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Neurologic complications of COVID-19

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ABSTRACT

Background: Much of the focus regarding the global pandemic of coronavirus disease of 2019 (COVID-19) has been on the cardiovascular, pulmonary, and hematologic complications. However, neurologic complications have arisen as an increasingly recognized area of morbidity and mortality.
Objective: This brief report summarizes the neurologic complications associated with COVID-19 with an emphasis on the emergency medicine clinician.
Discussion: COVID-19 has infected over 3.5 million people and killed over 240,000 people worldwide. While pulmonary complications are profound, the neurologic system is also significantly impacted, with complications including acute cerebrovascular events, encephalitis, Guillain-Barré syndrome, acute necrotizing hemorrhagic encephalopathy, and hemophagocytic lymphohistiocytosis. Additionally, patients on immunosuppressive medications for pre-existing neurologic issues are at an increased risk for complications with COVID-19 infection, and many of the currently proposed COVID-19 therapies can interact with these medications.
Conclusions: When caring for COVID-19 patients, emergency medicine clinicians should be aware of the neurologic complications from COVID-19.

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1. Introduction

First appearing in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease of 2019 (COVID-19), which the World Health Organization (WHO) declared a pandemic in March 2020 [1]. As of May 1, 2020, the COVID-19 pandemic has resulted in over 1 million cases and 62,406 deaths in the United States, and over 3.5 million cases and 240,000 deaths worldwide [1-3]. Despite the majority of the focus being placed on pulmonary and cardiovascular complications, emergency medicine clinicians must remain cognizant of the neurologic complications, which can present subtly and add substantially to the morbidity and mortality [4-7]. The following article reviews the neurologic complications from COVID-19, with an emphasis on the emergency medicine clinician.

2. Methods

Authors searched PubMed and Google Scholar for articles using the keywords "COVID-19", "SARS-CoV-2", "neurologic", "brain", "cerebral", "cerebrovascular accident", "HLH", "hemophagocytic lymphohistiocytosis", "stroke", "altered level of consciousness", "decreased level of consciousness", "encephalopathy", "cerebrovascular disease". Authors included case reports, retrospective studies, prospective studies, systematic reviews and meta-analyses, clinical guidelines, and narrative reviews focusing on COVID-19 and neurologic effects and complications. Preprinted articles were also included. The literature search was restricted to studies published in English. Emergency medicine physicians with experience in critical appraisal of the literature reviewed all of the articles and decided which studies to include for the review by consensus, with a focus on emergency medicine-relevant articles. A total of 60 articles were selected for inclusion.

3. Discussion

3.1. Pathophysiology and clinical features

A member of the beta-coronaviridae family, SARS-CoV-2 is an enveloped, non-segmented, single-stranded, positive-sense RNA virus [8-10]. The mechanisms by which SARS-CoV-2 causes neurologic damage are multifaceted, including direct damage to specific receptors, cytokine-related injury, secondary hypoxia, and retrograde travel along nerve fibers [11-15]. Much like its expression on lung epithelial cells, the expression of angiotensin converting enzyme 2 (ACE2) on endothelial cells of the blood-brain barrier can allow viral binding at this important site, facilitating viral entry into the central nervous system by attacking the vasculature [16,17]. The binding of SARS-CoV-2 at the pulmonary epithelial cells also generates a global systemic inflammatory response (SIRS), producing increased levels of interleukin (IL)-6,

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IL-12, IL-15, and tumor necrosis factor alpha (TNF-α); activating glial cells; and producing a massive pro-inflammatory central nervous system state [13]. In particular, IL-6 levels have been correlated with increased disease severity in COVID-19 [11-13]. These systemic effects combined with localized lung alveolar damage result in severe hypoxia, which can lead to cerebral vasodilation and may decompensate into cerebral edema and ischemia [13,14]. Finally, SARS-CoV-2 travels retrograde along the olfactory nerve and bulb, which provides an avenue between the nasal epithelium and the central nervous system and may also explain the common complaint of anosmia [15].

The prevalence of neurologic symptoms in COVID-19 patients has become more apparent, though pre-existing neurologic conditions have been linked to more severe COVID-19 infections [4-7,18]. In a recent review of patients diagnosed and hospitalized with COVID-19, 8% of the 4014 patients had pre-existing neurologic diseases, though this analysis mainly focused on those with prior strokes [6]. Interestingly, patients with prior neurologic conditions have less improvement of respiratory symptoms over their first 10 days of hospitalization and had a significantly increased risk of developing acute respiratory distress syndrome as compared to controls without neurologic disease [19,20]. In a separate cohort of 179 patients with SARS-CoV-2 pneumonia, pre-existing cerebrovascular disease was also found to be associated with increased mortality [21]. A similar mortality trend has been demonstrated in those with Parkinson's Disease [22]. A systematic review and meta-analysis also identified a 2.5-fold increased risk of severe infection among patients with a prior stroke [23].

