Review

NeuroCOVID: Insights into Neuroinvasion and Pathophysiology

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Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may lead to acute and chronic neurological symptoms (NeuroCOVID-19). SARS-CoV-2 may spread from the respiratory tract to the central nervous system as the central nervous system (CNS) of certain patients dying from COVID-19 shows virus-related neuropathological changes. Moreover, a syndrome found in many patients having passed a SARS-CoV-2 infection, which is termed long COVID and characterized by lasting fatigue and other diverse clinical features, may well have some of its pathological correlates inside the CNS. Although knowledge on the routes of SARS-CoV-2 neuroinvasion and the pathophysiology of NeuroCOVID have increased, the molecular mechanisms are not yet fully understood. This includes the key question: to understand if observed CNS damage is a direct cause of viral damage or indirectly mediated by an overshooting neuroimmune response.

Keywords: SARS-CoV-2; COVID-19; neuroinvasion; vagal nerve; blood–brain barrier; neurovascular unit; neuropathology

1. Introduction

Coronavirus disease 2019 (COVID-19) has infected over 250 million people worldwide, leading to over 6 million deaths so far. However, because adequate testing regimes are not in place in many countries and COVID-19 infection rates are not openly communicated for political reasons, underreporting occurs; therefore, the officially reported figures are most likely a vast underrepresentation of reality. Additionally, considering the questionable political decision-making, limited access to vaccines in some areas, the low compliance of certain parts of society with vaccination campaigns in other countries, and the continued appearance of new virus strains, the pandemic itself and the associated deaths are unlikely to end soon.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a respiratory virus targeting the lower respiratory tract. In fatal courses of COVID-19, which occur at a frequency of less than 1%, lung damage manifesting as pneumonia, acute respiratory distress syndrome, and subsequent organ failure are common causes of death. Clinically, it presents as a multi-organ disease, since SARS-CoV-2 spreads throughout the body, causing organ damage in the cardiovascular system, kidneys, and the central nervous system. In fact, in some studies, viral RNA and viral proteins were observed in the brain and cerebrospinal fluid (CSF) of COVID-19 patients—although the majority of patients have no viral RNA and proteins and levels are comparably low in virus positive patients [1,2]—whereas other studies have failed to demonstrate viral RNA in the brain and CSF [3]. The neurological complications seen in COVID-19 occurring in the acute and chronic disease stages are grouped under the term NeuroCOVID-19.

Acute NeuroCOVID-19 includes cerebrovascular injury, ischemic brain damage, altered mental status, encephalitis, encephalopathy, dizziness, headache, hypogeusia, hypomnesia, and neuropsychiatric ailments [4–7].
Some COVID-19 patients also experience complications beyond the initial period of acute infection and, if these persist for more than 12 weeks after the start of acute symptoms, they are referred to as post-acute COVID-19 syndrome (PACS) or 'long COVID'. This condition presents with a wide range of non-CNS symptoms, such as tachycardia, persistent cough, shortness of breath, and metabolic and gastrointestinal disorders. About one-third of patients with long COVID suffer from CNS symptoms ('long NeuroCOVID') such as depression, insomnia, and a combination of cognitive dysfunctions: headache and dizziness, which are sometimes described under the non-medical term "brain fog" [8–15].

The pathophysiology of NeuroCOVID-19, including routes of neuroinvasion taken by the virus, is still unclear, yet as a result of a surprisingly quickly established global research effort—at a pace deemed impossible pre-COVID-19—and via the use of digital infrastructure and highly interdisciplinary research teams, the last year has seen enormous knowledge gains in this field, which will be summarized in the paragraphs below.

2. Neuroinvasion of SARS-CoV-2

Several well-controlled studies and case series or case reports have documented SARS-CoV-2, albeit in low quantities, in the CNS of patients dying from or with COVID-19 [2,16–19]. The presence may only be transient and may only occur in a subset of patients, yet it raises an important question about how the virus gains access to the CNS.

COVID-19 leads to viremia and SARS-CoV-2 may target brain endothelial cells where SARS-CoV-2 proteins can be found [20–22]. Thus, the entry of SARS-CoV-2, present in blood, into the CNS via the neurovascular system passing through the blood–brain barrier, is a conceivable route of neuroinvasion. In fact, studies using animal models of the disease have suggested this possibility early in the pandemic [23]. Recent data using human-induced pluripotent stem cell-derived brain capillary endothelial-like cells not only show the transcellular transport of SARS-CoV-2 through brain endothelial cells, but also that the virus can replicate in these cells [24]. Using a human-induced pluripotent stem-cell-derived blood–brain barrier model in this study, the ultrastructural data map attachment of the virus to the apical side and the release of virus particles from the basolateral side of capillary endothelial-like cells in vitro [25].

