Neurological Manifestations of SARS-CoV-2
A Narrative Review

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Background: Coronavirus disease 2019 (COVID-19) pandemic started as an outbreak in China and soon crossed borders to affect the populations in all countries of the world. During the initial course of the disease, COVID-19 was perceived as a pneumonia-like illness. However, recent findings of COVID-19 patients suggest that the virus has the potential to disseminate to different tissues and organs, and cause significant complications.

Summary: Neurological symptoms are of great significance as these usually present in and complicate critical cases. Many case reports and case series have documented the findings of neurological complications in COVID-19 patients. From the existing data, the most frequent symptoms in these patients were broadly classified into the central nervous system (CNS), peripheral nervous system, and skeletal muscular symptoms. CNS symptoms include meningitis, encephalitis, cerebrovascular complications, peripheral nervous system symptoms include anosmia, ageusia, and skeletal muscular symptoms include myalgias. It is postulated that the cause may be direct CNS injury through blood and neuronal pathways or indirectly because of an immune-mediated response, hypoxia caused by decreased oxygen saturation, or by the binding of subacute respiratory syndrome-coronavirus-2 to the host angiotensin-converting enzyme-2 receptors. Striking radiologic findings in COVID-19 patients with neurological symptoms have also emerged.

Conclusions: As subacute respiratory syndrome-coronavirus-2 may potentially have lethal implications on the nervous system, it is important that neurologists are better informed about the spectrum of clinical manifestations, radiologic findings, and likely mechanisms of injury. Understanding the symptoms and radiologic imaging allows clinicians to consider brain imaging in any patient with suspected COVID-19 and neurological symptoms.

Key Words: COVID-19, neurological, meningitis, encephalopathy, stroke, GBS, anosmia

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Coronavirus disease 2019 (COVID-19) was first identified in December 2019, when a considerable number of people became infected with an unusual respiratory infection after visiting a wet market in Wuhan, China. China's Centre for Disease Control later announced that the cause of this new infection was a novel strain belonging to the coronavirus family.[1] The origin of this new strain was traced down to be from a bat to a human. Previously members of the same family; subacute respiratory syndrome (SARS) in 2002 and middle eastern respiratory syndrome in 2011, have caused significant morbidity and mortality in humans. As most of the transmission was discovered to occur through the respiratory route, it was extremely hard to trace and contain the disease. Despite all measures, it managed to spread across countries and regions and was soon declared as a pandemic on March 11, 2020. The virus has an association and genomic relation with the previous strain; SARS, and hence named subacute respiratory syndrome-coronavirus-2 (SARS-CoV-2).[1]

The incubation period of the virus ranges from 2 to 14 days and most symptoms manifest within this time frame.[1] An individual may remain asymptomatic and yet continue to propagate the infection. Much is known about the common symptoms of COVID-19 including fever, cough, myalgia, and life-threatening symptoms leading to intensive care unit (ICU) admissions such as shock and respiratory support. Initially, the disease was perceived as a pneumonia-like illness needing respiratory support in extreme cases that present with acute respiratory distress syndrome. However, as more is being discovered about the new disease, many new and unusual symptoms of COVID-19 are being identified. These include cardiac, neurological, hematological, and in extreme cases multiorgan failure leading to ICU admission.[2,3]

A retrospective study on neurological symptoms because of COVID-19 reported that 36.4% (78/214) of patients had neurological complications.[1] Many case reports and studies have documented the neurological symptoms of the virus. Many viruses and other coronaviruses; SARS and middle eastern respiratory syndrome, have been associated with similar neurologic involvement.[3] This could also be further explained by evidence of viral antigens found in the cerebrospinal fluid (CSF) and brain cells.[3,4] The common symptoms include anosmia and ageusia, cerebrovascular disorders, muscular weakness among others.[3]

It is important for clinicians to recognize COVID-19 patients who may have nonspecific neurological manifestations.[4] This will require a profound understanding of the symptoms and their proposed management. In this review article, we aim to describe the possible mechanisms of injury to the nervous system by SARS-CoV-2, the clinical presentation of the disease, and constructive treatment options for complications.