While pre-existing neurologic conditions portend worse outcomes, the incidence of neurologic complications secondary to SARS-CoV-2 infection is also substantial. Among hospitalized COVID-19 patients, neurologic complications range from 6% to 36% [18,24]. Additionally, hypoxic ischemic encephalopathy was reported in 20% of patients in one series [25]. Focused efforts are also investigating the neurotropism of SARS-CoV-2 to account for the devastating brainstem-mediated complications in both the cardiovascular and pulmonary systems [16,26] (Fig. 1).

3.2. Neurologic complications associated with COVID-19 infection

3.2.1. Acute cerebrovascular disease

Acute cerebrovascular disease remains one of the more common and serious neurologic complications seen in COVID-19 populations. However, this final common manifestation has a multifactorial etiology. SARS-CoV-2 causes a global inflammatory response and a hypercoagulable state evidenced by increased D-dimers, prolonged prothrombin time, and disseminated intravascular coagulation [20,27]. In an Italian cohort of COVID-19 patients admitted with confirmed infection, the rate of ischemic stroke was 2.5%, despite venous thromboembolism prophylaxis on admission [28]. In comparison, the rate of ischemic stroke in hospitalized COVID-19 patients in China was estimated to be as high as 5% [24]. Similarly, there was a 3.7% incidence of ischemic stroke in Dutch COVID-19 patients in the intensive care unit (ICU) despite venous thromboembolism prophylaxis [29]. Interestingly, COVID-19 has also led to younger patients presenting with ischemic stroke, including large vessel occlusions [30]. Additionally, COVID-19 patients can develop significant hypoxia leading to decreased cerebral oxygenation and infarcts, particularly in those with pre-existing cerebrovascular disease [13,14]. Infection, inflammation, and hypercoagulable states can further increase the risk of ischemic stroke, which can be even more pronounced in older patients [31-33].

When evaluating COVID-19 patients with stroke-like symptoms, it is important to protect the healthcare team while expediting this time-sensitive emergency. The American Heart Association has addressed this with guidelines for a protected code stroke, emphasizing screening guidelines, personal protective equipment, and crisis resource management [34]. However, once diagnosed with ischemic stroke, patients should still receive the standard of care based on their institution with consideration of intravenous thrombolytic medications and endovascular thrombectomy in the appropriate clinical scenarios, without any alteration to intervention criteria [35,36].

