Journal of Integrative Neuroscience

*J. Integr. Neurosci.* **2022**; 21(3): 77
https://doi.org/10.31083/j.jin2103077

*Review*

# Neurological Sequelae of COVID-19

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Academic Editors: Rafael Franco and Mila Emerald
Submitted: 6 December 2021 Revised: 31 January 2022 Accepted: 21 February 2022 Published: 6 April 2022

**Abstract**

**Background**: Though primarily a pulmonary disease, Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus can generate devastating disease states that affect multiple organ systems including the central nervous system (CNS). The various neurological disorders associated with COVID-19 range in severity from mild symptoms such as headache, or myalgias to more severe symptoms such as stroke, psychosis, and anosmia. While some of the COVID-19 associated neurological complications are mild and reversible, a significant number of patients suffer from stroke. Studies have shown that COVID-19 infection triggers a wave of inflammatory cytokines that induce endothelial cell dysfunction and generate coagulopathy that increases the risk of stroke or thromboses. Inflammation of the endothelium following infection may also destabilize atherosclerotic plaque and induce thrombotic stroke. Although uncommon, there have also been reports of hemorrhagic stroke associated with COVID-19. The proposed mechanisms include a blood pressure increase caused by infection leading to a reduction in angiotensin converting enzyme-2 (ACE-2) levels that results in an imbalance of the renin-angiotensin system ultimately manifesting inflammation and vasoconstriction. Coagulopathy, as demonstrated by elevated prothrombin time (PT), has also been posited as a factor contributing to hemorrhagics stroke in patients with COVID-19. Other neurological conditions associated with COVID-19 include encephalopathy, anosmia, encephalitis, psychosis, brain fog, headache, depression, and anxiety. Though there are several hypotheses reported in the literature, a unifying pathophysiological mechanism of many of these disorders remains unclear. Pulmonary dysfunction leading to poor oxygenation of the brain may explain encephalopathy and other disorders in COVID-19 patients. Alternatively, a direct invasion of the CNS by the virus or breach of the blood-brain barrier by the systemic cytokines released during infection may be responsible for these conditions. Notwithstanding, the relationship between the inflammatory cytokine levels and conditions such as depression and anxiety is contradictory and perhaps the social isolation during the pandemic may in part be a contributing factor to some of the reported CNS disorders. **Objective**: In this article, we review the current literature pertaining to some of the most significant and common neurological disorders such as ischemic and hemorrhagic stroke, encephalopathy, encephalitis, brain fog, Long COVID, headache, Guillain-Barre syndrome, depression, anxiety, and sleep disorders in the setting of COVID-19. We summarize some of the most relevant literature to provide a better understanding of the mechanistic details regarding these disorders in order to help physicians monitor and treat patients for significant COVID-19 associated neurologic impairments. **Methods**: A literature review was carried out by the authors using PubMed with the search terms "COVID-19" and "Neurology", "Neurological Manifestations", "Neuropsychiatric Manifestations", "Stroke", "Encephalopathy", "Headache", "Guillain-Barre syndrome", "Depression", "Anxiety", "Encephalitis", "Seizure", "Spasm", and "ICUAW". Another search was carried out for "Long-COVID" and "Post-Acute COVID-19" and "Neurological Manifestations" or "Neuropsychiatric Manifestations". Articles such as case reports, case series, and cohort studies were included as references. No language restrictions were enforced. In the case of anxiety and depression, attempts were made to focus mainly on articles describing these conditions in infected patients. **Results**: A total of 112 articles were reviewed. The incidence, clinical outcomes, and pathophysiology of selected neurological disorders are discussed below. Given the recent advent of this disease, the incidence of certain neurologic sequelae was not always available. Putative mechanisms for each condition in the setting of COVID-19 are outlined.

**Keywords:** COVID-19; ischemic stroke; hemorrhagic stroke; encephalopathy; encephalitis; brain fog; headache; Guillain-Barre syndrome; depression; anxiety; cerebral venous sinus thrombosis; Long COVID

## 1. Introduction

With more than five million world-wide deaths reported and new variants emerging, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has been a significant medical challenge. Symptoms of Coronavirus Disease 2019 (COVID-19) include cough, fever or chills, shortness of breath, fatigue, myalgia, headache, anosmia, ageusia, sore throat, and congestion or runny nose and may vary in severity from mild to life threatening. In severe disease, patients exhibit respiratory failure, acute renal failure, and eventually multi-system organ failure.

While many COVID-19 patients may exhibit mild neurologic symptoms, a small percentage of patients can develop severe neurologic disorders [1]. Soon after the discovery of the illness, and the World Health Organization declaring COVID-19 a global pandemic, clinicians began reporting delirium and encephalitis in acutely ill patients with confirmed infection [2], and early retrospective studies coming out of China [3] and France [4] indicated that significant proportions of patients were experiencing neurologic complications during COVID-19 hospitalization. As the pandemic spread globally, the impact of COVID-19 on brain health became increasingly relevant, with one large healthcare network in the USA reporting neurologic manifestations in 82.3% of both hospitalized as well as ambulatory COVID-19 patients [5].

While anosmia and ageusia have been recognized since the beginning of the pandemic as mild and temporary components of the COVID-19 syndrome, startling reports in the summer of 2020 estimated the incidence of stroke in COVID-19 to be as high as 6% in hospitalized patients. These individuals exhibited elevated pro-inflammatory markers, including ferritin and C-reactive protein (CRP), as well as elevated D-dimer levels [6]. Elevated D-dimer levels have also been found by another study to be associated with acute ischemic and especially cryptogenic stroke, as per the results of unsupervised machine learning cluster analysis of biomarkers [7]. Both overactive coagulation as well as hyper-inflammation have been proposed as mechanisms for endothelial damage and thrombus formation in COVID-19 [2,8].

The true incidence of neurologic manifestations of COVID-19 is likely underestimated in the literature, given the predominance of respiratory complications and the attention these issues command of patients and their providers. Furthermore, there is a tendency in published COVID-19 data to emphasize hospitalized patients [2]. Nonetheless, the scale of the pandemic means that in reality a very large population of COVID-19 patients, numbering in the tens to hundreds of thousands, have experienced or will experience neurologic complications in the course of their illness [2,6]. Importantly, the neurological complications in persistent COVID-19 disease appear to be more disabling relative to other organ system involvement [9]. The continuum of COVID-19 effects on the nervous system likely represents multiple pathogenic pathways and much remains to be elucidated in describing the pathogenicity and deleterious effects of SARS-CoV-2 on the nervous system [2,10]. Moreover, as indicated in the published literature, there is no consensus on the range of neurologic conditions that are formally recognized as associated with COVID-19. There is also a paucity of knowledge regarding which neurologic manifestations and disabilities are likely to persist in the post-acute phase of infection and beyond [8], and an objective characterization of the neurologic complications of COVID-19 is needed to facilitate surveillance as well as selection of treatment candidates [11].

Herein we review the current literature pertaining to the common neurological disorders such as stroke, encephalopathy, encephalitis, headache, Long COVID, Guillain-Barre syndrome, depression, and anxiety in the setting of COVID-19. We summarize some of the most relevant literature to provide a better understanding of the mechanistic details regarding these disorders with a goal to help stimulate creative thinking and improve patient management and outcomes in Table 1 (Ref. [1,9,12–52]), with the supporting references included.

