Review

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Long-term cognitive dysfunction after the COVID-19 pandemic: a narrative review

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Introduction: SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has brought a conglomerate of novel chronic disabling conditions described as 'Long COVID/Post-COVID-19 Syndrome'. Recent evidence suggests that the multifaceted nature of this syndrome results in both pulmonary and extrapulmonary sequelae,chronic dyspnoea, persistent fatigue, and cognitive dysfunction being the most common, debilitating symptoms. Several mechanisms engender or exacerbate cognitive impairment, including central nervous system and extra-central nervous system causes, although the exact mechanism remains unclear. Both hospitalized and non-hospitalized patients may suffer varying degrees of cognitive impairment, ranging from fatigue and brain fog to prolonged deficits in memory and attention, detrimental to the quality-of-life years post-recovery. The aim of this review is to understand the underlying mechanisms, associations, and attempts for prevention with early intervention of long-term cognitive impairment post-COVID-19.

Methodology: A systematic search was conducted through multiple databases such as Medline, National Library of Medicine, Ovid, Scopus database to retrieve all the articles on the long-term sequalae of cognitive dysfunction after SARS-CoV-2 infection. The inclusion criteria included all articles pertinent to this specific topic and exclusion criteria subtracted studies pertaining to other aetiologies of cognitive dysfunction. This search was carefully screened for duplicates and the relevant information was extracted and analysed.

Results/discussion: To date, the exact pathogenesis, and underlying mechanisms behind cognitive dysfunction in COVID-19, remain unclear, hindering the development of adequate management strategies. However, the proposed mechanisms suggested by various studies include direct damage to the blood-brain barrier, systemic inflammation, prolonged hypoxia, and extended intensive care admissions. However, no clear-cut guidelines for management are apparent.

Conclusion: This review of the COVID-19 pandemic has elucidated a new global challenge which is affecting individuals' quality of life by inducing long-term impaired cognitive function. The authors have found that comprehensive evaluations and interventions are crucial to address the cognitive sequelae in all COVID-19 patients, especially in patients with pre-existing cognitive impairment. Nevertheless, the authors recommend further research for the development of relevant, timely neurocognitive assessments and treatment plans.

Keywords: Brain, cognitive dysfunction, coronavirus, COVID-19

Introduction

COVID-19, caused by the SARS-CoV-2, has reportedly affected an estimated 510 million people globally. No doubt that COVID-19 predominantly affects the respiratory tract, but this virus has shown to affect multiple systems in the body, one such system being the nervous system[1]. Approximately 10–35% of patients who endured mild COVID-19[2] reported having their life affected by post-COVID-19 complications[3]. The National Institute for Health and Care Excellence has defined such complications as "Post-COVID Syndrome", new symptoms that have developed either during or post-COVID-19, which have persisted for more

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than 12 weeks and not explained by a clear diagnosis[4]. Some of these complications reported are anosmia, ageusia, cough, dyspnoea, headache, and cognitive dysfunction[5].

Cognitive dysfunction caused by COVID-19 has been detailed to affect memory recall and encoding, category fluency, processing speed, executive functioning, and issues in concentration effort[6]. Such cognitive deficit has been observed in both patients that were hospitalized and non-hospitalized due to COVID-19[7].

However, evaluating a large population via standardized cognitive assessment is arduous since numerous variables might affect cognitive functioning of individuals in said population[7]. A systematic review and meta-analysis demonstrated that the proportion of individuals ($n = 13\ 232$) that complained of cognitive dysfunction post-COVID-19 was 0.22 with a P value less than <0.001 shown to be statistically significant[8]. Another study conducted showed decreased cognitive function in patients who recovered from COVID-19 (extending 7 months post-COVID infection) in comparison to healthy individuals[9].

The aim of this review is to understand the underlying mechanisms, associations, and attempts for prevention with early intervention of long-term cognitive impairment post-COVID-19.

HIGHLIGHTS

- SARS-CoV-2 has resulted in a new set of chronic disabling conditions called long COVID/post-COVID-19 syndrome.
- Chronic dyspnea, persistent fatigue, and cognitive dysfunction are some of the most common and debilitating symptoms associated with long COVID/post-COVID-19 syndrome.
- The exact pathogenesis and underlying mechanisms behind cognitive dysfunction in COVID-19 remain unclear.
- Proposed mechanisms for cognitive dysfunction include direct damage to the blood-brain barrier, systemic inflammation, prolonged hypoxia, and extended intensive care admissions.
- Comprehensive evaluations and interventions are crucial to address cognitive sequelae in all COVID-19 patients, especially those with pre-existing cognitive impairment. Further research is needed for the development of relevant neurocognitive assessments and treatment plans.

