Neuropathogenesis of severe acute respiratory syndrome coronavirus 2

Payal B. Patel[a] *and David Bearden*[b]

Purpose of review
The purpose of this review is to address our current understanding of the pathophysiology of neurologic injury resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection on the developing nervous system.

Recent findings
SARS-CoV2 may enter the brain through three potential mechanisms: transsynaptic spread from the olfactory bulb following intranasal exposure, migration across the blood–brain barrier through endothelial cell infection, and migration following disruption of the blood–brain barrier from resulting inflammation. SARS-CoV2 does not appear to directly infect neurons but rather may produce an inflammatory cascade that results in neuronal injury. Additionally, autoantibodies targeting neuronal tissue resulting from the immune response to SARS-CoV2 are present in select patients and may contribute to central nervous system (CNS) injury.

Summary
These findings suggest that neuronal injury during SARS-CoV2 infection is immune mediated rather than through direct viral invasion. Further multimodal studies evaluating the pathophysiology of neurologic conditions in pediatric patients specifically following SARS-CoV2 infection are needed to improve our understanding of mechanisms driving neurologic injury and to identify potential treatment options.

Keywords
brain, maternal–fetal transmission, neurologic injury, pathophysiology, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerged as pathogen causing a global pandemic of unforeseen proportion. Although pulmonary manifestations of the disease remain the most prominent presentation, neurologic symptoms occur in approximately 30–40% of patients with acute SARS-CoV2 infection [1]. Recent publications have shed light on the mechanisms by which SARS-CoV2 causes neurologic complications. This review will address our current understanding of the pathophysiology of neurologic invasion and injury resulting from acute SARS-CoV2 infection.

NEUROPATHOLOGIC EVIDENCE OF CENTRAL NERVOUS SYSTEM INJURY FROM PRIOR CORONAVIRUS STRAINS

Currently, there are seven known coronavirus strains, which have been shown to infect humans. Of these strains, three, severe acute respiratory syndrome coronavirus 1 (SARS-CoV1), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and SARS-CoV2, have been associated with severe neurologic disease and both Human Coronavirus OC43 (HCoV-OC43) and SARS-CoV1 have demonstrated neuroinvasive potential in murine models [2,3]. Acute infection with HCoV-OC43 produces productive infection in oligodendrocytes, astrocytes, and neurons in animal models [4]. Similar to one of the proposed mechanisms of spread of SARS-CoV2, HCoV-OC43 invades the CNS following intranasal inoculation in animal models [4]. Resultant neuronal injury appears to be virally mediated and clinical presentations include encephalitis and flaccid paralysis in mice. There have been pediatric case reports of HCoV-OC43 encephalitis in children with a history

[a]Seattle Children's Hospital, University of Washington, Seattle, WA and [b]Department of Neurology, University of Rochester School of Medicine, Rochester, NY, USA

Correspondence to Payal B. Patel, MD, Acting Assistant Professor, University of Washington, Seattle, USA. Tel: +1 832 967 7066; e-mail: Payal.patel@seattlechildrens.org

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KEY POINTS

- Potential mechanisms of CNS entry of SARS-CoV2 include: transsynaptic spread from the olfactory bulb following intranasal exposure, migration across the blood–brain barrier through endothelial cell infection, and migration following disruption of the blood–brain barrier from resulting inflammation.
- Postmortem analyses and animal models suggest an inflammatory-mediated process for neuronal injury following SARS-CoV2 infection rather than direct viral invasion of neurons.
- Autoantibodies to neuronal tissue have been found in select cases of patients experiencing neurologic symptoms following infection with SARS-CoV2.
- Vertical transmission of SARS-CoV2 infection from mother to child seems to be rare. The long-term neurologic consequences of in-utero SARS-CoV2 exposure remain to determined.

of severe immunosuppression and metagenomic sequencing has confirmed the presence of HCoV-OC43 in cerebral tissue in these cases [5,6]. Additionally, postmortem autopsy studies on individuals living with multiple sclerosis (MS) demonstrate a higher prevalence of HCoV-OC43 RNA in cerebral tissue of individuals living with MS compared with controls without neurologic disease [7]. These data suggest that HCoV-OC43 is neuroinvasive and has the potential to present as a variety of neurologic disorders.

