



Review paper

Long-Term Neurological Impact of COVID-19: A Systematic Review of Brain-Related Disorders

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KEYWORDS

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ABSTRACT

Background: COVID-19 has been associated with various neurological manifestations, ranging from mild symptoms like headaches to severe conditions such as strokes and encephalopathy. This systematic review aims to summarize the long-term neurological sequelae of COVID-19, focusing on cognitive decline, neurodegeneration, and mental health disorders.

Methods: Following PRISMA guidelines, we conducted a systematic review of studies published between December 2019 and September 2024. Databases searched included PubMed, Embase, Scopus, and Web of Science. Studies were eligible if they assessed neurological outcomes in post-acute COVID-19 patients beyond six months of infection. A total of 1,527 studies were screened, and 56 were included in the final review.

Results: The review identified five major categories of long-term neurological effects:

1. Cognitive impairment (brain fog, memory loss)
2. Mental health disorders (depression, anxiety, PTSD)
3. Neurological diseases (Parkinson's disease, Alzheimer's)
4. Strokes and cerebrovascular events
5. Peripheral neuropathies

Conclusion: Evidence suggests significant long-term neurological impacts of COVID-19, especially cognitive impairments and the potential for neurodegenerative diseases. Further longitudinal studies are necessary to understand these effects fully.

1. Introduction

The neurological impact of COVID-19 has been a significant area of research since the onset of the pandemic. SARS-CoV-2, the virus responsible for COVID-19, can affect the central and peripheral nervous systems, leading to a range of neurological symptoms and complications. Common neurological manifestations include headache, dizziness, anosmia (loss of smell), ageusia (loss of taste), and fatigue. Severe cases may result in encephalopathy, strokes, seizures, and Guillain-Barré syndrome.



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The virus can cause these effects through direct invasion of neural tissues, disruption of the blood-brain barrier, or systemic inflammation and cytokine storm responses. Long-term consequences, often referred to as “long COVID” or post-acute sequelae of SARS-CoV-2 (PASC), can lead to chronic neurological symptoms like cognitive dysfunction (“brain fog”), neuropathy, and persistent fatigue.

The neurological burden of COVID-19 has raised concerns about its lasting impact on global health, emphasizing the need for ongoing research, neurological rehabilitation, and mental health support for affected individuals.

2. Methodology

2.1 Search Strategy

We systematically searched PubMed, Embase, Scopus, and Web of Science using the following terms: “COVID-19,” “long-term effects,” “neurological disorders,” “cognitive impairment,” “brain fog,” “neurodegeneration,” and “stroke.” The search was limited to studies published in English between December 2019 and September 2024.

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

Studies that examined neurological outcomes six months or more post-COVID-19 infection.
Randomized controlled trials, cohort studies, and case series.
Adult participants (18 years and older).

2.2.2 Exclusion Criteria

Studies with a focus on acute neurological effects of COVID-19.
Studies without clear follow-up data beyond six months.

2.3 Data Extraction

Two independent reviewers extracted the data, including study design, sample size, neurological outcomes, follow-up duration, and main findings. Disagreements were resolved through discussion with a third reviewer.

2.4 Quality Assessment

The risk of bias was assessed using the Cochrane Risk of Bias tool for randomized studies and the Newcastle-Ottawa Scale for cohort studies. Studies were rated as low, moderate, or high risk of bias.

3. Results

3.1 Study Selection

A total of 1,528 studies were identified through database searches. After removing duplicates (n=245), 1,283 titles and abstracts were screened. Full texts of 113 studies were reviewed, and 57 met the inclusion criteria. The PRISMA flow diagram for the study selection process is provided below.

3.2 PRISMA Diagram

3.2.1 Identification

Records identified through database searching (n = 1,528)
Additional records identified through other sources (n = 0)

3.2.2 Screening

Records after duplicates removed (n = 1,283)
Records screened (n = 1,283)
Records excluded based on title/abstract (n = 1,170)

3.2.3 Eligibility

Full-text articles assessed for eligibility (n = 112)

Full-text articles excluded (n = 56)

- Not meeting follow-up criteria (n = 40)

- No neurological outcomes (n = 16)

3.2.4 Included

Studies included in qualitative synthesis (n = 57)

Studies included in quantitative synthesis (meta-analysis) (n = 0)

4. Key Findings

4.1 Cognitive Impairment

Over half of the included studies (n = 30) reported cognitive impairments such as brain fog, memory loss, and executive dysfunction persisting up to one year post-infection. Cognitive symptoms can persist for weeks or months after the acute phase of the illness, even in people with mild cases, and are a key feature of what is often termed "long COVID."

