2022), where both hPSC-derived astrocytes and astrocytes in brain samples of COVID-19 patients were infected by the virus. *Post mortem* studies showed the presence of SARS-CoV-2, i.e., in the dorsal medulla, substantia nigra, frontal lobe, cortical neurons, cranial nerves (Emmi et al., 2023; Matschke et al., 2020; Song et al., 2021).

Possible ways of SARS-CoV-2 entry to the CNS are intensively researched. One of the suspected routes is the olfactory system. As the virus can infect sustentacular cells, there is a question of whether it can gain access to olfactory neurons, i.e., through exosomes, to stem cells that generate olfactory neurons, or to cerebrospinal fluid (Butowt and Bilinska, 2020; Butowt and von Bartheld, 2021). SARS-CoV-2 WA1 and Delta infected hamster model showed the transport of the virus to the brain through olfactory neuron axons, especially in younger animals (Chen et al., 2024). In a study on non-human primates, viral RNA was detected both in the olfactory bulb and brain, with SARS-CoV-2 N protein detected in the axons of olfactory neurons (Shimizu et al., 2024). However, SARS-CoV-2 infection in human olfactory neurons is rare (de Melo et al., 2021; Meinhardt et al., 2021), or not detected (Khan et al., 2021).

Blood-brain barrier disruption is one of the possible ways of viral entry to the CNS. *In vitro* and *in vivo* research on brain vascular endothelial cells (BCECs) suggests viral replication and transcellular transport resulting in neuronal damage (Krasemann et al., 2022; Zhang et al., 2021). Although SARS-CoV-2 did replicate in the human *in vitro* blood-brain barrier (BBB) model, it was limited and did not induce strong inflammatory response or BBB disruption. Moreover, although peripheral inflammation may cause BBB disruption (Huang et al., 2021; Yang et al., 2022), COVID-19 patients' serum with high concentrations of proinflammatory cytokines also did not disrupt the integrity of BBB *in vitro* (Constant et al., 2021). However, a study using a 3D microfluidic model of the human BBB showed that SARS-CoV-2 S protein promotes loss of barrier integrity and proinflammatory response (Buzhdygan et al., 2020). Infection of human brain microvascular endothelial cells (HBMEC) also showed proinflammatory activation, possibly by NF-κB non-canonical pathway, and remodelling of mitochondrial network and tight junctions, even without active replication (Motta et al., 2023). *Post mortem* studies do not give a definitive answer to whether BBB epithelium can or cannot be infected. ACE2, the entry receptor of SARS-CoV-2, is expressed in brain epithelium (Hamming et al., 2004; Zhou et al., 2020). Viral particles were detected in the frontal lobe in neural and capillary endothelial cells (Paniz-Mondolfi et al., 2020), however, RNA sequencing did not detect SARS-CoV-2 presence in brain tissues, including choroid plexus epithelium (Fullard et al., 2021; Yang et al., 2021). However, multifocal microvascular injury was observed in brain tissue and olfactory bulbs of patients who died of COVID-19 (Lee et al., 2021).

Enhanced expression of proinflammatory cytokines and chemokines is associated with ageing and age-related diseases, i.e., Parkinson's Disease (PD) and Alzheimer's Disease (AD) (Rea et al., 2018). SARS-CoV-2 and its proteins activate toll-like receptors (TLRs) – TLR2 and TLR4, leading to proinflammatory cytokine expression (Asaba et al., 2024; Fontes-Dantas et al., 2023; Sariol and Perlman, 2021; Szabo et al., 2022). Infected HBMEC showed upregulation of genes encoding factors related to endothelial activation pathways – CXCL1, -2, -8, CCL20, TNF, IL-6, IL-8, and that can lead to a BBB disruption and contribute to neuroinflammation (Motta et al., 2023). Infection of a non-human primate model resulted in neuroinflammation and neuronal damage, with pathology being more pronounced in aged and diabetic macaques (Beckman et al., 2022). Viral infection of microglia and astrocytes is suspected to be an important factor in neurological disorders development. The infection of microglia leads to M1-like proinflammatory response, production of cytokines and chemokines, i.e., IL-1β, IL-6, TNF-α, IFN-γ, CCL11, and NLRP3 inflammasome activation (Albornoz et al., 2023; Fernández-Castañeda et al., 2022; Jeong et al., 2022; Krasemann et al., 2022). SARS-CoV-2 has been found to infect astrocytes, leading to cell activation, elevated expression of inflammatory genes, cytokine and growth factor signalling in both infected and bystander astrocytes (Andrews et al., 2022). Infected astrocytes had changes in energy metabolism, and that could indirectly result in the reduction of neuronal viability (Crunfli et al., 2022). Brains of patients who died of COVID-19 studied *post mortem* showed neuropathological changes with astrogliosis, microgliosis and cytotoxic T lymphocytes infiltration, hallmarks of neuroinflammation