## 2. Ischemic Stroke

Incidence: Ischemic stroke is one of the most feared neurological complications of COVID-19. A retrospective cohort study of 236,379 patients with COVID-19 concluded that approximately 34 percent of patients developed neurological or psychiatric conditions within 6 months of diagnosis, whereas the incidence of ischemic stroke was 2.10 percent [53]. Other studies have found similar incidence of stroke in patients with COVID-19. A retrospective case series containing 214 hospitalized COVID-19 patients demonstrated a 5.7 percent incidence of ischemic and hemorrhagic stroke in severe infection [3]. Another study found that 2.3 percent of patients suffered from ischemic stroke [12].

COVID-19 stands out among respiratory diseases including influenza when it comes to ischemic stroke. Stroke is nearly twice as likely to occur in non-hospitalized COVID-19 patients compared to influenza with a hazard ratio (HR) of 1.80 [53]. Incidence of stroke has been shown to be concordant with severity of illness. For example, a meta-analysis found that 61 percent of stroke cases occurred in severe infection [54]. A retrospective cohort study found a 4.38 percent incidence of ischemic stroke in those hospitalized, as compared to an overall 6-month rate of 2.10 percent [53]. Patients who were admitted to the intensive treatment unit and patients with encephalopathy had an incidence of 6.92 and 9.35 percent, respectively. The HR for developing ischemic stroke for hospitalized versus non-hospitalized patients was 1.65.

Clinical Outcome: Studies have demonstrated that COVID-19 associated stroke patients experienced an approximately 5 times greater in-hospital mortality rate than

**Table 1. COVID-19 associated neurological sequalae and proposed mechanisms.**

| Neurological sequalae | Putative mechanism | Ref. |
|---|---|---|
| Ischemic stroke | Cytokine overproduction; Vascular endothelial damage, Endothelial dysfunction; Hypercoagulable state | [12–20] |
| Hemorrhagic stroke | Decrease in ACE-2 levels; Blood pressure increase; Coagulopathy; CVST | [21,23,24] |
| Encephalopathy, encephalitis | Cytokine overproduction; Vascular endothelial damage; Direct CNS invasion; Hypoxia; Autoimmunity | [9,22,25–35] |
| ICUAW | Cytokine overproduction; Myofiber atrophy; Direct viral damage | [42–47] |
| Myoclonus | Autoimmune cerebellar/brainstem damage; Hypoxia | [41] |
| Brain fog/Long COVID | Autoimmune; Neuroinflammation; Neurodegeneration | [9,26,35–37] |
| Headache | Hypoxia; Activation of peripheral trigeminal nerve endings; Cytokine overproduction; Direct CNS invasion; Hypercoagulable state | [38,39] |
| Guillain-Barre syndrome/Polyneur opathy | Autoimmunity/Molecular mimicry | [40] |
| Depression, anxiety and sleep disorders | Cytokine overproduction/Neuroinflammation; Direct CNS invasion | [48–51] |
| Seizure | Hypoxia; Multiorgan failure; Metabolic derangements; Cytokine overproduction; Direct CNS invasion | [1,52] |

that of others (odds ratio (OR) = 5.21) [54]. Patients who suffered emergent large-vessel occlusion who were also COVID-19 positive were much more likely to succumb compared to COVID-19 negative patients with emergent large-vessel occlusion (63% vs. 9% mortality) [55].

Enhanced mortality in COVID-19 patients with stroke compared to non-infected stroke patients has also been found by another study (39.3% vs. 16.1% mortality) [56]. Moreover, researchers assessed the functional outcomes of these patients as measured by Modified Rankin Score (mRS) initially and three months post-stroke. There was a significant difference in the proportion of infected and non-infected stroke patients who achieved favorable outcomes, with infected patients demonstrating a relative risk for poor functional outcome of 1.25. Yet, after adjusting for age, baseline National Institutes of Health Stroke Scale (NIHSS) score, admission to the ICU, and history of diabetes in multivariable logistic regression analysis, no significant difference in the probability of achieving a functional outcome was found between these two groups. Infected patients' NIHSS scores were significantly greater both at baseline and post-72 hours. NIHSS score itself was significantly associated with mortality. Infected patients were also more likely to be admitted to the ICU, which itself was associated with poor functional outcome (OR = 3.30). Thus, the apparent less favorable outcomes in this study may be attributed to the severe disease state found in COVID-19. Furthermore, the authors failed to find a significant link between COVID-19 and large-vessel occlusion. Both groups of patients had similar baseline NIHSS scores and the rates of successful recanalization in infected and non-infected patients did not differ significantly. No significant difference in favorable outcome was detected between infected and non-infected patients. Yet, the mortality rate of infected patients exceeded that of non-infected patients, with a HR of 2.96.

Pathophysiology: COVID-19 induced stroke may be better understood through the lens of its proposed mechanism. The infection is thought to promote a systemic inflammatory response, with monocyte-derived macrophages releasing cytokines that bring about endothelial cell dysfunction and general coagulopathy [13]. Macrophages also release tissue factor (TF), thereby activating the extrinsic coagulation pathway. Biopsy results have highlighted the microthrombotic and microangiopathic nature of COVID-19 [57]. The prothrombotic state of patients with COVID-19 may explain at least in part their elevated risk of ischemic stroke.

Coagulopathy has been well documented in COVID-19. One study found that 7.2 percent of patients experienced thromboembolic events [12]. Furthermore, 2.10 percent of patients suffered from disseminated intravascular coagulation (DIC), wherein sepsis and other conditions generate widespread coagulation that ultimately exhausts the supply of clotting factors, promoting bleeding.

The exact mechanism behind COVID-19 associated stroke has yet to be elucidated for a plurality of cases. Cryptogenic stroke comprised 44.7 percent of cases of ischemic stroke, whereas cardioembolic stroke made up 21.9 percent of cases. There appears to be a male predisposition to ischemic stroke in COVID-19, with 71.9 percent of COVID-19 associated ischemic stroke patients being male compared to 45 percent in the case of historical controls [14].

Female sex has been repeatedly shown to be protective against viral ailments. Estrogen stimulates the immune system while also inhibiting viral replication [15]. Furthermore, when exposed to 17$\beta$-estradiol, human atrial tissue expression of LOX-1 and ICAM-1, both of which are *NF-$\kappa$B* target genes, decreased significantly [16]. ICAM-1 and LOX-1 are pro-inflammatory and pro-oxidative, respectively. Estrogen exposure also decreased the ratio of ACE to ACE2 on a mRNA and protein level, providing a

potentially protective effect. ACE2 has in fact been shown to be protective against pulmonary hypertension, with the gene for ACE2 residing within the X-chromosome [14].

Studies have shown that female mice display greater resistance to the SARS-CoV virus. It was found that male mice infected with 5000 plaque-forming units (PFU) of mouse-adapted SARS-CoV (MA15) suffered a mortality rate as high as 90 percent, with a significantly lower rate for females (20 percent) [14]. Estrogen appears to be the source of females' relatively low mortality. The mortality rate of females that underwent bilateral oophorectomy increased to 85 percent. The differential in mortality rates between the sexes is reflected by the more severe male lung pathology results, which included alveolar edema, hyperemia, and vascular leakage. Male mice were also found to have 2 to 3 times the amount of inflammatory monocyte macrophages (IMMs) in their lungs compared to female mice on day 3 post-infection. A greater percentage of male IMMs produced inflammatory cytokines, such as IL-6 and IL-1-$\beta$. When the males were depleted of their IMMs using an MC21 antibody, mortality significantly decreased.