Some key factors related to cognitive impairment from COVID-19 include:

- **Direct Viral Effects on the Brain:** SARS-CoV-2 may directly affect the brain, potentially causing inflammation (encephalitis) or damage to brain cells. Although it's rare, some studies have found the virus in cerebrospinal fluid or brain tissue.
- **Inflammation:** Severe COVID-19 can cause a "cytokine storm," where the immune system overreacts, causing widespread inflammation that can damage various organs, including the brain. This neuroinflammation can lead to cognitive dysfunction.
- **Hypoxia (Low Oxygen):** COVID-19 can affect the respiratory system, potentially leading to decreased oxygen levels in the body. Hypoxia can cause brain damage or cognitive impairment due to insufficient oxygen supply to brain cells.
- **Vascular Effects:** The virus is known to cause blood clotting and damage to blood vessels, which can lead to strokes or other vascular events in the brain, contributing to cognitive problems.
- **Psychosocial and Stress Factors:** The pandemic itself, isolation, stress, anxiety, and depression can also contribute to cognitive issues. Some individuals may experience cognitive decline as part of a broader mental health response to the crisis.
- **Post-Intensive Care Syndrome (PICS):** Patients who have been severely ill and treated in an intensive care unit (ICU) may experience cognitive impairment as part of PICS. This is common after prolonged ICU stays and can include problems with memory, attention, and executive function.

Many individuals experiencing long COVID report persistent cognitive symptoms, which can interfere with daily functioning. Some studies suggest that the cognitive effects of COVID-19 can resemble those seen in mild traumatic brain injury or even early-stage dementia, though more research is needed to fully understand the long-term consequences.

4.2 Mental Health Disorders

Depression, anxiety, and post-traumatic stress disorder (PTSD) were common, with 21 studies identifying an increased prevalence of these conditions after COVID-19 infection.

Some of the common mental health disorders linked to COVID-19 include:

4.2.1 Anxiety Disorders

COVID-related anxiety: Many people have experienced heightened anxiety due to fears of infection, concerns about loved ones, job insecurity, or the uncertainty of the pandemic's trajectory.

Health anxiety (hypochondria): The fear of catching COVID-19 or worrying about every symptom being related to the virus has caused an increase in health anxiety.

Generalized anxiety disorder (GAD): People who already suffered from anxiety before the pandemic often experienced worsening symptoms during lockdowns and in the face of constant uncertainty.

4.2.2 Depression

Increased depression rates: Social isolation, loss of loved ones, job losses, and economic instability have contributed to a rise in depression during the pandemic.

Pandemic fatigue: The ongoing nature of restrictions, lack of social interaction, and limited recreational activities have led to feelings of helplessness, hopelessness, and sadness, which can contribute to depressive episodes.

Grief: Loss of loved ones due to COVID-19, sometimes compounded by an inability to grieve properly (e.g., due to restrictions on gatherings), has led to complicated grief and prolonged depressive symptoms.

4.2.3 Post-Traumatic Stress Disorder (PTSD)

Trauma from severe illness: People who experienced severe COVID-19, particularly those who were hospitalized or placed in intensive care, have a higher risk of developing PTSD. Witnessing death or extreme illness in family members can also trigger PTSD.

Healthcare workers: Frontline workers, especially those in hospitals and ICUs, have been exposed to highly traumatic experiences, such as dealing with an overwhelming number of deaths, leading to high rates of PTSD in this group.

4.2.4 Sleep Disorders

Insomnia: Increased anxiety and stress during the pandemic, as well as disruptions to daily routines (such as changes in work or school schedules), have led to a rise in sleep disorders, including insomnia.

Nightmares: People with anxiety, depression, or PTSD linked to COVID-19 may also experience nightmares and disrupted sleep due to the heightened stress levels.

4.2.5 Substance Use Disorders

Increased substance use: Many people have turned to alcohol or drugs to cope with the stress and isolation brought on by the pandemic. Studies have shown an increase in alcohol consumption, drug use, and relapse rates among those with pre-existing substance use disorders.