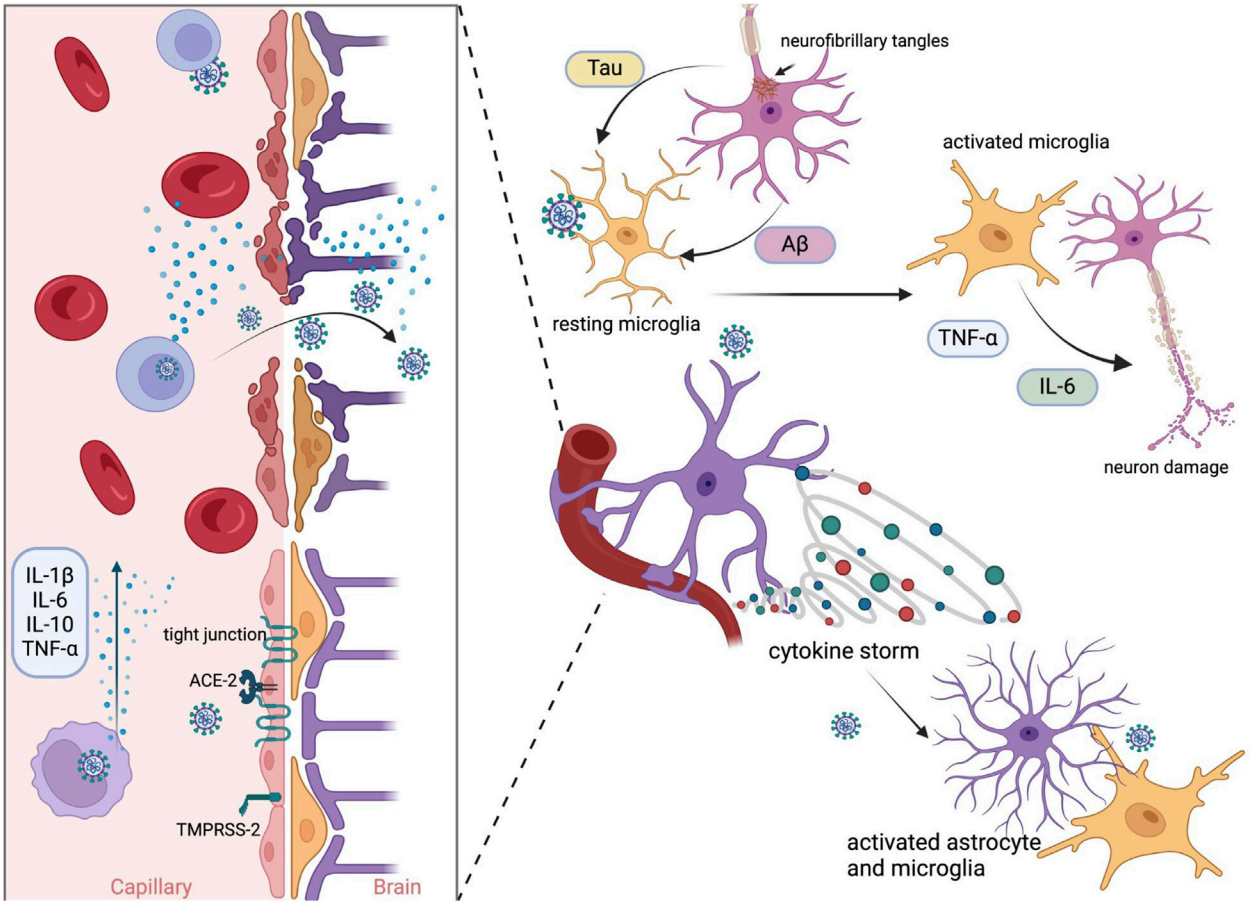

FIGURE 1
Possible mechanism of SARS-CoV-2 neuroinvasion by BBB disruption. Infection begins with proteolytic activation of the S protein by furin protease-TMPRSS-2 and binding to the ACE2 receptor in epithelial cells. Viral replication promotes the activation of inflammatory mechanisms. The release of primary proinflammatory cytokines, such as IFN-γ and TNF-α, leads to the activation of immune cells, astrocytes, and microglia. Activated microglial cells induce the release of cytokines such as IL-1, IL-6, and TNF-α, which further activate astrocytes. Activated astrocytes release mediators, which lead to neuroinflammation. These events and viral particles evade the host immune system, resulting in chronic infection and the subsequent deposition of Aβ (amyloid-beta) and phosphorylated tau in the brain. Created in BioRender. Bartak, M. (2023) BioRender.com/q85y420.

(Matschke et al., 2020). What is more, SARS-CoV-2 infection outside of CNS can lead to cytokine storm (Hu et al., 2021), and as a result, cytokines and chemokines in the blood may cause BBB disruption and consequently lead to microglia and astrocyte activation (Meinhardt et al., 2023) (Figure 1).

Moreover, ORF6 and ORF10 fragments and S protein fragments form amyloid assemblies causing neuronal death (Charnley et al., 2022; Nyström and Hammarström, 2022). PD's onset and progression are tightly connected to α-synuclein (α-syn) aggregation, which was observed to be promoted by both S and N proteins of SARS-CoV-2 (Semerdzhiev et al., 2023; Wang et al., 2023; Zilio et al., 2023). SARS-CoV-2 infection can also lead to tau phosphorylation, a key factor in tauopathies such as AD (Di Primio et al., 2023; Eberle et al., 2023). Moreover, AD patients seem to be more prone to severe course of infection, which could possibly exacerbate already existing neuropathology (Ciaccio et al., 2021; Meinhardt et al., 2023).

Discussion

