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Neurological Implications and Sequelae of COVID-19: A Brief Literature Review

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ABSTRACT

Coronavirus disease (COVID-19) is an infectious viral zoonotic disease that emerged in late 2019 with the index case reported in Wuhan, China. The etiology of this disease is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since 2019, it has spread rapidly worldwide and was declared a pandemic in March 2020 by the World Health Organization. As of May 2023, the number of confirmed cases has been over 750 million worldwide. While the main presenting signs and symptoms are respiratory and gastrointestinal, recent reports suggest that more than 35% of the infected individuals developed neurological symptoms during the acute phase or post recovery. The pathophysiology involved in the neurological complications include overt damage to specific receptor sites mediated by cytokines, secondary hypoxia and retrograde axonal transport. Neurological complications range from Acute cerebrovascular disease, encephalitis, and Guillain Barret Syndrome to fatigue, anosmia and ageusia. The objective of this article is to briefly review the literature about the neurological manifestations and complications of COVID-19 to educate primary care clinicians about the possible neurological sequelae of this disease.

Keywords: Neurological; COVID-19; SARS-CoV-2; Coronavirus; Sequelae; Complications

Introduction

Coronavirus disease (COVID-19) is an infectious viral zoonotic disease that emerged in late 2019 with the index case reported in Wuhan, China. The etiology of this disease is the SARS-CoV-2. Since 2019, it has spread rapidly worldwide and was declared as a pandemic in March 2020 by the World Health Organization. As of May 2023, the number of confirmed cases has been over 750 million worldwide. (Franke, et al. [1]). While COVID-19 typically manifests with respiratory and gastrointestinal symptoms, like cough, respiratory distress, fever, fatigue, diarrhea and vomiting, recent reports suggest that more than 35% of those individuals infected with COVID-19 develop neurological symptoms during the acute phase or post recovery. The reported neurological signs and symptoms which may include concentration and memory deficits, headache, fatigue, vertigo, neuropathy, myalgias, anosmia and ageusia (Franke, et al. [1]).

Search Method

Google Scholar was used to search keywords, "Coronavirus", "neurological", "COVID-19", SARS-CoV-2, "implications", "sequelae", and "complications" for this review. The search was performed on 20th May 2023 and was limited to English manuscripts published from 2019 to present and yielded literature reviews, meta-analyses, case reports, retrospective studies, systematic reviews and clinical guidelines.

Pathophysiology

The means by which COVID-19 causes neurologic damage is complex and includes overt damage to specific receptor sites, cytokine related injury, secondary hypoxia and retrograde axonal transport (Bridwell, et al. [2]). The expression of high affinity ACE2 receptors by the endothelial cells make the lungs and blood brain barrier vulnerable sites of attack. The cell bodies of neurons also express ACE2 receptors.

The retrograde axonal transport along the olfactory nerves provides a potential explanation for the common complaint of anosmia and may provide a portal of entry to the central nervous system (Bridwell, et al. [2]). Current research suggests possible pathways of COVID-19 entry into the central nervous system to be either via hematologic pathways or through peripheral nerves (Mahalakshmi, et al. [3]). It is suspected that via the hematologic route, COVID-19 invades white blood cells and enters the blood stream, eventually breaching the blood brain barrier (BBB). Many experimental animal studies have yielded evidence that the spread of COVID-19 from the respiratory tract to the central nervous system occurs via retrograde axonal transport from peripheral nerves, especially, the olfactory nerves. (Mahalakshmi, et al. [3]).

Neurological Sequelae of COVID-19

One of the more common and serious neurologic complications of COVID-19 is Acute Cerebrovascular Disease (ACVD), caused by a disseminated inflammatory response and hypercoagulable state. Elevated D-dimers, prolonged clotting times and disseminated intravascular coagulation are all thought to play roles in the progression to ACVD, and not just in the elderly population, as COVID-19 has also been implicated in ischemic stroke presentation in younger populations as well (Bridwell, et al. [2]). COVID-19 is thought to increase D-dimers in the blood, capable of precipitating thrombotic vascular events. Prior studies have yielded cases of secondary cerebral infarction, raising suspicion that COVID-19 may induce cerebral venous/arterial infarctions (Wang, et al. [4]). While direct viral invasion of the CNS has certainly been of concern in the neurological sequelae of COVID-19, para-infectious neurological diseases have also been implicated.

Specifically, Guillain-Barre Syndrome (GBS) and encephalopathy have been identified in COVID-19 patients (Needham, et al. [5]). GBS, with its hallmark of ascending flaccid paralysis, has been linked to COVID-19 infection, with patients typically reporting upper respiratory symptoms 5-14 days prior to the development of weakness (Bridwell, et al. [2]). Additionally, GBS patients, following COVID-19 infection, appear to experience more long term neurological effects, including fatal outcomes in some cases (Camargo Martínez, et al. [6]). Encephalitis is suspected to be secondary to inflammatory injury precipitated by the disease, rather than direct viral infection (Bridwell, et al. [2]). A recent study suggests that patients who develop encephalopathy secondary to COVID-19 have a worse prognosis and a much lower survival rate (Camargo Martínez, et al. [6]). Another study found that more than one third of patients experienced altered consciousness and delirium during the acute phase of the disease (Camargo Martínez, et al. [6]).

Peripheral Nervous System (PNS) manifestations of COVID-19 appear to be less severe, with the most common PNS symptoms being anosmia and ageusia which typically occur suddenly (Niazkar, et al. [7]). These symptoms are present in either the asymptomatic population or as initial presentation of the virus with no other associated findings which suggests that people with such symptoms should isolate themselves as potential carriers of COVID-19 (Niazkar, et al. [7]). Furthermore, numerous cases of COVID-19 associated epilepsy have been reported. These cases were recurrent transient generalized tonic-clonic seizures, with patients having no personal or family history of seizure disorders (Niazkar, et al. [7]). Hypothetical pathogenesis of COVID-19 induced epilepsy include the release of inflammatory cytokines and the granulocyte colony-stimulating factor, both of which may promote neuronal hyperexcitation via activation of glutamate receptors (Niazkar, et al. [7]). While some researchers believe seizures to be secondary to encephalitis, no definitive research currently exists to confirm that COVID-19 can cross the BBB. Others theorize that seizure activity could also be related to adverse drug reactions of antiviral medications used to treat COVID-19 (Niazkar, et al. [7]).

Conclusion

While COVID-19 predominantly manifests with respiratory and gastrointestinal symptoms, neurological sequelae cannot be ignored and may procure significant complications if not identified early. Clinicians should be aware and remain cognizant of the wide spectrum of neurological complications associated with COVID-19, to promote early diagnosis and intervention, especially in the context of life threatening manifestations.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Ethic Statement

This article does not contain any studies involving human participants performed by the authors.

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