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Review

Acute and long-term neurological manifestations of Covid-19: insights from virology and neurology

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Introduction
This literature review examines the profound impact of Covid-19, caused by SARS-CoV-2, on the nervous system. While the virus is predominantly associated with respiratory complications, emerging evidence highlights its strong neurotropic potential, leading to a broad spectrum of neurological disorders. This review explores the convergence of virology and neurology, emphasizing both acute and long-term neurological consequences of the disease.

Methods
A systematic review following PRISMA guidelines was conducted using databases such as PubMed, Scopus, and Web of Science. Studies were selected based on their relevance to the pathophysiology, clinical presentations, and prolonged neurological effects of Covid-19. Preference was given to peer-reviewed research, including meta-analyses and clinical case reports published between 2020 and 2024.

Results
The review identifies various pathways through which SARS-CoV-2 affects the nervous system, including direct neuroinvasion and systemic inflammatory responses. Acute neurological conditions such as encephalitis, stroke, and Guillain-Barré syndrome have been frequently reported, while chronic complications include cognitive dysfunction, neurodegenerative disorders, and psychiatric disturbances. These findings highlight the intricate and enduring neurological burden of Covid-19.

Conclusion
Neuro-Covid presents an ongoing challenge in the post-pandemic landscape. A deeper understanding of its neurological implications is essential for enhancing patient management and shaping future research directions. This review highlights the importance of increased clinical vigilance and a multidisciplinary strategy to effectively address the complex and evolving spectrum of Covid-19-related neurological disorders.

Keywords:
Neuro-Covid
SARS-CoV-2
Neurological manifestations
Long Covid
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Introduction

The emergence of SARS-CoV-2, the virus responsible for Covid-19, has had a profound impact on global health, causing millions of fatalities and straining healthcare infrastructures worldwide. Although initially recognized for its respiratory complications, it has become evident that the virus can also affect multiple organ systems, including the nervous system. This realization has led to an increasing focus on the neurological consequences of Covid-19 (1).

The global burden of Covid-19 has been unprecedented. As of 2024, more than 770 million confirmed cases and nearly 7 million deaths have been reported worldwide. The rapid transmission of SARS-CoV-2 and its potential to cause severe complications, particularly in high-risk populations, have posed a significant public health crisis (2). In response, researchers have extensively investigated the disease's systemic effects, including its impact on the nervous system.

Viral infections have long been associated with neurological complications. Neurotropic viruses such as herpes simplex virus and West Nile virus have the ability to directly invade the central nervous system (CNS), leading to conditions such as encephalitis and meningitis. Additionally, some viruses induce neurological damage through immune-mediated processes or systemic effects, such as hypoxia and coagulopathies. SARS-CoV-2 appears to exert its neurological effects through multiple mechanisms, including direct viral invasion, inflammatory responses, and vascular involvement, resulting in a wide range of neurological symptoms (3).

The motivation for studying Covid-19's neurological impact stems from the diverse spectrum of reported symptoms, which range from mild headaches and anosmia to severe conditions such as stroke, encephalitis, and Guillain-Barré syndrome (3). Understanding these neurological manifestations is critical for enhancing patient care and improving clinical outcomes. Early detection of neurological symptoms may facilitate timely intervention, potentially reducing morbidity and mortality. Moreover, investigating the mechanisms through which SARS-CoV-2 affects the nervous system could provide valuable insights into the broader field of neurovirology, contributing to advancements in the treatment of other neurotropic viral infections (2).

This review aims to explore the acute and long-term neurological effects of Covid-19 by analyzing existing literature and identifying key mechanisms contributing to neurological complications. We hypothesize that SARS-CoV-2 induces neurological manifestations through direct viral invasion, systemic inflammation, and immune-mediated mechanisms, leading to both acute and chronic effects.

Methodology

This literature review was conducted using a systematic methodology in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This approach ensured a thorough and unbiased selection of relevant studies examining the neurological manifestations of Covid-19.

Search Strategy

A comprehensive literature search was performed across four major databases: PubMed, Scopus, Web of Science, and Google Scholar. The search covered studies published between January 2020 and December 2024, ensuring an extensive review of available literature. The strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords, including "Neuro-Covid," "SARS-CoV-2," "*Neurological manifestations,*" "*Long Covid,*" *and* "*Neuroinvasion*." Boolean operators (*AND, OR*) were applied to refine the search results and maximize the inclusion of relevant studies.

Inclusion and Exclusion Criteria

To ensure the relevance and reliability of the included studies, the following criteria were applied:

Inclusion Criteria

- Language: Only studies published in English were included to minimize language bias.
- Population: Studies focusing on patients diagnosed with Covid-19 and experiencing neurological symptoms.
- Focus: Articles that specifically examined neurological manifestations of Covid-19.
- Study Design: Peer-reviewed studies, including case reports, cohort studies, cross-sectional studies, systematic reviews, and meta-analyses.

