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COVID-19 Pandemic and Neurological Disease: A Critical Review of the Existing Literature

Shervin Assari[1*]

[1]Department of Family Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, CA 90059, USA

***Corresponding Author:** Shervin Assari, M.D., M.P.H., Department of Family Medicine, Charles R Drew University of Medicine and Science, Los Angeles, CA 90059, USA. Email: +1-734-363-2678, Email: assari@umich.edu

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Abstract

Most of what we know about the coronavirus disease 2019 (COVID-19) is limited to the severe acute respiratory syndrome, epidemiology, fatality, and acute care. However, infection with COVID-19 may also involve the central nervous system (CNS), which may or may not be due to a multi-organ injury. Our aim in this paper is to briefly summarize the main aspects of the growing literature on neurological manifestations of the COVID-19 infection. As such, after mentioned some general background on the economic and medical pandemic on the populations, the healthcare system, and the society, we summarize some common aspects of the published literature on neurological manifestations of the COVID-19 infection. We also highlight the existing gaps in the literature, which requires additional work. The most common neurological manifestation of COVID-19 infection is the olfactory deficit. However, it is still unknown if it is inflammatory or degenerative in nature. Still, the incidence of neurological involvement, and also mechanisms and their treatments are unknown. This literature is predominantly composed of opinions and reviews rather than original articles, so the patients' data are not used for a majority of the studies. Multi-center studies that not only conduct chest CT or MRI but also brain CT or MRI are needed. Randomized trials are still required on the management of acute and chronic neurological conditions due to COVID-19 infection. Cohort studies may also determine the natural history of the conditions and factors that are prognostic. Furthermore, while disparities in COVID-19 infections are known, inequalities in neurological manifestations are unknown. Besides, the efficacy of specific treatments on CNS involvement is still unknown. We will discuss the health care needs of patients with chronic neurological conditions. We end the paper with a few recommendations for practice and research.

Keywords: Coronavirus Disease 2019 (COVID-19), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Neurology, Neurological Disease, Brain, Central Nervous System (CNS)

1. Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), has generated a full-blown global pandemic in 2020.[1,2] By July 2020, there have been 15 million confirmed cases of COVID-19, which includes more than six hundred thousand deaths, reported by the World Health Organization (WHO).[3] The current paper first reviews some general aspects of the pandemic and then summarizes the literature which has been published on neurological manifestations of the COVID-19. We will discuss the health care needs of patients with chronic neurological conditions. We end the paper with a few recommendations for practice and research.

2. COVID-19 Impacts the Individuals, the Health Care System, and the Society

The COVID-19 pandemic has generated societal disorder that is beyond clinics. In the US, and under Trump administration,[4] it has become a political rather than a health issue. Having masks, shot downs, and closure of bars and restaurants have been opposed by conservative parts of the county. The negative impact of the politicization of public health challenges are well known, and COVID-19 is only one example.[5]

The economic impact of the pandemic is immense.[3] Based on the World Bank estimation, COVID-19 is likely to push 71-100 million people worldwide into extreme poverty in 2020. At the same time, the global extreme poverty rate would increase by 1% from 8.23% in 2019 to 9.18% in 2020. This would be the first increase in the global extreme poverty rate since 1998. This will also effectively wipe out all the progress that the world experienced in tackling extreme poverty since 2017.[3] Most new cases who would experience extreme poverty would be concentrated in countries that are already poor (countries in South Asia, and Sub-Saharan Africa).[3]

3. Unequal Burden

The burden of COVID-19, similar to all other aspects

of health, were unequal, with the poor and minorities carrying a double burden of the diseases. COVID-19 disproportionately impacts individuals with poverty and racial and ethnic minorities.[6] It widened the gaps that already existed between the top and the bottom part of the society.[7] A large body of research has shown us that in many countries such as the US,[7] Canada,[8,9] the UK,[7] marginalized, and minority individuals were at the highest risk. Thus the effect of COVID-19 should not be reduced to people as it impacts communities, particularly communities of color.[6] While we know that COVID-19 disproportionately impacts the most vulnerable people, this is better known for the overall rate of infection and outcomes,[10] and less is known about neurological conditions.

