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Neurological Complications of COVID-19

Bharati K*

UNESCO, India

***Corresponding author:** Kaushik Bharati; COVID-19 Research Trackers- UNESCO; New Delhi- 110059, India, Tel: +91-9910331170; Email: dr.kaushik.bharati@gmail.com

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Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has claimed the lives of over seven million people. Millions more are living with its consequences. COVID-19 has wreaked havoc across the globe without respect for international borders and sparing none. It has affected rich-poor, young-old, men-women - literally everyone. The etiologic agent of COVID-19 is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that has the ability to infect all organs of the body, although the respiratory system is the primary site of infection. The nervous system is also vulnerable. Infection of the brain leads to neurological complications, including cognitive dysfunction and psychiatric problems. Difficulty remembering, thinking and confusion, often collectively termed as 'brain fog', are very common neurological symptoms of SARS-CoV-2 infection of the brain. The present review has aimed to describe the various neurological complications associated with COVID-19, highlighting the mechanisms of neuroinvasion and neurological damage, common neurological symptoms, and the major neurological disorders.

Keywords: Coronavirus; COVID-19; Neurological Complications; Pandemic; Brain; Nervous System

Abbreviations

MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; CNS: Central Nervous System; PNS: Peripheral Nervous System; BBB: Blood-Brain-Barrier; ACE2: Angiotensin Converting Enzyme 2; DIC: Disseminated Intravascular Coagulation; PTSD: Post-Traumatic Stress Disorder; CVST: Cerebral Venous Sinus Thrombosis; ICU: Intensive Care Unit; AMS: Altered Mental State; GBS: Guillain-Barre Syndrome; EBV: Epstein-Barr Virus; CMV: Cytomegalovirus; MFS: Miller Fisher Syndrome; PRES: Posterior Reversible Encephalopathy Syndrome; LEMS: Lambert-Eaton Myasthenic Syndrome; MS: Multiple Sclerosis; OCD: Obsessive Compulsive Disorder.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been the deadliest in living memory and of a scale not seen since the Spanish Flu of 1918. Although coronavirus infections are primarily associated with respiratory disease, neurological manifestations are also being increasingly recognized, which provides evidence of neuroinvasion and neurovirulence. The presence of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) and abnormal magnetic resonance imaging (MRI) findings provide further evidence of viral spread into the central nervous system (CNS). Since both the CNS and the peripheral nervous system (PNS) are highly susceptible to SARS-CoV-2 infection, it could explain the occurrence of multiple neurological manifestations, such as headache, dizziness, malaise, impaired consciousness, ataxia, seizures [1] and even neuropsychiatric disorders [2]. Notably, these neurological complications can occur even in the absence of typical features of COVID-19, such as respiratory problems. The neurotropism of SARS-CoV-2 is either mediated through infection of the peripheral nerves or the hematogenous route. Also, immune dysregulation or respiratory insufficiencies have been found to affect

the nervous system indirectly. Moreover, 'cytokine storm' and hypoxic states often lead to blood-brain-barrier (BBB) disruption, coagulation abnormalities, and autoimmune neuropathies [3].

Mechanisms Involved in Neuroinvasion

SARS-CoV-2 has been detected in CSF [4], as well as post-mortem brain tissue of infected patients [5], indicating its neuroinvasive property. Invasion of the brain and other parts of the CNS may occur through a number of mechanisms, which are briefly highlighted below and in Figure 1.

Hematogenous Route: A plausible mechanism of the 'Hematogenous Route' is binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) receptors on BBB endothelial cells, passage through endothelial cells by transcytosis, and then finally reaching the brain [6].

Trojan Horse Mechanism: This involves infection of immune cells expressing ACE2 receptors, such as monocytes, granulocytes, and lymphocytes. These immune cells uptake the virus particles and transport them into the CNS, resulting in infection of the brain [7].

Anterograde Transport: SARS-CoV-2 may be transported by the peripheral nerves into the CNS. These primarily involve the olfactory sensory neurons and is also known as the 'Transcribrial Route' [8]. The olfactory epithelium and olfactory bulb express high levels of ACE2 receptors and transmembrane serine protease 2 (TMPRSS2), which can promote anterograde viral transport [9]. Notably, occurrence of early anosmia also suggests viral neuroinvasion via the olfactory bulb.

Paracellular Route: This involves passage of the virus through the tight junctions of disrupted endothelial cells due to inflammation caused by the viremia.