Exclusion Criteria

- Non-peer-reviewed articles, including preprints, editorials, commentaries, and opinion pieces.
- Studies lacking primary data, such as letters to the editor and conference abstracts.
- Animal or in vitro studies that did not provide direct clinical relevance.
- Studies focusing on general Covid-19 complications without discussing neurological involvement.

Study Selection and Screening Process

An initial search yielded 168 studies, which were reviewed in multiple stages:

1. Duplicate Removal: After eliminating duplicates, 120 unique studies remained.
2. Title and Abstract Screening: Two independent reviewers assessed the relevance of these studies based on their titles and abstracts. Articles not meeting the inclusion criteria were excluded.
3. Full-Text Review: The remaining 70 studies underwent a detailed full-text review to ensure they specifically addressed neurological manifestations of Covid-19. This process led to the exclusion of 30 additional studies that did not sufficiently focus on neuro-Covid.

Following this screening process, 40 studies met all inclusion criteria and were incorporated into the final review. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Data extraction and synthesis

Key information was systematically extracted from each included study using a standardized data extraction template. The collected data included:

- Study characteristics (author, publication year, study design, sample size).
- Patient demographics (age, gender, comorbidities).
- Neurological manifestations (acute and long-term symptoms).
- Pathophysiological mechanisms and outcomes associated with neuro-Covid.

The extracted data were synthesized to provide a comprehensive overview of Covid-19's impact on the nervous system.

Quality assessment

To evaluate the reliability of the included studies, the Newcastle-Ottawa Scale was used for observational studies, while the Cochrane Risk of Bias tool was applied to randomized controlled trials. This ensured that the findings presented in this review were based on high-quality evidence.

To illustrate the study selection process, a PRISMA flow diagram (Figure 1) is included, detailing the number of records identified, screened, and excluded at each stage.

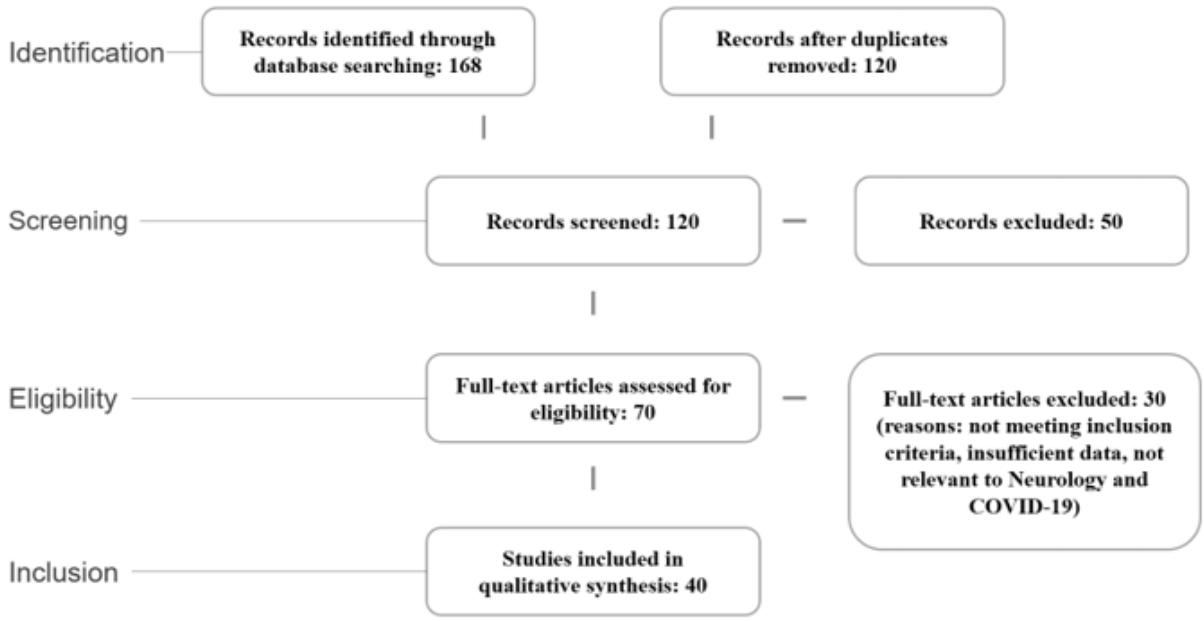

Figure 1. Illustrates the PRISMA flow diagram

Results

A total of 40 studies met the inclusion criteria and were analyzed to assess the neurological manifestations associated with Covid-19. The findings indicate a wide range of both acute and long-term neurological complications linked to SARS-CoV-2 infection (Table 1).