Materials and methods

A systematic search was conducted through multiple databases such as Medline, National Library of Medicine, Ovid, Scopus database to retrieve all the articles on the long term sequalae of cognitive dysfunction after SARS-CoV-2 infection. The inclusion criteria included all articles pertinent to this specific topic and exclusion criteria subtracted studies pertaining to other aetiologies of cognitive dysfunction. This search was carefully screened for duplicates and the relevant information was extracted and analysed.

One-third of COVID-19 survivors showed evidence of cognitive impairment as well as motor deficits at time of hospital discharge[10]. However, the exact mechanism of how COVID-19 causes long-term cognitive dysfunction is unknown[11].

Proposed mechanisms of cognitive dysfunction after COVID-19 infection

The proposed mechanisms, alone or in combination, hypothesize how COVID-19 infection has long-term consequences on the brain: direct viral encephalitis, systemic inflammation, peripheral organ dysfunction (i.e. liver, kidney, lung), and cerebrovascular changes[12]. The resulting damage to the brain has been linked to cognitive impairments. For instance, an investigative study on cognitive impairments 3–4 months post-COVID-19 hospital discharge found that 59–65% of subjects showed clinically significant cognitive impairment[13].

A case report showed the direct invasion of SARS-CoV-2 into the central nervous system (CNS)[14]. Direct invasion is suggested to occur through haematogenous spread and via axonal transport through certain cranial nerves such as the olfactory nerve[15]. It is also hypothesized that SARS-CoV-2 infects the neuroglial cells in the CNS by crossing the blood-brain barrier (BBB)[16]. Notably, demyelination of the neurons has also been documented post-coronaviruses infection[17].

Host immune response to the SARS-CoV-2 virus leading to systemic inflammation has been demonstrated by sustained high levels of pro-inflammatory cytokines in COVID-19 patients[18]. The "cytokine storm" has been shown to promote cognitive decline making it likely that survivors will experience neurodegeneration years following infection[18–21].

Acute respiratory distress is the most frequent clinical presentation of organ dysfunction in COVID-19 patients[22]. Acute respiratory dysfunction often requiring chronic ventilation has been shown to cause cognitive decline months to years after hospital discharge[18]. It has been noted that hypoxia, a noteworthy respiratory system mechanism of COVID-19, could impact long-term cognitive functioning[16].

Acute cerebrovascular changes such as ischaemic stroke and cerebral haemorrhage were experienced by some patients. A study in Wuhan showed that 5% of patients with severe infection had cerebrovascular disease. Cognitive impairment due to cerebrovascular disease are due to vascular and parenchymal changes that impair brain perfusion[23].

Post-COVID-19 has been proven to cause cognitive decline long-term. These can be attributed to both CNS and non-CNS-originated pathologies. These complications occur in both hospitalized and non-hospitalized patients and these mechanisms have been discussed below:

Post-COVID-19 cognitive complications due to CNS causes

COVID-19 is best recognized for its effects on the respiratory system, but evidence exhibiting organ dysfunction, including the CNS, is mounting. Complications involving the CNS and mental health, including cognitive impairment, are becoming more common. Direct neurotoxicity or the host's immune system are two of the most common causes of cognitive deficits[24]. The patient's consciousness is also affected by direct inflammation of the CNS due to SARS-CoV-2 and extracranial cardiorespiratory illness. In addition, systemic inflammation, direct viral encephalitis, peripheral organ dysfunction, and cerebrovascular variations are all pathogenic-associated disturbances in the CNS[12].

Infected brains show structural variances over time above and beyond any apparent baseline differences, according to Gweanaelle Douaud, the study's first author and a Professor at the University of Oxford[25]. Most notably, people who had no or

just minor symptoms with COVID-19 showed unique abnormalities, although cortical damage appears to happen independently of illness severity, age, or sex[25]. Furthermore, even after 6 months of recovery, a loss in the amount of grey matter in the limbic system, which comprises multiple structures necessary for creating behavioural and emotional responses, was exposed[26]. The left parahippocampal gyrus and the entorhinal cortex showed the greatest changes, with decreases ranging from 0.2 to 2%[26]. Because these areas are critical in the hippocampus memory system, grey matter loss might indicate future memory problems. New data suggest that SARS-CoV-2 can infect the brain itself[27]. According to Stevens, numerous recent studies have confirmed that the developing coronavirus may cross the BBB[28]. MRI confirmed that the presence of viral meningitis, and cerebrospinal fluid analysis revealed signs of the developing coronavirus disease[28]. The virus was found in the cerebral fluid of a 56-year-old patient with severe encephalitis, according to Chinese experts[28].