PATHOGENESIS AND MECHANISMS OF INJURY IN THE NERVOUS SYSTEM

Not much is known about the pathogenesis by which the virus causes neurological injury.[5] However, Wu et al[6] broadly classified the mechanisms into 2 main pathways; direct and indirect injury (Fig. 1).

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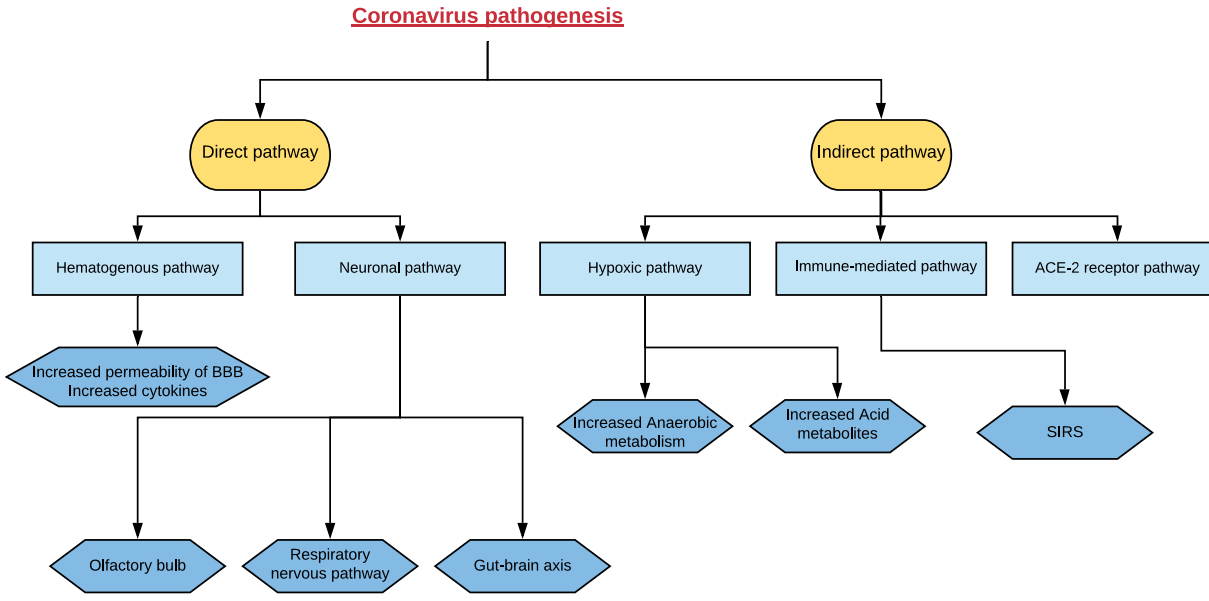

FIGURE 1. Pathogenesis and mechanisms of injury of SARS-CoV-2. ACE-2 indicates angiotensin-converting enzyme-2; BBB, blood-brain barrier; SIRS, severe inflammatory response syndrome.

Direct Injury

This involves a direct introduction of the virus into the brain either through the hematogenous or the neuronal pathways.[6,7] The neuronal route can further be divided into olfactory, respiratory, and gut-brain axis routes.[6,8,9]

(1) Hematogenous pathway: there is little evidence of SARS-CoV-2 affecting the brain tissues through this pathway,[6] however, the postulated mechanism can be explained by the angiotensin-converting enzyme-2 (ACE-2) receptor expression on the endothelial cells of the capillaries. The presence of COVID-19 in the systemic circulation slows the movement of blood in the capillaries allowing the binding of SARS-CoV-2 with ACE-2 receptors. This in turn causes subsequent endothelial damage and increased permeability of the blood-brain barrier because of increased cytokines can give way for nervous access.[7]

(2) Neuronal pathway: the retrograde or anterograde movement of the virus through different peripheral nerves is one possibility by which the virus may gain access.[6] The most vulnerable pathway is the olfactory bulb pathway, which is through the cribriform plate.[7] As demonstrated in an investigation, the removal of olfactory bulbs in mice models subsequently halted the infection from reaching the central nervous system (CNS). Once it enters, it is postulated to cause inflammation and demyelination.[6]

The second important neuronal pathway is the respiratory pathway. The presence of viral antigens has been found in the brainstem, which has connections to the respiratory tract.[8] Viral entry in the brainstem could trigger death by alteration of these neuronal groups.