Studies have found that COVID-19 produces lingering prothrombotic effects. Infection with COVID-19 results in the release of IL-1, IL-6, and TNF-$\alpha$, which trigger the release of TF [17]. PAI-1 expression also increases, inhibiting fibrinolysis. Endothelial cell damage that arises from cytokine storms triggers the release of von Willebrand factor (vWF), promoting platelet adhesion to the endothelium. Inflammation of the endothelium during viral infection may also preferentially destabilize atherosclerotic plaque, inducing thrombotic stroke in the case of even mild carotid disease [18].

Research shows that some of the prothrombotic changes may be sustained even months after initial infection. A study of 52 COVID-19 patients found that patient ex vivo thrombin-generating potential remained elevated 4 months post-discharge [19]. PAI-1 expression was elevated both at admission and 4 months post-discharge. Elevated PT, factor V, vWF, fibrinogen, D-dimer, and thrombin-antithrombin complex were present on admission, but normalized 4 months later. Factor VIII remained elevated at 4 months post infection, which may explain the sustained hypercoagulable state found in convalescent COVID-19 patients. In fact, cases of delayed COVID-19 associated stroke, though rare, have been documented in the literature. A study of 18 men up to 50 years old with asymptomatic infection found a median of 54.5 days between initial infection and stroke [20].

Discussion: COVID-19 related stroke is an inflammatory process driven by cytokine-release, endothelial cell dysfunction, unregulated vasoconstriction, and a general thrombogenic state. While the exact mechanism remains unclear, histopathological studies conducted in deceased COVID-19 patients support brain tissue damage related to abnormal immune response [58]. COVID-19 associated stroke has been associated with elevated D-dimer as well as CRP [59]. Furthermore, stroke has been found to confer greater odds of mortality, with an OR of 3.49. Most COVID-19 associated cases of stroke occur in the early stages of infection. However, the continued elevation of prothrombotic factors such as factor VIII, PAI-1, and ex vivo thrombin-generating potential are testament to a lasting risk of virus-related ischemic events. Recrudescence, or recurrence, of stroke symptoms has also been observed. For example, one woman who suffered ischemic stroke two months after a mild case of COVID-19 demonstrated an old infarct in the left middle cerebral artery territory on imaging [60]. The patient presented with cognitive dysfunction, sensory deficits, and new-onset right-sided weakness. In one study of 153 patients with post-stroke recrudescence, researchers found recrudescence to be associated with infection, hypotension, and hyponatremia, occurring a median of 3.9 years post-stroke [61].

During the height of the pandemic, the quality of healthcare was generally compromised due to the sudden influx of severely ill patients. Patients with emergent large-vessel occlusion during the pandemic were significantly less likely to receive thrombolysis administration and mechanical thrombectomy compared to a prepandemic cohort. Yet, no significant difference in poor functional outcomes or mortality was observed [62]. Furthermore, COVID-19 is a global health issue that impacts every race and ethnicity. A retrospective analysis of COVID-19 positive patients admitted to New York City hospitals failed to find significant interracial differences in the prevalence of stroke and other thrombotic events [63]. However, other studies have suggested instead that African Americans are at significantly higher risk of developing COVID-19 associated stroke even when controlling for co-morbidities such as hypertension as well as smoking status [64].

## 3. Hemorrhagic Stroke

Incidence: A retrospective cohort study of New York City hospital patients found that 0.67 percent of COVID-19 positive individuals developed subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), or intracerebral hemorrhage [21]. A meta-analysis of 108,571 patients found a 1.4 percent cumulative incidence of acute cerebrovascular events with 87.4 percent ischemic and 11.6 percent hemorrhagic stroke [54]. Studies have shown that COVID-19 associated hemorrhagic stroke is less prevalent than ischemic stroke. A study determined the incidence of intracranial hemorrhage (ICH) to be approximately one-fourth that of ischemic stroke [22]. The HR of developing hemorrhagic stroke in the setting of COVID-19 for non-hospitalized patients compared to influenza was 1.87 [53]. Intensity of illness was also found to be correlated with incidence of hemorrhagic stroke. The HR for developing intracranial hemorrhage for hospitalized versus non-hospitalized patients was 3.09.

Clinical Outcome: A retrospective study of COVID-19 associated hemorrhagic stroke found infected patients had a significantly greater chance of death compared to non-infected controls [23]. Infected patients with ICH had an OR of 2.64 for mortality, after adjusting for variables such as sex, age, smoking, renal failure, and acute coronary syndrome. Infected patients with SAH had a greater mortality rate than non-infected controls (42.9% vs. 14.8%). The adjusted OR for mortality in infected compared to non-infected patients was 1.81 [23].

Pathophysiology: Regarding hemorrhagic stroke, a virus-induced unregulated increase in blood pressure is thought to be a crucial pathophysiologic mechanism. The angiotensin-converting enzyme-2 (ACE-2) receptor, found on lung and brain smooth muscle and endothelial cells, is a binding target of the SARS-CoV-2 spike (S) protein. By binding to ACE-2, the virus invades cells and eliminates ACE-2 via endocytosis. ACE-2 cleaves angiotensin I into angiotensin 1–9, which is ultimately cleaved into angiotensin 1–7 (a vasodilator with anti-inflammatory properties) by ACE. ACE-2 also cleaves angiotensin II into angiotensin 1–7 [24]. Angiotensin II acts as a vasoconstrictor while simultaneously promoting inflammation. The decrease in available ACE-2 increases the amount of angiotensin II and decreases the amount of angiotensin 1–7, thereby upregulating vasoconstriction and inflammation, ultimately leading to hypertension and potentially hemorrhagic stroke. Coagulopathy, as evidenced by PT elevation, has also been posited as an etiology of hemorrhagic stroke [21].

Discussion: Hemorrhagic stroke, though a less common COVID-19 sequelae than ischemic stroke, has been found to be significantly associated with SARS-CoV-2 infection [53]. Infected patients have experienced a greater risk of mortality compared to their non-infected counterparts, even after controlling for age, sex, and renal failure [23]. There has been an increased usage of anticoagulants in COVID-19 patients due to the enhanced risk of thrombotic events. Given the fact that a significantly greater percentage of infected patients with intracerebral hemorrhage (69.8%) received anticoagulation compared to non-infected controls (55.4%), this increased utilization of anticoagulants may be partly to blame. COVID-19 associated cerebral venous sinus thrombosis (CVST) has also been shown to induce hemorrhagic stroke.

A retrospective cohort study of 537,913 patients with COVID-19 found an incidence rate of CVST (42.8 per million people) that was significantly greater than that of either vaccine or influenza associated CVST in matched cohorts. The relative risk of developing CVST following COVID-19 infection compared to the mRNA vaccine was 6.33. Moreover, the relative risk of developing CVST following COVID-19 infection compared to influenza infection was 2.67 [65]. CVST is a rare cerebrovascular disease that generally affects young adults, particularly women of childbearing age [66]. While symptoms of CVST include blurred vision, fainting, and seizures, the most common symptom is headache. Headache is also the most common neurological symptom of COVID-19, which makes diagnosis of CVST more difficult.