4. COVID Impact on Mental Health

COVID-19 has resulted in a surge in suicide,[11,12] anxiety,[13] and depression.[11] It is unknown if these effects are due to the fear of the disease,[14] social isolation, unemployment,[11] economic burden, exacerbation of existing conditions, or biological changes in the brain.[15] There has also been a concern about the mental health and psychological sequels of the COVID-19 infection.[16] One of the areas that is concerning is a rise in suicide.[17,18]

5. Existing Reviews

Absullahi et al, conducted a review to summarize the evidence on the neurological symptoms of the COVID-19 infection. The authors used the following data sets MEDLINE, EMBASE, Web of Science, and Google Scholar (first 100 hits) until April 17, 2020. The key search terms used were "coronavirus" and "signs and symptoms." Authors could find 60 studies that included 11, 069 patients from which 51 studies entered to the meta-analysis. The prevalence of neurological and musculoskeletal manifestations was 35% for smell impairment, 33% for taste impairment, 19% for myalgia, 12% for headache, 10% for back pain, 10% for dizziness, 3% for acute cerebrovascular disease, and 2% for impaired consciousness. The authors concluded that clinicians should be vigilant for the diagnosis and treatment of patients with neurological symptoms.[19]

Another existing systematic review written by Asadi and Simani could only locate two articles and none of those articles were data driven. They, however, proposed that future research in the field should include[20]:

> *"Precise and targeted documentation of neurological symptoms, detailed clinical, neurological, and electrophysiological investigations of the patients, attempts to isolate SARS-CoV-2 from cerebrospinal fluid, and autopsies of the COVID-19 victims may clarify the role played by this virus in causing neurological manifestations."*[20]

Most other review studies are narrative or scoping reviews. For example, Collin Herman and colleagues searched MEDLINE/PubMed, CINAHL (EBSCO), and Scopus databases and showed that 322 of 4,014 (8.0%) of hospitalized patients diagnosed and treated for COVID-19 had a preexisting neurologic illness. They showed that four retrospective studies had linked COVID-19 to an increased risk of secondary neurologic complications in hospitalized patients (incidence rates varied from 6% to 36% across studies).[21]

6. COVID Causes Multi-organ Damage

COVID-19 generates multi-organ involvement. Comorbid conditions involving various organs, including central nervous system (CNS), are the most common risk factors for the severity of illness and mortality. Multi-organ damage may be the result of the hyperinflammatory response of the body,[22-24] which may be mainly responsible for a wide range of COVID complications. Heart failure, renal failure, liver damage, shock, and multi-organ failure have precipitated death. Acknowledging the comorbidities and potential organ injuries throughout the course of COVID-19 is crucial in the clinical management of patients. This paper aims to add to the ever-emerging landscape of medical knowledge on COVID-19, encapsulating its multi-organ impact.

Most of the research community's attention has been on overall infections, intensive care needs, treatment, development of vaccination, fatality, and policy. Severe acute respiratory syndrome, acute respiratory distress syndrome, and respiratory failure are among the main domains of studies. Lungs, and the respiratory system, however, are not the only organs involved in COVID-19. From both the epidemiological work as well as work in the clinical domain, we know more about epidemiology of respiratory conditions than other organs such as heart,[25] kidney,[26] and brain.[27]

In addition to the major respiratory distress, characteristic neurological manifestations are also described, indicating that SARS-CoV-2 may be an underestimated opportunistic pathogen of the brain. Based on previous studies of neuroinvasive human respiratory coronaviruses, it is proposed that after physical contact with the nasal mucosa, laryngopharynx, trachea, lower respiratory tract, alveoli epithelium, or gastrointestinal mucosa, SARS-CoV-2 can induce intrinsic and innate immune responses in the host involving increased cytokine release, tissue damage, and high neuro-susceptibility to COVID-19, especially in the hypoxic conditions caused by lung injury. In some immune-compromised individuals, the virus may invade the brain through multiple routes, such as the vasculature and peripheral nerves.[27]

7. Acute Neurological Conditions

There have been several studies and reports that have convinced us regarding the involvement of the CNS as a result of SARS-CoV-2 infection. SARS-CoV-2, the etiologic agent of COVID-19, can result in damage and neurologic alterations, which can be grouped into several categories. For example, some scholars have categorized the acute conditions as those that are nonspecific and moderate

symptoms such as myalgia, headache, or hyposmia to more severe symptoms such as intracranial infections or cerebrovascular disease. Based on our current knowledge, severe neurologic conditions (e.g., acute cerebrovascular disease) are rare and only occur in a minority of patients who have multiple risk factors. These severe types of neurological involvement are commonly associated with poor outcomes. Most COVID-19 patients either do not have or have minor to mild neurologic symptoms.[19,28]