Furthermore, many authors have suggested that the gut-brain axis entry is a potent route since there is an abundance of ACE-2 receptors on the gut epithelial cells.[9] The enteric nervous system makes an extensive network of connecting brain and enteric glial cells. They also express many immune cells that release inflammatory mediators including interleukin 6 (IL-6). Therefore, cytokine storm with elevated IL-6 observed in COVID-19 infection can lead to late CNS symptoms.

Indirect Pathway

The indirect pathways can be broadly classified into hypoxic, immune-mediated, and ACE-2 receptor pathways.

(1) Hypoxic pathway: this is mainly attributed to less oxygen saturation that is caused by acute respiratory distress syndrome in critical patients with COVID-19. Loss of oxygen causes mitochondria of the brain cells to carry out anaerobic metabolism. An increase in the acid then may lead to cerebral edema, cerebral vasodilation, and swelling of the brain cells, further exacerbating CNS complications.[6]

(2) Immune-mediated pathway: other viruses have also caused significant mortality because of severe inflammatory response syndrome (SIRS)-induced multiorgan failure just like SARS-CoV-2. The activation of the immune response in the brain can result in chronic injuries. Studies on glial cells have shown large amounts of IL-6 secretion, which is also seen in the COVID-19 cytokine storm.[6]

(3) ACE-2 receptor pathway: investigations on the human brain conclude that the human brain cells, especially the glial and neuronal cells express ACE-2 receptors and are the likely targets of SARS-CoV-2. Once inside the neuronal cells, a cycle of budding is initiated causing neuronal damage without further inflammation just like SARS-CoV-1. This subsequently causes nervous tissue damage.[7]

SPECTRUM OF NEUROLOGICAL CLINICAL PRESENTATION

There is a wide variety of neurological manifestations and these can be broadly classified into 3 categories: CNS (headache, altered levels of consciousness, cerebrovascular disease, and seizures); peripheral nervous systems (anosmia and ageusia); and skeletal muscular symptoms.

Headache and Meningitis

Headache has been reported to be one of the most common CNS manifestations in COVID-19 patients.[10] According

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to a case series by Mao et al,[11] 24.8% of the patients experienced CNS manifestations, of which 13.1% suffered from headaches.

It has also been assumed that headaches may be suggestive of viral meningitis instead of being a constitutional symptom.[12] A case of meningitis/encephalitis has been described in which a patient had fever and headache on the first day of symptoms. These symptoms progressively worsened and the patient developed a sore throat. On the ninth day, the patient was found unconscious and while being transferred to the hospital suffered transient generalized seizures. The chest computed tomography (CT) showed evidence of small ground-glass opacities. Despite the fact that SARS-CoV-2 RNA was not detected in the nasopharyngeal swabs, it was detected in the CSF.[13] This highlights the fact that despite having a negative real-time polymerase chain reaction using a nasopharyngeal swab, it does not rule out the possibility of infection with SARS-CoV-2. Upon admission, endotracheal intubation and mechanical ventilation were carried out because of the seizures. The patient was transferred to the ICU, where empirical treatment with intravenous (IV) ceftriaxone, vancomycin, acyclovir, steroids, and IV levetiracetam for seizures was started.[13]

However, in another patient (who was positive for SARS-CoV-2) with signs of meningeal irritation and altered consciousness, the virus was not isolated in the CSF. The patient also had a fever, shortness of breath, myalgias, and altered consciousness. The chest CT showed multiple ground-glass opacities, whereas head CT was unremarkable. However, the CSF pressure was elevated and this was treated with mannitol infusions, arbidol, and oxygen therapy. The CSF pressure was gradually decreased and the patient regained consciousness. Given the neurological symptoms, a presumptive diagnosis of encephalitis was made.[14] New-onset seizures are also suggestive of encephalitis.[15]

Therefore, it is imperative to perform a CSF analysis in suspected meningitis/encephalitis.