Opioid crisis worsening: In some countries, the opioid crisis worsened during the pandemic, with increased rates of overdose due to stress, economic hardship, and disrupted access to treatment.

4.2.6 Obsessive-Compulsive Disorder (OCD)

Increased contamination fears: The heightened focus on cleanliness, handwashing, and avoiding contamination during the pandemic has led to a worsening of symptoms in people with OCD, particularly those who have contamination-related obsessions.

New cases of OCD: Some individuals without a prior history of OCD developed obsessive behaviors related to hygiene and virus prevention during the pandemic.

4.2.7 Loneliness and Social Isolation

Impact of isolation: Social distancing measures, lockdowns, and quarantine have led to widespread loneliness, particularly among the elderly and people living alone. Loneliness is a significant risk factor for depression and anxiety.

Lack of social support: The reduction in face-to-face interaction has diminished the availability of emotional and social support, leaving people feeling isolated and vulnerable.

4.2.8 Suicide Risk

Increased suicide risk: The pandemic's emotional toll, along with financial stress, job loss, and social isolation, has led to concerns about increased suicide risk, especially among vulnerable populations such as those with pre-existing mental health conditions, the elderly, and frontline workers.

Global disparities: While some countries have seen an increase in suicide rates during the pandemic, others have reported stable or even decreased rates. However, long-term effects on suicide rates may take time to manifest as the mental health consequences of the pandemic continue to unfold.

4.2.9 Children and Adolescents

Disrupted development: The pandemic has had a profound impact on the mental health of children and adolescents, who have experienced interruptions to schooling, socialization, and extracurricular activities. This has led to increased anxiety, depression, and behavioral issues.

Academic pressure: Remote learning and the uncertainty around education have contributed to heightened academic pressure and stress in young people.

4.3 Neurodegenerative Disorders

Emerging evidence links COVID-19 to an increased risk of neurodegenerative diseases such as Parkinson's and Alzheimer's.

While more research is needed to establish definitive links, early findings suggest that the virus may play a role in triggering or accelerating certain neurodegenerative processes, especially in vulnerable populations. Here are some key points related to neurodegenerative disorders and COVID-19:

4.3.1 Potential for Triggering or Accelerating Neurodegenerative Diseases

COVID-19 may not directly cause neurodegenerative diseases, but the inflammatory response it induces in the body could exacerbate underlying conditions or increase the risk of developing them. Some potential mechanisms include:

Neuroinflammation: COVID-19 can cause widespread inflammation, including in the brain. Chronic inflammation is a known risk factor for neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis (MS).

Blood-Brain Barrier Disruption: The virus may compromise the blood-brain barrier, allowing harmful substances (e.g., cytokines, immune cells) to enter the brain and damage neurons, potentially contributing to the development of neurodegenerative conditions.

Microvascular Injury: The virus can cause damage to blood vessels, leading to microvascular injuries in the brain. This damage could contribute to the onset of neurodegenerative diseases by reducing blood flow to brain tissue, increasing the risk of neurodegeneration.

4.3.2 Parkinson's Disease (PD)

Viral Infections as a Risk Factor: Previous studies have shown that viral infections can increase the risk of developing Parkinson's disease later in life. Some researchers hypothesize that COVID-19 could act similarly, potentially triggering or accelerating Parkinsonian symptoms in susceptible individuals.

COVID-19 and Dopamine Systems: COVID-19 could potentially damage neurons that produce dopamine, a key neurotransmitter that is deficient in Parkinson's disease. This could accelerate the progression of the disease in people who are already predisposed to it.

Case Reports: There have been anecdotal reports of patients developing Parkinson's-like symptoms after contracting COVID-19, though these cases are rare and more research is required to determine if there is a direct link.

4.3.3 Alzheimer's Disease (AD)

Inflammation and Alzheimer's: Chronic inflammation is believed to play a role in the development and progression of Alzheimer's disease. Since COVID-19 induces a strong inflammatory response (including in the brain), there is concern that it could accelerate the onset or progression of Alzheimer's in older adults.

Cognitive Decline: Many COVID-19 survivors, particularly those with long COVID, report persistent cognitive symptoms (e.g., memory loss, confusion). There is speculation that these symptoms may overlap with early stages of Alzheimer's or other forms of dementia, though it is too early to say whether the virus can directly cause Alzheimer's.

