Neuropathogenesis of Acute COVID-19

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Word count: 2553/2500

Funding: NIH 1R01AI157488-01 (SFF), NIH 5K23MH118999 (SFF)

Conflicts of Interest: none

Abstract (150/200 words structured):

Purpose of review: Over the course of the COVID-19 pandemic, it has become increasingly clear that there is a high prevalence of neurological complications in people infected with SARS-CoV-2.

Recent findings: Studies of central nervous system tissue in brain model systems and from adults with acute SARS-CoV-2 infection have begun to uncover potential mechanisms for neurological damage during COVID-19. These studies suggest that direct viral invasion of the CNS occurs in a subset of cases but does not frequently cause overt viral meningoencephalitis. Vascular abnormalities including microvascular thrombi and endothelial activation, as well as parainfectious processes, including CNS specific immune responses, may contribute to neurological symptoms during acute SARS-CoV-2 infection.

Summary: Neuroimmune perturbations and vascular inflammation observed in people with COVID-19 may warrant investigation of immune modulating interventions to ameliorate neurological complications associated with acute SARS-CoV-2 infection. These therapies may also impact the trajectory of potential long-term complications of COVID-19.

Keywords: Neuro-COVID; SARS-CoV-2; Neuroinflammation; COVID-19; Neuropathogenesis

Introduction

The novel coronavirus SARS-CoV-2 has now spread across the globe to cause pandemic coronavirus disease (COVID-19). As caseloads rise, extrapulmonary manifestations of COVID-19 are increasingly identified, with neurological symptoms reported in as many as 50% of hospitalized patients with acute COVID-19 [1]. While the wide-spectrum of neurological symptoms in patients with acute COVID-19 has been well-documented, the pathological mechanisms underlying these diverse symptoms remain poorly understood (figure 1). During the initial months of the COVID-19 pandemic, autopsy and magnetic resonance imaging were limited in COVID-19 patients out of concern for operator safety. However, studies from central nervous system (CNS) models, those utilizing cerebrospinal fluid and neuroimaging from patients, as well as more recent post-mortem series have begun to illuminate potential modes of neuropathogenesis.

In this review we focus on current evidence supporting potential mechanisms of neurological dysfunction during acute SARS-COV-2 infection: systemic metabolic and inflammatory abnormalities; CNS vascular damage; direct infection of neurons and neighboring cells; and dysregulated host immune responses within the CNS. Gaining a clear understanding of the pathophysiology underlying neurological disorders in COVID-19 is needed to develop targeted treatments to ameliorate acute neurologic disease and manage symptoms. Furthermore, concerns are now emerging about neurological and psychiatric manifestations that may develop after the acute infection, or symptoms that may linger for many months following the initial illness. Understanding the pathogenesis of SARS-CoV-2 in the nervous system is a first critical step in optimizing the neurologic health of survivors of COVID-19 worldwide.

Systemic illness during COVID-19

Most neurological reports and clinical studies of COVID-19 have focused on moderately to severely ill patients who are observed or sampled in the inpatient hospital setting, either on floor units, or in intensive care settings. While patients on standard hospital units may not have life-threatening critical illness, many have systemic laboratory derangements, poor oxygenation, fever and multisystem organ dysfunction that are associated with mental status changes, delirium, seizure, headache, and other neurological manifestations in a range of illnesses. These metabolic and systemic factors are non-specific and thus such associations would not be necessarily due to SARS-CoV-2 effects on the nervous system, but rather ‘metabolic encephalopathy’ due to pulmonary, renal, cardiac, or gastrointestinal system involvement. Indeed COVID-19 leads to more severe multi-organ system dysfunction than respiratory viruses such as influenza, evidenced by rates of renal involvement requiring dialysis, for example, or frequency of myocarditis detected in hospitalized patients [2,3]. Thus, the observation that encephalopathy is more frequent in hospitalized COVID-19 compared to viral infections more typically limited to respiratory dysfunction may in part relate to the more extensive extra-pulmonary involvement of this pathogen and associated immune responses. It is likely that a significant proportion of the high burden of neurologic signs and symptoms reported in hospitalized patients with COVID-19 are thus due to systemic illness and ‘metabolic encephalopathy.’