## 4. Encephalopathy

Encephalopathy is defined as a disease state that leads to impaired brain functioning as evidenced by reduced mentation or frank delirium.

Incidence: Occurrence of encephalopathy in COVID-19 has varied a great deal, ranging from 7 percent to 69 percent [5,6,25,67]. Luigetti *et al*. [22] reported encephalopathy in 32.4 percent of hospitalized patients, whom they further divided into encephalopathy related to fever (>39.5 °C), hypoxia (SpO2 <85%), and idiopathic encephalopathy. While encephalopathy was the most frequently encountered manifestation in the cohort, most of these cases were related to respiratory complications resulting in hypoxemia [22].

Clinical Outcome: Studies have shown that COVID-19 associated acute encephalopathy or encephalitis without severe hypoxia or metabolic derangement is a self-limiting condition that responds well to intravenous corticosteroid therapy followed by oral steroid taper [26,27]. Moreover, a review of published cases of encephalopathy found that 83.3 percent (30/36 cases) of patients improved following medical management. Patients suffering from encephalopathy in the setting of COVID-19 have required mechanical ventilation and ICU care.

Altered mentation has been found to confer greater odds of mortality, with an OR of 1.61 [59]. Importantly, elevated procalcitonin and D-dimer levels were associated with both severe COVID-19 infection and altered mentation. Despite controlling for various biomarker levels, patients with altered mentation continued to demonstrate increased risk of mortality.

Pathophysiology: A case series examined 7 hospitalized patients with positive COVID-19 nasopharyngeal swabs who presented with acute changes in cognition and behavior, focal neural deficits and/or new onset seizures. All patients showed similar results on positron emission tomography (PET) evaluation. Fluorine-19 magnetic resonance imaging and positron emission tomography (19F-FDG-PET) imaging revealed hypometabolism in a cerebral network containing the prefrontal cortex, anterior cingulate, insula and caudate nucleus. These changes in brain metabolism were present despite only 28.6 percent (2/7) of these patients developing acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation. These PET disturbances persisted at 6 months of follow up in all patients, though mild improvement in mentation was observed in some patients. RT-PCR was negative for SARS-CoV-2 in the CSF for all patients. In addition, CSF levels of IL-6 levels were elevated in all patients tested [22].

Another case series followed 31 hospitalized patients with a diagnosis of "COVID-19 induced encephalopathy" [28]. This cohort was divided into two groups, mild and severe encephalopathy. No difference in severity of pneumonia was observed between both groups, with 90.3 percent of (28/31) patients developing ARDS. Brain MRI analysis revealed abnormalities in 92 percent of (23/25) patients with no difference between groups. In addition, contrast enhancement of intracranial vessels, a sign of endothelial damage, was observed in 85 percent of (17/20) patients. Elevated serum CRP was found to be associated with presence of intracranial vessel enhancement. Taken together, these reports suggest an indirect, proinflammatory effect of SARS-CoV-2 that results in intracranial, endothelial dysfunction and encephalopathy.

Though pulmonary dysfunction leading to poor oxygenation of the brain can help explain encephalopathy in the acute phase of COVID-19 hospitalization, other hypotheses have been proposed implicating viral invasion of the CNS as well as an overwhelming cytokine response to the virus crossing the blood-brain barrier [22,29,30]. Moreover, there is evidence suggesting that the etiology of the encephalopathy may influence the duration of impairment.

Discussion: The pathophysiology of SARS-CoV-2 induced encephalopathy remains unclear. A recent case series described three pediatric patients who had tested positive for SARS-CoV-2 with mild COVID-19 symptoms but presented with severe neuropsychiatric symptoms including psychosis, paranoia, and agitation. All 3 had abnormal CSF and 2 of these patients were observed to have anti-SARS-CoV-2 IgG in addition to antineuronal antibodies. These findings support the possibility of viral CNS invasion as well as autoimmunity as explanations for these symptoms [31]. Thus, COVID-19 may pose a unique threat to the neuropsychiatric wellbeing of even young individuals without previous mental health history.

## 5. Encephalitis

Encephalitis is defined as encephalopathy with evidence of brain inflammation on either MRI or CSF, with $>$5 white blood cells/$\mu$L and $>$0.45 g protein/dL in the CSF [68]. COVID-19 encephalitis is defined as meeting these criteria in the presence of CSF PCR or viral culture positive for SARS-CoV-2, and/or intrathecal viral antibodies in the absence of other pathogens within the CSF [6].

Incidence: A recent systematic review and meta-analysis of encephalitis in 23 studies of 129,008 total patients with COVID-19 found an average incidence of encephalitis of 0.215 percent [69]. However, an estimated incidence as low as 0.05 percent has also been demonstrated [70]. Encephalitis is only rarely a presenting symptom of COVID-19. Patients initially present with respiratory symptoms followed by encephalitis 14.5 days later on average. Severity of illness also impacts incidence of encephalitis. Patients with severe cases of infection had a 6.7 percent incidence of encephalitis.

Clinical Outcome: Though an uncommon complication of COVID-19, encephalitis can significantly increase morbidity and mortality. A meta-analysis of over 100,000 patients from 23 studies demonstrated an average mortality rate of 13.4 percent [69]. Following specific encephalitis treatment protocols that included antibiotics, antivirals, high-dose steroids and immunoglobulins or plasmapheresis, a multicenter study reported high mortality in patients with alterations in MRI imaging (vs. negative neuroimaging) [70]. Patients with encephalitis had a variety of presenting symptoms, such as delirium, aphasia, and dysarthria. Seizure was also reported in approximately one-third of patients. Spontaneous recovery was achieved by 24 percent of patients. A mortality rate of 16 percent was observed [70].

Pathophysiology: The same ACE-2 enzyme which facilitates SARS-CoV-2 entry into nasal mucosa, lung and other body tissues is also expressed throughout the central nervous system, particularly in the thalami, cerebellum and inferior olivary nuclei [32]. It is therefore important to differentiate the encephalopathy that develops in response to metabolic derangement and hypoxemia in the setting of critical pulmonary illness versus true viral encephalitis in treating these encephalopathic patients [25]. Case reports of altered mental status combined with signs and symptoms of meningeal irritation in the setting of normoxia and without metabolic derangement highlight the inherent potential of SARS-CoV-2 infection to cause encephalopathy or encephalitis independent of respiratory function in patients with COVID-19 [27].

The first confirmed case of SARS-CoV-2 encephalitis was a 24-year-old Japanese male who presented in February 2020 with generalized seizures and nuchal rigidity following a weeklong flu-like prodrome. Radiographic examination revealed paranasal sinusitis, right lateral ventriculitis and right mesial encephalitis. Preexisting mesial temporal pathology was unlikely in this young adult who had no prior history of epilepsy or other neurodevelopmental disorders. RT-PCR was negative for SARS-CoV-2 RNA on nasopharyngeal swab but positive in the CSF [33]. It is now known that detection of SARS-CoV-2 in nasopharynx requires the patient to be actively shedding, whereas patients without respiratory symptoms may exhibit a false negative swab [9,34]. Although the clinical outcome of that patient was not included in the report, this case highlights the importance of suspecting CNS invasion of SARS-CoV-2 even with a negative nasopharyngeal swab.

