Dear Editor

Since the beginning of the COVID-19 pandemic, SARS-CoV-2 caused near one hundred million confirmed cases and over two million deaths worldwide, until 2021 February. Although SARS-CoV-2 primarily targets the human respiratory system, it has also shown neurotropic and neuroinvasive properties. Evidence of neuroinvasion in post-mortem COVID-19 patients has been reported (Reichard et al. 2020; Song et al. 2020). A range of various neurological manifestations is reported so far in SARS-CoV-2 infection, from mild symptoms such as headache, dizziness, impaired consciousness, smell/taste impairment, and neuralgia to more severe complications, including seizures, psychosis, acute ischemic stroke, and acute cerebrovascular diseases (Guadarrama-Ortiz et al. 2020; Liu et al. 2020; Valiuddin et al. 2020).

Patients with neurodegenerative disorders who are usually older potentially have a higher risk of developing COVID-19. However, comorbidity, severity, and duration of their neurodegenerative disease are considered more important factors. The morbidity and mortality of COVID-19 in the severe stages of Parkinson’s, Alzheimer’s, and Huntington’s disease might be higher because of respiratory muscle rigidity, dementia, and difficulties in secretion clearance from lungs, respectively (Ferini-Strambi and Salsone 2021). Since the number of patients with neurodegenerative disorders and COVID-19 who have been studied is small, the results of these studies are sometimes inconsistent and not generalizable (Del Prete et al. 2021; Yu et al. 2021).

Finding a more in-depth insight into biological processes and pathways involved in neurological manifestations of COVID-19 seems necessary. Only two high-throughput datasets are available in the gene expression omnibus database (GEO, http://www.ncbi.nlm.nih.gov/geo) (GSE157424 and GSE159812) so far, which has attempted to analyze the SARS-CoV-2 infection impacts on neural cells, and no high-throughput data on neurons treated with SARS-CoV-2 are available in the ArrayExpress databank (https://www.ebi.ac.uk/arrayexpress/).

Several hypotheses have been proposed about the routes of SARS-CoV-2 neuroinvasion, including neuronal retrograde, hematogenous, lymphatic rout, and trans-synaptic (Fig. 1). In the retrograde neuronal pathway, the virus can penetrate from the respiratory tract to the central nervous system (CNS) through the olfactory bulb (Desforges et al. 2019; Baig et al. 2020; Li et al. 2020). Damage of the olfactory endothelium could be related to anosmia or hyposmia symptoms. In the hematogenous route, the virus uses the bloodstream to reach cerebral circulation, damages endothelial cells of the blood–brain-barrier (BBB), and enters the CNS. Other respiratory viruses can also contaminate leukocytes and spread to the brain through cerebral circulation (Hamming et al. 2004; Desforges et al. 2019; Li et al. 2020). Lymphatic routes are physiological routes connected to the cervical and olfactory lymphatic vessels. The virus can use it to reach the CNS (Louveau et al. 2015; Iroegbu et al. 2020). The last suggested route is the trans-synaptic exchange of virus particles from peripheral nerves to the CNS (Li et al. 2020). Moreover, hyper-inflammation and hyper-coagulation can increase BBB permeability and entrance of the viral particles to the brain, which results in local hypoxia, ischemic infarcts, and BBB breakdown (Battaglini et al. 2020; Song et al. 2020).
In the CNS, microglial cells function similarly to macrophages that respond to virus infection. Microglia inductively express the pattern-recognition receptors (PRRs) that recognize viral pathogen-associated molecular patterns (PAMPs) (Li et al. 2004). After receptor-mediated endocytosis of SARS-CoV-2, Toll-like receptor (TLR) 7/8 and TLR 3 can recognize viral RNA and Double-stranded RNA intermediates, respectively (Kircheis et al. 2020). Then inflammatory cascades initiate by activating the IFN and NF-kB signaling pathways (Sabroe et al. 2008; Totura et al. 2015). In viral infection of the human central nervous system (CNS), type I IFN (IFN-α and IFN-β) is produced by infected cells, and type-II IFN (IFNγ) is expressed by activated immune cells (Kulkarni et al. 2017). In the NF-kB pathway, activation of IKKα and IKKβ leads to phosphorylation and ubiquitination of the cytoplasmic inhibitor factor IκBα. Then p50/p65 dimers are released and translocate to the nucleus. NF-kB dimers can regulate gene expression by binding to kB sites in promoter regions of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and IL-8 (Catanzaro et al. 2020; Kircheis et al. 2020). The virus is...
also recognized by cytoplasmic NOD-like receptors (NLRP3) that is a PAMP sensor. After binding to the virus, it forms an inflammasome complex with caspase-1 (Casp-1) and cleaves pro-IL-1β and pro-IL-18 to their mature forms (Battagello et al. 2020; Guadarrama-Ortiz et al. 2020). Hyper-cytokinemia plays an essential role in systemic inflammatory response syndrome (SIRS) that can cause brain damage (Catanzaro et al. 2020). TNF binds to its receptors and activates TNF receptor-associated factor (TRAF) and receptor-interacting protein (RIP) that leads to induce NF-kB and MAPK pathways (Battagello et al. 2020). From three prominent families of mitogen-activated protein kinases (MAPKs) in mammalians (ERKs, JNKs, and p38 MAPKs), some reports showed the p38s involvement in SARS-CoV-2 infection. Proinflammatory factors can induce the p38MAPK pathway, and in turn, it can regulate immune responses. Increased MAPK signaling activity can regulate neuronal survival and homeostasis in the CNS (Feng et al. 2019; Grimes and Grimes 2020). In the JAK/STAT pathway, IL-6 binding to IL-6 receptor mediate JAK proteins phosphorylation, leading to activation of STAT proteins. Phosphorylated STATs dimerize and translocate to the nucleus, where they act as transcription factors to regulate gene expression (O’Shea et al. 2015). SARS-CoV-2 infection down-regulates ACE2 expression, similar to SARS Coronavirus. Decreased level of ACE2 changes the balance of Ang-II / Ang-I and causes inflammation and vascular permeability (Kuba et al. 2005; Gheblawi et al. 2020). Accumulated Ang-II binds to Angiotensin-II type I receptor (AT1R) and induces inflammation and fibrosis via the JACK-STAT pathway. Since the Renin-Angiotensin system plays a vital role in regulating water balance and blood pressure in the brain, an increase in Ang-II level may lead to encephalitis and meningitis (Xiao et al. 2013; Groß et al. 2020). Pathways involved in SARS-CoV-2 neuroinvasion are summarized in Fig. 1.

Direct and indirect effects of SARS-CoV-2 on the brain endothelium (especially BBB) and vascular permeability, in addition to hyper-inflammation, hyper-coagulation, and disturbance of hemostasis in the brain, can justify CNS injury in COVID-19 patients. Some of these injuries are encephalopathy, encephalitis, encephalomyelitis, meningoencephalitis, demyelination, hypoxic injury, and hydrocephalus (Kotfis et al. 2020; Moriguchi et al. 2020; Paterson et al. 2020; Zanin et al. 2020).

Conflict of Interest Authors declare no conflict of interest.

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