SARS-CoV1 is associated with neurologic disease, as well. Typically SARS-CoV1 infection of the CNS presents as encephalitis. Autopsy studies have demonstrated the presence of SARS-CoV1 in the neuronal cytoplasm of the cortex and hypothalamus [2]. Specimens from patients with encephalitis display necrosis of neurons with surrounding edema and inflammatory infiltration of monocytes and T cells [3]. Intranasal inoculation of SARS-CoV1 in transgenic murine models with human ACE2 expression results in transsynaptic viral spread via the olfactory bulb [8]. This finding is of particular significance given the shared morphology between SARS-CoV1 and SARS-CoV2 including preferential angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane serine protease 2 (TMPRSS2) receptor binding, which are present in the nasal endothelium [9▪▪].

NEUROINVASIVE POTENTIAL OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

SARS-CoV2 targets ACE2 receptors and transmembrane serine protease 2 (TMPRSS2) receptors on cellular surfaces and within the cytoplasm [9▪▪]. These receptors are expressed on select regions in the central nervous system (CNS) to varying degrees. A study by Chen *et al.* [10] utilized spatial distribution analyses of publicly available human transcriptome databases in cerebral tissue and identified that ACE2 receptors were highly expressed in cytoplasm of neurons in the prefrontal cortex, hippocampus, posterior cingulate cortex, the middle temporal cortical gyrus, and paraventricular regions of the thalamus, similar to regions of ACE2 receptor expression in murine brains. In contrast, a recent publication by Zhou *et al.* [11▪] and her group utilized a multiomic approach, which included single cell RNA sequencing, proteomics, and interact-onomics (protein–protein interaction) analyses of postmortem cerebral tissue following SARS-CoV2 infection, and demonstrated low levels of expression of ACE2, TMPRS22, and various other SARS-CoV2 entry receptors across multiple brain regions and cellular types. The same group found alteration in genetic expression of inflammatory markers including those associated with cytokine profiling and monocyte translocation suggesting that immunologically mediated injury rather than direct, virally mediated injury is likely to be the cause of neurologic symptoms in patients with SARS-CoV2 [11▪].

Potential mechanisms of entry into cerebral tissue have been explored by various studies. These mechanisms include: transsynaptic spread from the olfactory bulb following intranasal exposure, migration across the blood–brain barrier (BBB) through endothelial cell infection, and migration following disruption of the BBB from resulting inflammation. Murine models of mouse hepatitis virus and HCoV-OC43 provide support for causal pathway of intranasal inoculation resulting in CNS infection. Pathologic studies have identified a high prevalence of SARS-CoV2 RNA and surface protein structures in olfactory mucosa through quantitative PCR and RNAScope in-situ hybridization techniques [12]. Further evaluation identifying surface proteins of SARS-CoV2 through electron microscopy documented that endothelial cells in these regions were the primary target of infection. SARS-CoV2 was not detected in axons in the olfactory bulb, although authors of the study note the limitation of current technology to detect low level viral particles in the small regional area, such as the olfactory nervous system [12]. In the largest autopsy study published to date, Bryce and colleagues found evidence of endothelial dysfunction in multiple organ systems. This dysfunction resulted in a hypercoagulable and hyperinflammatory state with immune-mediated injury noted in neurons surrounding vascular tissue in the brain

Table 1. Summary of key studies on severe acute respiratory syndrome coronavirus 2 infection neuropathology

Reference	Number of cases	Macroscopic evaluation	Microscopic evaluation
Matschke *et al.* [27]	43	Edema, infarcts	Ischemic infarct; astrogliosis, microgliosis, perivascular and leptomeningeal T cells
Solomon *et al.* [29]	18	Atherosclerosis	Hypoxic/ischemic injury; rare foci of perivascular lymphocytes and leptomeningeal inflammation
Hanley [30]	10	Ischemia; 1 brain with evidence of brainstem encephalitis	Activation of glial cells, perivascular T-lymphocyte activation
Remmelink *et al.* 2020 [31]	17	Ischemia, hemorrhage, edema	Spongiosis, vascular congestion

