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LETTER TO THE EDITOR

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Update on the neurology of COVID-19

To the Editor,

Though infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus predominantly manifests in the lung as an interstitial pneumonia ("ground glass opacities"), there is increasing evidence that the virus invades all compartments of the body, particularly the eyes, heart, skin, kidneys, and the central nervous system (CNS).[1] Neurological manifestations of coronavirus disease-2019 (COVID-19) can be generally classified as primary or secondary. Primary manifestations result from direct affection of the CNS or the peripheral nervous system (PNS) by the virus. Secondary manifestations result from affection of organs other than the CNS by the virus, which then causes disease in the CNS/PNS.

In a recent systematic review, six studies were included, which reported on the presence of neurological manifestations in patients with COVID-19.[2] These include dizziness, impaired consciousness, confusion, headache, ataxia, seizures, ischemic stroke, sinus venous thrombosis, and cerebral hemorrhage.[2] The study did not mention encephalitis, meningitis, neuritis, or radiculitis, manifestations which are most conceivable in the context of this viral infection.

A more intense search for neurological involvement, however, revealed that CNS/PNS are indeed much more severely involved than so far anticipated. There is now clear evidence that SARS-CoV2 can cause meningitis and encephalitis.[3,4] The first case of meningoencephalitis was reported in a 24 years male who experienced fever and generalized fatigue, took laninamivir and antiypyretics, but was found unconscious 9 days later and developed seizures during admission.[3] Specific SARS-CoV2 RNA was found in the cerebrospinal fluid (CSF) but not in the naso-pharyngeal swab.[3] Cerebral magnetic resonance imaging revealed hyperintensity along the wall of the right lateral ventricle and in the right mesial temporal lobe and hippocampus, suggesting meningitis.[3] Duong et al[4] reported meningoencephalitis in a 41 year female who presented with fever (38.1°C), a stiff neck, and pleocytosis of 70/3 and was tested positive for COVID-19. Unfortunately, the presence of virus-RNA in the CSF was not confirmed.[4] A third patient with SARS-CoV2 meningitis from India has been recently described but the report is not yet published. The presence of virus-RNA in the CSF was already reported in a retrospective analysis of 214 Chinese patients with COVID-19.[1]

Seizures have been occasionally reported in SARS-CoV2 infected patients (Table 1).[1] Whether seizures in these patients are the manifestation of ischemic stroke, meningitis, or cerebral hypoxia, or due to noninfection related causes, such as hypocalcemia or drug-induced, remains speculative. In the study by Mao et al[1] 0.5% of the infected patients had seizures. In a systemic investigation of 304 patients with COVID-19 without a previous history of seizures only two of them had seizure-like manifestations in association with hypocalcemia.[5] One patient with meningitis presented initially with seizures.[3]

TABLE 1 CNS and PNS disease caused by SARS-CoV2

CNS/PNS	Abnormality	Evidence level	Reference
CNS	Meningitis/encephalitis	Case reports	Mao et al,[1] Asadi-Pooya and Simani,[2] and Duong et al[4]
	Ischemic stroke	Case reports and RCS	Mao et al,[1] Yang et al,[6] Li et al,[7] Avula et al[8]
	Seizures	Case reports and RCS	Mao et al,[1] Moriguchi et al,[3] and Lu et al[5]
	Headache	Case reports and RCS	Mao et al[1]
	Cerebral bleeding	RCS	Li et al[7]
	Sinus venous thrombosis	RCS	Li et al[7]
	Optic neuritis	Murine and Felline model	Seah et al[9]
	Reduced alertness	RCS	Mao et al,[1] Wang et al,[10] Chen et al,[11] and Yin et al[12]
PNS	Guillain-Barre syndrome	Case report	Virani et al,[13] Sedaghat et al,[14] Toscano et al,[15] and Zhao et al[16]
	MFS	Case report	Gutiérrez-Ortiz et al[17]
	Polyneuritis cranialis	Case report	Gutiérrez-Ortiz et al[17]
	Hyposmia/hypogeusia	Case reports and RCS	Mao et al[1] and Gutiérrez-Ortiz et al[7]
	Neuralgia	RCS	Mao et al[1]
	Myalgia	Case report and RCS	Mao et al[1] and Fiorino et al[18]

Abbreviations: CNS, central nervous system; MFS, Miller-Fisher syndrome; PNS, peripheral nervous system; RCS, retrospective cohort studies; SARS-CoV2, severe acute respiratory syndrome coronavirus-2.

