



Unmasking the long-term effects: unravelling neuropsychiatric and neurological consequences of COVID-19

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Abstract

The COVID-19 pandemic has not only burdened healthcare systems but has also led to a new emerging medical enigma that is post-COVID-19 syndrome or “long COVID.” Characterized by persistent symptoms that extend beyond the acute phase of the illness, long COVID has rapidly become a public health concern with ambiguous neurological and neuropsychiatric dimensions. This narrative review aims at synthesizing available research to decode the long-term impacts of COVID-19 on neurological and mental health. Drawing from a multitude of studies, this review synthesizes evidence on various neuropsychiatric and neurological symptoms, including cognitive deficits, mood disorders, and more. The narrative delves into potential pathogenic mechanisms, hoping to fill existing research gaps and offering directions for future inquiry. The objective is not just academic; it has immediate real-world implications. Understanding these long-term effects is crucial for developing effective treatments and interventions, thereby better serving the millions of individuals living with these lingering symptoms. As healthcare systems continue to grapple with the fallout from the pandemic, this review provides much-needed context and insights into an area that demands urgent research and action.

Keywords: Antibody-mediated complement activation, Fc receptor, long-COVID, PASC, SARS-CoV-2

Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 has emerged as a global health crisis, affecting millions of people worldwide. While the primary focus of the pandemic has been on the acute respiratory symptoms, it has become increasingly evident that COVID-19 can have significant long-term consequences on the neurological and psychiatric well-being of affected

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HIGHLIGHTS

- The “long COVID” or post-COVID-19 syndrome, which is characterized by extended symptoms beyond the acute phase of the sickness may include neurological and neuropsychiatric components, posing a serious threat to the public’s health.
- The long-term consequences of COVID-19 significantly affect the neurological and psychiatric well-being of patients. Manifestations include cognitive deficits, mood disorders (such as depression, anxiety, and post-traumatic stress disorder), and severe neurological effects like encephalopathy and stroke. The susceptibility to these symptoms varies based on factors like age, sex, pre-existing conditions, and socioeconomic factors.
- Urgent need for research and treatment development: There is a substantial gap in the current literature regarding the clear understanding of COVID-19’s pathophysiology, especially in the context of long COVID. Comprehensive research is essential to develop specific treatments, enable early detection, and strategize prevention methods for the many individuals suffering from these persistent symptoms.

individuals. Exploring and understanding the neuropsychiatric and neurological sequelae of COVID-19 is essential for comprehensive patient care and informed public health strategies.

Studies have reported a wide spectrum of neurological complications associated with COVID-19, ranging from mild symptoms like headaches and fatigue to more severe events such as stroke and arrhythmias^[1,2]. These complications can persist long after the acute phase of the infection, leading to long-term neurological and neuropsychiatric consequences^[1,3,4]. Post-COVID-19 syndrome, commonly known as “long COVID,” has emerged as a recognized condition characterized by persistent symptoms and functional impairments beyond the acute phase of the infection^[5].

The neurological manifestations of COVID-19 are diverse and encompass various conditions, including encephalopathy, stroke, Guillain-Barré syndrome, anosmia, and other neurologic sequelae^[1,3,6]. Furthermore, emerging evidence suggests the presence of psychiatric symptoms such as post-traumatic stress disorder (PTSD), depression, anxiety, and cognitive impairment in individuals recovering from COVID-19^[4,6]. These neuropsychiatric symptoms can significantly affect the quality of life of affected individuals and pose long-term challenges to healthcare systems.