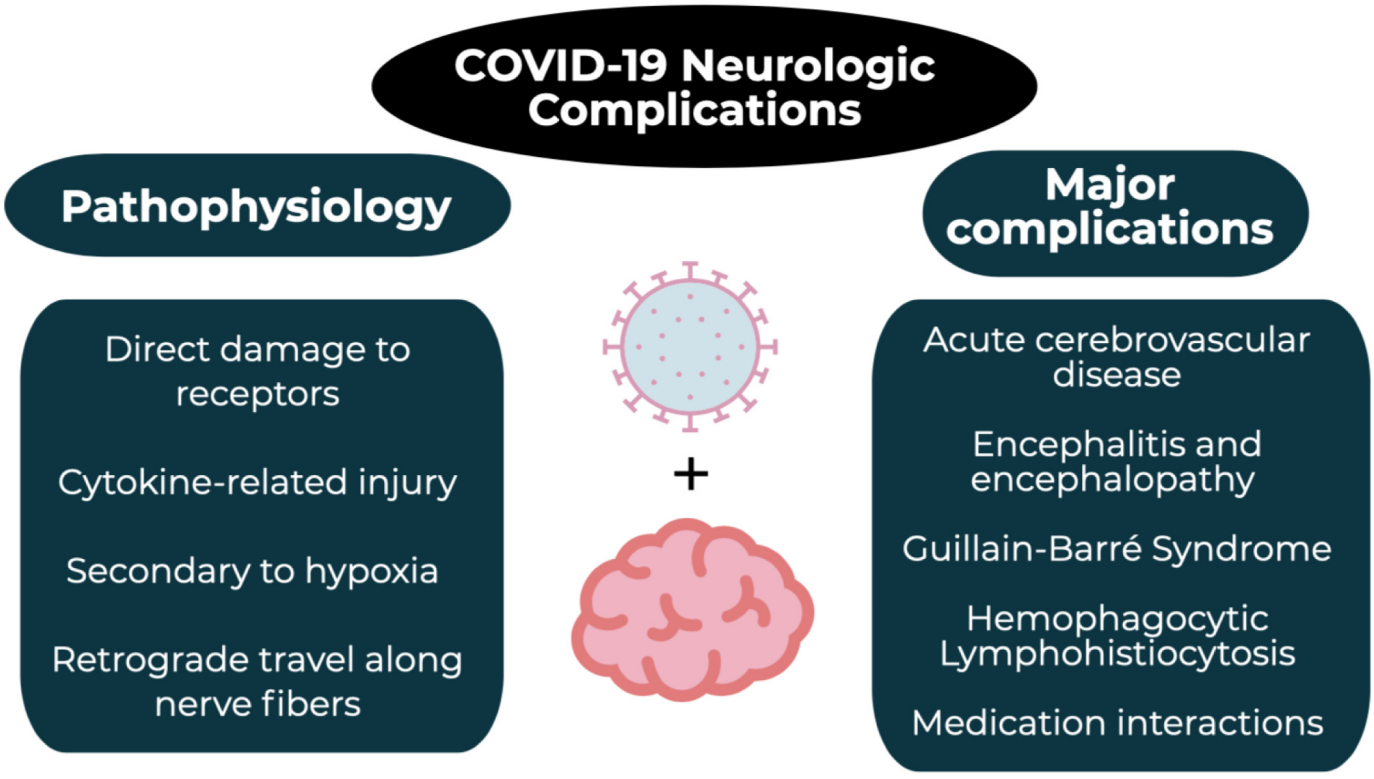

Fig. 1. COVID-19 and the neurologic system.

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3.2.2. Encephalitis and encephalopathy

Encephalitis is characterized by acute onset of fever, vomiting, seizures, and decreased or changed consciousness [37]. While rare, SARS-CoV-2 encephalitis has been reported in several cases, though this was based on clinical and imaging findings as there has been no cerebral spinal fluid (CSF) evidence of SARS-CoV-2 to date [38,39]. The pathophysiology is unclear but may be related to edema secondary to inflammatory injury versus direct viral infection [39]. Similar to other cases of encephalitis, aggressive supportive care and treatment of increased intracranial pressure are paramount.

Acute necrotizing encephalopathy (ANE) is a rare neurologic complication caused by cytokine storm and damage to the blood-brain barrier [40]. Unlike other viral central nervous system infections, demyelination is not present in ANE [38]. Non-contrast head computed tomography (CT) can initially demonstrate symmetric, multifocal lesions, while magnetic resonance imaging (MRI) with T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) may show hyperintense signal and internal hemorrhage [41]. The thalamus, brainstem, cerebellum, and cerebral white matter are the most common areas affected [41]. While this is more commonly associated with influenza or Zika infection, SARS-CoV-2 has also been associated with this condition [13]. The pathogenesis of ANE is poorly understood, but with the hyperinflammatory state, treatment with intravenous immunoglobulin (IVIG) and steroids can be attempted [42,43].

3.2.3. Guillain-Barré Syndrome (GBS)

GBS is a symmetric, ascending flaccid paralysis, often preceded by respiratory or gastrointestinal infections from a virus or bacteria [44]. This progressive neuropathy has recently been linked to SARS-CoV-2 infection, with 5 cases reported in Italy and 2 additional cases from Wuhan, China [45-47]. All patients experienced a prodrome of an upper respiratory infection ranging from 5 to 14 days prior to the development of symmetric weakness, with 3 patients developing respiratory failure [45-47]. All patients had a positive nasopharyngeal polymerase chain reaction (PCR) test and chest imaging characteristic of SARS-CoV-2, but all cerebrospinal fluid (CSF) samples had a negative SARS-CoV-2 PCR [45-47]. While all of the patients received IVIG, those who developed respiratory failure had poor outcomes [45]. Interestingly, brain and spine MRI did not show abnormalities in half of the patients, highlighting the importance of consultation and additional testing, such as nerve conduction studies, when there is a high clinical suspicion even in the absence of radiographic findings [45-47].