Severe COVID-19 requiring intensive care associates with myriad conditions that may underlie clinical neurologic syndromes and lead to CNS injury. The acute respiratory distress syndrome (ARDS) caused by COVID-19 and respiratory or cardiac arrest are independently associated with diminished neurologic function in patients who survive these events [4,5]. In addition, interventions such as mechanical ventilation requiring prolonged sedation, vasopressor therapy

for cardiovascular support, prone positioning, and at the extreme, extra corporeal membrane oxygenation, all are associated with impairment or injury in diverse components of the neuroaxis [6]. These complications are important and must be identified and understood in order to prevent and ameliorate neurologic injury and dysfunction, but likely are not specific to effects of SARS-CoV-2 or the immune response in the CNS, rather to the severity of disease.

Little systematic information exists about neurological manifestations in patients with mild forms of COVID-19 who convalesce in outpatient settings. Headache at the time of initial fever is frequent, but this symptom is also common in many other acute viral infections and may be non-specific, perhaps associated with the systemic immune response. Moderate to severe or prolonged headache as a primary manifestation of acute COVID-19 has been reported, however, and may potentially reflect a different pathophysiology, such as aseptic meningitis, vascular derangement, or increased intracranial pressure, though evidence is currently lacking. However, anosmia, a more focal symptom in many with mild disease, is unlikely to be due to systemic effects and suggests localized inflammation or infection of the nasal epithelium and perhaps the olfactory nerves[7].

Neurovascular injury during COVID-19

Systemic COVID-19 disease associates with coagulopathy and clinically significant thrombotic disease in a subset of infected patients [8]. These COVID-19 coagulation disturbances share similar features with disseminated intravascular coagulation seen in other forms of sepsis, including elevation of D-dimer and fibrinogen degradation products, but differ in displaying profound endothelial cell damage with subsequent release of plasminogen activators. Clinically, COVID-19 patients have higher rates of cerebrovascular thrombotic events, even in patients without known risk factors for stroke [9]. Though some increased stroke risk may be attributable to severe systemic illness afflicting patients requiring hospitalization and intensive care, comparisons between rates of stroke in patients presenting to two hospitals in New York with COVID-19 as compared to influenza A/B indicated a substantially elevated risk of cerebrovascular events with COVID-19 above influenza (odds ratio, 7.6; 95% CI, 2.3-25.2). This finding suggests that pathophysiology specific to SARS-CoV-2 or the host immune response to this pathogen contributes to increased vascular events in these patients [10].

ACE2, the canonical cell-surface receptor for SARS-CoV-2, is expressed on endothelial cells, suggesting that endothelial cells of the brain may be susceptible to SARS-CoV-2 infection. Outside of the brain, autopsy studies demonstrate the presence of viral particles within endothelial cells of the heart and kidneys; this endothelial cell infection is, in turn, associated with an accumulation of inflammatory cells [11]. Overall endothelial activation and injury may be a widespread process in individuals with acute COVID-19, involving multiple tissues and organ systems [12]. Cardiac autopsy has revealed evidence of small vessel endotheliitis, with lymphocyte and monocyte invasion into endothelial cells lining the capillaries in cardiac tissue, but not in the coronary arteries themselves [13]. Endothelial injury and viral infection of endothelial cells may be central to some of the observed pediatric manifestations of COVID-19 including chilblains or ‘COVID toes’ and multisystem inflammatory syndrome in children [14,15].

Blood biomarkers of endothelial and vascular inflammation are commonly elevated in COVID-19, especially in severe disease and those with evidence of end-organ injury.
Elevated levels of blood biomarkers suggesting endothelial activation or altered interactions between blood cells and endothelial cells, including von Willebrand factor antigen, soluble P-selectin, soluble thrombomodulin, factor VIII and fibrinogen have been detected in COVID-19 patients with severe disease, in addition to more generalized markers of systemic inflammation

[16]. Tissue injury and vascular complications may result from thrombotic microangiopathy resulting from combined effects of platelet activation and red blood cell abnormalities in the setting of inflammatory mediators and underlying endothelial derangement [17].