Olfactory deficits. It is known that SARS-CoV-2 has the potential to injure olfactory nerve terminals in the nasal cavity. This pathology explains the observations on a decreased sense of smell in COVID-19 patients. There is still a debate on whether COVID-19 related olfactory deficits are neurodegenerative disorders such as Alzheimer's and Parkinson's diseases or are reversible inflammatory conditions.[29-31] Although olfactory deficits are not specific to COVID-19 and have been commonly reported for other viral infections including coronavirus, olfactory deficits should be regarded as one of the most common neurological manifestations of COVID-19 infection.[32] Regarding research, there are hundreds of papers that have investigated or addressed the change in the sense of smell or olfactory deficits. As such, olfactory deficits can be regarded as the most described neurological disorder due to COVID-19.

Stroke. COVID-19 is a risk factor for stroke.[33] Although some of the publications are case reports that have minimal impact on clinical care and generating guidelines,[34] there are other studies with larger samples and case series.[35] Although case series generate more reliable knowledge than case reports, they still are among the lowest levels of evidence, in the hierarchy of knowledge and evidence-based medicine.[36] We are not aware of any randomized clinical trials or cohorts on COVID-related stroke.

Encephalopathy. Patients who acquire COVID-19 may develop encephalopathy, however, this is a rare event. The SARS-CoV-2 virus does not seem to cross the blood-brain barrier. However, there have been a few cases of encephalopathy associated with the SARS-CoV-2 virus in the literature. In most cases, CSF analysis of these patients is within normal limits. The MRI findings are compatible with a diagnosis of encephalopathy in the absence of structural damage to the brain.[27]

8. Management of Neurological Disease a Challenge During the COVID Era

One of the major challenges that COVID-19 has made for the community of neurological patients is that health care system itself imposes a risk to individuals, and elective cases and non-emergency patients have been advised to reduce attending the health care system, particularly at the time of COVID-19 peaks. Health care providers are also needed to cancel some of the non-emergent care, which includes care for dementia, and some other chronic neurological conditions. As such, a large proportion of patients who required care to manage their conditions faced extra difficulty receiving care. This is well-discussed in the literature, however, most of the papers are opinion pieces that do not have survey or administrative data which could document the extend of this burden on neurological patients.[37]

9. Telehealth as the Solution

There is need to move to telemedicine and telehealth [38] for care of chronic neurological conditions so patient management for non-emergent are can be delivered from distance. This will reduce the burden to the healthcare system and reduce the risk of exposure of patients who are highly vulnerable. There are many clinics across the world that have already implemented, so there are lessons to be learned. Clinics and health care systems may share their experiences and challenges of the transition to telehealth. However, clinics widely vary in their budget, and their political and administrative support.[39] They also differ in the infrastructure that they already have in place.[40] A major challenge toward moving to telemedicine is that by canceling elective cases and surgeries, the healthcare system has been already pressed, both in terms of financial status and their human capacity. The health care system has been operating, in some parts of the world, at close to full capacity, which makes it difficult to adopt a new technology, at the middle of a health crisis.[41]

10. Deterioration of Baseline Chronic Neurological Diseases

Certain medications that have indication for a wide range of neurological conditions are immunomodulators, with little to some immunosuppression abilities, whilst others are considered definitive immunosuppressants. Receiving immunomodulators has the potential to alter the risk and course COVID-19, which operates through inflammation and change of immune function.[42]

Neuromuscular diseases. Neuromuscular diseases such as motor neuron disease and myasthenia gravis, autoimmune or inflammatory neuropathies, or inflammatory myopathies are shown to be associated with an increased risk of COVID-19 infection. The potential cause is still unknown, but most likely might be comorbid conditions as well as receiving immunosuppressive therapies.[43,44]

Multiple Sclerosis. Multiple Sclerosis is one of the conditions that can potentially deteriorate by immunomodulation due to COVID-19. In addition, the medications used by patients with multiple sclerosis may increase the risk of COVID-19 infection as well as undesired outcomes.[45] Research in this area is mainly case series and case reports.