3.2.4. Hemophagocytic Lymphohistiocytosis (HLH)

HLH is a severe dysregulation of T-lymphocyte, natural killer cell, and macrophage over-activation causing a massive cytokine storm and multiorgan injury [48]. This condition is often secondary to hematologic malignancy, immunosuppression, or critical infection, but has also been described in patients with SARS-CoV-2 [48]. HLH patients present with unremitting fevers, pancytopenia, coagulopathy, hepatic dysfunction, hypertriglyceridemia, and an elevated ferritin [48-50]. HLH is an underrecognized complication among COVID-19 patients as the innate immune system may result in uncontrolled cytokine storm, characterized by severely increased levels of IL-2, IL-6, IL-7, and TNFα. Up to one-third of COVID-19 patients with HLH develop neurologic abnormalities. Early recognition and scoring with the HScore allows for prompt consideration of immunosuppressive treatments (Table 1); an HScore of 200 predicts an 88% probability of HLH, while a score of 130 predicts a 9% probability of HLH [51]. Treatments include steroids and tocilizumab, both of which are currently under investigation for treatment in COVID-19 patients [51].

Table 1
HScore.

Category	Number of points
Temperature	
<38.4 °	0
38.4–39.4 °C	33
>39.4 °C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides	
<1.5 mmol/L	0
1.5–4.0 mmol/L	44
>4.0 mmol/L	64
Fibrinogen	
>2.5 g/L	0
</=2.5 g/L	30
Ferritin	
<2000 ng/mL	0
2000–6000 ng/mL	35
>6000 ng/mL	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Hemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression	
No	0
Yes	18

3.3. Medication interactions

Many of the recently proposed medications have significant drugs interactions and side effects [4]. Azithromycin, corticosteroids, plasma exchange, biologic agents (tocilizumab), antivirals (e.g., remdesivir, ribavirin, lopinavir/ritonavir, favipiravir), and antimalarials (e.g., hydroxychloroquine, chloroquine) are all currently under investigation, with a recent announcement for an accelerated trial devoted to remdesivir [52-54]. Lopinavir/ritonavir and azithromycin interact with many common medications in patients with prior strokes including antihypertensives, antiplatelets, statins, and anticoagulants [52-55]. These also carry an increased risk of neurocognitive impairment in longer courses [55-57]. Ribavirin and interferon alpha have both neuropathic and neuropsychiatric sequelae, while interferon caries a risk of retinopathy [58,59]. Similarly, antimalarials also carry the risk of neuropsychiatric side effects and less commonly ataxia, seizures, and limbic encephalitis [60]. A complete summary of mechanism of action, neurologic effects, and medication interactions can be found in Table 2.

4. Limitations

There are several limitations of this current literature review evaluating neurologic complications and effects connected to COVID-19. These include potential risk of bias, low patient numbers largely based on case reports, as well as heterogeneity in study design, outcomes, comparators, and patient populations. In this time of ultimate knowledge translation, a substantial portion of the literation is released as preprint without complete peer review; this highlights the need for further data to delineate these neurologic manifestations and complications secondary to SARS-CoV-2.

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Table 2
Medications and the nervous system.

Medication	Mechanism	Neurologic effects and medication interactions
Remdesivir	Nucleotide-analog inhibitor of RNA polymerases	- Unknown
Ribavirin	RNA and DNA virus replication inhibitor	- Interacts with anticoagulants - Neuropathy
Lopinavir/Ritonavir	Lopinavir inhibits protease Ritonavir inhibits CYP3A metabolism	- Interacts with anticoagulants, antiplatelets, statins - Cognitive and motor disturbances
Favipiravir	Inhibits RNA-dependent RNA polymerases	- Interacts with anticoagulants, statins, antiarrhythmics
Chloroquine and Hydroxychloroquine	Endosomal/organelle pH modifications	- Neuropsychiatric side effects - Ataxia, seizures
Azithromycin	Binds to 50s ribosome, inhibiting protein synthesis	- Interacts with anticoagulants, statins, antiarrhythmics
Interferon	Activates immune system	- Neuropsychiatric side effects - Retinopathy - Neuropathy
Methylprednisolone	Inflammation reduction	- Interacts with anticoagulants - Delirium
Tocilizumab	IL-6 inhibitor	- May increase medication metabolism (e.g., statins)

RNA, ribonucleic acid; DNA, deoxyribonucleic acid; IL, interleukin.

5. Conclusions

Significant neurologic complications are associated with COVID-19, such as impaired level of consciousness, cerebrovascular disease, encephalitis, encephalopathy, and GBS. Some of the medications utilized to treat COVID-19 also have potential neurologic effects and may interact with medications of pre-existing neurologic disease. Emergency medicine clinicians must be cognizant of these neurologic complications when treating COVID-19.

Conflicts of interest

None.

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