[13▪▪]. These data suggest that, in select patients, SARS-CoV2 can lead to disruption of vascular function and physiologic barriers potentially resulting in viral spread and inflammation. ACE2 receptors provide a means of communication between endothelial cells and astrocytes and allow for BBB maintenance. Microglia also play an important role in BBB regulation and systemic inflammation may result in disruption of these processes [14,15]. Additionally, circumventricular brain regions are surrounded by fenestrated capillaries and may be areas that are susceptible to SARS-CoV2 and inflammatory substrate translocation following systemic infection. These findings have important implications in the developing brain, given the increased permeability of the BBB at younger ages and differential maturation of microglia as individuals age [16,17].

SARS-CoV2 infection may cause neurologic injury through three possible mechanisms: direct infection of neurons resulting in cellular necrosis, immune-mediated injury either through an inflammatory response to the viral infection or the generation of autoantibodies, which target neurons directly, and/or hypoxic/ischemic injury resulting from respiratory compromise or direct injury to the cerebrovascular supply. Pathologic and laboratory evidence for these potential pathways are discussed in detail below.

PATHOLOGIC FEATURES OF NEUROLOGIC INJURY FOLLOWING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION

Almost all neuropathology studies of SARS-CoV-2 have been performed in adult patients, and thus little is known regarding specific manifestations in children [18]. In addition, the majority of pathology studies have been completed on patients who died after prolonged mechanical ventilation, with many patients having been treated with extracorporeal membrane oxygenation (ECMO). Finally, deaths from COVID-19 and autopsy studies have over-represented older adults and those with preexisting conditions, and thus studies of COVID-19 neuropathology often reflect comorbid disorders common in these populations, such as amyloid deposition and cerebrovascular disease. Thus, it is challenging to sort out specific neuropathologic effects of COVID -19 vs. nonspecific effects of aging, critical illness, and mechanical ventilation [18–21]. Neuropathology studies in adults display diverse manifestations, with the most common being hypoxic/ischemic changes, reactive gliosis, astrocytosis, and microglial nodules accompanied by neuronophagia [18,22–24,25▪▪,26]. In addition, T lymphocytes have been noted to accumulate in perivascular regions [26]. Of note, some studies have identified neuronal damage in the medulla, suggesting that brainstem disorder may play a role in respiratory failure [27,28]. A summary of some key neuropathology studies is shown in Table 1.

A single case series of autopsy neuropathology studies of pediatric patients has been published [32]. In this series from Brazil, the most common neuropathology findings were similar to those described above in adults, including reactive microglia and ischemic changes. Of note, a single patient in this series, who had been diagnosed with MIS-C had SARS-CoV-2 identified in the cerebral endothelium and in perivascular astrocytes.

There is little evidence that SARS-CoV-2 typically results in a CNS vasculitis or encephalitis, although there have been rare case reports of this clinical presentation [24,28]. Viral RNA can be detected in select brain tissue, albeit at very low levels [33,34]. Viral RNA has been detected in brain tissue by reverse transcription–quantitative real-time PCR but not by in-situ hybridization. This suggests that at least in many cases, the presence of viral RNA may represent contamination by vasculature in leptomeninges and Virchow–Robin spaces [34]. SARS-CoV-2 protein has been found

in brain vascular endothelium but not typically in neurons or glia on electron microscopy. These findings suggest that the presence of microglial activation, microglial nodules, and neuronophagia observed in the majority of brain tissue does not result from direct viral infection of brain parenchyma but is more likely to be the result of systemic inflammation and hypoxic ischemia [34].