11. Future Areas of Research

Our primary criticism of the literature on neurological disease as a function of COVID-19 infection is that this research is predominantly composed of opinions and reviews rather than original articles, so the patients' data are not used for most studies. From review papers, most are narrative, and there are very few systematic reviews.[19]

The existing systematic reviews have used a search strategy that is not comprehensive and is mainly focused on symptoms rather than disorders and treatments.[19] A minimal proportion of the small number of the data-driven papers is on the efficacy of modalities for the prevention of treatment. This literature, thus, needs to be improved in multiple ways. One review study mentioned that "*Inconsistent reporting and limited statistical analysis among these studies did not allow for assessment of comparative outcomes.*"[21]

We also highlight the existing gaps in the literature and list the areas that require additional investigation. Still, the incidence of the neurological involvement overall and based on their sub-types are unknown. We do not know what percentage of the neurologic burden in COVID-19 cases is due to general immunological responses that generate multi-organ damage and what percentage is due to the brain's specific involvement without the brain being part of the multi-organ response.

Besides, the mechanisms behind the involvement of CNS such as stroke, brain inflammation, and even loss of the sense of smell are not fully known. Although endothelial damage[46] and hyper-reactivity of the immune response are a part of the picture, we do not have a clear picture of why only some but not all patients develop neurological manifestations. Preliminary data also exist on the efficacy of treatments that block endothelial damage[46] and hyper-reactivity of immune response[47] on brain involvement of the disease.

Multi-center studies that not only conduct chest CT or MRI but also brain CT or MRI are needed. Randomized trials. Cohort studies may also determine. Furthermore, while inequalities in COVID are known, inequalities in neurological manifestations are unknown. In addition, the efficacy of specific treatments on CNS involvement is still unknown. We will discuss the health care needs of patients with chronic neurological conditions.

12. Clinical and Public Health Recommendations

Preparedness is key. Neurologists should be fully educated and prepared so they can timely reorganize their consultative practices to serve the neurologic needs of patients during this pandemic.[21]

Several neurological diagnoses to be kept in mind. As neurological manifestations of COVID-19 are not rare and are many clinicians should have a wide range of neurological conditions inn their toolkit, when they provide consultation for patients with COVID-19 infections.

Increased surveillance and monitoring of patients. Healthcare providers need to assume that patients with chronic neurological diseases such as bulbar/respiratory muscle weakness (e.g., myasthenia gravis or Lambert Eaton myasthenic syndrome) are at higher risk of contracting the infection or experiencing severe manifestations of COVID-19.

Medication profile of neurological patients is important. Aggressive screening of neurological patients particularly those who receive high dosage immunosuppressive therapies is needed.

Closer observation of patients with other risk factors. Older patients, individuals with social isolation, individuals with poverty, patients with racial and ethnic minority status, and individuals with other comorbid conditions may require some extra attention, as they are more likely to acquire the COVID-19 infection, or be prone to the undesired outcomes following an infection.

Telemedicine. The pandemic that was experienced was a call for application of telemedicine for chronic care delivery and disease management of a wide range of conditions including but not limited to neurological conditions. Policymakers should fund, equip, and educate clinics and hospitals so they can better leverage the strengths of distant care and telemedicine for patients with neurological conditions.

Review Highlights

What Is Already Known?

Opinion papers, narrative review papers, and scoping review papers have been published on the implications of COVID-19 pandemic for the field of neurology.

What This Study Adds?

This paper synthesizes the existing knowledge on neurological conditions that may develop due to a COVID-19 infection. We discuss how COVID-19 may cause encephalopathy and stroke, and how it may worsen the course of pre-existing neurological conditions such as MS. We have also provided a list of suggestions for clinical practice as well as future research.

Conclusion

In summary, our review first generated a brief overview of what is known about the topic and then discussed the limitations of the existing literature. We also provided a list of recommendations for clinical work and research in the area of neurological conditions due to COVID-19. We hope that this document can help with research and public health and clinical care of COVID-19 patients and reduce morbidity and mortality as well as the economic pressure of the COVID-19 on patients, health care systems, and the society. Using a more comprehensive view with access to the existing knowledge researchers, policymakers, and clinicians may be better able to manage patients with acute neurological conditions due to COVID-19 infection.

Conflict of Interest Disclosures

The author declares no conflict of interest.

Ethical Approval

Not applicable.

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