Acute neurological manifestations

• Central Nervous System (CNS): Neurological complications such as encephalitis, meningitis, acute disseminated encephalomyelitis (ADEM), and ischemic stroke were commonly reported. Symptoms ranged from mild cognitive disturbances (e.g., confusion, headaches) to severe cases involving coma and large-vessel strokes. Notably, stroke emerged as a major concern in younger individuals, with the hypercoagulable state induced by SARS-CoV-2 acting as a significant contributing factor. Recent studies report that the incidence of stroke among hospitalized Covid-19 patients ranges between 1.2% and 6.9%, with a higher prevalence among those with severe disease.

• Peripheral Nervous System (PNS): Guillain-Barré Syndrome (GBS) and its variants were frequently observed, manifesting as ascending paralysis. Additionally, anosmia (loss of smell) and ageusia (loss of taste) were among the most prevalent early symptoms, often linked to viral invasion of the olfactory nerve. Studies suggest that up to 60% of Covid-19 patients experience anosmia or ageusia during the acute phase of infection.

Long-term neurological sequelae

• Cognitive and Psychiatric Disorders: Many individuals who recovered from Covid-19 reported persistent cognitive deficits, commonly referred to as "brain fog." These symptoms, which include memory impairment, chronic headaches, fatigue, and dizziness, were frequently associated with Long Covid. Additionally, an increased prevalence of anxiety (30–40%), depression (25–35%), and post-traumatic stress disorder (PTSD, 10–20%) has been documented in post-Covid-19 patients.

• Neurodegenerative Concerns: Emerging evidence suggests that SARS-CoV-2 may exacerbate or contribute to the development of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Persistent neuroinflammation and immune dysregulation have been proposed as potential mechanisms underlying these effects.

• Pediatric Considerations: Children diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) have exhibited severe neurological complications, including encephalopathy and cerebrovascular events. Long-term neurodevelopmental outcomes in children who experienced severe Covid-19 remain under investigation, but concerns regarding cognitive and behavioral impairments have been raised.

Immunological and Molecular Insights

The review highlights the critical role of immune dysregulation in Covid-19-related neurological damage. The cytokine storm, a hyperinflammatory response observed in severe cases, significantly impacts the blood-brain barrier (BBB), increasing permeability and leading to neuroinflammation. Additionally, autoimmune mechanisms triggered by molecular mimicry have been implicated in the development of GBS and other post-infectious neuropathies, raising concerns about long-term neurodegenerative risks in recovered patients.

Diagnostic Challenges

Diagnosing Covid-19-related neurological conditions remains complex due to overlapping symptoms with other neuroinflammatory and vascular disorders. Neuroimaging techniques, including MRI and CT scans, have been valuable in detecting abnormalities such as white matter lesions, microhemorrhages, and cortical atrophy. Additionally, biomarkers such as neurofilament light chain (NfL) and S100B have shown promise in assessing neuronal injury, though their specificity requires further validation in large-scale studies.

Therapeutic Approaches

Management strategies for neurological complications of Covid-19 have evolved over time. Corticosteroids, particularly dexamethasone, have proven effective in reducing inflammation and improving neurological outcomes in severe cases. Long-term care for patients with persistent neurological symptoms often involves cognitive rehabilitation and neuropsychiatric support. Additionally, ongoing research is exploring neuroprotective therapies, including anti-inflammatory agents, antioxidant compounds, and immunomodulators, to mitigate long-term neurological damage.

Table 1. Shows a summary of key findings

Neurological Manifestation	Prevalence/Key Findings
Stroke	Reported in 1.2–6.9% of hospitalized Covid-19 patients, higher in severe cases.
Anosmia & Ageusia	Affects up to 60% of Covid-19 patients in the acute phase.
Cognitive Impairment ("Brain Fog")	Persistent in 20–30% of post-Covid-19 patients.
Anxiety & Depression	Documented in 30–40% (anxiety), 25–35% (depression) of Long Covid patients.
Neurodegenerative Disease Risk	Increased risk of Parkinson's & Alzheimer's due to chronic neuroinflammation.
Guillain-Barré Syndrome (GBS)	Frequently reported post-Covid-19, linked to autoimmune dysregulation.
Multisystem Inflammatory Syndrome in Children (MIS-C)	Associated with neurological complications, encephalopathy, and developmental concerns.

Discussion

Pathophysiology of SARS-CoV-2

The interaction of SARS-CoV-2 with the central nervous system (CNS) is a complex process involving both direct and indirect mechanisms of neuroinvasion. A key factor contributing to neurological manifestations is the virus's ability to penetrate the CNS, a process referred to as neuroinvasion. This can occur via direct viral entry, systemic inflammatory responses, or a combination of both mechanisms.

