NEURO-COVID: THE HIDDEN BATTLE OF THE BRAIN AMIDST THE PANDEMIC

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Abstract. The COVID-19 pandemic has revealed itself as more than just a respiratory illness, bringing to light significant neurological implications that are still being unraveled. SARS-CoV-2, the causative agent of COVID-19, demonstrates a capacity for neuroinvasion, resulting in a broad spectrum of acute and chronic neurological manifestations. This review synthesizes current knowledge on the pathophysiology, clinical presentations, and management strategies of neuro-COVID, highlighting the brain's hidden battle amidst the pandemic. A comprehensive literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, focusing on studies published between January 2020 and August 2024. Relevant articles were selected based on their contribution to understanding the neurological impact of COVID-19, including pathophysiological mechanisms, clinical manifestations, neuroimaging findings, and therapeutic approaches. Case studies and reports were also incorporated to illustrate the diversity of neuro-COVID presentations. The analysis revealed that SARS-CoV-2 can infiltrate the central nervous system via multiple pathways, including direct viral invasion through ACE2 receptors and indirect mechanisms such as cytokine storms. Acute neurological symptoms range from mild (e.g., anosmia, headaches) to severe (e.g., encephalitis, stroke). Long-term sequelae, including cognitive impairments and neuropsychiatric disorders, are increasingly recognized as significant challenges in post-COVID care. Current therapeutic strategies focus on symptom management, with ongoing research into targeted neurotherapeutics. Neuro-COVID represents a significant and evolving challenge in the context of the pandemic. Understanding the neurological implications of COVID-19 is crucial for improving patient outcomes and guiding future research. This review underscores the need for heightened clinical awareness and a multidisciplinary approach to effectively address the complex neuro-COVID spectrum.
Keywords: *Neuro-COVID, SARS-CoV-2, neurological manifestations, neuroinflammation, long COVID*

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has triggered an unprecedented global health crisis, impacting millions of people and leading to significant morbidity and mortality. Initially characterized as a respiratory illness, COVID-19 soon revealed its far-reaching implications beyond the lungs, affecting multiple organ systems, including the nervous system. The neurological implications of COVID-19 have become a critical area of study, with reports of various neuropsychiatric and neurological manifestations becoming increasingly common among COVID-19 patients. Neurological symptoms associated with COVID-19 vary widely, ranging from mild conditions such as headaches and dizziness to severe outcomes like stroke, encephalopathy, and neuroinflammatory syndromes. These symptoms may result from direct viral invasion, immune-mediated damage, or the hypercoagulable state induced by the infection. The brain, with its complex network of neurons and supporting cells, appears particularly vulnerable to the multifaceted attack by the virus and the body's immune response (Dale, 2022; Ellul et al., 2020). One of the primary pathways through which SARS-CoV-2 affects the nervous system is by crossing the blood-brain barrier (BBB). This can occur through direct viral invasion via the olfactory nerve or through BBB disruption caused by the systemic inflammatory response known as the cytokine storm. This hyperinflammatory state can lead to microglial activation and subsequent neurotoxicity, contributing to neurological symptoms such as cognitive dysfunction, mood disturbances, and potentially long-term neurodegenerative changes (Baig, 2020; Natoli et al., 2020).

The rationale for focusing on the brain's involvement in COVID-19 extends beyond understanding the immediate neurological symptoms to comprehending the potential long-term consequences. As the pandemic continues, there is growing concern about the chronic neurological sequelae that might affect a significant portion of the population, leading to what is being termed "Neuro-COVID" or the neurological dimension of Long COVID. Understanding these mechanisms is crucial not only for managing current patients but also for developing strategies to mitigate long-term impacts on brain health globally (Frontera et al., 2021).

Materials and Methods

Search strategy

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify studies published on the neurological manifestations of COVID-19 (Neuro-COVID) from the inception of the pandemic in December 2019 until May 2023. The search strategy employed a combination of controlled vocabulary (e.g. MeSH terms) and free-text terms related to "COVID-19", "SARS-CoV-2", "neurological symptoms", "neuroinflammation", "neuroimaging" and "neurotherapeutics". To ensure comprehensive coverage, the search terms were adjusted for each database, and Boolean operators (AND, OR) were used to combine keywords. The initial search was supplemented by a manual review of the references cited in the included studies to identify additional relevant articles.