Neuroinvasion of SARS-CoV-2 and evidence from neuropathology of COVID-19

The neuroinvasive potential of coronaviruses has been demonstrated through studies of other coronaviruses, including mouse hepatitis virus (MHV; a coronavirus of laboratory mice) and human coronavirus OC43 (HCoV-OC43). In murine models, both MHV and HCoV-OC43 invade the CNS intranasally [18-20]. Neuronal damage appears to be caused by direct virus-mediated effects in HCoV-OC43 infection, and through immune-mediated injury during MHV infection [20,21]. More recently, case series undertaken during the SARS pandemic of 2008 demonstrated the presence of SARS-CoV-1 RNA in brain tissue specimens of SARS autopsy donors [22,23]. Like SARS-CoV, SARS-CoV-2 likely gains entry to neurons via ACE2, which is widely expressed in the human brain [24,25].

Studies in CNS model systems, including induced pluripotent stem cell derived human neural progenitor cells and brain organoids, provide in vivo evidence for the neuroinvasive potential of SARS-CoV-2 [25-28]. The human brain organoid model suggests potential mechanisms of tissue injury in the brain, wherein SARS-CoV-2 infection of neurons leads to cell death and metabolic changes in both infected and neighboring neurons.

Despite the early interest in central nervous system involvement, neuropathological studies of COVID-19 have remained relatively few in number, no doubt because of the difficulty in giving the indication of a brain biopsy and the small number of autopsies carried out across the world. Limited SARS-CoV-2 infection of brain cells has been confirmed through recent brain pathological studies from donors who died from COVID-19 related causes [29-31]. One of the largest autopsy series involved 43 patients, and concluded that neuropathological changes are generally minimal, most often characterized by inflammatory brainstem involvement[29]. The fear of seeing a multiplication of necrotizing bitemporal encephalitis like those encountered in herpes has not been confirmed [32,33]. Nevertheless, Meinhardt et al demonstrated the presence of SARS-CoV-2 in the olfactory mucosa and observed colocalizations with markers of neurons crossing the cribriform plate of the ethmoid bone. They deduce that SARS-CoV2 follows neuro-anatomical structures to enter the central nervous system and target the respiratory and cardiovascular control centers located in the brainstem. [30]. They also observe recent infarctions which they relate to microthrombi.

As suggested by clinical and biomarker studies, endothelial cell damage in the brain is a feature of CNS pathology in a subset of patients with severe COVID-19 [24]. An autopsy case series of 67 patients who died in hospital from COVID-19 revealed profound vascular damage, including microthrombi and associated areas of infarction in 6/20 patients [34]. This suggests the possibility that SARS-CoV-2 induces endothelial cell damage and microinfarctions, leading to bystander neuronal death from localized tissue hypoxemia, even in the absence of clinically apparent stroke. The pathophysiology of these lesions, often multiple and hemorrhagic, is debated in the literature. The hypothesis of a secondary perivenous encephalomyelitis [35] seems to be supplanted by that of lesions of the small arteries [36-38].

The role of SARS-CoV-2 neuroinvasion in COVID-19 is all the more intriguing since overall it is difficult to detect SARS-CoV2 in post-mortem brains [39]. The specificity of previous observations of viral particles in endothelial cells is questioned [40]. The presence of spike protein has been detected in endothelial cells [30] and endothelial cell damage can be induced

by the injection of its S1 subunit in a mouse model [41]. Overall, besides nonspecific cerebral lesions due to hypoxia and resuscitation maneuvers, two types of lesions caused by infection with SARS-CoV 2 appear to emerge: inflammatory lesions predominantly in the brainstem, correlated with penetration of the virus into the central nervous system; and later, more diffuse vascular lesions unrelated to viral replication. These lesions could be caused by circulating factors, vectors of inflammation or viral products, such as the spike protein.

Dysregulated host immune responses in the CNS during COVID-19

The lack of tissue damage associated with viral infection of neurons observed in autopsy studies suggests that immune-mediated processes, rather than or in addition to direct virus effects, contribute to the pathogenesis of CNS symptoms and syndromes associated with SARS-CoV-2. Studies of cerebrospinal fluid obtained from living patients with acute COVID-19 support this hypothesis.

Most reports of CSF from COVID-19 patients with neurological symptoms demonstrate an absence of any marked pleocytosis, while noting markers of blood brain barrier disruption, such as increased CSF to plasm albumin ratio and increased CSF protein, in a subset of patients [42-44]. However, while these CSF studies do not show findings typical for meningoencephalitis, single cell transcriptome analyses of immune cells in the CSF in patients with COVID-19 suggest marked perturbations of the normal CSF immune milieu during COVID-19 [45,46]. Heming and Li and colleagues report a clonal expansion of T cells within the CSF, as well as an expanded population of exhausted CD4 T cells [45]. Likewise, in a study of single cell transcriptomics comparing blood and CSF immune cells in COVID-19 patients and uninfected controls, Song and Bartley and colleagues found increased markers of T cell activation in the CSF of COVID-19 patients when compared to peripheral blood cells [46].