SARS-CoV-2, like other coronaviruses, has neurotropic properties, meaning it can infect neuronal tissues. There are two primary mechanisms through which the virus invades the CNS: (1) Direct viral entry, where the virus infiltrates the brain tissue, and (2) Systemic inflammatory pathways, which cause widespread neuroinflammation. Direct viral invasion can occur through hematogenous spread, in which SARS-CoV-2 enters the bloodstream, crosses the blood-brain barrier (BBB), and reaches the CNS. Another route of entry is retrograde neuronal transport, where the virus travels along peripheral nerves such as the olfactory nerve to gain access to the brain (4).

Hematogenous dissemination plays a crucial role in neuroinvasion. After infecting the respiratory system, the virus can enter the systemic circulation and potentially disrupt the BBB, which typically restricts pathogens from reaching the brain. SARS-CoV-2 binds to ACE2 receptors on the endothelial cells of the BBB, leading to increased permeability and facilitating viral penetration into the CNS. This disruption of the BBB can also cause inflammatory responses and cerebral edema, further exacerbating neurological damage (5).

The olfactory route represents another significant entry pathway for SARS-CoV-2. The olfactory nerve, which extends from the nasal cavity to the brain, provides a direct conduit for viral invasion. SARS-CoV-2 can infect olfactory epithelial cells that express ACE2 receptors, allowing the virus to travel directly into the CNS. This pathway has been closely linked to anosmia (loss of smell), which is one of the most frequently reported neurological symptoms of Covid-19 (5,6).

The exact role of the BBB in neuroinvasion remains debated, with conflicting evidence in the literature. Some studies suggest that the BBB remains largely intact in mild Covid-19 cases, while others report significant BBB disruption in severe cases, leading to increased neuroinflammation. Additionally, the extent of BBB impairment appears to vary by patient population, with elderly individuals and those with pre-existing neurological conditions (e.g., multiple sclerosis, Alzheimer's disease) being at higher risk for severe neurovascular involvement (7).

Furthermore, the inflammatory response triggered by SARS-CoV-2, known as the cytokine storm, plays a pivotal role in neurological damage. The excessive release of pro-inflammatory cytokines (such as IL-6 and TNF-α) can compromise BBB integrity, allowing immune cells and inflammatory mediators to infiltrate the CNS. This process is linked to severe neurological complications, including encephalopathy, stroke, and neurodegeneration. However, some studies suggest that immune-mediated neuroinflammation, rather than direct viral entry, may be the primary driver of Covid-19-related neurological damage, highlighting ongoing debates in the scientific community (7).

Acute neurological manifestations

The neurological complications of Covid-19 can be classified into central nervous system (CNS) and peripheral nervous system (PNS) manifestations. These acute neurological symptoms range from mild cognitive disturbances to severe life-threatening conditions, such as stroke and encephalitis.

Among CNS complications, encephalitis and meningitis have been frequently reported. These conditions are characterized by altered mental status, confusion, and, in severe cases, coma. Another reported condition is acute disseminated encephalomyelitis (ADEM), an inflammatory attack on the brain and spinal cord, likely triggered by an abnormal immune response to SARS-CoV-2 (8).

Ischemic stroke is another major neurological concern in Covid-19 patients, often linked to the hypercoagulable state induced by the virus. Clinical reports from China and the United States suggest that large-vessel strokes are occurring at an increased frequency among younger patients, raising concerns about the long-term cerebrovascular impact of Covid-19 (8,9). The risk of stroke is significantly higher in individuals with pre-existing cardiovascular disease, diabetes, and hypertension, as these conditions exacerbate coagulation abnormalities associated with SARS-CoV-2 infection.

Additionally, seizures and status epilepticus have been observed in severe Covid-19 cases. While less common than other CNS complications, these findings suggest that SARS-CoV-2 may exacerbate pre-existing seizure disorders or trigger new-onset epilepsy in some patients (10).

Covid-19 has also been associated with peripheral nervous system (PNS) disorders, most notably Guillain-Barré Syndrome (GBS) and its variants, such as Miller Fisher syndrome. GBS is a post-infectious autoimmune disorder that manifests as ascending paralysis and can lead to severe respiratory failure in critical cases. The proposed mechanism for Covid-19-associated GBS is molecular mimicry, in which the immune system mistakenly attacks

peripheral nerves due to similarities between viral antigens and host proteins (11,12).

Beyond GBS, SARS-CoV-2 has been linked to neuropathy and myopathy, with affected individuals reporting muscle pain, weakness, and sensory deficits. These symptoms may result from either direct viral invasion of muscle tissues or secondary inflammatory processes triggered by Covid-19 (11).

