Review

Neuroscience

Neurological Mechanisms of Long COVID

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Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection, refers to a condition where individuals continue to experience a range of symptoms weeks to months after the acute phase of COVID-19 has resolved. While respiratory symptoms are commonly associated with COVID-19, emerging evidence suggests that neurological manifestations play a significant role in the long-term effects of the disease. This article explores the neurological basis of long COVID, delving into the various symptoms, pathophysiological mechanisms, impact on cognitive function, neuroimaging findings, current treatment approaches, long-term prognosis, and future research directions in understanding and managing the neurological sequelae of long COVID.

Keywords: Long COVID; Neurological Manifestations; Mechanisms; Interventions; Prognosis

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Introduction

LONG COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a condition in which individuals continue to experience symptoms for an extended period of time after their initial COVID-19 infection has resolved (Liu et al., 2023). Neurological symptoms are a predominant characteristic of long-term COVID, and they can significantly affect an individual's quality of life (Ewing et al., 2024). It is essential to comprehend the neurological mechanisms that underlie long COVID in order to create effective treatments and interventions that can assist in the management of these symptoms.

Neuroinflammation is one of the primary neurological mechanisms that contribute to the protracted nature of COVID-19. Studies have demonstrated that individuals who have had a long COVID disease experience elevated levels of inflammatory markers in the brain, which can result in neuronal injury and dysfunction (Churchill et al., 2023; COVID-19, 2022). This chronic neuroinflammation is believed to be a contributing factor to the cognitive impairments, memory issues, and fatigue that are frequently reported by long COVID patients (Warren et al., 2022).

The dysregulation of the autonomic nervous system is another critical neurological mechanism in the long-term effects of COVID. The autonomic nervous system regulates a variety of bodily functions, such as digestion, blood pressure, and pulse rate. Dysregulation of this system in long COVID patients can result in symptoms such as gastrointestinal issues, cardiac palpitations, and dizziness (Becker, 2021; Dani et al., 2020; Jammoul et al., 2023). This dysautonomia can have a substantial effect on an individual's daily activities and overall well-being.

Additionally, the blood-brain barrier (BBB) is another neurological mechanism that may be compromised during long COVID. The BBB is a protective barrier that controls the movement of substances between the circulation and the brain (Erickson et al., 2021). Neuroinflammation and cognitive dysfunction may result from the entry of toxic toxins and immune cells into the brain in long COVID patients due to damage to the BBB (Chen et al., 2022; Shi et al., 2023). Researchers can develop targeted therapies to restore the BBB's integrity and alleviate neurological symptoms by comprehending the impact of long-term COVID on the BBB.

Furthermore, neuroimaging investigations have demonstrated structural and functional modifications in the brains of patients who have been afflicted with COVID for an extended period (COVID-19 and the Nervous System, 2024; Yasir et al., 2024). These changes may encompass abnormal patterns of neural activity, decreased gray matter volume, and alterations in white matter integrity. Researchers can acquire valuable insights into the underlying neurological mechanisms of long COVID and devise personalized treatment approaches to address these specific brain abnormalities by investigating these neuroimaging findings.

Recent research has stressed the potential role of viral persistence in the development of long COVID-related neurological symptoms (Buonsenso & Tantisira, 2024). It is posited that the SARS-CoV-2 virus may persist within the central nervous system, resulting in persistent inflammation and harm to brain tissue. Researchers may alleviate neurological symptoms in long COVID patients by devising strategies to target and eradicate viral reservoirs in the central nervous system (CNS) by comprehending the virus's interactions with the brain and its ability to evade the immune response.

Neurological Symptoms Associated with Long COVID

The emergence of the COVID-19 pandemic has undoubtedly had a far-reaching impact on global health, with the long-term sequelae of the disease, commonly referred to as long COVID, becoming a subject of increasing importance and concern (Albaqer et al., 2023; Leng et al., 2023). We herein will delve into the current understanding of the neurological symptoms associated with long COVID, synthesizing the latest research and evidence to provide a comprehensive overview of this evolving field (Crunfli et al., 2022; Miranda et al., 2022; Rivas-Vazquez et al., 2022; Reiss et al., 2023).

