Scholars Academic Journal of Biosciences
Abbreviated Key Title: Sch Acad J Biosci
ISSN 2347-9515 (Print) | ISSN 2321-6883 (Online)
Journal homepage: https://saspublishers.com
NLM ID:101629416
OPEN ACCESS
Unani Medicine

Peripheral Analysis of COVID-19's Effects on the Nervous System

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DOI: https://doi.org/10.36347/sajb.2025.v13i07.013 | **Received:** 02.06.2025 | **Accepted:** 26.07.2025 | **Published:** 31.07.2025

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Abstract | **Review Article**

Background: The COVID-19 pandemic, driven by SARS-CoV-2, has profoundly impacted global health, primarily as a respiratory illness but with significant neurological consequences in both acute and post-acute phases. ***Objective:*** This review synthesizes global and regional COVID-19 prevalence data and examines the neurological manifestations, underlying mechanisms, and long-term implications of SARS-CoV-2 infection on the nervous system. ***Methods:*** A systematic review of peer-reviewed literature, clinical studies, and epidemiological data from 2019 to 2025 was conducted, focusing on neurological outcomes, prevalence, and rehabilitation strategies. ***Results:*** Neurological manifestations range from mild symptoms (e.g., headache, anosmia) to severe conditions (e.g., stroke, encephalopathy). Mechanisms include direct viral invasion via ACE2 receptors, cytokine-mediated neuroinflammation, and blood-brain barrier disruption. Long COVID is associated with persistent cognitive, psychiatric, and autonomic dysfunction. ***Conclusion:*** The neurological impact of COVID-19 is significant and multifaceted, necessitating early diagnosis, targeted interventions, and further research to address long-term sequelae.

Keywords: COVID-19; SARS-CoV-2; Neurological Manifestations; Unani Medicine; Long COVID; Pandemic; Epidemic; CNS; Coronavirus.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in Wuhan, China, in December 2019 and rapidly evolved into a global pandemic. As of July, 2025, more than 778 million confirmed cases and over 7.1 million deaths have been reported globally, with substantial socio-economic and healthcare disruptions.[1] While COVID-19 was initially recognized as a respiratory illness, subsequent studies have shown that COVID-19 has since been acknowledged as a multisystemic disease, affecting not only the lungs but also the cardiovascular, renal, gastrointestinal and nervous Systems [2]. It is the largest and most severe pandemic since the 1918 influenza pandemic [3,4]. The involvement of the nervous system in COVID-19 has raised significant concern among clinicians and researchers. Neurological symptoms such as headache, anosmia, ageusia, dizziness, encephalopathy, stroke and seizures have been reported across all age groups.[3,4] Furthermore, an increasing number of patients experience persistent neurological symptoms long after recovery, a condition now widely referred to asLong COVID or post-acute sequelae of SARS-CoV-2 infection (PASC).[5] The pathophysiology behind the neurological involvement is complex and multifactorial. Proposed mechanisms include direct viral invasion via angiotensin-converting enzyme 2 (ACE2) receptors expressed in neural tissues, cytokine storm-induced neuroinflammation, disruption of the blood-brain barrier, and hypoxia-related brain injury. In addition, the psychosocial stress and systemic inflammation associated with COVID-19 have been linked to neuropsychiatric outcomes such as depression, anxiety and cognitive decline.

This review aims to provide a comprehensive understanding of the prevalence of COVID-19 across global and regional levels and to explore its diverse impacts on the nervous system. By synthesizing current clinical and epidemiological data, the review seeks to inform future research and improve clinical outcomes in COVID-19 patients presenting with neurological complications.

