Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System

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Abstract

Emerging evidence indicates that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, can cause neurological complications. We provide a brief overview of these recent observations and discuss some of their possible implications. In particular, given the global dimension of the current pandemic, we highlight the need to consider possible long-term impacts of COVID-19, including on the incidence of neurological and neurodegenerative disorders.

Coronaviruses, SARS-CoV-2, and their impact on multiple organ systems

Coronaviruses (CoVs) are the largest group of viruses causing respiratory and gastrointestinal infections, and have been responsible for three pandemics in the past 18 years: Severe Acute Respiratory Syndrome (SARS) in 2002/2003, Middle East Respiratory Syndrome (MERS) in 2012 and, currently, coronavirus disease 2019 (COVID-19). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, is a novel member of the human coronavirus family that emerged in China in late 2019. The symptoms of COVID-19 can include fever, cough, loss of smell and taste, sore throat, leg pain, headache, diarrhea, and fatigue. While most patients infected with SARS-CoV-2 are asymptomatic or develop mild to moderate symptoms, a subset of patients develops pneumonia and severe dyspnea, and require intensive care. Because acute respiratory syndrome is the hallmark feature of severe COVID-19, most of the initial studies on COVID-19 have been focusing on its impact on the respiratory system. However, accumulating evidence suggests that SARS-CoV-2 also infects other organs and can affect various body systems. As many scientists have already noted, these emerging findings call for investigating short- and long-term consequences of COVID-19 beyond the respiratory system. In the next sections, we briefly discuss recent observations suggesting an association between SARS-CoV-2 infection and neurological complications. We place these findings in the context of previous studies that demonstrated effects of various viruses, including CoVs, on the central nervous system (CNS). Lastly, we highlight the possibility that SARS-CoV infection could favor or enhance susceptibility to other forms of CNS insults that may lead to neurological syndromes. Given scope limitations, we offer only a sample of the substantial literature on CNS impacts of viral infection, with the purpose of underscoring some of the

sequelae and mechanisms that may be involved in the context of COVID-19, and that require further investigation.

Possible neurotropism of SARS-CoV-2

Cerebrovascular diseases are among the comorbidities of patients with confirmed COVID-19 who develop severe respiratory complications [1]. One study, for instance, reported hypoxic-ischemic encephalopathy in approximately 20% of 113 deceased patients with COVID-19 [2]. A recent study evaluated 214 patients diagnosed with COVID-19 from China and found that 36% had neurological manifestations, including acute cerebrovascular diseases and impaired consciousness [3]; a case of acute hemorrhagic necrotizing encephalopathy has been reported as well [4]. Connections between viral infections and CNS pathologies are not new. The aforementioned observations on COVID-19 are in line, for instance, with a report of severe neurological manifestations associated with MERS-CoV infection in Saudi Arabia [5]. With regards to SARS-CoV-2 specifically, current evidence is still scarce and additional work is needed on whether neurological manifestations occur in COVID-19 patient populations beyond those of the initial studies. It will also be important to determine whether SARS-CoV-2 is detected in the cerebrospinal fluid (CSF) of patients that develop neurological alterations, and/or whether other CSF alterations are present (see Box 1). CSF studies are needed, in part, to better understand SARS-CoV-2's neurotropism and whether its impact on the CNS is through direct infection or via secondary effects relating to enhanced inflammatory/pro-inflammatory signaling.

Human CoVs and other neurotropic viruses affects the CNS

While studies testing whether SARS-CoV-2 targets the brain in humans or in animal models are not yet available, well-established literature has demonstrated that other viruses target the central nervous system (CNS) and cause neurological alterations, including brain inflammation and encephalomyelitis [6]. One example comprises human CoV OC43, which has been associated with fatal encephalitis in children [7,8]. Detection of SARS CoV RNA in the CSF of a patient with severe acute respiratory syndrome has been reported [9]. Preclinical studies have further shown that human coronaviruses (e.g., HCoV OC43) as well as animal CoVs reach the CNS and cause encephalitis [6]. In addition, coronavirus antigen and RNA have been found in human brain tissue and CSF in Multiple Sclerosis (MS) patients [10], and CoVs have been implicated as putative etiologic agents of CNS autoimmunity, including MS. There are also indications of possible relevance to neurodegenerative diseases. CoV OC43 and CoV-229E, for instance, have been found in the CSF of Parkinson's disease patients [11]. Of note, early preclinical studies showed that intranasal/ocular inoculation in non-human primates [12] led to detection of coronavirus RNA or antigen in the brains, and post-mortem analyses indicated the presence of brain pathology, including inflammation and white-matter edema. Future studies may reveal whether the intranasal route of infection is connected to anosmia (loss of sense of smell), described as a frequent and early symptom of COVID-19 [13].

