UJEMI PERSPECTIVES

The two pronged approach: The direct and indirect mechanisms mediating SARS-CoV-2 effects on the central nervous system

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SUMMARY Neurological symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported in addition to primarily respiratory symptoms. These symptoms range from mild chronic effects including headaches and fatigue to acute consequences including stroke and encephalitis. Although a crucial field of research, mechanisms as to how SARS-CoV-2 exerts these effects remains unclear. However there is growing evidence to suggest underlying mechanisms are likely multifactorial. Thus examining the impact of SARS-CoV-2 on the central nervous system (CNS) is key because of its wide array of noted neurological effects, vexing underlying mechanisms and its potential relationship with long-COVID. Assessing leading hypotheses for proposed mechanisms by which SARS-COV-2 mediates neurological symptoms is an emerging field. This article will examine the effects and support for potential mechanisms of SARS-CoV-2 direct neuroinvasion of the CNS. We will also explore the effects and support for means by which SARS-CoV-2 can indirectly contribute to neurological symptoms without the virus entering the CNS, through the host response. Examining this field provides context in understanding neurological effects alongside their contributing viral and host mechanisms to assess neurological impact and develop potential remedies for both acute and chronic symptoms. This article found direct mechanisms of neuroinvasion of SARS-CoV-2 include transversal of the blood brain barrier (BBB) by means of endothelial cells and astrocytes as well as passage through the olfactory pathway. Indirect effects on the CNS mediated by the host's response consist of excessive neuroinflammation and hypoxic damage to brain tissue. The impact of this work in characterizing CNS effects and underlying mechanisms strengthens the foundation and provides new avenues for which areas, cells, and processes could be used to develop novel diagnostics and therapeutics. The emergence of SARS-CoV-2 variants of concern (VoC) also pose a concern for neurological impacts, emphasizing our need to advance this field.

INTRODUCTION

SARS-CoV-2 confirmed infections have continued to climb since the declaration of the pandemic by the World Health Organization (WHO) in March 2020 (1). SARS-CoV-2 is a positive sense single stranded RNA coronavirus responsible for the associated disease, coronavirus disease 2019 (COVID-19) (2). Neurological symptoms of COVID-19 have been reported since the onset of the pandemic and have raised concern for the potential neurotropic nature of the virus (3). Although primarily limited the respiratory tract, a recent literature review noted that approximately one third of all COVID-19 patients report neurological symptoms (4). COVID-19 exhibits a wide array of neurological manifestations (4). Mild common symptoms include fatigue, myalgia, dysgeusia, anosmia, and headaches (4). Though in more acute cases evidence of acute delirium, confusion, encephalitis, and stroke are present (4). Furthermore, brain fog and fatigue are chronic neurological symptoms associated with long-COVID (5). These aforementioned neurological symptoms can be mediated by the virus's effect on the central nervous system (6).

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The CNS is a neural network consisting of the brain and spinal cord (7). This complex system is responsible for processing of thoughts, homeostasis, and movement among other attributes (7). Although cranial nerves including the olfactory nerve are considered part of the peripheral nervous system (PNS) they are still structurally connected to the CNS (7). The CNS is also not without defenses against neurotropic viruses (8-9). The BBB forms a formidable impediment preventing microorganisms from entering the brain from hematogenous spread (8). In addition microglia are resident immune cells of the CNS which can activate a robust inflammatory response (9).

The mechanisms by which SARS-CoV-2 exerts these neurological effects are contested and unclear, likely due to their multifactorial intertwined nature (10-12). Of particular concern is that evidence of proposed mechanisms can vary between COVID-19 patients afflicted with neurological symptoms which can cloud conclusions (10-12). Thus there is considerable interest in examining the support for leading hypotheses of the underlying mechanisms including the direct neuroinvasion of the virus into the CNS and the indirect impact of the host's response (10-12). Elucidating these mechanisms are key towards developing novel CNS targets for diagnostics and therapeutics to detect and minimize neurological impact.

PROPOSED RESEARCH QUESTIONS

The lack of consensus within and the evolving multifaceted mechanisms by which SARS-CoV-2 mediates neurological impacts through the CNS warrants examining the proposed pathways and their support (10-12). This article will first examine the effects and support for potential mechanisms of SARS-CoV-2 direct neuroinvasion of the CNS. Second, this paper will address the effects and mechanisms by which SARS-CoV-2 can indirectly contribute to neurological symptoms through the host's response. These research questions aim to bridge the gap between two prominent areas of research on how SARS-CoV-2 mediates neurological effects.

PROPOSED PROJECT NARRATIVE

What are the effects and mechanisms of SARS-CoV-2 direct neuroinvasion of the CNS?

Direct neuroinvasion is when SARS-CoV-2 enters neurons of the CNS (13-14). SARS-CoV-2 RNA and proteins have been found in neurons and brain tissue of autopsies of COVID-19 patients with neurological symptoms (13-15). Preeminent proposed mechanisms of neuroinvasion outlined in FIG. 1 include disruption of the BBB and the utilization of the olfactory pathway (16-26). Exploring the effects of neuroinvasion alongside their underlying mechanisms is crucial in determining how to best approach measuring a patient's neurological impact and in looking forward to develop or repurpose therapeutics for neurological symptoms.