LITERATURE REVIEW

Global and Regional Prevalence of COVID-19:

Since its emergence in late 2019, COVID-19 has spread rapidly across the world. As of July, 2025, the World Health Organization has reported more than 775,917,102 confirmed cases and 7,058,381 deaths globally.[1] The highest burden has been observed in countries like the United States, India, Brazil and parts of Europe. As of 25 July 2025, according to Indian government figures, India has the second-highest number of confirmed cases in the world after the United States with 45,055,381reported cases of COVID-19 infection and the third-highest number of COVID-19 deaths after the United States and Brazil at 533,795 deaths.[6] In India alone, over 533,626 deaths have been officially reported due to COVID-19, making it one of the most affected nations in terms of total mortality.[7] The pandemic has seen multiple waves of infections, primarily driven by emerging variants of concern such as Alpha, Delta, Omicron and most recently, XBB sublineages, each demonstrating differences in transmissibility and severity.[2] Prevalence patterns varied across time and region, with densely populated urban areas witnessing high transmission rates due to increased contact. Rural regions, though initially less affected, eventually saw spikes in cases, partly due to migration and limited healthcare access.

Furthermore, longitudinal studies indicate that a substantial proportion of patients including those with mild or asymptomatic COVID-19develop post-acute neurological sequelae, contributing to the long-term burden of disease.[8]

Table 1: Global and Regional COVID-19 Case and Death Statistics (as of July 2025)

Region	Confirmed Cases	Deaths
Global	775,917,102	7,058,381
United States	Data not specified	Highest
Brazil	Data not specified	Second Highest
India	45,055,381	533,795

Mechanisms of Nervous System Involvement in COVID-19:

Although SARS-CoV-2 was initially identified as a respiratory pathogen, accumulating evidence demonstrates its ability to affect the central and peripheral nervous systems through multiple mechanisms. The neurological involvement is complex and multifactorial, involving both direct viral neuroinvasion and indirect immune-mediated responses.

Neuro-invasion via ACE2 Receptors:

SARS-CoV-2 gains entry into host cells primarily through the angiotensin-converting enzyme 2 receptor, which is abundantly expressed not only in pulmonary tissue but also in the central nervous system (CNS), including neurons and glial cells.[9] The virus may cross the blood-brain barrier or access the CNS via retrograde axonal transport through the olfactory nerve, explaining early symptoms such as anosmia.[10]

Disruption of the Blood-Brain Barrier (BBB):

Inflammatory cytokines such as IL-6, TNF-α and IL-1β, released during the systemic immune response, can disrupt BBB integrity, allowing viral particles, immune cells, or toxic metabolites to penetrate the CNS.[11] This leads to neuroinflammation, which contributes to symptoms such as encephalopathy, delirium and seizures.

Cytokine Storm and Neuroinflammation:

Severe COVID-19 is associated with a cytokine storm, a hyperinflammatory state marked by elevated levels of pro-inflammatory cytokines. This systemic inflammation can cause neuroinflammation, leading to brain swelling, demyelination and neuronal injury.[12] This mechanism is implicated in both acute and long-term neurological manifestations.

Hypoxic Brain Injury:

Severe respiratory dysfunction in COVID-19 often leads to hypoxemia, which can result in hypoxic-ischemic injury to the brain, particularly affecting areas such as the hippocampus and basal ganglia.[13] Patients with critical illness may also develop metabolic encephalopathy.

Autoimmune-Mediated Injury:

Some neurological manifestations may occur via post-infectious autoimmune responses as observed in conditions such as Guillain-Barré Syndrome, acute disseminated encephalomyelitis and transverse myelitis, which have been reported in post-COVID-19 patients. [14]

Acute Neurological Manifestations of COVID-19

COVID-19 has been increasingly associated with a variety of acute neurological complications, both central and peripheral, which may occur during the early phase of infection. These manifestations range from mild symptoms such as headache and dizziness to life-threatening events like stroke and encephalitis.

Headache and Dizziness:

Headache is one of the most commonly reported early neurological symptoms in COVID-19 patients, occurring in approximately 13% to 34% of cases.[15] Dizziness or light headedness is also frequently observed and may be linked to systemic hypoxia or direct CNS involvement.

