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Commentary

Pathophysiology of CNS disease related to SARS-CoV-2

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Commentary

With interest we read the review article by Mahalakshmi et al. about the repercussions of an infection with SARS-CoV-2 (COVID-19) on the central nervous system (CNS) [1]. It was concluded that neurons and glial cells express ACE2-receptors, that activated glial cells contribute to neuroinflammation, and that SARS-CoV-2 triggers immune-mediated demyelinating disease, cerebrovascular damage, neurodegeneration, and depression [1]. We

have the following comments and concerns.

The main limitation of the review is that it is assumed that CNS compromise from SARS-CoV-2 only results from invasion of the virus in the CNS or the response of the immune system against the virus [1]. However, the infection may not only result in primary damage of neurons or glial cells by the invasion of the virus or secondary due to the reaction of the global immune system or glial cells to the viral attack, but also tertiary due to primary or secondary affection of organs other than the CNS, which may lead to tertiary CNS compromise due to the close connection between the CNS and these other affected organs. The organ most closely connected to the CNS is the heart. This is why primary or secondary affection of the heart by SARS-CoV-2 can lead to CNS disease. Affection of the kidneys may cause renal hypertension, which may be responsible for intracerebral bleeding or ischemic stroke. Gastro-intestinal involvement may lead to electrolyte disturbances and consecutively to arterial hypertension [2].

A pathophysiological mechanism of ischemic stroke in COVID-19 patients not considered is cardiac embolism. There are several reports showing the SARS-CoV-2 may cause myocarditis [3, 4]. Since myocarditis may go along with intra-cardiac thrombus formation [5], it is conceivable that intra-cardiac thrombi are transported to cerebral arteries where they may occlude small or large intra-cerebral arteries. Intra-ventricular thrombi may also result from heart failure. Since myocarditis may be complicated by arrhythmias, including atrial fibrillation [6], it is conceivable that cardio-embolism may also originate from the left atrium due to impaired contractility.

Another source of cardio-embolism not addressed in the review is Takotsubo syndrome (TTS). There is an increasing number of reports demonstrating that SARS-CoV-2 can trigger TTS [7]. Since TTS is attributed in one third of the cases to emotional triggers and in another third to physical triggers, it is conceivable that TTS in SARS-CoV-2 infected patients is triggered by anxiety or by stress from hypoxia, dyspnoea, or mechanical ventilation.

The spectrum of CNS disease associated with a SARS-CoV-2 infection is broader than anticipated in the review. SARS-CoV-2 may not only induce cerebrovascular disease, demyelinating CNS, or neurodegenerative disease, but also virus-related meningitis/encephalitis, immune encephalitis, myoclonus-ataxia syndrome, immune-response related myelitis, acute, disseminated encephalomyelitis (ADEM), sinus venous

thrombosis (SVT), vasoconstriction syndrome, cerebral vasculitis, intracerebral bleeding, psychosis, epilepsy, or headache. Among the demyelinating CNS disorders, SARS-CoV-2 may even precipitate multiple sclerosis [8].

Overall, the appealing review about pathophysiologic mechanisms involved in the development of CNS disease due to SARS-CoV-2 has several limitations. Tertiary causes of CNS disease, particularly cardiologic involvement, should be considered in the discussion about the pathophysiology of CNS compromise in COVID-19 patients. Particularly, cardio-embolism should be added to the discussion. There are also a number of CNS disorders, which are not explained by the pathophysiological scenarios depicted in the review.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest.

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