Among the most frequently reported neurological symptoms are anosmia (loss of smell) and ageusia (loss of taste). These symptoms are believed to result from viral invasion of the olfactory nerve or damage to supporting cells in the nasal epithelium. Notably, anosmia and ageusia have been documented even in mild Covid-19 cases, emphasizing the virus's ability to affect the nervous system early in the disease course (13).

Certain populations exhibit distinct neurological vulnerabilities when infected with SARS-CoV-2:

• Elderly patients have been found to experience higher rates of stroke, delirium, and cognitive dysfunction following Covid-19 infection. Studies suggest that pre-existing neurodegenerative conditions (e.g., Alzheimer's and Parkinson's disease) may be exacerbated by Covid-19-induced neuroinflammation, accelerating cognitive decline (9).

• Patients with pre-existing neurological disorders, including multiple sclerosis, epilepsy, and migraine disorders, have reported worsening symptoms following SARS-CoV-2 infection. This may be due to either direct viral effects on neural tissues or immune-mediated flare-ups triggered by systemic inflammation.

• Individuals with metabolic disorders, such as diabetes and obesity, are at a higher risk of severe neurological complications, including stroke and neuropathy, due to underlying vascular dysfunction and inflammatory responses (10).

While substantial evidence supports the neuroinvasive potential of SARS-CoV-2, some studies challenge the extent of direct viral entry into the CNS. Several neuropathological analyses have failed to detect viral RNA or proteins in brain tissues, suggesting that inflammatory and immune-mediated processes may play a more significant role in neurological damage than direct viral invasion. Additionally, inconsistencies exist regarding the prevalence of stroke and GBS in Covid-19 patients, with some reports indicating no significant increase in these conditions compared to non-Covid-19 viral infections (12). Further longitudinal studies are needed to clarify these disparities and establish a more definitive understanding of neuro- Covid mechanisms.

Long-term neurological sequelae

The long-term neurological consequences of Covid-19, commonly referred to as "Long Covid," have become an area of increasing concern in the post-pandemic era. Collectively termed Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), these complications manifest as persistent neurological symptoms that continue beyond the acute phase of infection. Among the most frequently reported symptoms are cognitive impairments, often described as "brain fog," along with chronic headaches, fatigue, and dizziness (14). These cognitive difficulties include impaired concentration, memory deficits, and executive dysfunction, significantly affecting daily functioning and overall quality of life. The underlying mechanisms of these symptoms remain under investigation, with hypotheses suggesting that they result from prolonged neuroinflammation, immune system dysregulation, or direct viral effects on the central nervous system (CNS) (15).

Beyond cognitive and sensory impairments, Long Covid has been associated with an increased burden of mental health conditions, including anxiety, depression, and post-traumatic stress disorder (PTSD). Many patients report ongoing psychological distress, which exacerbates the already complex neurological sequelae of SARS-CoV-2 infection. The bidirectional relationship between neurological symptoms and psychiatric disorders creates a significant challenge for both patients and healthcare providers, emphasizing the need for a multidisciplinary approach to management (16). Furthermore, there is growing evidence that Covid-19 may accelerate or contribute to the onset of neurodegenerative diseases such as Parkinson's and Alzheimer's disease.

The suspected mechanisms behind these associations include sustained neuroinflammation and chronic immune system activation, which may exacerbate pathological processes linked to neurodegeneration (17). The potential role of blood-brain barrier (BBB) dysfunction in facilitating neuroinflammatory cascades further strengthens the concern that Covid-19 could increase susceptibility to neurodegenerative conditions over time (18). While some studies support these findings, conflicting evidence suggests that not all Covid-19 survivors experience persistent neurological dysfunction, highlighting the need for longitudinal studies to clarify the long-term risks (19). Given the significant uncertainties, continued research and clinical monitoring of recovered individuals, particularly those with lingering neurological symptoms, are essential to better understand and mitigate long-term complications.
Immunological and molecular insights

The immunological and molecular mechanisms responsible for the neurological impact of Covid-19 are complex and multifaceted. One of the primary contributors

to these complications is the "cytokine storm," an excessive inflammatory response triggered by the immune system in reaction to SARS-CoV-2 infection. This hyperinflammatory state involves the overproduction of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, which have been implicated in disrupting the CNS. The integrity of the BBB is compromised during this inflammatory process, allowing inflammatory mediators and immune cells to infiltrate the CNS. This infiltration results in widespread neuroinflammation, neuronal damage, and a range of neurological symptoms that can persist even after the acute infection has resolved (20,21).