Inclusion and exclusion criteria

Studies were selected based on pre-specified eligibility criteria: (1) inclusion criteria: original research articles, case series, clinical trials, and systematic reviews focusing on the neurological implications of COVID-19; studies involving human subjects of all ages and genders; articles published in peer-reviewed journals in English; and studies that provided clear data on neurological symptoms, diagnostic findings, or treatment outcomes related to COVID-19. (2) exclusion criteria: non-peer-reviewed articles, editorials, commentaries, and letters to the editor; studies focused exclusively on non-neurological aspects of COVID-19; articles without full-text availability or those published in languages other than English.

Study selection

The study selection process involved two independent reviewers who screened the titles and abstracts of all retrieved articles. Full texts of potentially eligible studies were obtained and assessed against the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion, and if necessary, a third reviewer was consulted.

Data extraction and synthesis

Data from the included studies were extracted using a standardized data extraction form. The extracted information included study characteristics (e.g., author, year of publication, study design, sample size), patient demographics, neurological symptoms, diagnostic methods, and treatment outcomes. Given the heterogeneity of the included studies, a narrative synthesis approach was employed to summarize the findings. This approach allowed for the integration of diverse study designs and outcomes, providing a comprehensive overview of the neurological manifestations of COVID-19. The results were categorized into key themes: acute neurological manifestations, long-term neurological sequelae, neuroinflammation, and neuroimaging findings. These themes were then discussed in relation to the underlying pathophysiology and clinical management of Neuro-COVID.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for clinical trials. This assessment helped identify potential biases and ensured the reliability of the conclusions drawn from the reviewed literature. To provide a clear overview of the study selection process, a PRISMA flow diagram (*Figure 1*) is included, illustrating the number of records identified, screened, and included in the review, along with reasons for exclusion at each stage.

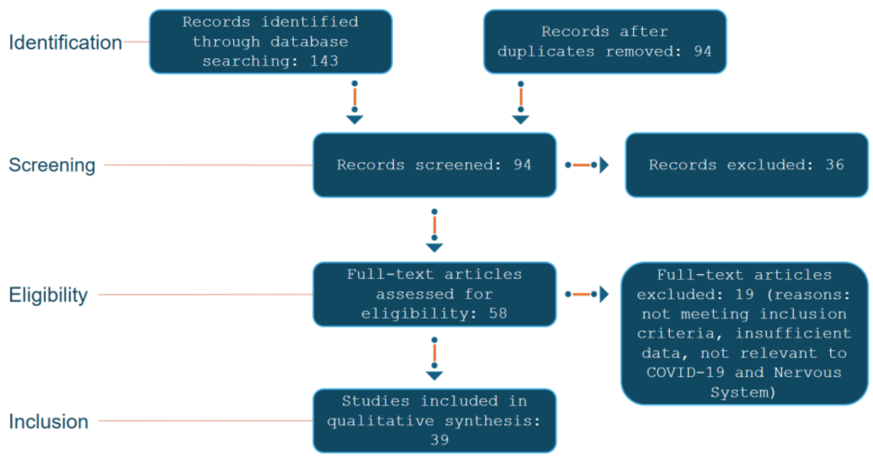

Figure 1. *The PRIMSA flow diagram.*

Results and Discussion

Overview of neurological manifestations of COVID-19

The reviewed literature consistently highlights a broad spectrum of neurological manifestations associated with COVID-19, ranging from mild symptoms such as headaches and dizziness to more severe outcomes like encephalopathy, strokes, and Guillain-Barré syndrome (GBS). Anosmia and ageusia were among the most commonly reported early neurological symptoms, serving as potential indicators of SARS-CoV-2 infection. The severity and variety of these symptoms reflect the virus's multifaceted impact on the nervous system, often correlating with the overall severity of the disease.