Encephalopathy

Encephalopathy encompasses a range of symptoms from mild (memory loss, personality change) to severe (dementia, seizure, coma, or death). Encephalopathy is a rare complication of viral infections and leads to adverse outcomes. Although the exact mechanism by which SARS-CoV-2 causes encephalopathy is still not certain, a suggested pathway is for the virus to move retrogradely through olfactory nerve to CNS.[14] Since SARS-CoV-2 preferentially ails elderly patients with chronic and/or pre-existing conditions, patients with acute respiratory symptoms, and prior neurological conditions are at an increased risk of encephalopathy.[16] In a case reported by Filatov and colleagues, a 74-year-old male with multiple comorbidities and COVID-19 developed encephalopathy with no verbal expression intact. He was unable to follow commands, however, mobility in his extremities and reaction to noxious stimuli were preserved.[16] In a study conducted in Wuhan, China comprising 214 patients, 14.8% patients with severe disease had impaired consciousness versus only 2.4% with milder disease symptoms.[11]

Acute necrotizing encephalopathy (ANE) is a rare complication related to intracranial cytokine storm. It can cause a breakdown in the blood-brain barrier and dissemination of disease.[17] In a case report by Poyiadji et al,[18] a female in her late fifties with COVID-19 presented with symptoms of fever, cough, and altered mental status and developed acute necrotizing hemorrhagic encephalopathy, which was the first case of its type. Another report by Dixon and colleagues had a 59-year-old woman with pre-existing transfusion-dependent aplastic anemia who presented with seizures and altered consciousness. She was later diagnosed with ANE and died on the eighth day of admission.[19] The disease course was severe, indicating a need for in-depth analysis of encephalopathy in every patient with neurological symptoms.

In a report by Filatov and colleagues, the patient was treated prophylactically with antiepileptic medication along with antiviral and antibiotic medications. Following recent leads, hydroxychloroquine and ritonavir were added to the treatment. However, despite the medications and care in ICU, the patient remained critically ill.[16] For the treatment of ANE, Poyiadji and colleagues, used intravenous immunoglobulin (IVIG). Because of the concerns of respiratory failure, the use of high-dose steroids were avoided.[18] However, in the case reported by Dixon and colleagues, they used levetiracetam and IV antibiotics along with transfusion of human leukocyte antigen-matched platelets to avert the risk of hemorrhage. The patient was intubated and placed on a mechanical ventilator, however, she died a few days later.[19]

Cerebrovascular Disease

Stroke is another sequalae of COVID-19 infection. SARS-CoV-2 has a specific affinity for ACE-2 receptors[20] causing blood pressure variations in patients with hypertension increasing the risk of intracranial hemorrhage. Furthermore, some critical patients develop severe thrombocytopenia, which can increase the risk of a cerebral hemorrhage.[10]

A study by Avula and colleagues reported 4 COVID-19 patients with cerebrovascular events. This study shows evidence of cerebrovascular events early in the disease course.[21] In contrast, Mao et al[11] showed that 5.7% of patients with severe infection developed the acute cerebrovascular disease later in the course of illness. Another retrospective study in Wuhan, China, showed that the incidence of stroke among severe COVID-19 patients was ~5%; with the youngest patient being 55 years old. These patients had comorbidities including diabetes, hypertension, and previous cerebrovascular disease. Laboratory testing showed elevated levels of D-dimer and C-reactive protein. This indicated abnormalities in coagulation along with a high inflammatory state, which potentially leads to an acute cerebrovascular event at an average of 12 days after diagnosis of COVID-19.[22] In New York City, 5 patients with COVID-19 presented with large-vessel stroke.[23] According to a letter by Wang et al,[24] the number of reported cases of COVID-19 patients with intracerebral hemorrhage is rising, making early diagnosis necessary for better prognosis of patients.