Anosmia and Ageusia:

Loss of smell and tasteare hallmark neurological signs of SARS-CoV-2 infection. These symptoms often appear early and may occur even in the absence of respiratory symptoms.[16] The virus likely affects the olfactory bulb and neurons, possibly through ACE2 receptor expression in the nasal epithelium.

Stroke and Cerebrovascular Events:

COVID-19 has been associated with a hypercoagulable state, leading to ischemic and haemorrhagic strokes, particularly in patients with severe illness or comorbidities.[17] Notably, large-vessel stroke has also been reported in young, otherwise healthy individuals.

Encephalitis and Encephalopathy:

Several case reports and series have described acute encephalitis and meningoencephalitis in COVID-19 patients, with findings of elevated inflammatory markers and cerebrospinal fluid abnormalities.[18] In severe cases, acute necrotizing encephalopathy has been observed, likely triggered by cytokine storms.

Guillain-Barré Syndrome (GBS)**:**

COVID-19 has been implicated in immune-mediated neuropathies, particularly GBS, which typically presents with ascending muscle weakness and areflexia a few days to weeks after infection.[19]

Table 2: Acute Neurological Manifestations of COVID-19

Symptoms	Prevalence	Mechanism
Anosmia/ Ageusia	Common	Olfactory nerve invasion
Headache	13-34%	Systemic hypoxia, Neuro-inflammation
Stroke	1-5%	Hypercoagulability
Encephalitis	Rare	Cytokine storm, BBB disruption
Guillain-Barré Syndrome	Rare	Autoimmune response

Post-Acute and Chronic Neurological Sequelae of COVID-19:

While most individuals recover from the acute phase of COVID-19, a substantial number experience persistent or new-onset neurological symptoms weeks to months after recovery. This condition is now termed Long COVID or post-acute sequelae of SARS-CoV-2 infection.[5] These neurological sequelae may occur even in patients with mild or asymptomatic initial infection, making them a significant public health concern. Commonly reported chronic neurological symptoms include:

Cognitive Dysfunction (Brain Fog)**:**

Patients often report reduced concentration, memory problems, and executive dysfunction, collectively referred to as brain fog. Neuropsychological testing in some studies has revealed deficits in attention and processing speed, particularly in previously hospitalized patients.[20]

Fatigue and Sleep Disturbances:

Severe, prolonged fatigue is among the most frequently reported post-COVID complaints. Sleep disorders including insomnia, fragmented sleep, and restless leg syndrome have been documented in more than 30-40% of Long COVID cases.[21]

Psychiatric Sequelae: Anxiety, Depression and PTSD:

Patients with Long COVID often develop anxiety, depression, and in some cases, post-traumatic stress disorder. This may be due to direct CNS inflammation, social isolation, ICU experiences, or loss of livelihood.[22]

Neuropathy and Autonomic Dysfunction:

Some patients develop peripheral neuropathies, presenting with tingling, numbness, or burning pain. Dysautonomia (e.g. postural orthostatic tachycardia syndrome) has also been observed as part of the post-COVID syndrome.[23]

DISCUSSION

The neurological impact of COVID-19 arises from a complex interplay of direct viral effects, immune responses, and systemic complications. The high prevalence of Long COVID underscores the need for long-term monitoring and rehabilitation. Vulnerable populations, including the elderly and those with comorbidities, face elevated risks. The limitations outlined above highlight the need for standardized methodologies and improved healthcare access to fully understand and address the neurological burden of COVID-19. Multidisciplinary approaches, integrating neurology, psychiatry, and rehabilitation, are essential for comprehensive care.

CONCLUSION

SARS-CoV-2's neurological effects are diverse, ranging from mild sensory deficits to severe, life-altering conditions. Understanding these manifestations is critical for optimizing clinical management and developing rehabilitation protocols. Addressing research and clinical limitations will be key to mitigating the long-term burden of Long COVID. Future studies should prioritize longitudinal data collection, standardized reporting, and targeted therapeutic interventions.

Disclosure statement: No potential conflict of interest was reported by the author(s).

Funding: Nil

Conflict of Interest: Nil

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