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Commentary

Response to Commentary on: “The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients”

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Running title: **The possible involvement of nervous system in COVID-19**

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Abstract

In a recent review, we have suggested a neuroinvasive potential of SARS-CoV-2 and its possible role in the causation of acute respiratory failure of COVID-19 patients (J Med Virol doi: 10.1002/jmv.25728), based upon the clinical and experimental data available on the past SARS-CoV-1 and the recent SARS-CoV-2 pandemic. In this article, we provide new evidences recently reported regarding the neurotropic potential of SARS-CoV-2 and respond to several comments on our previously published article. In addition, we also discuss the peculiar manifestations of respiratory failure in COVID-19 patients and the possible involvement of nervous system.

KEYWORDS

cell susceptibility, coronavirus, dissemination, nervous system

Based upon the clinical and experimental data available for coronaviruses (CoVs), we have suggested a neuroinvasive possibility of SARS-CoV-2 and its possible role in the acute respiratory failure seen in COVID-19 patients (J Med Virol doi: 10.1002/jmv.25728), given that most CoVs share a similar viral structure and infection pathway among them ¹.

Coraci et al. ² have commented the significance of the treatment options suggested by us. However, the treatment options have not been incorporated in the final edition of our paper ¹. Turtle L. is cautious about our suggestions, especially about our views on the use of masks. He also doubts the neuroinvasive possibility, as in his views, he thinks that many viruses can only occasionally gain entry into human central nervous system ³.

Mr. Turtle appears to have overlooked the fact that the neuroinvasive propensity has been very well documented for almost all the β CoVs. Among the six known human CoVs, at least four (HCoV-229E, HCoV-OC43, SARS-CoV, and MERS-CoV) have been shown to possess such property ^{4~7}.

In less than a month after our article got published online, several pieces of evidence have been reported regarding the neurotropism of SARS-CoV-2, which is generally consistent with our prediction.

The first-hand evidence became available in medRxiv⁸, which reported that 36.4% among 214 COVID-19 patients had neurologic manifestations, and that severe patients were more likely to display neurologic symptoms, such as acute cerebrovascular diseases (5.7%), impaired consciousness (14.8%) and skeletal muscle injury (19.3%).

Moreover, another neurological symptom, loss of smell and taste, has been reported in COVID-19 patients in several countries⁸, for example, in the Heinsberg district, Germany (<https://www.pfalz-express.de/bonner-virologe-entdeckt-neue-covid-19-symptome>).

In addition, a piece of more direct evidence has been obtained in two different countries. A COVID-19 male patient in his 20s in Yamanashi, Japan who along with fever had been diagnosed with meningeal irritation (<https://headlines.yahoo.co.jp/hl?a=20200308-00000503-san-hlth>). Another case with encephalitis was reported for a male patient aged 56 years on March 16, 2020 on the website of Beijing Ditan Hospital Capital Medical University, China (<http://www.bjdth.com/html/1/151/163/3665.html>). Importantly, PCR analysis showed that the cerebrospinal fluid samples from both patients turned positive for SARS-CoV-2.

The mechanisms underlying the neurological symptoms are unclear, which deserves further study, but the isolation of SARS-CoV-2 RNA in the cerebrospinal fluid elucidates that the SARS-CoV-2 may be naturally neuroinvasive in humans.

Since a comprehensive understanding of SARS-CoV-2 is still lacking, a high degree of vigilance should be kept for the possible involvement of nervous system in COVID-19 patients, despite only rare cases are currently being reported with COVID-19 related encephalitis or meningitis.

Based upon the recent evidence, the extent and characteristics of lung lesions were similar between symptomatic and asymptomatic patients, but most of the patients showed only mild flu-like symptoms, which gave clinical staff an impression of improvement so that some patients who suddenly deteriorated had missed timely treatment^{9~11}. It is also still unclear why some survivors had lost their natural breath during respiratory failure.

As a possible mechanism, skeletal muscle injuries and poor expectoration have been reported for some COVID-19 patients^{8~9,12}. Similarly, some SARS patients have

already been found to develop axonopathic polyneuropathy after onset of illness, while some experienced myopathy or rhabdomyolysis^{13~14}. The neuromuscular disorders in SARS patients have previously been considered as critical illness neuropathy and myopathy, but the possibility of direct attack by SARS-CoV on the nerves and muscles could not be excluded¹³.

Besides, the loss of smell and taste in some COVID-19 patients provided another possibility that SARS-CoV-2 infection may lead to a reduced sensitivity of neurosensory reflexes. A similar olfactory dysfunction has also been described for a SARS patient early in 2006¹⁴.

Therefore, it is possible that injured respiratory muscles and/or poor sensory response may play a role in the respiratory failure induced by SARS-CoV-2, though severe lung lesions and airway obstruction may bear most of the responsibility. Considering the possible involvement of nerves and/or muscles, neurophysiological assessment may be considered during the management of the patients with peripheral neurological symptoms.

On the other hand, studies on the samples from patients with SARS have demonstrated the presence of SARS-CoV particles in the brain, where they were located almost exclusively in the neurons^{5~6,15}. Either SARS-CoV or MERS-CoV, when given intranasally, could enter the brain of experimental animals, possibly via olfactory nerves, and thereafter rapidly spread to some specific brain areas. Among the involved brain areas, the brainstem has been demonstrated to be heavily infected by SARS-CoV^{16~17} or MERS-CoV⁷. Consistently, the olfactory and taste disorder reported for some COVID-19 patients may at least partially supports this possibility.

Baig et al. in a recently published an article have suggested a putative transcribrial route of the SARS-CoV-2 to brain and have emphasized that the isolation of SARS-CoV-2 RNA in the cerebrospinal fluid would be the most conclusive evidence to document the neurovirulence of SARS-CoV-2¹⁸.

The potential invasion into the central nervous system by SARS-CoV-2 indicates a central mechanism underlying the acute respiratory failure in COVID-19 patients, which may coexist with the peripheral factors without contradiction¹. Autopsies and detailed

analysis of nerve tissue from COVID-19 patients will be an effective measure to clarify the role of the central factors in the respiratory failure ¹⁸.

So far, several pieces of evidence have emerged showing the involvement of nervous system during SARS-CoV-2 infection. According to WHO, SARS-CoV-2 has caused a worldwide pandemic, and there is an urgency to clarify the mechanisms underlying the respiratory failure of COVID-19 patients in order to prioritize and individualize the treatment protocols based on the severity of the disease and predominant organ involvement ¹⁸.

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