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COMMENTARY

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Comment on "Central Nervous System Involvement by Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2)"

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We read the article "Central Nervous System Involvement by Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2)" with great interest. There are many earlier reports demonstrating the neuroinvasiveness of 2003 SARS-CoV virus.[1,2] Although there have been several reports previously suggesting that the similar SARS-CoV-2 virus could infect neuronal cells and cause central and peripheral neurological morbidities in coronavirus disease 2019 (COVID-19) patients,[3-5] few direct detection of virus by reverse transcription polymerase chain reaction (RT-PCR) in cerebrospinal fluid (CSF) has casted earlier doubt whether there is indeed a direct infection of the central nervous system (CNS). In this report,[6] the authors were able to directly demonstrate the presence of viral RNA by RT-PCR of both structural and nonstructural genes. More interestingly, an electronic microscopy analysis of frontal lobe brain sections from postmortem examinations detected pleomorphic spherical virus-like particles in endothelial cells. The quality of the electronic micrographs needs to be improved to ascertain the small vesicles are indeed virion particles. An immune electron microscopy or immune-histochemistry staining will be required to address this question.

This is the first demonstration of virus-like particles in blood vessel endothelial cells of blood-brain barrier (BBB). It is not clear whether SARS-CoV-2 viruses can be similarly detected in endothelial cells from other severe COVID-19 patients with central neurological involvement.[3] Neither is it clear whether this discovery has anything to do with this particular patient's pre-existing central neural disease, Parkinson's disease.[6] Nevertheless, at least in this reported patient, the viral replication in BBB endothelial may point to a hematogenous route for virus infection of CNS.

It is worthy to point out that one very recent report from a Chinese case demonstrating the presence of SARS-CoV-2 virus sequence in the CSF fluid of a COVID-19 patient is presenting viral encephalitis.[7] Together with the current report, the results are all suggestive of a direct CNS infection by SARS-CoV-2. A computed tomography/magnetic resonance imaging scanning result of a COVID-19 patient showed acute necrotizing encephalopathy (ANE), a rare encephalopathy typically associated with viral infection of the brain tissue.[8] Nevertheless, ANE is frequently associated with intracranial cytokine storms,[9] which leads to breakdown of BBB and shedding of viruses. The causative relationship between cytokine storm and SARS-CoV-2 viral infection of CNS will clearly warrant further investigation. It is known that cytokine storm frequently occurs in COVID-19[10] and certainly it is particularly interesting to dissect the kinetic relationship between cytokine storm and CNS infection. To identify cases that have CNS infections in the absence of cytokine storm will likely provide even stronger evidence of direct infection of CNS. Furthermore, inflammatory cells such as macrophages can penetrate BBB and bring many viruses including human immunodeficiency virus and other viruses to the brain in a "Trojan horse mechanism."[11,12] It will be important to investigate whether SARS-CoV-2 has evolved to possess this mechanism for CNS infection.

The infection of neuronal system can explain a lot of clinical cases with neurological involvement,[3] both central and peripheral. As a result, as pointed by Dr Baig,[13] it is urgent to develop means and technologies to pinpoint whether the patient has CNS involvement during COVID-19, which will be critical for diagnosis and prognosis of

the affected patients. There are at least three possible routes for viral infection of CNS: hematogenous, lymphatic, and transsynaptic transfer.[14] The current report is suggestive of a hematogenous route. The transsynaptic transfer route is particularly interesting considering the frequently reported peripheral neuronal manifestations in COVID-19 including loss of smell and taste.[3,13] It is currently unknown how much likelihood the peripheral neurological manifestation will lead to CNS infection, which warrants further investigation. On the other hand, it may not be unreasonable to assume that the infection of CNS through three different routes may affect different regions of the brain and eventually lead to different functional impairments from CNS. For example, in an earlier study from COVID-19 patients in China, it was discovered that although patients with cardiovascular comorbidity were more likely to develop severe cardiac complications, acute cardiac injury and heart failure were more common in deceased patients regardless whether there is history of.[15] Many case reports showed loss of involuntary process of breathing in severe patients.[14] Whether the SARS-CoV-2 virus affected the same or different regions of cardiorespiratory center in the brain deserves further investigations.

No matter which routes the virus reaches the CNS area through, the consequence may be beyond the current pandemic. It is not clear now exactly how long the SARS-CoV-2 virus can remain in the CNS. It is unlikely that this coronavirus has the same mechanism as the neurotropic DNA viruses, such as herpes simplex viruses, to stay permanently in the brain. Nevertheless, an interesting report by Dr Talbot's[16] group showed that the viral RNA of another human betacoronavirus, human coronavirus OC43, can exist in the mice for at least a year after the initial virus-induced acute encephalitis and continuously cause pathology in the mice. In light of this, it will be worthy to take into account of the neuronal reservoir of SARS-CoV-2 virus in the recurrent cases of COVID-19 disease.[17,18] For these cases, previous neurological manifestations will be an important factor for prognosis.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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