A protected code stroke has been proposed by Houman et al[25] to be followed in this pandemic, which encompasses all key elements like personal protective equipment, screening guidelines, and crisis resource management. Oxley and colleagues used antiplatelet therapy initially and switched to anticoagulation therapy later. After CT angiography showed a complete resolution of the thrombus, the patient was discharged to a rehabilitation facility.[26] Monitoring clinically stable stroke patients after thrombolysis in non-ICU has been suggested by Umapathi et al.[26] Avula et al[21] highlighted effective communication was hampered while treating acute stroke patients because of speech problems and altered mental status.

Anosmia and Ageusia

Smell and taste disorders are common following viral infections.[27] Anosmia and ageusia are 2 of the predominant symptoms with which most COVID-19 patients present. Mice models have shown that SARS-CoV-2 penetrates transneuronally through the olfactory bulb, resulting in access and spread through

the brain. Damage to the olfactory nerve may also occur directly, which reflects why COVID-19 patients have anosmia in the absence of nasal congestion. This is in contrast to infection with other respiratory viruses, in which anosmia is accompanied by nasal congestion. Moreover, the lining cells of the oral mucosa express the ACE-2 receptor, which is the host cell receptor for SARS-CoV-2. This facilitates viral penetration and may be responsible for causing ageusia.[28,29]

In a series conducted by Patel et al,[29] 77 of 141 patients had both anosmia and ageusia, 9 reported that they had ageusia only, and 3 with anosmia only. These symptoms generally begin during the early phase of the disease, hence should be solicited as important early diagnostic predictors.[30] There is a high rate of transmission before the onset of symptoms and during the early phase of the disease, so people should be cautioned to immediately isolate themselves if they develop these symptoms.[31] These are more common among females and younger individuals. The median time to recover from both anosmia and ageusia was reported to be 7 days and most patients recovered within 3 weeks.[28]

Because of the current limitations and rapid evolvement of the pandemic, the World Health Organization and Centers for Disease Control and Prevention do not classify anosmia as a screening symptom.[32] Yet, it is imperative that emergency department physicians consider such symptoms as the initial manifestation of COVID-19.[33]

Guillain-Barre Syndrome (GBS)

GBS is an acute immune-mediated disease usually elicited by various infections. It is a disease of peripheral nerves and nerve roots (polyradiculoneuropathy). It presents as progressive, ascending, symmetrical flaccid limb paralysis in addition to hyporeflexia or areflexia, with or without cranial nerve involvement.[34] Sedaghat and Karimi,[35] reported the first case of GBS as a neurological complication of COVID-19 infection after 2 weeks of clinical onset.

In a case report by Zhao et al,[36] a patient presented to the hospital with acute weakness in both legs and severe fatigue progressing from day 1, developing symptoms of COVID-19 on day 8 of hospital admission. Contrary to this, in another case report by Ottaviani et al,[37] a patient developed GBS symptoms (ascending paralysis leading to quadriplegia along with bilateral facial paralysis) a week after the onset of respiratory symptoms. Another case report by Virani and colleagues stated that a patient presented to the hospital with complaints of numbness and weakness in lower extremities and a 10-day history of fever and nonproductive cough. The patient was diagnosed with Clostridium difficile colitis 2 days before hospital admission and subsequently later tested positive for COVID-19. GBS in this case may or may not be because of COVID-19 since Clostridium difficile infection is also associated with GBS.[38] However, all 3 studies stated its progression to have a para-infectious profile with symptoms increasing simultaneously with the disease.

Another series of case reports from Italy by Toscano et al[39] reported 5 patients who presented with weakness and paresthesia as their main symptoms. Four of these patients tested positive for COVID-19 on their first visit, whereas 1 tested negative during the initial visit and later turned positive. Three patients had features of axonal polyneuropathy, whereas 2 patients had demyelinating polyneuropathy. Since COVID-19 is a relatively emerging disease, no confirmed association has yet been established.