Numerous studies have reported a wide range of neurological manifestations in patients recovering from acute COVID-19 infection. These include altered consciousness, such as confusion or disorientation, as well as debilitating fatigue, seizures, and changes in the perception of smell and taste, which can significantly impact a person's quality of life and daily functioning (Cho et al., 2022; Rivas-Vazquez et al., 2022. Furthermore, in-hospital neurological complications, such as stroke, central nervous system infection, and seizures, have been documented in both adult and pediatric COVID-19 patients (Cho et al., 2022).

The underlying mechanisms behind these neurological symptoms are not yet fully understood, but researchers have proposed various pathways through which the SARS-CoV-2 virus may directly or indirectly affect the nervous system. One hypothesis suggests that the virus may disrupt the blood-brain barrier, leading to increased inflammation and potential neuronal damage (Ciaccio et al., 2021). Additionally, direct viral invasion of the central nervous system has been observed in some cases, potentially contributing to the observed structural changes and neuropsychiatric dysfunction.

Interestingly, these neurological sequelae have been reported not only in individuals with severe COVID-19 infections, but also in those with mild or even asymptomatic cases, highlighting the widespread and potentially persistent nature of the neurological impact of this disease (Crunfli et al., 2022; Reiss et al., 2023). Ongoing research continues to elucidate the underlying mechanisms and risk factors associated with these neurological manifestations, as well as the long-term prognosis and potential interventions to mitigate the burden on individual patients and the healthcare system.

However, some researchers have expressed skepticism about the prevalence and severity of neurological symptoms associated with long COVID. They argue that the reported neurological manifestations may not be directly caused by the SARS-CoV-2 virus and could be influenced by a range of other factors, such as the psychological and socioeconomic impacts of the pandemic (Quan et al., 2023). These researchers suggest that more rigorous and controlled studies are needed to establish a clear causal relationship between COVID-19 and the observed neurological symptoms. They also highlight the potential for misattribution, as some individuals may experience neurological issues unrelated to their COVID-19 infection, but associate them with the disease due to heightened awareness and anxiety (Ellul et al., 2020; Varatharaj et al., 2020; Zhao et al., 2021). While the neurological impact of long COVID remains an important area of investigation, the opposing view emphasizes the need for cautious interpretation of the available evidence and further research to conclusively determine the extent and mechanisms of these neurological sequelae.

Pathophysiology of Long COVID in the Nervous System

The underlying pathophysiology of the neurological manifestations of long COVID is not fully understood, but emerging research has shed light on some of the potential mechanisms involved. Notably, studies have suggested that the SARS-CoV-2 virus may be able to directly invade the central nervous system, potentially leading to neuroinflammation and neural damage (Leng et al., 2023; Reiss et al., 2023). Additionally, the disruption of the blood-brain barrier, which can occur due to the systemic inflammatory response triggered by the virus, may allow for the entry of inflammatory mediators and potentially harmful substances, further exacerbating neur neurological symptoms (Albaqer et al., 2023; Leng et al., 2023; Xu et al., 2022).

Another proposed mechanism for the neurological manifestations of long COVID is the indirect effects of the virus on the nervous system. The COVID-19 infection can lead to hypoxia, coagulopathies, and autonomic dysregulation, all of which can have deleterious effects on the brain and nervous system. Furthermore, the virus may trigger an autoimmune response, leading to the production of antibodies that cross-react with neuronal proteins, potentially contributing to neurological symptoms. The broad array of neurological symptoms associated with Long COVID can include persistent fatigue, cognitive difficulties (known as "brain fog"), impairments in sensory and motor function, and disruptions in sleep patterns (Albaqer et al., 2023; Leng et al., 2023; Reiss et al., 2023; Xu et al., 2022). Indeed, numerous studies have reported that a significant proportion of patients with Long COVID experience these debilitating neurological complications, underscoring the need for further research and the development of targeted interventions to address this pressing public health issue (Albaqer et al., 2023; Leng et al., 2023; Reiss et al., 2023; Xu et al., 2022).