Conversely, there have been instances of COVID-19 positive (by nasopharyngeal swab) patients with signs of meningeal irritation (e.g., Nuchal rigidity, Kernig and Brudzinski signs) and/or altered mentation, from whose CSF no virus or antibodies were isolated [27,71]. Some authors have suggested CSF testing is not sensitive enough for detecting SARS-CoV-2, stating intrathecal viral prolif-

eration is a transient phenomenon and a negative CSF result may be due to below-detectable CSF titers while sufficient virus is nonetheless present to cause CNS disease [22]. Other authors have argued that cases of encephalitis occur via invasion of the olfactory tract or through a local breakdown in the blood brain barrier [26,35].

Discussion: RT-PCR testing of CSF has successfully detected SARS-CoV-2 in a handful of encephalopathic COVID-19 patients, even though the true incidence of CNS invasion is believed to be much greater [72]. Improved sensitivity over conventional RT-PCR methods of detecting SARS-CoV-2 invasion of the CSF need to be tested and validated in order to rapidly assess and treat patients with COVID-19 who become encephalopathic [73,74]. Alternatively, next-generation sequencing for SARS-CoV-2 in the CSF has shown promising results. A recent study applied high-throughput RNA sequencing and proteomics to CSF samples from 8 COVID-19 patients with varying severities of neurologic symptoms. RNA sequencing unequivocally confirmed SARS-CoV-2 RNA in half of the (4/8) subjects and indicated "high likelihood" of positivity in the remaining patients. Importantly, RT-PCR and antiviral antibody tests in the CSF samples were negative in all cases [75]. While the strength of a small, single center cohort study is limited, this report provides strong evidence that SARS-CoV-2 invasion of the CSF space likely eludes detection by conventional means and instead requires amplification of the materials for confirmation.

## 6. Brain Fog and Long Covid

Incidence: While many patients with COVID- associated encephalopathy or encephalitis make a full neurologic recovery with steroid therapy and supportive care, there are individuals who develop prolonged cognitive symptoms. According to a study from Northwestern University's Neuro-COVID-19 Clinic, brain fog was the most reported persistent (>6 weeks) neurologic symptom in survivors (81%) without history of severe illness, hypoxia, or respiratory compromise [9]. Brain fog persisted as long as 5 months and females were much more likely than males (2.3:1) to exhibit "long hauler COVID-19" symptoms [9,76].

Clinical Outcome: A recent systematic review assessing prevalence of symptoms of Long COVID affecting all body systems found fatigue to be the most reported ailment (58%). Effects on cognition were found to be 31% and 27% for persistent difficulty with concentrating and attention deficits, respectively [76,77]. Patients with brain fog who underwent cognitive testing as part of another study displayed short-term memory (32%) and attention (27%) deficits [9]. Fatigue was found in 85 percent of patients. Time from the onset of illness was not significantly correlated with subjective recovery.

Pathophysiology: Research has suggested that so-called brain fog might represent a sub-acute form of post-COVID encephalopathy. In addition, elevated antinuclear antibody (titer >1:160) was more prevalent in the long hauler cohort relative to the general population (33% vs. 5%), suggesting an autoimmune etiology of post-acute cognitive symptoms in COVID-19 long haulers [9].

One proposed mechanism for persistent dysfunction following mild COVID illness has been neuroinflammation causing hypometabolic lesions [36]. Hugon *et al*. [35] showed that hypometabolism in the cingulate cortex was associated with diminished executive control and loss of attention in a patient with a history of mild COVID. Similarly, a PET study examining 7 patients with persistent cognitive and emotional impairment 6 months after recovery from COVID-19 encephalopathy found hypometabolism in the frontal, anterior cingulate and insular cortices as well as the caudate. The results of these studies suggest that COVID can have lasting negative effects on cognitive networks and that clinicians should maintain an index of suspicion for prolonged neurocognitive symptoms in patients who have recovered from the acute phase of COVID encephalopathy [37]. Some authors have also suggested that neuroinflammation caused by mild COVID infections could lead to neurodegenerative illness [26]. Accordingly, long-term follow up is recommended in all patients who experience neurologic derangement during COVID infection to detect persistent symptoms [35].

Discussion: A recent systematic review reported a total 55 long-term effects associated with COVID-19 lasting at least 2 weeks after the acute phase of the illness [77]. It is estimated that one or more of these prolonged symptoms is present in up to 30% of COVID-19 survivors [71,78]. Several definitions for the term "Long COVID" have been proposed, though there has been no consensus [77]. Sapkota *et al*. [76] define "Long COVID" as an uninterrupted continuation of the original COVID-19 syndrome or a relapsing-remitting pattern of symptoms, following COVID-19 recovery as indicated by negative PCR swab. The UK health system has formally defined the condition as "post-COVID-19 Syndrome" [NICE guideline (NG188)], and the World Health Organization has applied the term Long COVID to individuals who have symptoms 3 months after suspected or confirmed COVID diagnosis which last for 2 months without any other likely diagnosis.

Neurological impairment following SARS-CoV-2 infection presents both patients and physicians with short and long-term challenges. The most common neurologic symptoms of Long COVID are a cognitive dysfunction referred to as brain-fog as well as fatigue. In a study of non-hospitalized COVID-19 individuals with Long COVID, certain preexisting conditions such as autoimmune disease and depression/anxiety were prevalent suggesting increased vulnerability to SARS-CoV-2 infection [9].

The pathophysiology underlying persistent cognitive impairment in Long COVID remains unclear. Despite many reports indicating that delirium caused by a hyper-

inflammatory response to viral CNS invasion is temporary and responds well to steroid therapy [27,71] prolonged cognitive symptoms following recovery from acute COVID-19 illness is a well-documented finding [9]. Aside from the direct cytotoxic effects of neuronal infection, invasion of the CNS by SARS-CoV-2 activates patrolling microglia. The role played by microglia as neuroprotective versus aggressive effectors of cytotoxicity is dependent on the balance between anti- and pro-inflammatory markers released during viral invasion. Microglial detection of SARS-CoV-2 is believed to trigger the release of pro- inflammatory cytokines, proteases and neurotropic factors resulting in either transient or lasting secondary damage to the CNS [29].

As the COVID-19 pandemic persists, more patients will likely develop Long COVID, the majority of whom are unlikely to ever be hospitalized or sick enough to visit a specialist [9]. These patients are at risk of suffering the effects of Long COVID without evaluation or treatment by overtaxed health systems which are less likely to focus on post-acute COVID-19 patients who are not seriously ill. Moreover, the majority of Long COVID symptoms, such as attention and memory impairment, are highly subjective. Accordingly, patients may be discouraged from seeking treatment due to perceived stigma, an issue that has historically been observed with other subjective disorders primarily affecting women such as chronic fatigue syndrome and fibromyalgia [9]. An increased awareness of the prevalence of Long COVID and education on the multi-organ nature of the disorder is key to ensuring COVID survivors are properly screened and assessed for these complications [76]. The prospect of patients with Long COVID being left with suboptimal or no treatment due to these barriers highlights the need to standardize the evaluation of post-acute COVID patients and to generate a universal terminology in categorizing these individuals and their symptoms. It is also important that providers encourage their patients to continue monitoring and reporting symptoms to their primary care providers beyond the acute window of illness and/or after negative follow-up testing. Further prospective studies are needed to continue documenting the incidence of Long COVID complications, the natural progression of these complications, and any responses to therapies.