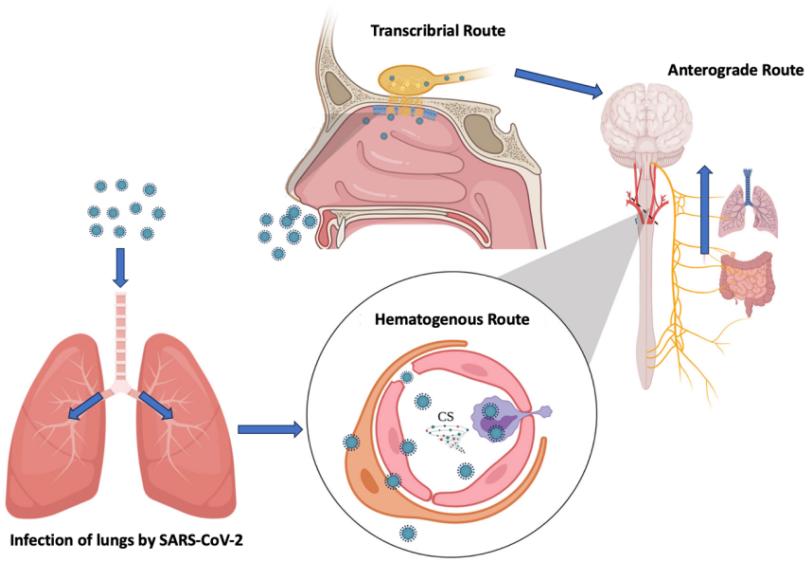

Figure 1: Routes of entry of SARS-CoV-2 into the CNS.

Mechanisms of Neurological Damage

SARS-CoV-2 mediated neurological damage primarily occurs by two mechanisms, namely, hypoxic brain injury and immune mediated brain injury, which are briefly described below:

Hypoxic Brain Injury: Systemic hypoxia may result from severe pneumonia. Some of the contributory factors include hypoxia, hypercarbia, peripheral vasodilation, and anaerobic metabolism, leading to accumulation of toxic compounds. These significantly contribute to neuroinflammation and brain edema, leading to brain damage [10].

Immune Mediated Brain Injury: Immune mediated brain injury primarily occurs due to 'cytokine storm'. In this phenomenon, there are elevated levels of proinflammatory cytokines, along with activation of T-cells, macrophages, and endothelial cells. This is accompanied by release of IL-6, leading to vascular leakage, activation of complement and coagulation cascade, disseminated intravascular coagulation (DIC), and end organ damage [11].

Common Neurological Symptoms Associated with COVID-19

There are many neurological symptoms associated with COVID-19, of which the major ones are highlighted below:

Headache: This is one of the most common, non-specific neurological symptoms in COVID patients and can persist

for over four weeks post-infection. In some cases, it is the first symptom to be observed. Headache occurs in 6-25% of COVID patients and is usually of moderate to severe intensity. Severe headache may be accompanied by photophobia and neck stiffness [12]. It is brought about by SARS-CoV-2 infection of the trigeminal nerve endings in the nasal cavity and subsequent passage into the brain [13].

Dizziness: This is another common neurological symptom, which occurs in 8-9% of COVID patients. Dizziness can occur even in the absence of fever, cough, and headache [14]. Therefore, the occurrence of dizzy spells in the absence of respiratory symptoms could hint at COVID-19.

Myalgia and Fatigue: These symptoms have been frequently reported in COVID patients. Fatigue has been reported in 26-51% of patients, whereas the figure for myalgia lies in the range of 3-64% [15]. Myalgia can occur in COVID patients due to severe inflammation and elevated levels of proinflammatory cytokines [16]. Since myocytes express ACE2 receptors, direct entry of SARS-CoV-2 into muscles is also a possibility.

Anosmia and Ageusia: Loss of smell (anosmia) and taste (ageusia) are among the most common early symptoms of COVID-19 [17,18]. Anosmia and ageusia may result from SARS-CoV-2 infection of the olfactory bulb and trigeminal nerves [19]. These prominent symptoms have been reported in 88% of COVID patients having mild to moderate disease. Therefore, these could be used as clinical diagnostic markers for COVID-19 [20].