Human induced pluripotent stem cell organoid models have demonstrated the capability of SARS-CoV-2 to dysregulate the BBB (17). The BBB normally functions to prevent microorganisms including viruses circulating in the bloodstream from entering the brain while trafficking necessary substances (8). Endothelial cells form tight junctions which prevent paracellular transport through the BBB (8). SARS-CoV-2 was found to infect and replicate within induced endothelial cells of the BBB with apical viral takeup and basolateral shedding (17). This demonstrates a potential transcellular pathway by which SARS-CoV-2 can penetrate the BBB after initial hematogenous spread (17, 24). Hematogenous spread can occur with severe COVID-19 infection through damage to lung blood vessels (24, 26). Anti-angiotensin converting enzyme 2 (ACE2) and anti-neuropilin 1 (NRP1) antibodies reduced the observed infectivity of endothelial cells, suggesting they may play a role in viral entry (17). In addition K18-hACE2 mice models have demonstrated presence of SARS-CoV-2 in the brain without infection of the olfactory bulb hinting transversal of the BBB (21).

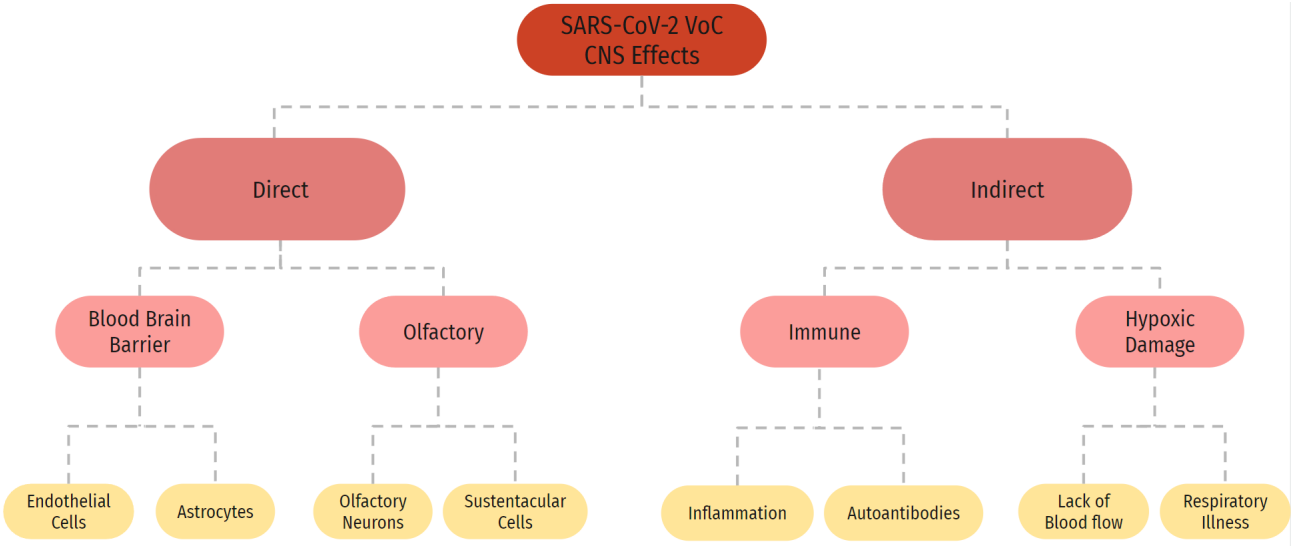

FIG. 1 Flow chart outlining effects and mechanisms mediating SARS-CoV-2 effects on the CNS. The gray dotted line indicates links between proposed mechanisms and effects.

Clinical autopsies of COVID-19 patients with brain necrosis and neuroinflammation alongside brain organoid models have indicated evidence of preferential infection of astrocytes (22-23). Astrocytes are glial cells in the CNS which contribute to endothelial cell homeostasis and structure of the BBB (8). This indicates another potential pathway of SARS-CoV-2 to disrupt the BBB (22-23). Astrocytes are noted to have minimal ACE2 expression (22-23). Their infection is likely mediated by alternative receptors including NRP-1, dipeptidyl-peptidase 4 (DPP4), and cluster of differentiation 147 (CD147) based on receptor inhibition experiments (22-23). The altered secretory phenotype of infected astrocytes results in neuronal death (22).

The olfactory pathway of SARS-CoV-2 neuroinvasion extends from the nasopharynx to the brain as demonstrated in some clinical autopsies of COVID-19 patients with neurological symptoms (24-25). An observed pathway through visualizing RNA and immunohistopathology begins in the olfactory mucosa, followed by the olfactory sensory nerves, the olfactory bulb and ends in the brain (24-25). Greater amounts of ACE2 is expressed on basal cells which mature into olfactory sensory neurons (OSN), suggesting infection during maturation of basal cells could contribute to olfactory neuroinvasion (25). This route of infection also provides a link between a neurological symptom, anosmia and a mechanism as a result of infection and damage of sustentacular cells supporting OSNs (25).