The pathophysiology of the neurological manifestations of long COVID is complex and multifactorial, involving a combination of direct and indirect effects of the SARS-CoV-2 virus on the nervous system. While the exact mechanisms are still under investigation, the resulting neurological symptoms can have a significant impact on a patient's quality of life and daily functioning.

Neuroimaging Findings in Long COVID Patients

A prevalent neuroimaging observation in enduring COVID patients is the presence of cerebral inflammation. Magnetic resonance imaging (MRI) investigations have revealed elevated concentrations of pro-inflammatory cytokines in the brains of these patients, indicating persistent inflammation even after the resolution of acute infection (Crunfli et al., 2022; Ferrando et al., 2020). These symptoms, including brain fog, memory impairments, and attention difficulties, are frequently experienced by long COVID patients and may be attributed to this inflammation.

Another intriguing neuroimaging discovery in long COVID patients is the presence of microstructural alterations in the brain (Leng et al., 2023; Nouraeinejad, 2022). Analysis of diffusion tensor imaging has revealed changes in the structural integrity of white matter in these patients, maybe associated with ongoing neurological complaints (Crunfli et al., 2022; Planchuelo-Gómez et al., 2022). In long COVID patients, these alterations may impact the propagation of impulses between various brain regions, resulting in cognitive and emotional disruptions.

Several neuroimaging investigations have also detected cerebral hypoperfusion in individuals with long COVID. Perfusion imaging techniques, including arterial spin labeling, have demonstrated diminished blood flow in certain brain regions in these patients, potentially correlating with symptoms such as fatigue and headaches (Ajčević et al., 2023; Bondira et al., 2021; Kim et al., 2022). The decreased blood flow observed in long COVID patients may indicate the presence of continuous vascular dysfunction, which contributes to their ongoing symptoms.

Furthermore, neuroimaging investigations have identified alterations in the brain structure of individuals with long COVID, such as decreases in the volume of gray matter in specific areas (Churchill et al., 2023; Duan et al., 2021; Paula et al., 2022). The observed alterations in structure could potentially be associated with the cognitive and emotional symptoms reported by these persons, together with challenges in motor function and coordination. An analysis of these structural alterations could assist researchers in devising specific therapies for long COVID patients to enhance their quality of life.

Neuroimaging findings in long COVID patients offer significant insights into the mechanisms driving neurological symptoms in this population. By detecting cerebral inflammation, variations in microstructure, reduced blood flow, and structural modifications in patients with long COVID, scientists can gain a deeper understanding of the lasting impact of COVID-19 on the brain and devise specific treatments to enhance results for these individuals (Crunfli et al., 2022; Kim et al., 2022). To completely clarify the neuroimaging findings in long COVID patients and create successful therapies for this group, additional study is required.

Therapeutic Approaches for Neurological Manifestations of Long COVID

Pharmacological Interventions for Neurological Symptoms

An effective pharmaceutical treatment for the neurological symptoms of long COVID is the administration of cognitive enhancers, namely inhibitors of acetylcholinesterase (Hashimoto, 2023). These drugs exert their effects by augmenting the concentrations of acetylcholine in the brain, a vital neurotransmitter for memory, learning, and cognitive processes. By increasing acetylcholine levels, cognitive enhancers may ameliorate memory impairments and cognitive challenges in patients with long COVID.

Another potential pharmacological treatment for neurological symptoms of Long COVID is the use of antiviral therapy. Although the primary source of the first COVID-19 infection is the SARS-CoV-2 virus, other studies suggest that the continued neurological symptoms may be associated with a chronic viral infection in the brain (German et al., 2023; Turana et al., 2021). The administration of antiviral drugs has the ability to specifically target and eradicate any residual virus particles within the brain, therefore potentially mitigating inflammation and enhancing neurological symptoms.