Studies on CNS invasion by neurotropic viruses, and on the underlying mechanisms leading to neuroinflammation and neurological symptoms, have made significant strides in recent years (e.g. [14,15]). Those studies may provide guidance on key areas of investigation aimed to clarify whether and how SARS-CoV-2 affects the CNS. For example, brain inflammation has been shown to underlie, at least in part, CNS damage associated with infection by West Nile, Zika and herpes simplex viruses, conditions in which long-lasting inflammatory

processes develop within the CNS. In addition, the intense systemic inflammatory response linked to viral infection can lead to Blood Brain Barrier breakdown. This, in turn, can allow peripheral cytokines to gain access to the CNS, where they may trigger or exacerbate neuroinflammation leading to encephalitis [15].

Possible long-term CNS consequences of SARS-CoV-2 infection

Human neurodegenerative diseases often involve a gradual process that evolves, in some cases, over several decades. Large numbers of young adults worldwide are now infected, or will be infected in the near future by SARS-CoV-2. For some, the severity of the disease will require hospitalization, opening up the possibility of detailed medical examination, which could be leveraged for longitudinal studies, as discussed later. Literature on previously studied viruses raises the possibility that SARS-CoV-2 may affect the CNS. The inflammatory response elicited during infection or post-infection may trigger or accelerate early and sub-clinical mechanisms underlying the earliest stages of neurodegenerative disorders. Moreover, similar to findings in neurodegenerative diseases and other viral infections suggesting that systemic inflammatory mediators may access the CNS and trigger damage via impaired BBB function, systemic inflammation triggered by SARS-CoV-2 infection may further contribute to neuroinflammatory processes and increase susceptibility to neurological syndromes. CNS infections may thus favor the development of neurodegenerative disease in individuals already at risk. Longitudinal studies are urgently needed to determine whether the COVID-19 pandemic will lead to enhanced incidence of neurodegenerative disorders in infected individuals (see Box 2).

To conclude, emerging evidence suggests that SARS-CoV-2 is associated with neurological alterations in COVID-19 patients presenting with severe clinical manifestations.

Three general scenarios seem feasible. Specifically, the impact of SARS-CoV-2 on the CNS could (1) lead to neurological alterations directly; (2) worsen pre-existing neurological conditions; and/or (3) increase susceptibility or increase the damage caused by other insults. Given the global dimension of the current pandemic and high transmissibility of SARS-CoV-2, the evidence discussed above raises concerns regarding the potential long-term consequences of COVID-19 to the CNS (Box 2). We propose that follow-up of severe COVID-19 patients should include careful clinical, imaging and laboratory neurological assessment aimed to determine to what extent the interplay between central and systemic infection drives CNS damage and neurological alterations. From where we now stand, it seems possible that, as currently-infected individuals age in the coming years and decades, the systemic and/or brain inflammatory response elicited by SARS-CoV-2 infection may trigger long-term mechanisms leading to a widespread increase in incidence of neurological and neurodegenerative disorders.

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Text Box 1 – Outstanding questions

- Are specific groups of COVID-19 patients more prone to developing neurological alterations?

- Is SARS-CoV-2 present in post-mortem brain tissue or in the CSF of COVID-19 patients? Is there a preferential targeting of CNS structures in patients that develop neurological alterations?

- Is anosmia indicative of SARS-CoV-2 infection in the CNS or does it reflect an impact to the peripheral nervous system (e.g., olfactory nerve)? Can SARS-CoV-2 be found in olfactory or optic nerve, as potential conduits for invasion of the CNS?

- Considering potential neurological consequences, what strategies (clinical, imaging, biomarkers) should be adopted in the long-term neurological follow up of COVID-19 patients?

Text Box 2 – A roadmap to research into the CNS impact of SARS-CoV-2

- There is need to investigate whether and to what extent neurological alterations are observed in distinct COVID-19 patient groups, e.g., immunocompetent/immunosuppressed individuals, as well as patients with cardiovascular or metabolic disorders. In animal models, investigate if infection by SARS-CoV-2 via different routes (intravenous, intranasal) induces neuroinflammation and neurodegeneration.

- For patients under intensive care, who are likely to develop an intense systemic inflammatory response to viral infection, blood samples and CSF (whenever possible) should be collected longitudinally for evaluation of systemic and CNS inflammatory markers.

- It would be crucial to conduct detailed cognitive testing in COVID-19 patients to detect possible cognitive impairments, and to conduct longitudinal studies that includes brain imaging, neurological and neuropsychological evaluation examining multiple cognitive domains.

- In patients who develop severe neurological complications, whenever possible, investigation of cerebrospinal fluid samples for presence of viral antigen/RNA and inflammatory mediators would be valuable to determine direct CNS infection. In addition, the investigation of post-mortem brain and spinal cord tissue from deceased COVID-19 individuals (when possible) may provide evidence of parenchymal infection.

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