What are the effects and mechanisms by which SARS-CoV-2 can indirectly contribute to neurological symptoms?

Indirect mechanisms that can mediate SARS-CoV-2 neurological effects are based on the host's response to the virus (26-31). Patients with COVID-19 can have neurological symptoms without viral RNA or proteins detected in the CNS (13-15). This exemplifies how we must also look beyond direct neuroinvasion to fully understand SARS-CoV-2 neurological effects and mechanisms. Mechanisms by which the virus can mediate effects indirectly depicted in FIG. 1 include escalation of the host's immune response with neuroinflammation and self-reactivity in addition to hypoxic damage (26-31). Examining the effects and mechanisms of SARS-CoV-2 indirect contribution to neurological symptoms complements direct mechanisms to develop more complete neurological diagnostics and therapeutics.

Overreaction of the host's immune response to SARS-CoV-2 can explain neurological effects (26-27). The cytokine storm induced from proinflammatory cytokines originating from the primary respiratory infection could result in systemic effects which could lead to

excessive neuroinflammation (26-27). Cytokines including interleukins (IL) and tumor necrosis factor-α (TNF-α) are associated with both clinical COVID-19 and also disruption of the BBB (27). Neuroinflammation can be mediated by activation of glial cells including microglia and astrocytes in the CNS (22, 23, 26, 27). Activated astrocytes alongside microglia amplify neuroinflammation by releasing ILs, TNF-α, reactive oxygen species (ROS) and nitric oxide (NO). Neuroinflammation can be an appropriate inflammatory response within the CNS (27). However, disproportionate inflammation can lead to neuronal damage and some observed COVID-19 neurological effects including encephalitis (27).

Autoantibodies are antibodies that are reactive to a host's own tissues (28-29). Self-reactive antibodies have been found in cerebrospinal fluid of COVID-19 patients (28). Their affinity for neurons is particularly concerning as it could potentially lead to neuronal apoptosis and predisposition for autoimmune neurological diseases (28-29). Autoantibodies open the discussion to diagnostics markers of neurological effects and subsequent therapeutics based on host antibodies and B cells (29).

Hypoxic CNS during severe COVID-19 could also explain neurological effects (30). Evidence of local hypoxic injury and stroke could be a result of reduced oxygen uptake in severe cases of respiratory illness or blood clots (30). Additionally reduction in blood flow due to pericyte constriction could also simultaneously contribute to observed hypoxic injuries (31). A hamster model identified that SARS-CoV-2 affinity for ACE2 on pericytes competes against its normal vasodilation activity (31). A decrease in ACE2 activity results in vasoconstriction increasing the likelihood of blood clots and thus also hypoxic injury (30-31).

POTENTIAL IMPACT/CONCLUSIONS

In summary, SARS-CoV-2 infection mediates neurological effects on the CNS through both direct neuroinvasion and the indirect host immune response. Leading evidence for SARS-CoV-2 neuroinvasion suggests infiltration through the BBB and transmission along the olfactory pathway (16-26). Compelling evidence on indirect host mediated responses to COVID-19 include an excessive immune response and hypoxic brain damage (27-31).

Though direct and indirect mechanisms have been discussed separately in this article we need to recognize that they can act simultaneously within a COVID-19 patient. For example, cytokine storm from the host's immune response can contribute to disruption of the BBB making neuroinvasion more likely (27). By recognizing the combined implications of multiple mechanisms of SARS-CoV-2 affecting the CNS, we can improve our understanding of the vexing nature of COVID-19 neurological complications.

This field of research provides an opportunity to develop and improve diagnostic capability to determine a COVID-19 patient's neurological effects and their severity through assessing biomarkers of both the virus and host through establishing mechanistic pathways. Additionally this area of research lays the groundwork for developing therapeutics as better understood mechanisms provide potential therapeutic targets to prevent or mitigate the neurological impact of COVID-19.

Determining the impact of SARS-CoV-2 VoCs on the CNS is currently a limitation of this area of research. The literature selected in this review did not explicitly identify variants. Most included experimental studies are published between 2021-2022, suggesting a blend of variants is represented in the results. This is a challenge because different SARS-CoV-2 VoCs might exert contrasting neurological effects. For instance, the greater amount of inflammation associated with the Delta (B.1.617.2) Variant might pose greater likelihood for neuroinflammation as compared to the Omicron (B.1.1.529) Variant (32).

SARS-CoV-2 VoCs also segue into future directions that could continue to build upon this field of research. Comparing and contrasting the effects and mechanisms of SARS-CoV-2 VoCs in the CNS would be a logical next step as they differ transmissibility and severity which could play a role in neurological effects (32). Additionally, experimentally testing diagnostic markers and developing therapeutics with these mechanistic targets would be necessary for clinical use for COVID-19 neurological effects. Finally, as further longitudinal data becomes available, we could more readily examine the role of SARS-CoV-2 CNS effects and mechanisms in long-COVID.

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