Furthermore, researchers are investigating the potential of anti-inflammatory drugs alongside cognitive enhancers and antiviral drugs to address neurological symptoms in individuals with long COVID (Miller et al., 2016). It is widely recognized that inflammation in the brain contributes to the onset of cognitive impairments and memory deficits. Therefore, the use of anti-inflammatory drugs may be beneficial in mitigating inflammation and enhancing neurological performance. By specifically addressing the fundamental inflammatory mechanisms, these medicinal interventions have the potential to alleviate the symptoms experienced by persons grappling with Long COVID.

It is crucial to acknowledge that pharmaceutical treatments for neurological symptoms of long COVID are still in the first phases of study and development. Therefore, healthcare practitioners must meticulously oversee the safety and efficacy of these drugs in individuals diagnosed with long COVID. Successful identification of the most effective pharmacological treatments for neurological symptoms in persons with long COVID will require close collaboration among researchers, healthcare professionals, and patients.

Rehabilitation Strategies for Cognitive Impairments

Cognitive rehabilitation treatment is a therapeutic method used to treat cognitive impairment in long COVID patients (Houben & Bonnechère, 2022; Mathern et al., 2022). This therapeutic modality encompasses activities and exercises specifically developed to enhance cognitive function, including memory, attention, and problem-solving abilities. Targeted cognitive rehabilitation therapy can be customized to meet the unique requirements and objectives of the individual, therefore facilitating the restoration of mental clarity and concentration (Eslinger et al., 2013; Mukundan, 2013). Through the implementation of purposeful workouts, individuals can enhance the resilience of neural connections and gradually enhance their cognitive capacities.

Neurofeedback therapy is an alternative therapeutic method for addressing the neurological symptoms of long COVID (Warren et al., 2022). This non-invasive therapy entails the ongoing monitoring of brain activity and the provision of immediate feedback to assist individuals in acquiring the ability to control their brainwaves. Neurofeedback therapy has demonstrated efficacy in enhancing cognitive function, attention, and memory among individuals diagnosed with diverse neurological illnesses (Chmiel, 2013; Jiang et al., 2022; Marzbani et al., 2016). The enhancement of cognitive symptoms and overall brain health in those with long COVID can be achieved through the training of the brain to operate with greater efficiency.

Indeed, alongside cognitive rehabilitation and neurofeedback therapy, physical exercise has demonstrated advantageous effects in managing neurological symptoms of long COVID (Reiss et al., 2023; Rountree-Harrison, 2022). Studies have established a correlation between regular aerobic exercise and enhanced cognitive performance, mood, and general brain health. Physical activity has the potential to enhance cerebral blood circulation, stimulate neurogenesis, and mitigate inflammation, therefore facilitating improved cognitive function in individuals with long COVID (Cabral et al., 2019; Gómez-Pinilla et al., 2002). By integrating a consistent exercise regimen into their therapy regimen, persons diagnosed with long COVID can observe enhancements in cognitive symptoms and general state of health.

Moreover, mindfulness-based therapies have demonstrated potential in assisting those with long COVID in effectively managing cognitive impairment (Compagno et al., 2022; Rudofker et al., 2022). Engaging in mindfulness activities, such as meditation and deep breathing exercises, can effectively decrease stress levels, enhance concentration, and optimize cognitive abilities. Numerous studies have demonstrated that mindfulness-based therapies can effectively assist persons suffering with chronic health disorders, such as long COVID, in managing symptoms and enhancing their overall quality of life. By integrating mindfulness techniques into their daily regimen, persons suffering from long COVID can observe enhancements in cognitive performance and promote mental clarity.

Long-Term Prognosis and Management of Neurological Symptoms in Long COVID

The enduring presence of neurological symptoms in extended covid casts significant doubt on the long-term outlook for these individuals. Although there is still much uncertainty, preliminary studies indicate that neurological problems among those with long COVID may endure for a considerable duration (Baig et al., 2022). A study revealed that over 50% of individuals diagnosed with long COVID syndrome experienced neurological symptoms six months following infection (Perlis et al., 2022). The aforementioned symptoms were correlated with a diminished quality of life and heightened consumption of healthcare services. These findings indicate that neurological symptoms experienced after extended covid may have a long-lasting effect on the general well-being of patients.