Autoimmune responses have also been identified as a key factor in the neurological manifestations of Covid-19. SARS-CoV-2 has been shown to induce autoimmunity, where the immune system mistakenly attacks the body's own tissues, including neurons and glial cells. This phenomenon, known as molecular mimicry, occurs when viral antigens share structural similarities with human proteins, leading to immune cross-reactivity. In some cases, this process has been linked to the development of post-infectious neurological disorders such as Guillain-Barré Syndrome (GBS) and other autoimmune neuropathies (12,22). The long-term implications of this immune dysfunction remain an area of ongoing research, as some patients continue to exhibit signs of immune-mediated neurological damage long after their initial infection.

Molecular mimicry and cross-reactivity raise additional concerns regarding the potential for SARS-CoV-2 to accelerate or trigger chronic neurological conditions. Persistent immune system activation and prolonged neuroinflammatory states have been hypothesized as contributing factors to neurodegenerative diseases, including Parkinson's and Alzheimer's disease. While emerging research supports this hypothesis, conflicting studies suggest that the long-term risk of neurodegeneration may vary depending on factors such as genetic predisposition, pre-existing neurological conditions, and the severity of initial Covid-19 symptoms (23,24). Understanding these complex immune mechanisms is essential for developing targeted therapeutic interventions to mitigate the long-term neurological effects of Covid-19.

Pediatric neurological manifestations

The pediatric population has exhibited a distinct set of neurological manifestations related to Covid-19, primarily through conditions such as Multisystem Inflammatory Syndrome in Children (MIS-C) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). MIS-C is a severe hyperinflammatory disorder that can develop following SARS-CoV-2 infection, often presenting with neurological complications such as encephalopathy, cerebrovascular events, and acute demyelinating syndromes. The exact mechanisms underlying these neurological manifestations are still being investigated, but current evidence suggests that they may result from a combination of systemic inflammation, direct viral invasion of the CNS, and autoimmune responses (25,26).

In addition to MIS-C, PANS has emerged as a concerning post-infectious phenomenon in children following Covid-19. This syndrome is characterized by the sudden onset of neuropsychiatric symptoms, including obsessive-compulsive behaviors, motor tics, and severe behavioral disturbances. The pathophysiology of PANS is believed to involve immune dysregulation and molecular mimicry, where the immune system's response to SARS-CoV-2 cross-reacts with neural tissues, leading to neuroinflammation and psychiatric symptoms (26). The precise link between Covid-19 and PANS remains an area of active research, but the increasing number of reported cases suggests a potential role for SARS-CoV-2 in triggering immune-mediated neuropsychiatric conditions in children.

Beyond these acute neurological syndromes, concerns have been raised about the long-term cognitive and developmental consequences of Covid-19 in children. Preliminary studies suggest that children who experienced severe Covid-19 or MIS-C may be at increased risk for persistent cognitive deficits, memory impairments, and executive dysfunction. These effects are thought to be mediated by ongoing neuroinflammation, BBB disruption, and potential direct viral effects on developing neural circuits. However, the extent and duration of these cognitive impacts remain unclear, as long-term follow-up studies are still in progress (27,28). Given the critical period of brain development in childhood, continued monitoring and early intervention strategies are necessary to assess and address any lasting neurological effects in pediatric populations.

Diagnostic challenges and biomarkers

The neurological complications of Covid-19 pose significant diagnostic challenges due to their overlap with various other neurological conditions, necessitating a multifaceted approach involving advanced neuroimaging techniques and biomarker assessments. Imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans have played a crucial role in identifying Covid-19-related neurological abnormalities. MRI has been particularly effective in detecting white matter hyperintensities, microhemorrhages, and cortical abnormalities, which are indicative of neuroinflammatory processes associated with SARS-CoV-2 infection. PET scans, though less commonly employed, have revealed altered glucose metabolism in the frontal and temporal lobes, findings that correlate with cognitive impairments such as "brain fog" commonly observed in Long Covid cases (28).

In addition to imaging, cerebrospinal fluid (CSF) analysis has provided valuable insights into the immune response and neuronal damage associated with Covid-19. Elevated

levels of neurofilament light chain (NfL) in the CSF have been correlated with neuronal injury, suggesting its potential utility as a biomarker for assessing the severity of neurological involvement in Covid-19. Furthermore, the presence of oligoclonal bands (OCBs) in the CSF has been associated with intrathecal antibody synthesis, indicating an ongoing immune response within the CNS (29). Despite these advances, the interpretation of biomarker data remains complex. Conflicting reports exist regarding the specificity and sensitivity of biomarkers such as NfL and S100B, with some studies suggesting that these markers may not be exclusive to Covid-19-related neurological injury and could be elevated in other neuroinflammatory or neurodegenerative conditions(30). Consequently, further research is necessary to refine their diagnostic utility and establish standardized thresholds for clinical use (31).