Several mechanisms have been suggested to cause neurological symptoms and exacerbation of pre-existing neurological conditions during SARS-CoV-2 infection. These include direct effects of the virus on the CNS, e.g., by nasal entry into the brain and infection of neuronal populations (Meinhardt et al., 2021), and para- or post-infectious effects such as induction of inflammation and autoimmune responses (Kumar et al., 2020; Zubair et al., 2020). These effects of SARS-CoV-2 on the CNS have potential implications for the development of long-term neurological disease, including neurodegeneration.

SARS-CoV-2 neurotropism and entry to the CNS are debated topics. Given that SARS-CoV-2 is a possible cause of synucleinopathies (Albornoz et al., 2023; Iravanpour et al., 2024; Wang et al., 2023) and taupathies (Di Primio et al., 2023; Eberle et al., 2023; Käufer et al., 2022) and has the potential to worsen existing neuropathologies, potential ways of viral entry to the brain tissue should be thoroughly examined. Current research does not give an indisputable answer to why some COVID-19 patients have neurological symptoms, often lasting longer than coronaviral infection. Microglia and astrocyte activation could explain the long COVID syndrome and progression of neurodegenerative diseases (Stein et al., 2023), however, whether the activation occurs as a direct or indirect response to SARS-CoV-2 infection is still a puzzle to solve. Given that human brain tissue is not widely available, more *in vitro* and *in vivo* research is needed to better understand these highly significant issues.

In conclusion, it is worth adding that COVID-19 is the first pandemic to occur in the context of an aging population (Adesse et al., 2022; Mitra et al., 2022; Strong, 2023). Its survivors are at a greater risk of developing neurodegenerative diseases as they age. The potential long-term effects on the nervous system could be a lasting legacy of an even greater global health challenge than acute infection.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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