Neurologic manifestations of COVID-19

To the editor We read with interest the review article by Adamczyk-Sowa et al[1] on neurologic manifestations of coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was concluded that clinicians should pay attention to neurologic signs and symptoms in COVID-19 that suggest the involvement of the central or peripheral nervous system caused by the infection.[1] We have the following comments and concerns regarding this issue.

The authors claim that SARS-CoV-2 enters the cerebrospinal fluid (CSF) via olfactory epithelial cells and a trans-synaptic neural pathway in the olfactory bulb.[1] However, in most patients undergoing a spinal tap (particularly those with suspected polyradiculitis or meningitis / encephalitis) and investigations of the CSF for SARS-CoV-2, tests for viral RNA yielded negative results in the CSF.[2] Since the virus, nonetheless, has been found inside neurons, glial cells, and endothelial cells of the frontal lobe[3] and in other cerebral locations, hematogenous spread appears to be more likely than neuronal dissemination. Damage to the blood-brain barrier (BBB) may occur from the vascular side of the BBB by a direct attack or indirect immunological attack of endothelial cells. Of note, SARS-CoV-2 not only exhibits high affinity to the angiotensin-converting enzyme 2 receptors of olfactory epithelial cells and taste buds but also to vascular endothelial cells.[4] An argument against entry via the lymphatic system is that lymph node swelling is hardly reported in patients with COVID-19.

Neurologic signs and symptoms in addition to olfactory or gustatory disturbances, seizures, impaired consciousness, photophobia, hemiparesis, quadriparesis, facial weakness, aphasia, dysarthria, sensory disturbances, headache, and dizziness that should trigger the suspicion of neurologic involvement in COVID-19 include acute cognitive decline in the case of acute hemorrhagic necrotizing encephalitis (AHNE),[5] ataxia in the case of cerebellitis, transverse syndrome due to transverse myelitis, spasticity, myoclonus, neurogenic dysphagia, dysexecutive syndrome, memory impairment, and psychosis.

Neurologic disease, in addition to meningitis / encephalitis, stroke, and epilepsy associated with COVID-19, include AHNE,[5] cerebellitis, intracerebral bleeding, acute cerebral demyelination, vasculitis with endotheliitis of small or large cerebral arteries, acute disseminated encephalomyelitis, and posterior reversible encephalopathy syndrome.

Overall, the comprehensive review could benefit from a broader discussion about the hematogenous spread of the virus and dissemination to the brain as well as from considering other signs and symptoms and neurologic disorders as neurologic involvement in COVID-19.

ARTICLE INFORMATION

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Authors' reply We would like to thank Dr. Finsterer and Dr. Scorza for their interest in our article and important comments.

We agree with the observation that the hematogenous spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be the first route of viral dissemination in the host organism, considering the multiplicity of

organs affected during infection. Some reports have suggested that the virus may enter the central nervous system via endothelial cell infection of the blood-brain barrier or through infected monocytes or macrophages.[1] On the other hand, in view of the fact that neurologic symptoms, especially loss of smell and taste, very often precede all other symptoms or are even the only symptoms that occur, it is reasonable to anticipate neuronal retrograde dissemination. Indeed, in some reports, the presence of SARS-CoV-2 RNA has been shown in both oropharyngeal swab and cerebrospinal fluid specimens.[2,3] In our opinion, it is impossible to dissect the clinical relevance of those routes as well as a potential for others.

Certainly, the list of neurologic disorders that are associated with SARS-CoV-2 infection or could potentially be its sequelae will become much longer with new knowledge. Up to date, many of the suggested diseases and/or manifestations are based on case reports and it is crucial to consider them, but it is difficult to draw conclusions on their relevance in coronavirus disease 2019 (COVID-19). What adds to the complexity of the issue, neurologic involvement during SARS-CoV-2 infection results not only from the direct effect of the virus, but, in our opinion more importantly, should potentially be linked to defective immune activation and inflammation.[4] Finally, some disorders described, such as posterior reversible encephalopathy syndrome, could not be directly related to SARS-CoV-2 infection yet to its treatment, ie, the use of potentially neurotoxic off-label therapies or prolonged intensive care unit treatment.[5] On one hand, neural complications are among the most important complications of SARS-CoV-2 infection. On the other hand, reports on a specific disease should be treated with caution, as there have been only few of them and they need to be validated in large prospective datasets.

The aim of our review was to draw clinicians' attention to various neurologic symptoms that may be caused by SARS-CoV-2 yet not primarily being of neurologic origin. This may contribute to a faster diagnosis and treatment of COVID-19.

ARTICLE INFORMATION

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