Post-COVID Neurological Symptoms: These include body ache, weakness, sleep disturbances, anxiety, depression, and post-traumatic stress disorder (PTSD), which can last for months. Therefore, it is important to follow-up COVID patients even after the acute phase of the disease has passed [21]. Some of the neurological sequelae experienced by COVID patients are presented in Table 1 [22].

Neurological Sequelae	Mechanisms
Ischemic stroke	Cytokine overproduction, vascular endothelial damage, endothelial dysfunction, hypercoagulable state
Hemorrhagic stroke	Decrease in ACE2 levels, increased BP, coagulopathy, CVST
Encephalitis and encephalopathy	Cytokine overproduction, vascular endothelial damage, direct CNS invasion, hypoxia, autoimmunity
Cognitive dysfunction	Neuroinflammation, neurodegeneration, autoimmunity
Headache	Hypoxia, cytokine overproduction, direct CNS invasion, hypercoagulable state, activation of peripheral trigeminal nerve endings
Guillain-Barre syndrome	Autoimmunity, molecular mimicry
Depression, anxiety, and sleep disorders	Cytokine overproduction, neuroinflammation, direct CNS invasion
Seizures	Hypoxia, multiorgan failure, metabolic derangements, cytokine overproduction, direct CNS invasion

Table 1: COVID-19 associated neurological sequelae and their mechanisms.

Neurological Disorders Associated with COVID-19

The neurological disorders associated with COVID-19 are many. The major ones are highlighted below:

Cerebrovascular Diseases: Cerebrovascular disorders have been reported in 5% of COVID patients. Of these, 87.4% are due to ischemic stroke and 11.6% due to hemorrhagic stroke [23]. Stroke, in the context of COVID-19, is caused by endothelial cell dysfunction, cytokine overproduction, unregulated vasoconstriction, hyperinflammation, and hypercoagulable state [24]. Although the underlying mechanism has not been fully elucidated, histopathological studies on cadavers have suggested that brain tissue damage could occur due to a dysregulated immune response [25].

Ischemic Stroke: This type of stroke is one of the most dreaded neurological complications of COVID-19. Ischemic stroke has been reported in 2.3-5% of COVID patients [26]. It can elicit the production of proinflammatory mediators from activated immune cells. Moreover, ischemic brain tissue could further promote brain damage. It follows that suppression of inflammation is likely to ameliorate brain damage following ischemic stroke [27]. Notably, it has been found that COVID-associated stroke patients are 5-times more likely to die than others [23].

Hemorrhagic Stroke: Although hemorrhagic stroke is less common than ischemic stroke in the context of COVID-19, it has nevertheless been found to be significantly associated with SARS-CoV-2 infection [28]. An American study showed that 0.67% COVID patients developed subdural hemorrhage, subarachnoid hemorrhage, or intracerebral hemorrhage [29]. The underlying mechanism for the pathogenesis of COVID-associated hemorrhagic stroke is the virus-induced

unregulated increase in blood pressure (BP). Cerebral venous sinus thrombosis (CVST) can also induce hemorrhagic stroke in SARS-CoV-2 infected individuals. Notably, infected patients are more likely to die than their non-infected counterparts [30].

Coagulopathy and Vascular Thrombotic Complications: Coagulopathy has been studied in detail among COVID patients. Coagulation abnormalities are more prevalent in severe illness and indicate a poor prognosis. It has been reported that 7.2% patients experience thromboembolic events, while 2.1% are affected by DIC [31]. Sepsis-induced coagulopathy is observed in 21.6% patients suffering from severe COVID, while the incidence of arterial or venous thromboembolism varies between 8% and 31% in hospitalized patients [32].

Encephalitis

Encephalitis is the inflammation of the brain parenchyma, primarily due to an infection. Detection of virus in the CSF without any evidence of brain inflammation doesn't confirm encephalitis. Besides inflammation of the brain, other characteristic symptoms include headache, delirium, vomiting, aphasia, fever, convulsions, seizures, dysarthria, and impaired sensations [33]. Since SARS-CoV-2 has been detected in the brain and CSF of COVID patients with encephalitis, it indicates that the virus can directly cause brain injury, leading to encephalitis [34]. Encephalitis generally occurs in severe COVID cases, with an incidence of approximately 6.7% and mortality of 13.4% [35].

Encephalopathy

Encephalopathy is a condition characterized by impaired brain function with reduced mental capacity and delirium. The incidence of encephalopathy in COVID patients ranges between 7-69% with more in case of hospitalized patients [36]. The condition occurs more in COVID patients with underlying neurological problems. Encephalopathy can usually be managed by steroid therapy, although some patients may require supportive care in an Intensive Care Unit (ICU) [37].