SARS-CoV-2 is found in high quantities in the nasal cavity. Since dysfunction of the olfactory system, manifesting as hyposmia, is a prevalent and early symptom of COVID-19, the speculation on an olfactory route of SARS-CoV-2 neuroinvasion was raised very early in the pandemic. This scenario is openly discussed within the scientific community. In fact, there are patient- and animal-experiment-derived data showing that the virus, present in the olfactory mucosa, transits to the olfactory and sensory nerve endings contained within the olfactory mucosa, thereby gaining access to the CNS via the olfactory tract [22,26]. On the other hand, others contest this route of neuroinvasion; patient data show that, within the nasal cavity, SARS-CoV-2 is mainly found in the sustentacular cells within the respiratory mucosa; these studies neither found evidence of olfactory sensory neuron infection, nor of entry via the olfactory bulb [27,28].

Within the CNS, SARS-CoV-2-associated neuropathological alterations are most commonly seen in the brain stem [17]. In fact, in some patients dying with COVID-19, glial and neuroinflammatory reactions could be mapped to respiratory centers within the brain stem containing the nuclei of the vagal nerve [29]. These morphological data, together with clinical data suggesting vagal nerve dysfunction, led to the hypothesis that the vagal nerve may be involved in SARS-CoV-2 neuroinvasion. Moreover, the lung, as the prime target of SARS-CoV-2, is densely innervated by the vagal nerve. Although data from animal models are lacking, the fact that SARS-CoV-2 viral proteins can be found in the vagal nerve of patients dying with COVID-19 suggests a vagal route of SARS-CoV-2 CNS entry [17,29].
However, at present, no data demonstrate the involvement of the vagal nerve innervating in the gastrointestinal tract in SARS-CoV-2 neuroinvasion—although, since SARS-CoV-2 has been detected in rectal swabs, this additional possibility cannot be excluded [24].

The neuroinvasion of pathogens is a complex matter as it involves transitioning between different tissue compartments with tissue- and cell-type-specific replication cycles occurring in a well-defined spatial and temporal manner. Therefore, it is likely that further, more detailed studies of SARS-CoV-2 transport, and replication may yield novel routes of neuroinvasion; it is conceivable that the preferred route SARS-CoV-2 takes to gain access to the CNS very much depends on host- and pathogen-encoded factors, and redundancy may occur. Furthermore, it should be stressed that a considerable number of novel insights into SARS-CoV-2 neuroinvasion come from autopsy studies. As mentioned above, this population (i.e., patients having died from/with SARS-CoV-2) may not be fully representative of the milder clinical courses of COVID-19 seen in the vast majority of patients and rarely pictures the acute phase of SARS-CoV-2 infection.

3. The Pathophysiology of NeuroCOVID

Clinical and virological data argue in favor of CNS involvement in COVID-19, at least in a subset of patients; yet, mechanistic insights into the pathophysiology of neurological symptoms have not yet been fully elucidated. Indeed, even the key question has not been answered: is the observed CNS damage directly caused by SARS-CoV-2, or is this rather an indirectly mediated effect caused by an overshooting neuroimmune response? A putative sequence of events leading to both acute and long NeuroCOVID, backed by scientific data, could be as follows: In severe cases of COVID-19, SARS-CoV-2 is present in the blood, where it gains access to the CNS through the blood–brain barrier; alternatively or additionally, it can travel to the CNS using one of the aforementioned nerve-associated routes.

Once in the CNS, presence of the SARS-CoV-2 initiates several events (Figure 1). All of the below-mentioned pathways are corroborated by the experimental data, but need to be confirmed by other independent studies in a greater number of models and human participants.

- The main SARS-CoV-2 protease Mpro (identical with Nsp5 or 3CLpro) proteolytically processes the host protein nuclear factor (NF)-κB essential modulator (NEMO), thereby disturbing NEMO-mediated signaling cascades, some of them being critical for the survival of brain endothelial cells [30]. This signaling impairment has multiple consequences, one of which is necroptotic cell death of endothelial cells and, consequently, microvascular damage [30].
- The presence of SARS-CoV-2 in the CNS, specifically in the neurovascular unit, leads to neuroimmune activation of both the innate immune system (manifested as microglial activation with microglial nodules) but also of the adaptive immune system (presenting with an enhanced presence in the CNS of monocytes and T helper cells) [18,24,31,32].
- SARS-CoV-2 leads to the breakdown of the blood–brain barrier, either caused by CNS-specific effects or as a consequence of peripheral inflammation and/or peripheral overshooting immune responses [24,31,33].
- A misleading immune reaction against SARS-CoV-2 may initiate the production of autoantibodies targeting neural antigens [34,35].
Figure 1. Possible routes of SARS-CoV-2 neuroinvasion and potential modes of action concerning CNS damage, as seen in NeuroCOVID.

4. Conclusions

COVID-19 has not only massively challenged our health systems and societies (and continues to do so), it has also had a tremendous effect on how we conduct science. Through a better digital infrastructure, highly interdisciplinary research teams, and thanks to the renaissance of autopsy-driven research which makes full use of new powerful tools such as omics technologies and bioinformatic solutions, we now have the first insights into the pathophysiology of NeuroCOVID. Since COVID-19 will likely stay with us longer than we all hoped, investment into thorough (neuro)pathological assessments, as well as basic and translational research, will certainly pay off in the form of mechanistic insights to guide biomarker identification and therapy development in NeuroCOVID-19.

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