## 7. Headache

Incidence: Headache has been described in the literature as the most common non-specific neurological symptom found in COVID-19 patients. The reported incidence of headache has varied widely from 6 to 20 percent [79]. Garcia-Azorin *et al*. [80] found an incidence rate of 23.4 percent for 2194 infected patients. Headache was the most common first symptom reported in COVID-19. In fact, 5.8 percent of infected patients developed headache prior to any other symptom.

Clinical Outcome: The median onset of COVID-19 associated headache was within 24 hours of infection, with a median duration of 7 days [80]. However, 13 percent of patients developed persistent headache lasting over 1 month. Persistent headaches linked to COVID-19 have also been documented by Caronna *et al*. [81] with 28 of the 74 patients reporting ongoing headaches 6 weeks post-admission. Patients with COVID-19 associated headache endorsed a median severity of 7 out of 10, as well as a median duration of 7 hours per day. COVID-19 related headache demonstrated certain defining features. In a survey-based study of 3458 patients that included 262 positive patients, 79.5 percent of COVID-19 associated headache patients compared to only 37.3 percent of non-infected headache patients endorsed novel headache features [82]. COVID-19 associated headache was significantly more likely to be bilateral, long lasting, and analgesic-resistant, with ORs of 3.37, 1.93, and 2.61 respectively. Another study found that 80 percent of COVID-19 associated headaches were bilateral [80].

Furthermore, COVID-19 patients frequently report headache accompanied by abnormal sensory and systemic symptoms such as anosmia and ageusia, and gastrointestinal complaints such as diarrhea [82,83]. The ORs for concomitant anosmia and gastrointestinal complaints in infected patients with headache were 11.4 and 2.13, respectively [82].

Pathophysiology: The exact pathophysiological mechanism of COVID-19 associated headache remains unclear. However, activation of trigeminal nerve endings, overproduction of pro-inflammatory cytokines, direct CNS invasion as in the case of encephalitis, as well as virus mediated hypercoagulation and hypoxia all have been invoked as possible mechanisms in the setting of COVID-19 [38,39].

Discussion: While clinical and basic science research has suggested that the proinflammatory properties of COVID-19 are responsible for increased incidence of stroke and encephalopathy, studies of headache have revealed an entirely different pathophysiologic mechanism [84]. Patients with headache had lower mortality rates as well as lower levels of inflammatory biomarkers, including IL-6, procalcitonin, CRP, and ferritin. The link between lower mortality risk and decreased levels of markers such as CRP is not unexpected. When researchers endeavored to generate a severity score of certain clinical parameters that would predict COVID-19 associated mortality, they found CRP and the internal normalized ratio (INR, the ratio of a patient's PT to that of a control), to be critical components of the score [85]. Given the unique features of COVID-19 associated headache, as well as the other neurological disorders patients may suffer from, the virus' effect on the CNS with respect to these disorders remains relatively unexplored.

## 8. Polyneuropathy, Myopathy, and Neuromuscular Disease

Guillain-Barre syndrome (GBS), a progressive demyelinating autoimmune polyneuropathy usually preceded by infection, is the most common etiology of acute flaccid paralysis and has been linked to cytomegalovirus, Epstein-Barr virus, Influenza A virus, Mycoplasma pneumoniae, Haemophilus influenzae, and Campylobacter jejuni [86].

Incidence: Early on in the pandemic, the incidence of GBS and other inflammatory polyneuropathic syndromes following COVID-19 related hospitalization were reported in the literature. Concurrent cases of COVID-19 and GBS and it various subtypes have been reported in various countries including Italy, Japan, China, USA, Spain, and India, among others [87–89]. Despite numerous observations, an epidemiological link between COVID-19 and GBS has not been established. The incidence of GBS in northern Italy during March-April 2020 increased 2.6-fold when compared to the same time in 2019. Authors of the study recruited patients diagnosed with GBS from 12 hospitals across 7 cities and divided them into COVID-19 positive and COVID-19 negative groups based on nasopharyngeal swab PCR results. The same study showed that COVID associated GBS was more severe than non-COVID GBS on the basis of clinical scores of muscle strength [90]. The authors acknowledged that the number of total COVID-19 positive patients in the hospitals that were studied was likely higher than that reflected in the data, leading to the possibility of overestimating the incidence of GBS among COVID-19 patients. Nonetheless, these findings are discordant with a study from the UK that was unable to show a rise in GBS incidence during the pandemic, finding a decrease instead. This was a retrospective study which leveraged the UK National Immunoglobulin Database where all cases of GBS are required to be logged [40]. It is possible that quarantining protocols in the UK decreased the incidence of GBS associated infections. Further research is required to fully explore the relationship between COVID-19 and GBS.

Intensive care unit-acquired weakness (ICUAW), a clinical phenomenon defined as new-onset weakness associated with extended hospital stay in critically ill patients, has also been reported in COVID-19. One prospective study in Sweden showed that in a cohort of 111 COVID-19 positive patients, 9.9% developed ICUAW. A case series from a tertiary care center in Spain described 12 patients with COVID-19 who had developed generalized weakness and failed weaning off ventilator-assisted respiration in the ICU. 91.7 percent of patients showed abnormal results on nerve conduction studies (NCS) and electromyography (EMG) consistent with critical illness myopathy (CIM). No patients had preexisting neuromuscular disease [91].

Tremor or new-onset hyperkinetic movement disorders, though rare, have been reported in the setting of COVID-19. A literature survey by Brandao *et al*. [41] identified 93 cases in which myoclonus (63.4%) and ataxia (38.7%) were reported as the most prevalent disorders. Opsoclonus and ocular flutter were found in 20.4 percent of cases. Miller-Fisher syndrome, a rare variant of GBS in which patients suffer from sensory ataxia, areflexia, and ophthalmoplegia, occurred in approximately three percent of cases [41]. Albuminocytologic dissociation, commonly found in both GBS and Miller-Fisher syndrome, was found in one patient's CSF.

Clinical Outcomes: A review of 118 concurrent COVID-19 and GBS cases across 23 countries revealed a male predominance, with 67% of patients being male. 30% of cases resulted in poor outcomes and 6% in deaths. Most patients (75%) received intravenous immunoglobulin (IVIG), 8.5% received plasmapheresis, and 6.8% received some combination of both treatment modalities [92]. Another study found that 23.8% of patients were admitted to the hospital for COVID-19 and either developed GBS during hospitalization or were discharged and later readmitted due to neurologic symptoms. Most patients (76.2%) presented to the hospital with neurologic symptoms and during admission tested positive for SARS-CoV-2 infection. Respiratory failure was seen in 33.3 percent of cases. Furthermore, GBS was ascribed as the main in half of these cases. The median time of follow up was 14 days, with 18.9% reporting complete recovery, 62.1% reporting some or significant improvement in symptoms, and 10.8% of patients reporting no improvement [93]. Patients with polyneuropathy have also been found to develop sensory ataxia.