CEREBROSPINAL FLUID ABNORMALITIES IN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Standard cerebrospinal fluid evaluation in most patients with acute SARS-CoV2 infection and neurologic symptoms is usually unremarkable. PCR testing for SARS-CoV2 is often negative except in a few case reports of encephalitis [35]. These cases may represent false positives resulting from blood contamination. Often, there is no clear evidence of inflammation on conventional CSF testing, including a normal white blood cell count and protein in most patients [36▪▪,37]. These data seem to indicate that direct infection with SARS-CoV2 may not be the primary driver of neurologic symptomatology. An alternative explanation is that detection of SARS-CoV2 RNA may be limited because of low sensitivity of current PCR testing methods.

Biomarker analyses of cerebrospinal fluid consistently demonstrates abnormal CSF to plasma albumin ratio in a portion of patients with acute SARS-CoV2 infection suggesting breakdown of the BBB during acute infection, particularly in patients experiencing severe SARS-CoV2 infection. Additionally, neurofilament light chain, a marker of neuronal injury, is found to be elevated in the CSF of patients with acute SARS-CoV2 infection and is higher in individuals with severe SARS-CoV2 infection [38]. These data suggest that severe, acute SARS-CoV2 infection may result in BBB breakdown and that this process may allow for the extravasation of immune cells or inflammatory cytokines into the CNS space with the potential to cause neuronal injury.

Recent studies evaluating antibody specificity in patients with subacute SARS-CoV2 infection have demonstrated the presence of autoreactive antibodies to neuronal tissue in select patients [39▪▪,40▪]. SARS-CoV2 antibodies are able to neutralize pulmonary infection in animal models and also reproducibly bind to cerebral tissue in murine brains suggesting that an autoimmune process may play a role in neurologic injury following SARS-CoV2 infection. The binding pattern of antibodies indicate a predilection for the vessel wall endothelium, perinuclear antigens, astrocytes, and neurons in the basal ganglia and hippocampus, similar to prior reports of binding patterns in other antibody-associated autoimmune encephalitides [39▪▪]. Anti-NMDA receptor encephalitis has been reported following SARS-CoV2 infection in case reports including one pediatric patient [41–43]. These findings indicate that autoimmunity may play an important role in the pathophysiology of neurologic injury following SARS-CoV2 infection and a high degree of clinical suspicion for autoimmune encephalitis should be held in patients presenting with hyperexcitable neurologic symptoms, such as seizures or myoclonus, after SARS-CoV2 infection [39▪▪].

MATERNAL TO FETAL TRANSMISSION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

The data on the consequences of SARS-CoV-2 infection during pregnancy on both maternal and fetal outcomes is limited. A key concern has been whether SARS-CoV-2 may infect or cross the placenta [44]. A recent review including 1457 pregnancies concluded that the risk of premature birth, maternal death, fetal death, fetal distress, and neonatal asphyxia were all increased in pregnancies affected by SARS-CoV-2 [45]. However, these complications largely seem to result from maternal illness rather than a direct effect of SARS-CoV-2 on the placenta or the fetus [46,47]. There is some evidence of histopathologic effects of COVID-19 on the placenta [48,49]. In a cohort study of women infected late in pregnancy, SARS-CoV-2 viral RNA was detected in 23 out of 54 placentas [50]. Nevertheless, while vertical transmission of SARS-CoV-2 from mother to child has been described, it appears to be exceedingly rare [51–58]. Long-term neurodevelopmental outcomes of infants who were exposed to SARS-CoV-2 *in utero* remains an area for future targeted studies [59–61].

CONCLUSION

In this review, we summarized the current literature regarding the potential mechanism of SARS-CoV2 neuroinvasion and resulting neurologic injury. Although data from pediatric studies are limited, postmortem evaluation of cerebral tissue and CSF evaluation in adults and children and animal model studies suggest an inflammatory mediated process of neuronal injury following SARS-CoV2 infection rather than direct viral invasion of neurons. Further studies are needed in order to determine the pathophysiologic mechanism specific to pediatric patients, particularly in distinct clinical phenotypes, such as multisystem inflammatory syndrome

in children (MIS-C) and in cohorts of children born to mothers with exposure to SARS-CoV2 infection during pregnancy.

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Conflicts of interest

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