Patel *et al.*^[4], performed a systematic review and meta-analysis and examined the long-term neurological effects of COVID-19. The analysis included 3304 post-COVID-19 patients, with 20.20% experiencing symptoms beyond 2 weeks after the acute phase. Neurocognitive symptoms such as headache (27.8%), fatigue (26.7%), myalgia (23.14%), anosmia (22.8%), dysgeusia (12.1%), sleep disturbance (63.1%), confusion (32.6%), difficulty to concentrate (22%), and psychiatric symptoms like PTSD (31%), feeling depressed (20%), and suicidality (2%) were prevalent. The meta-analysis revealed that COVID-19 patients with severe symptoms had higher odds of headache and myalgia. However, relationships with other neurocognitive sequelae could not be established. Long-term follow-up may help mitigate the neurocognitive effects associated with COVID-19^[4].

Some of the growing concerns regarding the neuropsychiatric and neurological consequences of COVID-19 include acute neurologic complications of COVID-19 which can manifest as nonspecific neurologic symptoms such as headache, dizziness, myalgia, and fatigue. Symptoms more specific to COVID-19 include loss of smell (anosmia)^[7]. COVID-19 has been found to have a causal association with a plethora of neurological, neuropsychiatric, and psychological effects as well. Clinical features of both central and peripheral nervous system involvement are evident. These have been categorically analyzed briefly with literature support^[8]. As far as psychological effects are concerned, most of them are secondary to pandemic-associated regulatory, socioeconomic, and psychosocial changes^[8].

The neuropsychiatric consequences of COVID-19 can be ascribed to several factors, ranging from the direct effect of infection to the psychological sequelae of social isolation, unemployment, and fear for one's health and livelihood. These consequences can have a global impact^[9]. Emerging reports suggest a high frequency of neuropsychiatric symptoms after infection with COVID-19. These reports emphasize fatigue, cognitive dysfunction, and other persistent symptoms^[10]. COVID-19 is accompanied by a wide range of neurological and neuropsychiatric symptoms from the common, such as fatigue and anosmia, to the more severe, such as seizures, encephalitis, encephalopathy, and Guillain-Barré syndrome^[11]. There are potential neurotropic mechanisms that may explain the neuropsychiatric manifestations of COVID-19, including direct viral invasion, immune-mediated damage, and systemic inflammation^[12].

Overall, the neuropsychiatric and neurological consequences of COVID-19 are a growing concern and require further research to fully understand the long-term effects of the disease. Given the growing body of literature documenting the neurological and neuropsychiatric influence of COVID-19, it is crucial to consolidate the existing knowledge, identify research gaps, and shed light on the underlying pathogenic mechanisms. By understanding the breadth and depth of these sequelae, healthcare providers and policymakers can better anticipate, diagnose, and manage the long-term effects of COVID-19, ensuring comprehensive care for affected individuals. This review will provide valuable insights into the long-term consequences of COVID-19 on the nervous system, facilitating the development of targeted interventions and support strategies for individuals experiencing post-COVID neuropsychiatric and neurological sequelae.

Neuropsychiatric post-covid sequelae

The COVID-19 syndrome primarily targets the respiratory system, resulting in symptoms such as fever, headache, dry cough, dyspnoea, and dizziness^[13,14]. However, COVID-19 is accompanied by a wide range of neurological and neuropsychiatric symptoms from the common, such as fatigue and anosmia, headache, altered consciousness, and paraesthesia, depression, anxiety, cognitive impairment, and post-traumatic stress disorder (PTSD), were common and still reported months and years after initial diagnosis, to the more severe, such as psychosis, encephalopathy, Guillain-Barré syndrome, visual problems, delirium, and cerebrovascular accidents^[7,13–18].

It is known that SARS-CoV-1 and MERS have long-term neuropsychiatric effects, and it is speculated that COVID-19 may have similar effects based on the mechanisms of the virus on the CNS^[13]. Post-acute sequelae of COVID-19 (PASC) have been reported in up to 91% of patients with COVID-19 six months after hospitalization and in ~25% of non-hospitalized adults with COVID-19^[19]. However, long-term neuropsychiatric sequelae of COVID-19 are currently unknown. Some studies suggest that psychiatric deficits may persist after recovery from the primary infection^[20].