Observations of ICUAW have been seen in the post-acute phase. A case series followed 21 patients admitted to a rehabilitation center after hospitalization due to COVID-19. Strikingly, 90.5 percent of patients had clinical deficits suggestive of neuromuscular disease. 89.5 percent of patients were found to have abnormalities on EMG and NCS. ICUAW, particularly CIM, was the most common disorder among these patients. Two patients were found to have GBS [94].

COVID-19 associated myoclonus was accompanied by confusion and/or delirium [41]. One case of new-onset rigid-akinetic Parkinsonism was preceded by generalized myoclonus. Patients with myoclonus-opsoclonus-ataxia syndrome have shown improvement following IVIG administration. Myoclonus has also successfully been treated with antiepileptics (levetiracetam) and benzodiazepines (clonazepam).

Pathophysiology: In the case of Campylobacter jejuni induced GBS, a cross-reaction between antibodies against the bacterium's lipo-oligosaccharide surface epitopes and peripheral nerve glycolipids is thought to be responsible for patient neurologic deficits [86]. Antiganglioside antibodies including anti-GM2 have been implicated as the etiology of CMV induced GBS [40]. Yet, in the case of SARS-CoV-2, no known homology between viral and human proteins exists, making molecular mimicry less likely. Researchers have speculated that post-translational modifi-

cation of viral proteins by host cells may allow for significantly homologous and immunogenic SARS-CoV-2 proteins to arise. A link between GBS and another betacoronavirus, Mers-CoV, has been speculated [95]. Acute inflammatory demyelinating polyradiculopathy (AIDP), a motor and sensory demyelinating disorder, is the most common subtype of GBS observed in patients with COVID-19. Other subtypes, however, including rare variants such as Miller-Fisher syndrome, have also been observed [92].

ICUAW is subdivided into two major categories: critical illness polyneuropathy (CIP) or CIM with CIM being more commonly observed [42,43]. CIM is characterized by the selective loss of myosin causing myofiber atrophy and death while CIP is a result of peripheral nerve axonal dysfunction and death, importantly, without a major demyelinating component as seen in GBS. The cause of these pathological processes is not fully understood, however systemic inflammation, prolonged immobilization, and metabolic aberrations have all been proposed.

The first case report of COVID-19 as a cause of CIM was reported on a patient who had failed several spontaneous breathing trials after intubation. NCS were not consistent with GBS and CIP, favoring the diagnosis of CIM. The authors of this report warned that as cases continue to require long-term ventilation, more cases of ICUAW would be seen [44]. Muscle biopsies taken from 3 patients with CIM demonstrated degenerative processes without signs of autoimmune or vascular etiology. These findings were suggestive of direct viral damage, as has been observed with other viral infections including Influenza [45].

Myoclonus, which has previously been shown to occur following hypoxic or metabolic brain insults, frequently co-occurred with encephalopathy [41]. Encephalopathy, as previously discussed, is also commonly found with hypoxia. One possible pathophysiologic mechanism of COVID-19 associated myoclonus is a cross-reaction between anti-viral antibodies and brain stem or cerebellum neuronal proteins.

Discussion: A link between COVID-19 and autoimmune neuromuscular diseases has been difficult to establish. It is challenging to distinguish respiratory failure due to GBS from COVID-19 associated lung disease. Elzouki *et al*. [92] found that in the majority of cases of respiratory failure, GBS was the ascribed etiology. COVID-19 has been shown to bind sialic acid-containing glycoproteins and gangliosides, including those found in peripheral myelin [96]. Spike-protein bound gangliosides may have epitopes that are shared with peripheral nerve cell membrane sugar residues, raising the possibility of cross-reactivity due to molecular mimicry, an established mechanism of Campylobacter jejuni and Zika virus associated GBS [96]. However, it should also be noted that antibodies commonly associated with GBS, and related pathologies have not been found in most cases of COVID-19 associated GBS, suggesting another mechanism entirely may be at play [97].

An important facet of potential neuromuscular disease in the spectrum of COVID-19 complications is ICUAW given both the intense immunologic response and the extended hospitalization severe disease confers. *In vitro* models have shown that sera from CIM patients induce depolarization of muscle cell resting membrane potential, decrease time to action potential peak, and increase inward sodium current amplitude. This is thought to be in part due to prolonged cytokine induced depolarization, which reduces membrane excitability and the deceleration of muscle fiber conduction velocity [46]. This may help to explain the high degree of spontaneous activity measured on EMG reported previously [45]. A case series described two patients with COVID-19 pneumonia requiring intensive care treatment who went on to develop severe proximal weakness in all 4 limbs. Both patients were found to have elevated serum creatine kinase, indicating muscle damage, as well as elevated markers of inflammation (CRP and IL-6). These markers gradually normalized and both patients made partial recoveries in muscle strength after 6–8 weeks of rehabilitation. However, both patients reported persistent fatigue during physical activity [47]. A limitation of the reported studies here is that patients requiring standard intensive care treatment for severe COVID-19 disease receive medications (e.g., glucocorticoids and neuromuscular blocking agents) that have been proposed, though not conclusively shown, to be risk factors for developing ICUAW [98]. Regardless, the mechanistic findings from these and other studies should spur additional research and help clinicians identify cases and start appropriate rehabilitation.

## 9. Depression, Anxiety and Sleep Disorders

Incidence: COVID-19 has been associated with a significant increase in mental health disorders. A meta-analysis of 31 studies of infected patients found 45%, 47%, and 34% prevalence of depression, anxiety, and sleep disorders, respectively [99]. Mazza *et al*. [48] surveyed 402 COVID-19 survivors one-month post-discharge, finding that 55.7% of respondents scored in the clinical range of at least one psychiatric domain that included depression, anxiety, OCD, or PTSD. A retrospective cohort study of 273,618 COVID-19 survivors found that anxiety and depression are the most frequently cited complaints (22.82%), occurring more frequently 3 to 6 months post-infection [100]. Researchers found that females and younger patients were more predisposed to anxiety and depression.

Clinical Outcome: The majority of infected patients suffering from depression, anxiety, and sleep disorders have mild symptoms [99]. Mild depression (33%) had the highest prevalence, followed by moderate (14%), and severe (7%) depression. Similar trends existed for both anxiety and sleep disorders. The prevalence of mild, moderate, and severe anxiety was 29 percent, 12 percent, and 6 percent, respectively. The prevalence of mild, moderate, and severe sleep disturbances was 20 percent, 16 percent,

and 2 percent, respectively. Though mild symptoms predominated, moderate and severe depression were still more prevalent in infected patients than general society, in which the prevalence of moderate and severe depression is 5.1 percent and 1.5 percent, respectively. However, suicidality has not been shown to have necessarily increased during this pandemic, with a number of studies even finding instead an apparent decrease in the frequency of suicide attempts and self-harm [101].