Pathophysiology and mechanisms of neuroinvasion

The articles reviewed suggest several potential mechanisms through which SARS-CoV-2 invades the central nervous system (CNS). These include direct viral invasion via the olfactory nerve, hematogenous spread across a compromised blood-brain barrier (BBB), and neuroinflammation driven by the systemic immune response. The role of angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed on neurons and glial cells, is particularly emphasized as a key pathway for viral entry into the brain.

Acute and severe neurological complications

Many studies have documented severe neurological complications in COVID-19 patients, particularly in those with critical illness. Ischemic strokes, encephalitis, and acute disseminated encephalomyelitis (ADEM) are among the most significant findings. The literature also notes the occurrence of GBS as a rare but serious autoimmune response to SARS-CoV-2, typically presenting after the acute phase of the infection.

Long-term neurological sequelae

The concept of "Long COVID" or post-acute sequelae of SARS-CoV-2 infection (PASC) is prominent in the literature, with numerous studies reporting persistent neurological symptoms. Cognitive impairments, often described as "brain fog," along with chronic fatigue and neuropathic pain, are frequently mentioned. These long-term effects appear to affect a significant proportion of COVID-19 survivors, including those who experienced only mild to moderate initial symptoms. This indicates a need for further research into their underlying mechanisms and management strategies.

Diagnostic and therapeutic challenges

The literature review reveals significant challenges in the diagnosis and management of Neuro-COVID. Neuroimaging techniques, such as MRI and CT scans, have been instrumental in identifying CNS involvement, but variability in findings has made standardization difficult. Therapeutically, there is still no consensus on the most effective treatment strategies for Neuro-COVID, with current approaches often based on managing symptoms and underlying conditions rather than targeted antiviral or neuroprotective treatments.

Pathophysiology of SARS-CoV-2 in the nervous system

SARS-CoV-2, the virus responsible for COVID-19, exhibits significant neurotropism, meaning it has the ability to infect and impact neural tissue. Understanding the pathophysiology of how SARS-CoV-2 affects the nervous system is crucial for grasping the wide range of neurological manifestations observed in COVID-19 patients. The entry of SARS-CoV-2 into the central nervous system (CNS) is facilitated by multiple mechanisms. One of the primary routes is via the olfactory nerve, which provides a direct pathway from the nasal epithelium to the brain. The virus can invade the CNS by bypassing the blood-brain barrier (BBB) through the cribriform plate, a bony structure separating the nasal cavity from the brain. This route is supported by the frequent observation of anosmia (loss of smell) in COVID-19 patients, suggesting early viral involvement in the olfactory pathways (Meinhardt et al., 2021). Another significant entry mechanism is through the disruption of the BBB. The inflammatory response triggered by SARS-CoV-2 infection, characterized by the release of cytokines such as IL-6 and TNF-α, can lead to increased permeability of the BBB. This disruption allows the virus, along with immune cells and inflammatory mediators, to enter the brain parenchyma, contributing to neuroinflammation and the observed neurological symptoms. The cytokine storm associated with severe COVID-19 is a critical factor in this process, exacerbating the breakdown of the BBB and promoting neuroinvasion (Day et al., 2022; Alquisiras-Burgos et al., 2021).

SARS-CoV-2 exhibits a strong affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are widely expressed in various organs, including the brain. ACE2 receptors are present on neurons and glial cells, particularly in regions such as the brainstem, which plays a crucial role in respiratory and cardiovascular regulation. The binding of the virus to ACE2 receptors on these cells can lead to direct viral damage, resulting in cell death and contributing to the neurological complications seen in COVID-19 patients. Additionally, the downregulation of ACE2 due to viral binding may disrupt the renin-angiotensin system, leading to increased inflammation, oxidative stress, and further BBB disruption (Datta et al., 2020; Li et al., 2020). The direct invasion of the virus into neural tissue is compounded by secondary effects, such as hypoxia and systemic inflammation, which further aggravate neurological damage. Hypoxia, often seen in severe COVID-19 cases due to respiratory failure, can cause widespread neuronal injury. Moreover, systemic inflammation, driven by the cytokine storm, can result in widespread microglial activation within the CNS, leading to neuroinflammation, demyelination, and even long-term neurodegenerative processes (Pattanaik et al., 2023).