Epidemiology

Overall, survivors of COVID-19 are at risk of psychiatric sequelae, but symptoms generally improve over time^[20]. The lack of a standard definition of the syndrome and the heterogeneous grouping of neuropsychiatric symptoms and disorders in existing COVID-19 literature make it challenging to estimate the population at risk and the breadth of resources^[19].

Survivors of SARS-CoV-1 were clinically diagnosed with PTSD (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) at 31 to 50 months post-infection^[21–23]. 52.5% participants reported fatigue with cognitive impairment that gradually decreased over the period of one year^[24].

Etiology

The potential underlying mechanisms and pathophysiology of these neuropsychiatric effects are still being elucidated. So far, various widely accepted theories which have stronger scientific

evidence than others are under discussion for increasing the horizon of research in this domain (Table 1).

Vulnerable populations

Several factors may increase the likelihood of experiencing severe neuropsychiatric or neurological consequences post-COVID-19. Older adults are at a higher risk of experiencing severe neuropsychiatric or neurological consequences post-COVID-19^[19].

Individuals with pre-existing mental health conditions, such as anxiety or depression, may be more susceptible to persistent neuropsychiatric symptoms after COVID-19^[10,29,30]. The use of psychotropic medications in individuals with pre-existing mental health conditions and COVID-19 is a topic of interest. A retrospective cohort study using electronic health record data from the five largest private healthcare systems in New York City found that individuals with pre-existing psychiatric disorders may be more susceptible to severe forms of COVID-19 outcomes, but the use of antidepressants may reduce this risk^[31]. Pre-existing mental disorders were associated with the risk of severe COVID-19 clinical outcomes, such as hospitalization and intensive care unit (ICU) admission^[32]. A prospective cohort study found that a pre-existing psychological condition increases the risk of a poorer evolution of COVID-19 and may increase the likelihood of experiencing severe consequences post-COVID-19^[33]. People with pre-existing mental disorders may be considered a risk group similar to people with underlying physical conditions due to factors such as living accommodations with barriers to social distancing, cardiovascular comorbidities, psychotropic medications, and difficulties in accessing high-intensity medical care^[34]. The risks of drug–drug interactions involving psychotropic medications might be relevant in patients with COVID-19, and clinicians need to be vigilant when initiating psychotropic medications in this population^[35].

Comorbidities, such as hypertension, diabetes, and obesity, may increase the risk of experiencing severe neuropsychiatric or neurological consequences post-COVID-19^[10,32,34]. A multi-center study found that pre-existing mood and attention-deficit hyperactivity disorders have been reported to increase the susceptibility of contracting COVID-19^[31]. However, several

meta-analyses and reviews tempered the impact of pre-existing psychiatric disorders on susceptibility to contracting COVID-19, but reported that pre-existing psychiatric disorders might be associated with an increased risk for hospitalization and death after COVID-19 diagnosis^[31].

Some vulnerable populations that may be at a higher risk of experiencing severe neuropsychiatric or neurological consequences post-COVID-19. Healthcare workers are at a higher risk of contracting COVID-19 and may be more susceptible to persistent neuropsychiatric symptoms after COVID-19 due to the stress and trauma of working during the pandemic^[36]. Older adults are at a higher risk of experiencing severe neuropsychiatric or neurological consequences post-COVID-19^[16]. Individuals with pre-existing neurological disorders, such as dementia or Parkinson's disease, may be more susceptible to persistent neuropsychiatric symptoms after COVID-19^[37].

It is important to note that the literature on longer-term consequences of COVID-19 is still maturing, and more research is needed to better understand the risk factors and vulnerable populations.

