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SARS-CoV2 entry and spread in the lymphatic drainage system of the brain

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Dear Editor,

Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-CoV2) has been shown to invade brain tissue, but almost nothing is known with certainty about how it can invade. Researchers suppose that based on the evolutionary similarity between the coronaviruses responsible for the Middle East respiratory syndrome in 2012 and the severe acute respiratory syndrome epidemic in 2003, and SARS-CoV2, SARS-CoV2 could be a neurotrophic virus and that its neuroinvasive potential may explain the difference in the severity of SARS-CoV2-induced respiratory failure in patients with coronavirus infectious disease-19 (COVID-19) (Li et al., 2020). Therefore, the correspondences have focused on possible explanations of how SARS-CoV2 penetrates the olfactory bulb through the olfactory epithelium without asking whether it can. The presence of one similar word in two different books does not make those books similar; likewise, the evolutionary similarity between SARS-CoV and SARS-CoV2 does not prove these viruses has the same invasion mechanism. Moreover, SARS-CoV was not observed to spread in nervous system through nerve endings of olfactory bulb.

The first study investigates neurological signs of COVID-19 infection in 214 patients in Wuhan, China, indicated that 36% had neurological symptoms and the symptom frequency correlates with increased severity of the respiratory disease (Mao et al., 2020). Underlying events of these symptoms might be viral RNA-induced neural inflammation, coagulation causing a stroke or impaired clearance of the brain. More recently, postmortem histological evaluations revealed that SARS-CoV2 can infect endothelial cells and cause endothelial dysfunctions and lymphocytic endothelitis in the heart, kidney, lung, liver, and submucosal vessels of the small intestine (Varga et al., 2020). For many years, it has been thought that the brain has not classical lymphatic vessels. However, new findings revealed that functional lymphatic drainage does exist in the brain (Louveau et al., 2015). This brain-wide glymphatic pathway contain olfactory/cervical lymphatic vessels, which could provide a direct entry route for SARS-CoV2 to the brain.

The difference in respiratory distress in patients with SARS-CoV2 prompt researchers to suggest the neuroinvasive potential may account for this difference (Li et al., 2020). However, these rushed comments ignore the fact that recovering patients from COVID-19 do not show respiratory distress symptoms, which suggests that the impairment of dorsal root neurons in the brainstem by the virus is not the case in COVID-19 infection because recovering of neuroinflammation or neurodegeneration caused by viral infection is not as fast as recovering of the lung alveoli (Turtle, 2020).

Neurologic symptoms, i.e., impaired-consciousness and delirium, point out SARS-CoV2 entry and spread in neocortex of the brain. More recently, Paniz-Monodolfi et al. (2020) have reported SARS-CoV2 to be observed in frontal lobe tissue at transmission electron microscopy. Based on this finding, they have suggested the hematogenous route as the most likely pathway for SARS-CoV2 entry to the brain. Growing evidence indicates that the severity of viral infection correlates with increased frequency of neurological symptoms. Moriguchi et al. (2020) reported the first case of meningitis/encephalitis associated with COVID-19. Strikingly, their case was presented with significant paranasal sinusitis. They interpreted this finding to link paranasal conditions with the diagnosis of COVID-19. However, this paranasal sinusitis could be related to obstructed paranasal lymph vessels caused by the viral infection since, as I mentioned above, Varga et al. (2020) documented histologically that SARS-CoV2 can infect lymph endothelial cells branching to the nasal cavity from cervical lymph nodes and reaching to the brain. The other encephalitis case was reported by Ye et al. (2020), to which I am referring my comments. however, their case had presumptive diagnosis based on the physical evaluation of neurological symptoms not on virus isolation. The first systemic review also provided evidence on the occurrence of nervous system involvement and corroborated neurological symptoms of COVID-19 in the patients even though the standard of the review is arguable due to limited COVID-19 literature. Together, it is plausible to posit that SARS-CoV2 could infect the brain and cause neurological symptoms; however, putative entry side of SARS-CoV2 (angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TRPMSS2)) may not be olfactory sensory neurons because ACE2 or TRPMSS2 is expressed in the olfactory epithelium and not in the olfactory sensory neuron (Bagheri et al., 2020). In addition, case reports revealed that older patients are much more sensitive to SARS-CoV2 infection and anosmia. The literature bringing the view that the virus enters the brain through axons of olfactory bulb neurons under the cribriform plate into the forefront discusses that the ACE2 receptor provides a key for viral invasion from the olfactory epithelium to the brain (Li et al., 2020).

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However, aging is associated with the decline in ACE2 expression (Rodrigues Prestes et al., 2017) and the degeneration of olfactory receptor neurons. Severe COVID-19 infection and neurodegeneration in elders point out a different entry side, which is independent of neurons and molecular events.

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Declarations of interest

The author declares that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.04.080.

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