Acute neurological manifestations of COVID-19

The acute neurological manifestations of COVID-19 are diverse and can range from mild, transient symptoms to severe, life-threatening conditions. Among the most commonly reported neurological symptoms in COVID-19 patients are headaches, dizziness, anosmia (loss of smell), and ageusia (loss of taste). These symptoms often occur early in the course of the disease and may be some of the first indicators of SARS-CoV-2 infection. Headaches and dizziness are thought to result from the systemic inflammatory response and the virus's neuroinvasive properties, while anosmia and ageusia are directly linked to the virus's impact on the olfactory and gustatory pathways, potentially through the involvement of the olfactory bulb and related neural circuits (Lechien et al., 2020; Mao et al., 2020). Severe neurological manifestations are less common but carry significant morbidity and mortality risks. Encephalitis, an inflammation of the brain, has been documented in COVID-19 patients and can present with symptoms such as altered mental status, seizures, and focal neurological deficits. The pathogenesis of COVID-19-related encephalitis is believed to involve direct viral invasion of the CNS, as well as immune-mediated mechanisms, including cytokine storms that lead to widespread neuroinflammation and neuronal damage (Paterson et al., 2020). Stroke is another severe manifestation seen in COVID-19, particularly among patients with severe respiratory symptoms. SARS-CoV-2 infection can induce a hypercoagulable state, leading to an increased risk of thromboembolic events, including ischemic stroke. The hypercoagulability associated with COVID-19 is likely due to a combination of endothelial dysfunction, systemic inflammation, and the presence of antiphospholipid antibodies, all of which contribute to thrombus formation within cerebral arteries (Fifi and Mocco, 2020; Yaghi et al., 2020).

Guillain-Barré syndrome (GBS), a rare but serious neurological disorder, has also been reported in association with COVID-19. GBS is an autoimmune condition in which the body's immune response to the virus mistakenly attacks the peripheral nervous system, leading to muscle weakness, numbness, and in severe cases, paralysis. The onset of GBS in COVID-19 patients typically occurs within a few weeks of the initial infection and is thought to be triggered by molecular mimicry, where viral antigens resemble components of the nervous system, leading to an autoimmune response (Toscano et al., 2020). Case studies have provided detailed insights into the acute neurological presentations of COVID-19. For instance, a study documented a patient who developed acute necrotizing encephalopathy, a rare but severe form of encephalitis characterized by brain hemorrhages and swelling, following SARS-CoV-2 infection. This case highlighted the potential for COVID-19 to cause direct and profound neurological damage (Poyiadji et al., 2020). Another case involved a young patient with no significant medical history who suffered a large ischemic stroke shortly after contracting COVID-19, underscoring the virus's capacity to provoke severe cerebrovascular events even in those without traditional stroke risk factors (Oxley et al., 2020).

Long-term neurological sequelae of COVID-19

The neurological sequelae of COVID-19, particularly in the context of long-term effects, have emerged as a significant area of concern. Post-Acute Sequelae of SARS-CoV-2 infection (PASC), commonly referred to as Long COVID, includes a broad spectrum of persistent neurological symptoms that can endure for months or even years after the initial infection. These long-term effects have brought attention to the complex interplay between COVID-19 and the nervous system. One of the most notable neurological consequences of Long COVID is cognitive impairment, often described as "brain fog." This condition manifests as difficulties with memory, concentration, and executive function. Patients report challenges in processing information, which affects their daily functioning and quality of life. This cognitive decline is thought to result from several mechanisms, including persistent neuroinflammation, disruption of the blood-brain barrier, and direct viral effects on neural tissue. Studies have also highlighted the role of immune dysregulation in sustaining these symptoms, with altered immune cell profiles observed in affected individuals (Nouraeinejad, 2022).