Variables such as the severity of the original infection, the presence of underlying medical disorders, and the age of the patient may influence the long-term prognosis of neurological symptoms in long COVID. Studies indicated that elderly individuals and those with pre-existing neurological disorders may have a higher likelihood of experiencing long-lasting neurological symptoms after contracting COVID-19 (Mathern et al., 2022; Rodríguez-Morales et al., 2023). Moreover, the occurrence of intense respiratory symptoms during the initial stage of COVID-19 may potentially heighten the probability of enduring neurological adverse effects (Russell et al., 2021). A more comprehensive investigation is required to have a deeper understanding of the variables that impact the long-term outlook of neurological problems in extended covid.

Scholars have expressed apprehensions regarding the possible enduring ramifications of neurological symptoms in cases of long COVID. An investigation revealed that individuals with long COVID were more susceptible to the development of neurodegenerative diseases in their later years (Al-Aly, 2022). This underscores the need of closely monitoring and effectively controlling neurological symptoms in patients with long COVID in order to avoid significant long-term problems. Furthermore, timely intervention and suitable therapy might enhance the long-term outlook for these individuals.

Although neurological problems provide formidable obstacles in the context of extended covid, there are grounds for optimism. Further investigation is being conducted to gain a deeper understanding of the fundamental processes behind these symptoms and to formulate efficacious therapeutic approaches. The initial results indicate that rehabilitation and cognitive therapy have the potential to enhance cognitive function and quality of life in those suffering from long COVID (Tanti et al., 2023). To enhance the long-term outlook for patients with long COVID, healthcare providers should promptly and comprehensively address the neurological symptoms associated with this condition.

Future Directions in Research on the Neurological Basis of Long COVID

One potential area for future research in the neurological basis of long COVID is the virus's effect on the brain. Research has demonstrated that SARS-CoV-2 can enter the central nervous system through the olfactory nerve or the bloodstream, resulting in inflammation and injury to brain tissue (Felice et al., 2020). Insight into the neurological symptoms encountered by long COVID patients could be gained by comprehending the virus's interactions with the brain and its impact on various regions.

The immune system's role in long COVID is another critical area of research. Some individuals may experience persistent symptoms as a result of an overactive immune response to the infection. The identification of potential biomarkers for the condition and the identification of therapeutic intervention targets could be facilitated by the examination of the immune response in long COVID patients.

The long-term effects of the virus on the brain must also be understood, so research on the neuroinflammatory response in long COVID is crucial. A variety of neurological disorders, such as Alzheimer's disease and multiple sclerosis, have been associated with chronic inflammation in the brain. Investigation of the inflammatory response in long COVID patients may provide insight into potential pathways for intervention and treatment.

Moreover, studies on the neurovascular aspects of long COVID could offer valuable insights into the mechanisms that underlie cognitive impairment and other neurological symptoms. Study has demonstrated that SARS-CoV-2 can disrupt the blood-brain barrier and injure blood vessels, resulting in lower levels of oxygen and nutrients reaching the brain (Kempuraj et al., 2023). The identification of potential therapeutic targets could be facilitated by an examination of the virus's neurovascular effects.

Also, it is imperative to conduct research on the neurocognitive effects of long COVID in order to comprehend the virus's long-term effects on cognitive function. Studies have demonstrated that certain individuals with long COVID suffer from challenges with executive function, memory, and attention (Holdsworth et al., 2022; Vakani et al., 2022). The identification of strategies for rehabilitation and support for those affected could be facilitated by the investigation of the cognitive effects of the virus.

Conclusion

As our understanding of long COVID continues to evolve, it is evident that the neurological manifestations of this condition present unique challenges that require targeted research and clinical management strategies. By elucidating the pathophysiological mechanisms underlying the neurological symptoms, developing effective treatments, and implementing long-term care plans, healthcare providers can better support individuals experiencing the enduring effects of COVID-19 on the nervous system. Through ongoing research efforts and collaborative approaches, we aim to improve outcomes and quality of life for those impacted by the neurological sequelae of long COVID.■

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