Differentiating Covid-19-related neurological disorders from other conditions such as autoimmune encephalitis, stroke, and neurodegenerative diseases remains a pressing challenge. While neuroimaging and biomarker assessments provide critical diagnostic clues, population-specific factors also influence diagnostic complexity (31). Elderly patients, for instance, may present with neurological symptoms that resemble those seen in age-related neurodegenerative diseases such as Alzheimer's or Parkinson's, complicating the distinction between Covid-19-induced pathology and pre-existing cognitive decline(29). Similarly, individuals with pre-existing neurological conditions such as multiple sclerosis (MS) or epilepsy may experience exacerbations triggered by the inflammatory response to SARS-CoV-2, making it difficult to ascertain whether new neurological findings are a direct consequence of Covid-19 or part of an underlying disease progression (28). Understanding these nuances is crucial for developing targeted diagnostic algorithms that account for age, comorbidities, and pre-existing neurological vulnerabilities.

Therapeutic approaches and management

The management of Covid-19 related neurological complications requires a multidisciplinary therapeutic approach that addresses both acute and long-term neurological effects. Early recognition and intervention are crucial in the acute phase, particularly for severe manifestations such as stroke, encephalitis, and seizures. Among pharmacological treatments, corticosteroids such as dexamethasone have shown efficacy in mitigating neuroinflammatory responses and preventing severe neurological sequelae. Their ability to suppress the hyperinflammatory state associated with severe Covid-19 has been instrumental in reducing morbidity. Additionally, antiviral therapies like remdesivir, when used in conjunction with corticosteroids, have demonstrated a synergistic effect in limiting viral replication and decreasing the frequency of neurological complications (32).

As the pandemic has progressed, emphasis has shifted toward managing long-term neurological sequelae, particularly those associated with Long Covid or Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). Persistent symptoms such as cognitive impairment, chronic headaches, fatigue, and neuropsychiatric disorders (anxiety, depression, PTSD) require a comprehensive rehabilitation strategy. Cognitive rehabilitation techniques, aimed at improving memory, attention, and executive function, have been increasingly recognized as essential in managing cognitive dysfunction in post- Covid-19 patients. Similarly, neuropsychiatric rehabilitation, including psychotherapy and pharmacotherapy, is critical for addressing mental health complications associated with Long Covid (33).

Ongoing research is exploring the potential role of neuroprotective agents in preventing or mitigating the long-term neurological impact of Covid-19. Compounds such as N-acetylcysteine (NAC) and melatonin are under investigation for their antioxidant and anti-inflammatory properties, which may help reduce oxidative stress and neuronal damage. These agents have been proposed as potential therapies to preserve neuronal integrity and limit the progression of neurodegenerative diseases in individuals with a history of Covid-19 (34). However, the efficacy of these treatments remains uncertain, with conflicting findings in preliminary studies regarding their impact on long-term neurological outcomes.

Given the central role of chronic inflammation in Covid-19-related neurological complications, research has also focused on anti-inflammatory therapies beyond corticosteroids. Drugs targeting specific inflammatory pathways, such as interleukin-6 (IL-6) inhibitors (e.g., tocilizumab) and Janus kinase (JAK) inhibitors, are being evaluated for their ability to modulate prolonged neuroinflammatory responses and reduce the risk of long-term neurological deterioration (35). These approaches hold promise, but clinical trials are needed to confirm their safety and efficacy in neuro- Covid management.

Rehabilitation plays an integral role in recovery from Covid-19-induced neurological damage, particularly for individuals experiencing persistent cognitive and motor deficits. Multidisciplinary rehabilitation programs incorporating physical therapy, occupational therapy, speech therapy, and neuropsychological support have proven beneficial in helping patients regain lost function and enhance their quality of life. Telemedicine has emerged as an invaluable tool in providing rehabilitation services to individuals with Long Covid, ensuring continuous medical care while reducing the risk of exposure to infections(36).

Population-specific therapeutic considerations are crucial, as the impact of Covid-19 on neurological function varies among different demographic groups. Elderly patients, who are at increased risk for both acute neurological complications (e.g., stroke, encephalopathy) and long-term cognitive decline, require specialized rehabilitation

programs that balance cognitive training with management of pre-existing neurodegenerative conditions. Likewise, patients with underlying neurological disorders such as multiple sclerosis, Parkinson's disease, and epilepsy may need adjusted treatment regimens to account for disease-specific vulnerabilities and avoid exacerbation of symptoms. Further research is needed to tailor therapeutic strategies to these high-risk populations, ensuring that treatment protocols are optimized for different patient profiles.