In addition to cognitive impairments, Long COVID is frequently associated with chronic fatigue syndrome, characterized by overwhelming fatigue that is not alleviated by rest and is exacerbated by physical or mental exertion. The neurological underpinnings of this condition are linked to autonomic nervous system dysfunction, which can lead to issues such as orthostatic intolerance and postural tachycardia syndrome (POTS). This autonomic dysfunction further complicates the management of Long COVID and underscores the need for a multidisciplinary approach to treatment. Furthermore, the neuropsychiatric impact of Long COVID is profound, with many patients experiencing anxiety, depression, and post-traumatic stress disorder (PTSD). These conditions are not only reactive to the physical toll of the disease but are also believed to be driven by ongoing neuroinflammatory processes and disruptions in neurotransmitter systems. The persistence of these symptoms, even in patients who had mild initial infections, highlights the pervasive nature of COVID-19's impact on the brain (Almeria et al., 2024; Panagea et al., 2024).

Neuroinflammation and immune response in COVID-19

The neuroinflammatory response in COVID-19 is a complex interplay between the immune system and the central nervous system (CNS), significantly driven by the phenomenon known as a cytokine storm. This hyperactive immune response, characterized by the excessive release of proinflammatory cytokines like interleukins (IL-6, IL-1β), tumor necrosis factor-alpha (TNF-α), and interferons, has profound effects on the CNS. These cytokines can disrupt the integrity of the blood-brain barrier (BBB), allowing them to penetrate the CNS and trigger local inflammation. This process has been implicated in the acute and chronic neurological symptoms seen in COVID-19 patients (Ragab et al., 2020). In severe cases of COVID-19, cytokine storms are often linked to acute neurological manifestations such as encephalopathy, seizures, and cerebrovascular events. The pathophysiology behind this involves not only the cytokines crossing the BBB but also the activation of resident immune cells in the brain, such as microglia and astrocytes. Once activated, these cells can exacerbate neuroinflammation by releasing additional cytokines and chemokines, creating a vicious cycle that leads to neuronal damage (Braga et al., 2023).

Further complicating the neurological impact of COVID-19 is the phenomenon of molecular mimicry, where the immune system's response to viral antigens mistakenly targets self-antigens in the nervous system. This autoimmune response can lead to the development of conditions such as Guillain-Barré syndrome (GBS) and other autoimmune encephalopathies. GBS, in particular, has been frequently reported following SARS-CoV-2 infection and is characterized by rapid-onset muscle weakness and paralysis due to immune-mediated damage to the peripheral nervous system (Yesilkaya and Balcioglu, 2020). Another example of the immune system's role in COVID-19-related neuroinflammation is the persistent activation of the inflammasome, a multiprotein complex that plays a key role in innate immunity. The activation of inflammasomes, particularly the NLRP3 inflammasome, has been observed in COVID-19 patients and is associated with the release of IL-1β, a cytokine that drives further inflammation. The chronic activation of these inflammatory pathways is thought to contribute to the long-term neurological sequelae of COVID-19, such as cognitive decline and mood disorders, which are collectively referred to as Long COVID (Vanderheiden and Klein, 2022).

Neuroinflammatory markers such as C-reactive protein (CRP) and elevated levels of cytokines in the cerebrospinal fluid (CSF) have been correlated with disease severity in COVID-19 patients. These markers not only serve as indicators of the ongoing inflammatory process but also provide insight into the potential mechanisms underlying the neurological complications of the disease. For instance, elevated CRP levels have been associated with more severe encephalopathy and poorer cognitive outcomes, highlighting the need for early detection and intervention in neuro-COVID cases (Ragab et al., 2020). Moreover, studies have shown that the neuroinflammatory response in COVID-19 is not limited to the acute phase of the disease. Patients who recover from the initial infection can continue to experience neuroinflammation, leading to persistent symptoms such as "brain fog," chronic fatigue, and neuropsychiatric disorders. This prolonged inflammation is believed to be driven by a combination of factors, including the lingering presence of viral particles, persistent immune activation, and the dysregulation of the gut-brain axis (Braga et al., 2023; Yesilkaya and Balcioglu, 2020).