Amyloid Plaques: Some research has suggested that viral infections might contribute to the formation of amyloid plaques in the brain, a hallmark of Alzheimer's disease. This raises concerns that COVID-19 could have long-term effects on brain health, especially in elderly patients.

4.3.4 Multiple Sclerosis (MS)

Potential for Relapses: COVID-19's impact on the immune system may trigger relapses or worsen symptoms in people with multiple sclerosis (MS), a neurodegenerative disorder characterized by the immune system attacking the protective covering of nerves.

Autoimmune Response: In some cases, COVID-19 has been linked to an autoimmune response where the body mistakenly attacks its own tissues. For people with MS, this could worsen neurodegeneration or lead to the onset of more severe symptoms.

4.3.5 Amyotrophic Lateral Sclerosis (ALS)

Impact on Motor Neurons: While direct evidence linking COVID-19 to amyotrophic lateral sclerosis (ALS) is limited, there is concern that the virus could exacerbate ALS-like symptoms in patients by damaging motor neurons or inducing chronic inflammation in the central nervous system.

Worsening of ALS Symptoms: In individuals already diagnosed with ALS, severe COVID-19 could lead to respiratory complications, further impairing their motor functions and hastening disease progression.

4.3.6 Long COVID and Cognitive Decline

Cognitive Impairments: Many people with long COVID report cognitive difficulties such as brain fog, memory problems, difficulty concentrating, and slow information processing. These symptoms are reminiscent of cognitive decline seen in neurodegenerative diseases, though they are not necessarily permanent in all cases.

Overlap with Neurodegenerative Symptoms: The cognitive and neurological symptoms associated with long COVID resemble those seen in the early stages of neurodegenerative disorders, raising concerns about whether long-term COVID-19 effects might increase the risk of such diseases.

4.3.7 Indirect Effects on Neurodegeneration

Increased Stress: The pandemic itself has led to widespread stress, anxiety, and depression, all of which can have a negative impact on brain health. Chronic stress is a risk factor for many neurodegenerative diseases, and the psychological toll of the pandemic may increase susceptibility to these conditions over time.

Disruption of Healthcare Access: Many individuals with pre-existing neurodegenerative conditions have faced challenges in accessing regular care during the pandemic, potentially worsening their disease progression due to delayed treatment or lack of support.

4.3.8 Molecular Mechanisms of Concern

ACE2 Receptors in the Brain: The SARS-CoV-2 virus enters cells by binding to the ACE2 receptor, which is expressed not only in the lungs but also in the brain. This raises the possibility of direct viral invasion of the central nervous system, though this has not been definitively proven in neurodegenerative disorders.

Neurotropic Properties of SARS-CoV-2: The virus may have neurotropic properties, meaning it could potentially infect nerve cells or affect neurological functions. This could be particularly damaging in patients already prone to neurodegenerative disorders.

4.4 Cerebrovascular Events

Strokes and other cerebrovascular events were reported in 18 studies. The risk was highest among older adults and those with pre-existing cardiovascular conditions.

4.4.1 Increased Risk of Stroke

COVID-19 has been linked to an increased risk of ischemic stroke (caused by blood clots) and, to a lesser extent, hemorrhagic stroke (caused by bleeding). This risk is particularly high in severely ill COVID-19 patients, especially those requiring intensive care or mechanical ventilation.

4.4.2 Mechanisms Involved

Hypercoagulability: COVID-19 can trigger an excessive clotting response in the body, known as hypercoagulability, increasing the chances of blood clots that may lead to strokes.

Endothelial Damage: The virus can cause direct damage to the lining of blood vessels (endothelium), promoting inflammation and contributing to stroke risk.

Inflammation and Immune Response: COVID-19 causes a significant inflammatory response, including the release of cytokines (a "cytokine storm") that can lead to increased clot formation and vascular complications.

4.4.3 Risk Factors

People with pre-existing conditions like hypertension, diabetes, cardiovascular diseases, and obesity, as well as older adults, are at higher risk for cerebrovascular complications related to COVID-19.

4.4.4 Neurological Manifestations

Stroke is one of several neurological complications associated with COVID-19, alongside encephalopathy, seizures, and delirium. These are believed to result from both direct viral effects on the brain and the broader inflammatory and coagulative responses.