Activated and expanded lymphocyte and monocyte populations in the CNS may contribute to the production of inflammatory cytokines during COVID-19. Indeed single cell gene expression profiling predicted increases in IL-1 and IL-12 signaling in the CSF but not the peripheral blood[46], a finding consistent with cytokine analyses that demonstrate divergent inflammatory responses within the CNS of COVID-19 patients compared to the peripheral blood [47,48]. These studies suggest abnormal immune activation and cytokine activity within the CNS during COVID-19.

CNS autoimmunity during COVID-19

Increasingly, aberrant humoral immune responses have been implicated in SARS-CoV-2 systemic disease, with a significant proportion of COVID-19 patients displaying evidence for humoral autoimmunity[49-51]. Autoreactive processes may likewise contribute to neurological symptoms in COVID-19. In a series of seven patients with COVID-19 and neurological symptoms, Song and Bartley and colleagues found that five out of seven patients harbored high titers of anti-neural autoantibodies in the CSF[46]. Likewise, isolated case reports have demonstrated the presence of anti-neuronal antibodies in patients with COVID-19 associated autoimmune encephalitis and COVID-19–associated acute necrotizing encephalopathy[52,53].

While the mechanisms contributing to increased autoimmunity in COVID-19 remain incompletely understood, evidence is emerging for the potential for anti-viral antibodies to display aberrant autoreactive properties. Single cell analyses demonstrate that COVID-19 associates with a marked clonal expansion of B and plasma cells in the CSF; these CSF cells display divergent B cell receptor sequences when compared to cells found in the peripheral

blood of the same patients[46]. Monoclonal antibodies created from expanded B cell clones in the CSF demonstrated both anti-viral and anti-neural reactivity, including one monoclonal antibody that reacted against SARS-CoV-2 spike protein while also displaying anti-neural immunoreactivity. Likewise, researchers using a hamster model for SARS-CoV-2 found that anti-spike antibodies generated in this model displayed reactivity against mammalian tissue, including the brain[54]. Taken together, these studies suggest that patients with COVID-19 harbor intrathecal autoantibodies, including anti-neural autoantibodies, that may contribute toward neurological symptoms, although the clinical significance of these autoantibodies has not yet been proven.

Conclusion

Studies of central nervous system tissue from adults with acute SARS-CoV-2 infection have begun to uncover potential mechanisms for neurological damage during COVID-19. These studies suggest that, while direct viral invasion of the CNS occurs in a subset of cases, parainfectious processes, including CNS specific immune responses, are likely important contributors to neurological symptoms in these patients. However, it remains unknown how specific these findings are to SARS-CoV-2 infection, or whether they are features common to other systemic and respiratory infections. While research studies summarized here have shed important light on potential mechanisms of neurological symptoms during acute SARS-CoV-2 infection, increasingly there are reports of post-acute neurological sequelae occurring in people who have recently recovered from COVID-19. This includes reports of autoimmune encephalitis, memory loss, sleep disturbances, prominent mood disorders and persistent headaches in the weeks to months following acute infection with SARS-CoV-2. With an estimated more than one-hundred and twenty million people known to be infected with SARS-CoV-2, the problem of long-term neurological complications of COVID-19 has the potential to affect millions of people around the globe. Large-scale patient-based studies will be critical to understanding the pathophysiology of neurologic disorders seen in individuals after recovery from acute COVID-19 and to develop therapeutic strategies.

Key points:

- Neurological symptoms are commonly reported in hospitalized patients with acute COVID-19
- Autopsy and model system studies suggest that brain cells are susceptible to direct infection with SARS-CoV-2
- There is evidence for immune activation within the CNS, including increased intrathecal humoral autoimmunity in some patients with COVID-19.
- Future studies are urgently needed to understand whether neuroimmune perturbations persist in patients recovering from COVID-19

Figure 1. Potential causes of neurological complications of acute COVID-19

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