Neuroimaging and diagnostic challenges

The neuroimaging of COVID-19-related brain changes presents both promising advancements and significant diagnostic challenges, particularly in detecting and interpreting the neurological impacts of SARS-CoV-2. Advanced neuroimaging techniques such as MRI, CT, and PET scans have been instrumental in uncovering the structural and functional alterations in the brains of COVID-19 patients. These imaging modalities have revealed a range of abnormalities, including signs of ischemic stroke, microhemorrhages, and encephalitis, which are indicative of the diverse neurological sequelae associated with the infection. MRI has proven particularly valuable in identifying perfusion abnormalities and microstructural damage. For instance, a meta-analysis of neuroimaging studies found that around 55% of COVID-19 patients exhibited some form of brain abnormality on MRI, with perfusion-related injuries being most prevalent. These abnormalities are often associated with clinical symptoms such as cognitive impairment and neurological decline, especially in severe cases requiring ICU admission or mechanical ventilation (Boparai et al., 2023). Furthermore, CT and PET scans have also contributed to our understanding of neuro-COVID. CT scans are frequently used in acute settings to quickly assess for strokes and hemorrhages, while PET scans have helped in identifying metabolic dysfunctions in the brain. Notably, PET imaging has detected hypometabolism in specific brain regions, which correlates with symptoms like brain fog and chronic fatigue, frequently observed in long COVID (Katal dan Gholamrezanezhad, 2021).

Despite these advances, significant diagnostic challenges remain. One of the primary challenges lies in differentiating COVID-19-induced neurological damage from other conditions with similar imaging features. For example, differentiating between COVID-19-related encephalopathy and other viral encephalitides based solely on imaging can be difficult. Moreover, the heterogeneity in neuroimaging findings across different studies underscores the need for standardized imaging protocols and interpretation criteria (Douaud et al., 2022). As research continues, the integration of neuroimaging with clinical and biochemical data will be crucial in refining our understanding of the neurological impact of COVID-19 and improving diagnostic accuracy. The ongoing analysis of large datasets, such as those from the UK Biobank, promises to provide deeper insights into how COVID-19 affects brain structure and function over time, further aiding in the development of effective diagnostic and therapeutic strategies (Douaud et al., 2022).

Neurotherapeutics and management strategies

Managing the neurological complications of COVID-19 presents unique challenges, requiring a multifaceted approach that includes both established treatments and emerging therapies. The current treatments primarily focus on alleviating symptoms and managing severe neurological conditions such as encephalopathy, stroke, and seizures. Anti-inflammatory agents like corticosteroids are widely used to mitigate the excessive immune response seen in severe cases, particularly those involving cytokine storms. These agents help reduce inflammation in the central nervous system (CNS) and are crucial in managing acute neuro-COVID symptoms, though their efficacy varies depending on the timing and severity of the condition (Ellul et al., 2020; Zubair et al., 2020). Emerging therapies aim to address the broader spectrum of neuro-COVID complications. For instance, neuroprotective drugs such as nimodipine are being investigated for their potential to protect neural tissue from ischemic damage caused by COVID-19-related vascular events (Graham et al., 2021). Additionally, the use of intravenous immunoglobulins (IVIG) has shown promise in treating autoimmune neurological disorders triggered by SARS-CoV-2, such as Guillain-Barré syndrome (Wijdicks and Klein, 2017). These therapies highlight the need for personalized treatment plans based on the specific neurological manifestations in each patient.

Rehabilitation plays a critical role in the long-term management of neuro-COVID patients, particularly those suffering from persistent symptoms like cognitive impairment, chronic fatigue, and neuropsychiatric disorders. Multidisciplinary approaches that combine physical therapy, cognitive behavioral therapy (CBT), and neuropsychological interventions have proven effective in aiding recovery. For example, neurocognitive rehabilitation programs are designed to address cognitive deficits and "brain fog" by improving memory, attention, and executive function through targeted exercises and therapies (Geesler, 2022). Given the complexity and variability of neuro-COVID presentations, a multidisciplinary approach is essential. Collaboration between neurologists, immunologists, psychiatrists, and rehabilitation specialists ensures comprehensive care that addresses the full spectrum of neurological complications associated with COVID-19. This team-based approach not only improves outcomes but also provides the flexibility to adapt treatment strategies as more is learned about the long-term impacts of SARS-CoV-2 on the nervous system (Geesler, 2022).