Seizures

Some COVID patients exhibit seizures as a result of hypoxia, metabolic dysfunction, widespread inflammation, cerebral affection, and organ failure. Seizures can occur in patients with SARS-CoV-2 induced brain damage, often accompanied by encephalitis [38]. Viral infection in SARS-CoV-2-positive cases can reduce the threshold for seizures, as a result of which they can be provoked by lower intensity stimuli and particularly worsen the condition of epileptic patients. Importantly, seizures are sometimes one of the initial symptoms of COVID-19 and should be kept in the differential diagnosis by physicians [39]. Notably, seizures can occur even in children [40].

Altered Mental State

Altered Mental State (AMS) or altered sensorium is characterized by delirium and confusion and can present as an initial symptom in COVID patients, even in absence of classical respiratory symptoms. It has been found that around 9% of COVID patients exhibit AMS [41]. It is presumed that AMS could result from direct virus invasion of the brain or due to elevated inflammatory mediators released by the powerful and unrestrained immune response mounted against the virus.

Cognitive Dysfunction

This is commonly known as 'brain fog' and is the highest reported (81%) persistent neurologic symptom, lasting at least six weeks and as long as five months in COVID survivors. Studies have shown that females are more vulnerable than males (2.3:1) in developing 'brain fog' in the long haul. It has been found that 32% and 27% of these individuals exhibit short-term memory loss and attention deficit, respectively. It has been suggested that 'brain fog' could be a mild form of post-COVID encephalopathy or an autoimmune condition, given that antinuclear antibodies are significantly elevated, compared to the general population (33% vs 5%). This has been substantiated by the fact that individuals with cognitive dysfunction who have underlying autoimmune disease, are more vulnerable to infection by SARS-CoV-2 [42].

Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) in COVID patients is characterized by weakness in the lower limbs and paresthesia, often progressing to tetraparesis [43]. The nerve roots are typically involved and demyelinating polyradiculoneuropathy and axonal damage have also be reported. GBS symptoms can occur even before the appearance of the typical respiratory symptoms exhibited by COVID patients. COVID-19 GBS is more prevalent in the elderly and males, who have residual weakness, dysphagia, and extended ICU stay than other GBS types. It has been suggested that molecular mimicry could play a role in the pathogenesis of GBS in COVID patients. Since GBS has been linked to various viral infections, including Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and Influenza A virus, it is presumed that SARS-CoV-2 could be no exception. This is supported by the fact that GBS has been reported from many countries where SARS-CoV-2 was circulating at the same time, which suggests an etiological link between the two [44].

Some of the major neurological complications are depicted in Figure 2.

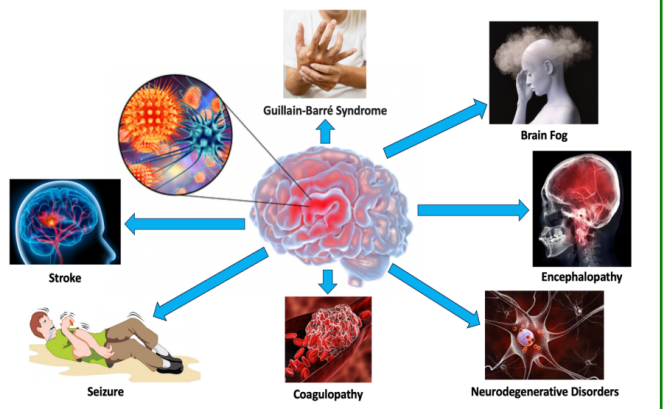

Figure 2: Major neurological complications of COVID-19.

Miller Fisher Syndrome

Miller Fisher Syndrome (MFS) is similar to GBS and its salient features include a triad of symptoms, including ophthalmoplegia, ataxia, and areflexia [45]. Similar to GBS, MFS symptoms are usually preceded by viral infections. It is suggested that MFS is associated with anti-GQ1b antibodies present in these patients. Likewise, it has also be suggested that MFS symptoms are caused by viral neurotropism and not immune-mediated damage [46]. Similar to GBS therapy, intravenous immunoglobulin (IVG) is the treatment of choice for MFS too [47].