Risk factors

Considering the diversity of population, lifestyle, environment etc, there are a lot factors which may affect COVID-19 outcomes. Low economic status results in reduced access to healthcare, also the added stress due to economic instability makes the individual more susceptible to the virus^[38]. Underlying medical conditions such as pulmonary and cardiovascular disease are directly related to the severity of the SARs-COV-2 infection^[39]. Densely populated cities result in more individuals per unit area thus increasing encounters resulting in a more rapid transmission of the virus^[40]. African Americans were more at risk due to social vulnerability; out of the 269 recorded deaths in the medical archive data, 62.9% were African Americans^[41]. Patients with eGFR less than or equal to 30 ml/min/1.73m² are associated with a progressive increase in susceptibility to SARs-COV-2^[42]. Alcohol users exhibit a myriad of risk factors such as metabolic and hepatic diseases that make them more susceptible to the SARs-COV-2 virus^[43]. Women's pre-existing vulnerabilities are aggravated in the wake of a

Table 1
Scientific theories as considerable etiologies of neuropsychiatric post-COVID sequelae

References	Year of publication	Study design	AETiology identified
Johansson <i>et al.</i> ^[25]	September 2021	Narrative review	Abnormal immune responses and respiratory insufficiency associated with COVID-19 which presumably affect the nervous system indirectly.
Mahboubi Mehrabani <i>et al.</i> ^[26]	November 2022		
Elmazny <i>et al.</i> ^[27]	January 2023	Cross-sectional analysis	The virus's neurotropic influence, dysregulation of the inflammatory response, and dysregulation of the vascular system, is also thought to favour mechanisms that can affect mental health, such as blood-brain barrier disruption and neuro-inflammation.
Newcombe <i>et al.</i> ^[28]	September 2021	Review article	Immunologic imprinting from previous coronaviruses.
Schou <i>et al.</i> ^[20]	October 2021	Systematic review	Multi-organ pathology is another justification that includes the brain and nervous system.
Kumar <i>et al.</i> ^[13]	March 2021	Perspective article	Neural and immune cells can host latent CoV, which could contribute to delayed neurologic and neuropsychiatric complications.
Ong <i>et al.</i> ^[29]	January 2023	Narrative review	Lingering damage and physiological perturbations caused by acute COVID-19 infection are recurring themes is another proposed mechanism of neurological complications of post-acute sequelae of COVID-19 (NC-PASC).
Newcombe <i>et al.</i> ^[28]	September 2021	Review article	Hypoxia-associated NC-PASC cerebral microbleeds and direct invasion of the central nervous system by the virus are also one of these proposed theories.
Ong <i>et al.</i> ^[29]	January 2023	Narrative review	

pandemic due to many factors such as school closures resulted in early marriages, pregnancies, hindering girls from returning to schools, lack of sexual and reproductive healthcare services in lockdowns and majority of women were responsible for their child's homeschooling and household responsibilities with zero payment/ financial gain in return^[44]. Syrian refugees in Lebanon and several vulnerability factors that directly or indirectly make them exponentially more susceptible to SARS-COV-2 such as inadequate water supply and sanitation, crowding, little to no access to healthcare, less preference given to them by the host nation and fear of legal consequences^[45].

Precisely, all these risk factors may increase the likelihood of experiencing severe consequences post-COVID-19. It is important to identify and examine populations who may be at greater risk, to avoid such sequels of COVID-19 infection.

Clinical management and treatment

Approaches and recommendations for managing and treating neuropsychiatric and neurological sequelae in post-COVID-19 patients are still being developed. However, some studies suggest that it is useful to encourage the development of systematic approaches for the diagnosis, management, and treatment of the cognitive aspects of COVID-19^[46]. Here are some therapeutic interventions that have been explored:

1. Pharmacological strategies

- **Melatonin:** Melatonin has been contemplated as a good choice in order to diminish the neurological sequelae from hypoxic-ischaemic brain injury as has also been studied as a potential neuroprotective agent for perinatal hypoxic-ischaemic encephalopathy^[47].
- **Hyperbaric oxygen therapy (HBOT):** Hyperbaric oxygen therapy has been used to treat delayed neuropsychiatric sequelae (DNS) of carbon monoxide intoxication^[48].
- **Psycho-pharmacotherapy:** Psycho-pharmacotherapy has been used to treat DNS in patients with carbon monoxide poisoning^[49].