The mainstay of treatment in the aforementioned cases was IVIG or plasmapheresis. However, in a case report by Ottaviani et al,[37] early treatment with IVIG was not beneficial and the patient progressively developed dysesthesia, unilateral facial palsy, and proximal weakness in all her limbs. Virani et al[38] mentioned that only upper extremity weakness responded to IVIG. Toscano and colleagues used IVIG for all his patients and followed-up with a second course of IVIG and/or plasma exchange. At 4 weeks of treatment, 2 patients remained on mechanical ventilators, whereas the other 2 underwent physical therapy for paraplegia, and only 1 patient was discharged and was able to walk independently.[39]

Myalgias

Another feature COVID-19 patients present with are myalgias. This may be attributed to the inflammatory reaction caused by SARS-CoV-2 or direct muscle damage by the virus and patients may experience limb aches and fatigue.[10] Patients with muscle symptoms also tend to have higher levels of serum creatine kinase and lactate dehydrogenase as opposed to those without muscle symptoms.[11] Rhabdomyolysis may also occur. Jin and colleagues reported that a 60-year-old, SARS-CoV-2 patient experienced pain and weakness in lower limbs on the ninth day of the hospital admission. The patient had elevated levels of myoglobin, creatine kinase, lactate dehydrogenase, and liver enzymes.[40] The patient was subsequently treated with hydration, alkalization, plasma transfusion, and gamma globulin. A follow-up chest CT demonstrated regressing pulmonary lesions. Fluid therapy was continued in addition to ongoing treatment with opinavir and moxifloxacin. The patient reported lesser limb pain and a second real-time polymerase chain reaction on the 12th hospital day came negative. The patient's condition improved thereafter.[40]

Neuroradiologic Features

If a confirmed COVID-19 case presents with deteriorating neurological symptoms, it is imperative that neuroradiologic investigations are performed. Clinically, altered mental status, syncope, and focal neurological defects are the most important indications for brain imaging.[41] With currently limited data, no characteristic radiologic findings have been attributed to COVID-19, however, some findings have emerged.

The first presumptive case of COVID-19 associated ANE demonstrated symmetrical, multifocal lesions in the medial thalamic region on CT.[18] Hyperintense lesions were seen bilaterally in medial temporal lobes, medial thalami, and subinsular region on magnetic resonance imaging (MRI) FLAIR. Multifocal hemorrhages were demonstrated as hypointense lesions on susceptibility-weighted MRI. The second presumptive case of COVID-19 associated ANE had similar results with an extension of symmetrical microhemorrhages in pons and medulla, and even striatum and subcortical perirolandic regions on susceptibility-weighted MRI.[19]

In the case report of the first COVID-19 associated meningitis/encephalitis, hyperintense lesions along the inferior horn of the right lateral ventricle were seen on MRI diffusion-weighted images. Upon MRI FLAIR images, right hippocampal atrophy and hyperintense signals in the right medial temporal lobe were reported.[13]

Multiple retrospective studies have discovered neuroradiologic findings in severe COVID-19 infections. Radmanesh and colleagues, in their study, identified nonspecific white matter changes characterized by hypodensities on CT and hyperintensities on T2-weighted MRI as the most common (55.4%) abnormal radiologic finding. Followed by chronic infarcts (19.4%), acute/subacute infarcts (5.4%) and acute intracranial hemorrhages (4.5%).[41] Another cohort conducted in France by Kremer and colleagues, discovered that the most frequent MRI findings in severe COVID-19 infections were involvement of medial temporal lobe,

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multifocal white matter lesions characterized by hyperintense signals on MRI FLAIR sequence, and hemorrhagic lesions including isolated white matter microhemorrhages. The presence of hemorrhage was associated with a worse prognosis.[42]

CONCLUSIONS

It is important for clinicians to remain cognizant that some COVID-19 patients can present with neurological symptoms as their primary presentation. Therefore, front-line physicians should have a suspicion of COVID-19 even in patients who do not have common flu-like symptoms but rather neurological manifestations. More awareness is needed regarding atypical presentations of COVID-19 infection as most people are only aware of the typical symptoms such as fever, cough, and shortness of breath. Early recognition of neurological symptoms is crucial to ensure appropriate triage and management.

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