Ischemic stroke has been repeatedly reported in patients with COVID-19. In a retrospective study of 304 infected patients, 27% developed an ischemic stroke during the infection.[5] In some of these patients seizures were reported.[5] Cerebral ischemic events in patients with COVID-19 have been reported also by others.[1] In a retrospective study of 184 patients with COVID-19, three experienced an ischemic stroke.[19] In a retrospective study of 92 patients who died from the virus, 10.8% had experienced a cerebrovascular event.[6] COVID-19 may predispose for ischemic stroke due to excessive inflammation, hypoxia, immobilization, or diffuse intravascular coagulation.[19]

In a single male with COVID-19, impaired consciousness and psychiatric abnormalities were observed. Impaired consciousness was also reported in 8% of the patients reported by Mao et al.[1] Headache was reported in 6% to 13% of these patients with COVID-19.[1] In the study by Li et al, 0.5% of the patients developed sinus venous thrombosis. Cerebral vasculitis or vasculitis of the PNS have not been reported as manifestations of a COVID-19 infection.

Evidence for involvement of the PNS comes from recent reports about the occurrence of Guillain-Barre syndrome in SARS-CoV2 infected patients.[13] Altogether four cases have been thus far reported (Table 1). In a 50-year-old male with COVID-19, Miller-Fisher syndrome developed 5 days after onset of the infection.[17] A 39-year-old male with COVID-19 developed polyneuritis cranialis 3 days after onset of the infection.[17]

In a Chinese study of 214 infected patients, 36.4% had neurological manifestations.[1] In this study, neurological manifestations, in addition to the ones mentioned above, included hyposmia, hypogeusia, visual impairment, and neuralgia.[1] Hyposmia/hypogeusia was reported in 5.1% respectively, 5.6% of the infected patients but has been repeatedly observed since this first description.[16] Hypogeusia/hyposmia may particularly occur in the early stages of a COVID-19 infection, most frequently before onset of pulmonary manifestations. Though a CNS/PNS cause cannot be definitively excluded, hyposmia/hypogeusia may be rather attributable to a direct contact of the virus with taste buds or olfactory receptors than meningitis or neuritis.[20] Other indications for affection of the PNS come from studies which reported neuralgia and myalgia in SARS-CoV2 infected patients (Table 1).

The pathway via which SARS-Cov2 enters the CNS is unknown but it has been speculated that the virus initially invades peripheral nerve terminals and later travels to the CNS via a synapse-connected route. The trans-synaptic transfer has been proven for HEV67 CoV and the avian bronchitis virus. In transgenic mice, SARS-CoV and Middle East respiratory syndrome-coronavirus entered the brain via the olfactory nerve and spreaded quickly to the brainstem and the thalamus.[21] This was explained by the expression of angiotensin converting enzyme 2 receptors on the surface of neurons and glial cells, which make them a potential target for SARS-CoV2. If the inoculum dosages in these mice were low, the virus was not found in the lungs but only in the CNS, suggesting that the high mortality due to respiratory insufficiency could be attributed to involvement of the brainstem.

A second route via which the virus could enter the CNS is the hematogenic pathway. Using arteries for accessing the CNS, the virus needs to overcome blood brain barrier. Indications for such a scenario have been recently provided by Paniz-Mondolfi et al,[22] who, in a postmortem study, found the virus in neurons and capillary endothelial cells of the frontal lobe of a patient who deceased from SARS-CoV2-associated acute respiratory distress syndrome. A third way of entry could be spreading of the virus via the lymphatic drainage system of the brain.

Overall, it is striking that the prevalence of neurological abnormalities in patients with COVID-19 is highly variable between studies and the types of abnormalities are considerably variable as well. However, neurological compromise is definitively part of COVID-19 infections and occurs in up to one third of the patients. The most frequent primary neurological manifestations of the COVID-19 infections are meningitis and seizures. Secondary neurological manifestations may be dizziness, confusion, headache, ischemic stroke, intracerebral bleeding, or sinus venous thrombosis. Ischemic stroke is regarded secondary as there is currently no indication for cerebral vasculitis or acute macroangiopathy of the intra- or extracerebral arteries. COVID-19 becomes also a challenge for the neurologist.

AUTHOR CONTRIBUTIONS

JF: assisted in design, literature search, discussion, first draft, and critical comments; CS: conducted literature search, critical comments, and revision.

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