Despite significant progress in understanding and managing Covid-19's neurological impact, gaps remain in our knowledge regarding the long-term effectiveness of various treatment approaches. While some studies support the use of anti-inflammatory and neuroprotective therapies, others question their ability to prevent irreversible neurological damage. Large-scale, longitudinal studies are essential to evaluate the long-term trajectory of neurological recovery in Covid-19 survivors and to refine therapeutic guidelines accordingly. Continued collaboration between neurologists, immunologists, psychiatrists, and rehabilitation specialists will be critical in shaping comprehensive care models for patients experiencing post-Covid-19 neurological complications.

Future directions and research gaps

The neurological impact of Covid-19 has exposed several critical gaps in current medical knowledge, highlighting the need for further research. One of the most pressing concerns is the lack of comprehensive longitudinal studies to assess the long-term neurological consequences of SARS-CoV-2 infection. While emerging evidence suggests that Covid-19 may contribute to the acceleration of neurodegenerative diseases such as Alzheimer's and Parkinson's, definitive conclusions remain elusive due to limited long-term follow-up data. Large-scale prospective cohort studies are needed to track the progression of cognitive decline and neurological dysfunction in recovered Covid-19 patients over extended periods (37,38).

In addition to understanding long-term sequelae, research efforts must focus on the development of targeted therapies for neuro-Covid. Anti-inflammatory treatments are a major area of interest, given that neuroinflammation has been implicated in both acute and chronic neurological manifestations of Covid-19. Immunomodulatory drugs that can selectively mitigate neuroinflammatory responses without compromising the body's ability to fight infection are under investigation. Furthermore, neuroprotective agents such as antioxidants, mitochondrial stabilizers, and agents that promote neurogenesis are being explored as potential strategies to prevent irreversible neuronal damage in severe cases (39).

Despite the urgency of finding effective treatments, conflicting findings in the literature have complicated the development of standardized therapeutic approaches. While some studies report a clear association between Covid-19 and increased neurodegeneration, others suggest that the observed cognitive impairments may be temporary post-viral effects rather than indicators of progressive neurodegenerative disease. Further research is required to determine whether SARS-CoV-2 is directly contributing to neurodegenerative pathologies or if these symptoms are the result of prolonged systemic inflammation and vascular dysfunction. Population-specific considerations must also be taken into account, as elderly individuals and those with pre-existing neurological disorders may be particularly susceptible to long-term cognitive deficits following Covid-19 infection. Future studies should focus on identifying risk factors for persistent neurological impairment, allowing for the development of personalized treatment approaches (40).

Ethical considerations are also crucial in ongoing neuro-Covid research. The urgency to develop effective treatments must be balanced against the need for rigorous testing to avoid unintended adverse effects. The complexity of SARS-CoV-2's neurological impact necessitates a multidisciplinary research approach, incorporating expertise from neurology, immunology, psychiatry, and virology to ensure a comprehensive understanding of the condition. Collaborative research efforts will be essential in developing evidence-based clinical guidelines that improve the diagnosis, treatment, and long-term management of Covid-19-associated neurological complications.

Conclusion

This review highlights the wide-ranging neurological effects of Covid-19, encompassing both acute conditions such as encephalitis, stroke, and Guillain-Barré syndrome, as well as long-term complications including cognitive impairment, neuropsychiatric disorders, and potential neurodegenerative progression. The underlying mechanisms involve direct viral invasion, systemic inflammation, immune-mediated responses, and blood-brain barrier disruption. Clinicians should prioritize early detection and intervention, utilizing neuroimaging and cerebrospinal fluid analysis to distinguish Covid-19-related neurological symptoms from other conditions. While biomarkers like neurofilament light chain (NfL) and inflammatory markers show promise in assessing neuronal injury, their clinical applicability requires further validation. Treatment strategies should be tailored to disease severity, incorporating corticosteroids, neuroprotective agents, and targeted anti-inflammatory therapies. For long Covid cases, multidisciplinary rehabilitation programs, including cognitive training, psychiatric support, and physical therapy, are essential for recovery and improving quality of life.

Future research should focus on longitudinal studies to track the long-term neurological impact of Covid-19,

particularly in high-risk populations such as elderly individuals and those with pre-existing neurological disorders. Determining whether SARS-CoV-2 contributes to chronic neurodegenerative diseases or if symptoms are transient post-viral effects remains a critical area of investigation. Additionally, further exploration of immune-modulating treatments, neuroprotective strategies, and personalized therapeutic interventions will be necessary to optimize patient outcomes. Addressing the neurological burden of Covid-19 requires a collaborative and interdisciplinary approach, involving specialists from neurology, infectious diseases, immunology, psychiatry, and rehabilitation sciences. Global research efforts must continue to enhance diagnostic precision, refine treatment protocols, and mitigate the long-term neurological consequences of Covid-19.

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