Pathophysiology: Social isolation during the pandemic has been posited as exacerbating chronic mental illness [102]. This phenomenon has been described previously in the context of other viral outbreaks, including other coronaviruses [49]. Depression and anxiety are commonly reported symptoms that persist beyond the infectious stage of COVID-19. It has been observed that pro-inflammatory cytokines such as IL-6 are elevated in individuals with major depressive disorder [50]. Elevation of inflammatory biomarkers has been associated with severity of depression and PTSD, as reported in another study [51]. Yet, another study failed to find a significant association between depressive symptom severity and inflammatory markers [48]. Baseline inflammatory markers, such as CRP, were not shown to be significantly associated with depression, anxiety, or insomnia. However, the systemic-immune inflammation index (SII) (SII = platelets X neutrophils/lymphocytes) was associated with depression and anxiety at follow-up. These contradictory results suggest the need for additional research to elucidate the mechanistic details of the impact of COVID-19 on these neuropsychiatric disorders. Furthermore, there are several literature reports including review articles that detail a general impact the pandemic has had on patients with preexisting mental health issues. The vulnerability of these patients with added stress factors such as social isolation and overstretched general and mental healthcare have been identified as factors exacerbating conditions such as anxiety and depression and other neuropsychiatric disorders such as Wilson Disease [103,104].

Discussion: Depression and anxiety have been reported in many COVID-19 patients months post-infection. This pandemic has introduced numerous stressors into the lives of countless individuals. The social isolation and decreased access to mental health services experienced by the general population may have contributed to the increased incidence of anxiety, depression, and sleep disorders found in COVD-19 patients. Though certain studies have suggested that a pro-inflammatory state is conducive towards general depression, a firm consensus has not been reached. Evidence regarding the link between the COVID-19 inflammatory state and the associated depression has also been contradictory. Furthermore, it is unclear at this time whether incidence of suicidal behaviors actually increased over the course of the pandemic.

## 10. Seizure

Incidence: Seizure, including status epilepticus and epileptiform discharges on electroencephalogram (EEG), has also been reported in the setting of COVID-19. In a study of EEG changes of infected patients admitted to the ICU, epileptiform discharges were identified in 37.9 percent of patients [105]. EEG abnormalities were detected in 93.1 percent of patients and specific abnormalities, including sharp, spike, and multi-spike, and ictal discharges, were detected in 37.9 percent of patients. Several studies, however, found the incidence of COVID-19 associated acute seizure to be less than one percent [106]. Further research is needed to accumulate evidence of COVID-19 induced epilepsy.

Clinical Outcome: Studies have found that 8 to 35 percent of patients with epilepsy who contracted COVID-19 experienced an increase in seizure frequency [106]. Yet, data from another study did not support a similar increase. Since older individuals are generally at greater risk of severe COVID-19 illness, it is important to note that one study with the lowest incidence of exacerbation underrepresented the proportion of elderly individuals in the sample.

Pathophysiology: Association of a history of clinical seizures, epilepsy, and stroke with specific EEG findings has been demonstrated in COVD-19 patients in intensive care [105]. The study shows that patients with chronic diseases such as hypertension and diabetes had abnormal EEG findings. A multifactorial etiology of seizure in infected patients is likely, as studies have found hypoxemia, multiorgan failure, and metabolic derangements to be present in many infected patients with seizure [52]. Two patients with encephalitis (SARS-CoV-2 RNA positive CSF) have also developed seizures. However, direct neuroinvasion as a cause of seizure is currently controversial, with a number of studies failing to find viral RNA in CSF. Elevated levels of inflammatory cytokines, including IL-6, IL-1$\beta$, and TNF-$\alpha$, have been found in patients following acute febrile seizures and a dysregulated cytokine surge in response to COVID-19 infection has been proposed as a possible etiology of seizure [1].

Discussion: Abnormal EEGs have been reported as a common finding in patients with COVID-19. This has been observed more frequently in those with a prior history of seizures. One meta-analysis of hospitalized patients' EEGs found a 20.3 percent prevalence of epileptiform discharges. This proportion was higher in infected patients with a history of epilepsy or seizures than in those without such a history (59.5% vs. 22.4%). Abnormal background activity was seen in 96.1% of all patients. The authors commented that patients who underwent such studies largely had altered mental status (68.4%) and that EEG changes, at least in part, may be explained by underlying severe illness [107]. Clinical seizures and status epilepticus, though much less frequently reported, have been the presenting feature of COVID-19. Clinicians should consider EEG moni-

toring critically ill patients with altered mental status and/or history of epilepsy.

## 11. Conclusions

The precise pathophysiology behind the COVID-19 associated disorders detailed above is multifaceted. Across the spectrum of these neurological sequelae exists a common theme of neurotropic invasion and concomitant systemic inflammation. Inflammation, hypercoagulation, and endothelial dysfunction are thought to contribute heavily to the evolution of acute ischemic stroke. Several studies have demonstrated greater mortality in COVID-19 associated stroke [15,54,108]. Interestingly, COVID-19 associated stroke was not found to result in worse functional outcomes. The elevated mortality rate among the infected may be due to virus-induced comorbidity.

Pulmonary dysfunction leading to poor oxygenation of the brain may explain encephalopathy in the acute phase. However, other hypotheses have been proposed. Viral invasion of the CNS, mass release of cytokines, and intracranial endothelial damage have all been implicated as potential etiologies of encephalopathy. Encephalitis has similarly been linked to neuroinvasion, possibly via the olfactory tract, and has been found to be a largely self-limiting condition that responds well to corticosteroids.

Headache, the most common non-specific neurological symptom found in COVID-19 patients may persist more than four weeks post infection, as in the case of long COVID. Activation of trigeminal nerve endings, overproduction of pro-inflammatory cytokines, direct CNS invasion, as well as virus mediated hypercoagulation and hypoxia all have been invoked as possible mechanisms.

GBS and related autoimmune polyneuropathies have been observed in a number of patients with COVID-19. Although a causal link has not been established between SARS-CoV-2 infection and GBS, molecular mimicry as a potential mechanism cannot be excluded. Similarly, IUAW and related neuromuscular diseases have also been reported in COVID-19 patients. Given the extended hospitalization patients with severe disease face, these findings are not entirely surprising. Cytokine overproduction has been shown to cause prolonged muscular depolarization and is therefore a likely mechanism in COVID-associated ICUAW and its subtypes.

As the COVID-19 pandemic evolves ultimately reaching the endemic stage, a significant number of patients will likely encounter Long COVID. A majority of these patients will not be sick enough to be hospitalized. Considering some of the symptoms associated with long COVID are highly subjective and may resemble chronic fatigue or fibromyalgia, a more in-depth knowledge and awareness of the multiorgan nature of these symptoms will ensure proper care of the survivors. Nonetheless, COVID-19 research is a rapidly shifting landscape in which the clinical observations of today may pave the road to advanced therapeutics, enhanced disease management, and improved overall outcomes.

## Abbreviations

SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; COVID-19, Coronavirus Disease 2019; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; TF, tissue factor; ACE-2, angiotensin-converting enzyme-2; S, spike protein; DIC, disseminated intravascular coagulation; OR, odds ratio; PFU, plaque-forming units; MA15, mouse-adapted SARS-CoV; IMMs, inflammatory monocyte macrophages; vWF, von Willebrand factor; GBS, Guillain-Barre syndrome; ICUAW, ICU-Acquired Weakness; CVST, Cerebral venous sinus thrombosis.

## Author Contributions

DJA conceived of, contributed to, and edited this paper; SJA wrote and compiled the manuscript in collaboration with co-authors CMF, JPV, and AJK.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

We thank our anonymous reviewers for taking the time out of their schedules.

## Funding

This research received no external funding.


## Conflict of Interest

The authors declare no conflict of interest.

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