Acute Myelitis

Acute myelitis cases have been observed during the ongoing COVID-19 pandemic, although the numbers were few. Myelitis is characterized by paresthesia and hypoesthesia of the feet, which are usually the first symptoms. This results in weak legs that progress to paraplegia, followed by total anesthesia [48]. It has been suggested that pathogenesis of myelitis in COVID patients might be immune-mediated. MRI is the diagnostic tool of choice for diagnosing acute myelitis [49]. Administration of corticosteroids like intravenous methylprednisolone, accompanied by plasmapheresis are the first line treatment options for acute myelitis [50].

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) often exhibits non-specific symptoms, including headache, altered sensorium, vision problems, seizures, and BP fluctuations. PRES is characterized by elevated inflammatory markers accompanied by 'cytokine storm', which leads to altered endothelial structure, BBB damage, and increased vascular permeability. The associated hemorrhage observed in COVID patients is due to coagulopathy and thrombotic complications, resulting from SARS-CoV-2 infection. The link between the virus and PRES is substantiated by the rising number of cases of this rare neurological disorder during the entire duration of the COVID-19 pandemic [51]. Notably, MRI is capable of clinching the diagnosis for this syndrome [52].

Myopathy and Neuromuscular Disorders

Neuromuscular junction dysfunction and myopathy is often seen in severely ill COVID patients with widespread inflammation, which is likely due to SARS-CoV-2 invasion of myocytes, which express the ACE2 receptor [53]. Additionally, pre-existing diseases, such as myasthenia gravis and Lambert-Eaton Myasthenic Syndrome (LEMS) may become aggravated in COVID patients.

Neurodegenerative and Demyelinating Disorders

Neurodegenerative complications may arise from direct viral invasion of the neurons by ACE2 receptor binding, as these receptors are highly expressed in the nervous system [54]. This type of SARS-CoV-2-mediated neurological damage is similar to that of multiple sclerosis (MS) [55]. It follows that SARS-CoV-2 infection could play a role in the development or exacerbation of MS. However, till date, no association between SARS-CoV-2 infection and development of other neurodegenerative diseases like Alzheimer's disease and Parkinson's disease have been reported.

Depression, Anxiety, and Sleep Disorders

Depression, anxiety, and sleep disorders have been reported in COVID patients during the pandemic. The prevalence of these three neuro-psychological problems has been found to be 45%, 47%, and 34%, respectively [56]. Anxiety and depression have been most frequently reported among COVID patients, especially between 3-6 months post-infection [57]. Female patients, adolescents, and young adults are particularly vulnerable to anxiety and depression. The prevalence of other psychiatric disorders, such as obsessive compulsive disorder (OCD) and PTSD is also much higher in this group. However, it is encouraging to note that the symptoms arising from depression, anxiety, and sleep disorders are relatively mild. For example, in the case of depression, the prevalence of mild symptoms was highest (33%), followed by moderate (14%), and severe (7%). The trend is similar for anxiety and sleep disorders as well. In the case of anxiety, the prevalence of mild, moderate, and severe symptoms were 29%, 12%, and 6%, respectively. Likewise, the prevalence of symptoms for sleep disorders was similar - mild (20%), moderate (16%), and severe (2%) [22].

Conclusion

Health systems worldwide and especially in resource poor countries have been crippled by the devastating COVID-19 pandemic for the past few years. Now the disease is slowly

transitioning from a pandemic to an endemic state. In these new circumstances, millions of survivors are living with various long-term sequelae of COVID-19, commonly known as Long COVID. Since many of these people will experience mild symptoms, they will not require hospitalization, but just supportive care. Hence, due to the subjective nature of the symptoms, many of them are likely to be missed by physicians. These healthcare professionals will need an in-depth understanding of the condition, including the multiorgan nature of the symptoms to ensure proper care for the survivors. A high index of suspicion is required, especially when diagnosing neurological complications of COVID-19. This will ensure prompt treatment and better case management, thereby reducing the morbidity and mortality.

Research in this area will still need to continue as the threat of another pandemic is very real - it's not a question of "if", but "when". Research will require collaboration between both the medical and scientific fraternities, having a wide range of clinical and research expertise, which will ensure harmonized research across the world. It should be kept in mind that prevention of a future pandemic will require increased long-term investments for strengthening health systems, proactive collaboration among international agencies, sustainable funding for research, and development of cost-effective tools to detect, treat, and prevent future biological calamities.

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