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

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Emerging evidence indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (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 the possible long-term impact of COVID-19, potentially including neurological and neurodegenerative disorders.

Coronaviruses, SARS-CoV-2, and Their Impact on Multiple Organ Systems

CoVs are the largest group of viruses that cause respiratory and gastrointestinal infections, and have been responsible for three pandemics in the past 18 years: SARS in 2002/2003, Middle East respiratory syndrome (MERS) in 2012 and, currently, COVID-19. SARS-CoV-2, the etiologic agent of COVID-19, is a novel member of the human CoV 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. Although most patients infected with SARS-CoV-2 are asymptomatic or develop mild to moderate symptoms, a subset of patients develop pneumonia and severe dyspnea, and require intensive care. Because acute respiratory syndrome is the hallmark feature of severe COVID-19, most initial studies on COVID-19 have focused 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 investigations into the 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 demonstrating that various viruses, including CoVs, can have effects on the central nervous system (CNS). Lastly, we highlight the possibility that SARS-CoV-2 infection could promote 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 the CNS impact 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]. For example, one study reported hypoxic/ischemic encephalopathy in ~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 disease and impaired consciousness [3]; a case of acute hemorrhagic necrotizing encephalopathy has also been reported [4]. Another recent study (from France) reported neurologic features in 58 of 64 patients with COVID-19, including encephalopathy, prominent agitation and confusion, and corticospinal tract signs [5]. Connections between viral infections and CNS pathologies are not new. The aforementioned observations on COVID-19 are in line with a report of severe neurological manifestations associated with MERS-CoV infection in Saudi Arabia [6]. With regards to SARS-CoV-2 specifically, current evidence remains 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 who develop neurological alterations, and/or whether other CSF alterations are present (see Outstanding Questions). CSF studies will be necessary, in part, to better understand the neurotropism of SARS-CoV-2 and to evaluate whether its impact on the CNS is through direct infection or via secondary effects relating to enhanced inflammatory/proinflammatory signaling.

Human CoVs and Other Neurotropic Viruses Affect the CNS

Although studies testing whether SARS-CoV-2 targets the brain in humans or in animal models are not yet available, it is well established in the literature that other viruses target the CNS and cause neurological alterations, including brain inflammation and encephalomyelitis [7]. For example, human CoV-OC43 has been associated with fatal encephalitis in children [8,9]. Detection of SARS-CoV RNA in the CSF of a patient with SARS has been reported [10]. Preclinical studies have further shown that human (e.g., HCoV-OC43) as well as animal CoVs reach the CNS and cause encephalitis [7]. In addition, CoV antigen and RNA have been found in human brain tissue and CSF in multiple sclerosis (MS) patients [11], and

CoVs have been implicated as putative etiologic agents of CNS autoimmunity, including MS. There are also indications of possible relevance to neurodegenerative diseases. For example, CoV-OC43 and CoV-229E have been found in the CSF of Parkinson's disease patients [12]. Of note, early preclinical studies showed that intranasal/intraocular inoculation in non-human primates [13] led to detection of CoV RNA or antigen in the brain, 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) that is described as a frequent and early symptom of COVID-19 [14].

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., [15,16]). These studies may provide guidance on key areas of investigation to clarify whether and how SARS-CoV-2 affects the CNS. Notably, 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 (BBB) breakdown. This in turn can allow peripheral cytokines to gain access to the CNS, where they may trigger or exacerbate neuroinflammation leading to encephalitis [16].

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 in acute or chronic infection may trigger or accelerate early and subclinical mechanisms that underlie the earliest stages of neurodegenerative disorders. Moreover, because findings in neurodegenerative diseases and other viral infections suggest 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 promote the development of neurodegenerative disease in individuals already at risk. There is an urgent need for longitudinal studies to determine whether the COVID-19 pandemic will lead to enhanced incidence of neurodegenerative disorders in infected individuals (Box 1).

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 are feasible. Specifically, the impact of SARS-CoV-2 on the CNS could (i) lead to neurological alterations directly, (ii) worsen pre-existing neurological conditions, and/or (iii) increase susceptibility to or aggravate damage caused by other insults. Given the global dimension of the current pandemic and the high transmissibility of SARS-CoV-2, the evidence discussed earlier raises concerns regarding the potential long-term CNS consequences of COVID-19 (Box 1). We propose that follow-up of

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 preferential targeting of CNS structures in patients who develop neurological alterations?

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

Box 1. A Roadmap for Research into the CNS Impact of SARS-CoV-2

There is a need to investigate whether and to what extent neurological alterations are observed in distinct COVID-19 patient groups, for example in immunocompetent/immunosuppressed individuals, as well as in patients with cardiovascular or metabolic disorders. In animal models, investigations should address whether 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 will be crucial to conduct detailed cognitive testing on COVID-19 patients to detect possible cognitive impairments, as well as longitudinal studies that include brain imaging, neurological, and neuropsychological evaluation to examine multiple cognitive domains.

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

severe COVID-19 patients should include careful clinical, imaging, and laboratory neurological assessment 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 the incidence of neurological and neurodegenerative disorders.

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Spotlight

Contextual Codes in the Hippocampus

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The hippocampus is thought to support memory and decisions by binding relevant aspects of experiences within a context. A recent paper by Gulli *et al.* studies how activity in the macaque hippocampus varies according to different contextual requirements in the same space. This study demonstrates how a hippocampal cognitive map can flexibly reflect both spatial and nonspatial task demands.

In his seminal piece 'Cognitive maps in rats and men' [1], Tolman proposed that animals may form internal, flexible representations of their spatial environment. In the following decades, neural recordings from the hippocampal formation identified place cells, direction cells, border cells, and grid cells, leading some to propose that the cognitive maps may be instantiated in the mammalian brain as a topological representation of particular spatial environments. According to this view, any spatiotemporal experience can be associated with a single map of the environment in the hippocampal formation [2]. To illustrate this view, consider the following two scenarios: you might enter your local grocery store with the goal of finding a specific item you know exactly where to find, or you might stroll between the aisles browsing for something sweet. The first scenario can be thought of as an 'associative memory' task, in which two distinct pieces of information, a location and an item, need to be associated in order to achieve your goal of eating a specific snack. The second scenario can be thought of as a 'foraging' task, in the sense that you are exploring a space, searching for an item, without a specific goal location in mind. Most of the research characterizing neural activity in the hippocampus is based on foraging experiments and fewer studies have investigated the influence of rules, goals, and learned associations on representations of space [3]. If cognitive maps reflect particular environments, then we would expect that both situations would be tied to the same neural representation of space, as long as you are walking along the same aisle, in the same