Implications for clinical practice and public health

The neurological implications of COVID-19 have profound consequences for both clinical practice and public health. Given the significant number of COVID-19 patients who exhibit neurological symptoms-ranging from mild issues like headaches and anosmia to severe conditions such as stroke and encephalitis-comprehensive neurological assessment has become a critical component of patient care. Early identification of these symptoms can significantly impact the management and outcome of the disease, allowing for timely intervention that may prevent the progression to more severe neurological damage (Ellul et al., 2020; Zubair et al., 2020). Integrating neuro-COVID considerations into pandemic response strategies is essential to effectively manage the long-term consequences of the virus. Public health policies must prioritize the recognition and treatment of neurological symptoms as part of the broader COVID-19 response. This includes training healthcare providers to recognize neuro-COVID symptoms, developing protocols for neurological assessment in COVID-19 patients, and ensuring that neurological care is accessible, especially in under-resourced areas. Such integration can improve patient outcomes and help in managing the burden of long-term neurological sequelae on healthcare systems (Paterson et al., 2020).

Research gaps and future directions

The study of neuro-COVID has highlighted numerous research gaps that demand attention to fully understand the neurological impacts of COVID-19. One of the key unanswered questions revolves around the precise mechanisms through which SARS-

CoV-2 causes long-term neurological damage. While acute neurological manifestations have been well-documented, the long-term effects, such as cognitive impairments and neuropsychiatric conditions, are still poorly understood. This necessitates more extensive longitudinal studies to track the progression of neurological symptoms in COVID-19 survivors over time, which could provide critical insights into the development of chronic conditions like "brain fog" and post-traumatic stress disorder (PTSD) (Ceban et al., 2021). Genetic susceptibility also represents a significant area of interest. Research has identified specific genetic polymorphisms, particularly in the ACE2 and TMPRSS2 genes, that may influence an individual’s susceptibility to SARS-CoV-2 and the severity of their neurological symptoms. Understanding these genetic factors could lead to personalized treatment approaches, optimizing therapeutic strategies based on an individual’s genetic makeup. However, there remains a need for global genetic studies that can account for the diverse genetic backgrounds across populations. This would help in identifying not only the genetic factors that confer risk but also those that might offer protection against severe neuro-COVID.

Another research gap lies in the exploration of potential biomarkers for neuro-COVID. Identifying reliable biomarkers could facilitate early diagnosis and intervention, potentially mitigating the long-term impact of the virus on the nervous system. Current studies have begun to explore the use of neuroinflammatory markers, but there is a clear need for more comprehensive research to validate these findings and develop practical clinical tools (Kanberg et al., 2020). The global nature of the COVID-19 pandemic underscores the importance of international collaboration in neuro-COVID research. Collaborative efforts, such as data sharing across different regions and pooling resources for large-scale studies, are crucial for overcoming the challenges posed by the pandemic. A coordinated global response could accelerate the development of effective treatments and preventive strategies, ensuring that discoveries are rapidly translated into clinical practice (Kousathanas et al., 2022).

Conclusion

The intersection of neuroscience and COVID-19 has unveiled a complex and multifaceted impact of SARS-CoV-2 on the nervous system, ranging from acute neurological symptoms to long-term sequelae that continue to challenge our understanding and treatment of the disease. The pathophysiology of neuro-COVID is characterized by the virus's neurotropism, its entry via ACE2 receptors, and the disruption of the blood-brain barrier, all of which contribute to a broad spectrum of neurological manifestations. Long-term effects, such as cognitive impairments, chronic fatigue, and neuropsychiatric disorders, underscore the critical need for ongoing research into the underlying mechanisms and potential treatments. Advances in neuroimaging and the development of targeted therapeutics offer promise for the future. However, significant research gaps persist, particularly in understanding genetic susceptibility and the broader implications for global public health. Addressing these challenges is essential for improving patient outcomes and preparing for the potential long-term impacts of neuro-COVID on public health. The need for global collaboration and a multidisciplinary approach is paramount as we strive to mitigate the enduring effects of this pandemic on the nervous system.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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