Other pharmacological strategies include use of Sphingosine, antivirals, immunomodulatory, analgesics and nutritional supplements^[29,50].

2. Non-pharmacological strategies

- **Rehabilitation programs:** Rehabilitation programs can be used to help patients recover from neurological and cognitive symptoms^[46].
- **Multidisciplinary care:** Multidisciplinary care, which involves a team of healthcare professionals from different specialties, can help provide comprehensive care for patients with neuropsychiatric and neurological sequelae^[51].

Others include music therapy, resistance exercise, neuromodulation, pilates^[52].

Overall, the pharmacological and non-pharmacological treatments both are still not conclusive entirely therefore a lot of research is essential for understanding the effects of these strategies. Somehow, it's essential to consider a combination of both approaches tailored to the patients for optimal treatment outcomes. It's crucial to note that specific treatments for post-COVID-19 neurological sequelae will vary depending on individual's symptoms, the extent of neurological involvement and

other medical factors. A multidisciplinary approach involving healthcare professionals from various specialties is often necessary to tailor the treatment plan to meet the unique needs of each patient.

Future directions and research implications

The current literature results do not contain conclusive information on the neuropsychiatric and neurological consequences of COVID-19 hence for identify gaps in the existing literature, more investigation is required^[53]. Longitudinal studies are essential for tracking the progression of COVID-19-related neurological and neuropsychiatric symptoms over time and identifying potential long-term consequences. In addition, collaborative research efforts are necessary to pool resources and expertise to better understand the mechanisms underlying COVID-19-related neurological and neuropsychiatric symptoms and develop effective treatments. Longitudinal studies and collaborative research efforts when combined, can help identify risk factors for COVID-19-related neurological and neuropsychiatric symptoms, develop effective prevention and treatment strategies, and improve the overall health outcomes of individuals affected by COVID-19. The impact of COVID-19 on vulnerable populations, such as older adults and those with pre-existing neurological or psychiatric conditions, needs to be further explored for better prevention in terms of developing a precautionary technique for any pandemic that occurs in future. Nonetheless, focusing on the idea of forming multidisciplinary teams to tackle such consequences including clinicians, psychiatrists and psychologists can help devise a proper approach for dealing with patients recovering from COVID-19 to avoid neuropsychiatric complications.

Conclusion

The long-term impact of COVID-19 on the neurological and mental well-being of those affected is substantial. Long COVID, in particular, can result in various conditions including depression, anxiety, PTSD, encephalopathy, and even stroke. The severity and variety of symptoms depend on factors such as age, gender, existing health conditions, economic status, population density, and access to healthcare. Although there are emerging pharmacological and non-pharmacological treatments for COVID-19, there is a significant gap in the literature and research that hinders a clear understanding of the virus's pathophysiology. A more comprehensive research approach is needed to develop specific and effective treatment methods, as well as to enable early detection and prevention of COVID-19-related neurological and psychiatric consequences.

Ethical approval

This is a Narrative review article hence ethics approval was not required for it.

Consent

Informed consent was not required for this review.

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Author contribution

M.T.: conceived the concept of study, did study designing and manuscript writing. FNU M.: literature search and manuscript writing. R.K.: literature search and manuscript writing. A.K.: literature search and manuscript writing. A.K.: literature search and manuscript writing. J.K.: manuscript editing, drafting and proofreading. M.A.M.: manuscript editing and drafting. U.M.: manuscript editing and drafting. K.M.M.: manuscript editing and drafting. F.S.T.: manuscript editing and drafting. A.G.: manuscript editing and drafting. A.J.: manuscript editing and drafting. S.S.: manuscript editing and drafting. M.H.W.: DATA Curation and methodology.

Conflicts of interest disclosure

There are no conflicts of interest.

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