4.5 *Peripheral Neuropathies*

Nerve pain and sensory disturbances were observed in 12 studies, with some cases lasting over a year.

4.5.1 Direct Viral Damage

Though primarily a respiratory virus, SARS-CoV-2 (the virus that causes COVID-19) has been shown to affect the nervous system, including peripheral nerves. The virus may infect nerve cells directly or trigger an autoimmune response that leads to nerve damage.

4.5.2 Inflammatory Response

COVID-19 can cause a significant inflammatory reaction, leading to immune system activation and, in some cases, an autoimmune attack on the nervous system. This can result in conditions like Guillain-Barré syndrome (GBS), a form of acute peripheral neuropathy where the immune system attacks the nerves, leading to weakness and sometimes paralysis. GBS has been reported in a small number of COVID-19 cases.

4.5.3 Post-Viral Syndrome (Long COVID)

Many people recovering from COVID-19 report ongoing neurological symptoms, including peripheral neuropathy. This can manifest as chronic pain, tingling, or numbness in the extremities, possibly due to persistent inflammation or immune-mediated nerve damage. These symptoms are part of "Long COVID," a condition where symptoms persist for months after the acute infection has resolved.

4.5.4 Thrombotic Complications

COVID-19 is associated with an increased risk of blood clots, which can reduce blood flow to peripheral nerves, causing ischemia and neuropathy.

4.5.5 Metabolic and Nutritional Factors

COVID-19 can exacerbate pre-existing conditions like diabetes, which is a major cause of peripheral neuropathy. Additionally, patients who have severe COVID-19 and are hospitalized may experience nutritional deficiencies, contributing to nerve damage.

5. Discussion

The long-term neurological effects of COVID-19 appear to be multifaceted and potentially debilitating. Cognitive impairments and mental health disorders are particularly prevalent, and there is concern about an increased risk of neurodegenerative diseases such as Parkinson's and Alzheimer's. Strokes and peripheral neuropathies also represent significant post-COVID complications.

Treating Long COVID (also known as post-acute sequelae of SARS-CoV-2 infection, or PASC) remains challenging due to the wide range of symptoms and how they affect individuals differently. Treatment approaches are typically personalized and focus on symptom management and improving quality of life. Here's an overview of common treatment strategies for Long COVID:

5.1 *Multidisciplinary Care*

Comprehensive Assessment: Patients with Long COVID often benefit from a multidisciplinary team, including primary care physicians, pulmonologists, cardiologists, neurologists, and mental health professionals.

COVID-19 Recovery Clinics: Many hospitals and health centers have set up specialized clinics to treat Long COVID patients, bringing together various specialists to address their complex symptoms.

5.2 Fatigue and Post-Exertional Malaise (PEM)

Energy Conservation: Patients with fatigue or PEM are encouraged to practice pacing—managing their energy by balancing activity and rest to avoid symptom flare-ups.

Graded Exercise Therapy (GET): Light and carefully monitored physical activity, when appropriate, can help improve energy levels, but it must be introduced cautiously to avoid worsening symptoms.

5.3 Neurological Symptoms (Brain Fog, Memory Issues, Headaches)

Cognitive Rehabilitation: Speech-language therapists or occupational therapists may assist with cognitive exercises to improve memory, focus, and brain function.

Medications: Some doctors may prescribe medications used for attention or memory problems, like stimulants, in cases of severe brain fog, although more research is needed on their effectiveness for Long COVID.

5.4 Mental Health (Anxiety, Depression, PTSD)

Counseling and Therapy: Cognitive Behavioral Therapy (CBT), supportive counseling, or other types of psychotherapy can be helpful for dealing with anxiety, depression, or post-traumatic stress.

Medications: Antidepressants or anti-anxiety medications may be prescribed to help manage mental health symptoms.

There is no approved medication specifically for long COVID, but existing medications may be used to treat symptoms (e.g., blood thinners for clotting issues, anti-inflammatory drugs for persistent inflammation). Proper nutrition, regular (but not overexerting) physical activity, and stress management can aid recovery. Future research should focus on understanding the mechanisms and developing interventions to mitigate these effects.

6. Conclusion

This review highlights the substantial burden of long-term neurological complications following COVID-19 infection. Continued monitoring and more longitudinal studies are essential to fully understand these effects and guide post-COVID care.

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