In Italy, researchers identified viral particles in the cells lining the arteries of the brain after autopsying a victim of the developing coronavirus[28]. Some experts believe that the virus causes respiratory failure and death not because of lung damage, but because of damage to the brainstem, the control centre guaranteeing continual breathing even during loss of consciousness[28]. The BBB is composed of unique cells that coat the arteries of the brain and spinal cord, protecting the brain from infectious diseases. This barrier keeps bacteria and other potentially harmful pathogens extracranially[28]. However, the current issue is that doctors do not have any medicines to avoid brain injury[28]. Despite the severity of lung and renal failure, patients are subjected to invasive conservative measures, such as mechanical ventilation or haemodialysis. However, no such equipment to filter the blood from poisons in the brain exists[28].

Post-COVID-19 cognitive complications due to non-CNS causes

(1) COVID-19 patients admitted to the ICU whatever the cause, have shown cognitive impairment presenting mainly as a decrease in speed of processing information, speech fluency, learning, and memory recall[29]. It is stipulated to be due to the various interventions (such as assisted ventilation) and complications (such as respiratory distress and elevated proinflammatory cytokines) that provoke this long-term cognitive decline post-COVID-19[12].

(2) Moreover, because of quarantine during the COVID-19 pandemic, the abundance of neuropsychiatric symptoms, such as depression, inattention, anxiety, and sleep disturbances, especially among adolescents, is on the rise. Also, quarantine worsened the behavioural condition of children with pre-existing attention deficit hyperactivity disorder or autism[30]. In addition, individuals who experienced multisystem inflammatory syndrome in children post-COVID-19 infection have a higher risk of neurological symptoms than others[31].

(3) COVID-19 has been attributed as a cause of brain damage, especially in people older than 70 years. Some patients who recovered from COVID-19 were found to have brain damage because of decreased oxygenation to the brain. Such hypoxia manifests as mild deficits in cognition such as inattention, shown to not necessarily affect daily life of affected individuals.

(4) COVID-19 infection is considered a long-term risk factor for Alzheimer's Disease (AD) as a complication of CNS causes (i.e. direct viral encephalitis) and non-CNS causes (i.e. systemic inflammation[32], damage to peripheral vital organs, and cerebrovascular events due to thrombosis).

Cognitive complications of hospitalized vs non-hospitalized patients

In the post-acute phase of COVID-19, neurological dysfunction may linger, resulting in the "Long COVID" syndrome[33]. Although more than half of COVID-19 patients have mild respiratory symptoms and do not warrant hospitalization[34,35], only some, known as COVID-19 "long haulers," suffer from the aftermath and develop neurological manifestations[35–38]. On the other hand, a wide range of neurological symptoms has been observed in 36.4–82.3% of individuals infected with COVID-19 and hospitalized globally[39–41].

Neuro-COVID-19 clinic conducted a study among non-hospitalized patients to assess the variety of neurological symptoms that manifested in SARS-CoV-2 laboratory-positive patients[32,36]. Those patients had neurological symptoms persevering no less than 6 weeks from symptom onset. After an average of 4.72 months following symptom onset, patients were assessed[42]. Per history, 85% of patients had four or more neurological symptoms with "brain fog" being the most common, while others displayed non-specific cognitive symptoms such as headache (68%), numbness/tingling (60%), dysgeusia (59%), anosmia (55%), myalgia (55%), dizziness (47%), pain (43%), blurred vision (30%), and tinnitus (29%)[41]. Per neurological examination, around half of the patients had neurological impairments with short-term memory and attention functioning being the most common. All in all, SARS-CoV-2-positive "long haulers" had considerably lower quality of life in the domains of cognition and memory, which was consistent with their medical histories and examination findings[43].

Among hospitalized COVID-19 patients, toxic-metabolic encephalopathy (52%), hypoxic-ischaemic encephalopathy (21%), stroke (11%), and seizure (11%) were the most common diagnoses within the neurological cohort (11%). When compared to COVID-19 patients without neurological issues, patients identified with new neurological complications during hospitalization had a two-fold greater risk of a worse 6-month functional outcome (as per modified Rankin Score). Furthermore, more than half of these patients were unable to resume their fundamental daily activities independently, and 59% of those who were working before COVID-19 infection were unable to return to work within 6 months[44]. Because of the high likelihood of encephalopathy in hospitalized COVID-19 patients, one would wonder if "brain fog," with or without fatigue, is a mild type of post-COVID-19 encephalopathy[41].

Progression of cognitive impairment after COVID-19 infection in patients that have pre-existing cognitive impairment

Although patients with mild cognitive impairment MCI or AD have not shown any clear evidence of being susceptible to COVID-19 infection, these patients do become victims of the virus due to increased age and dementia-like associated health conditions.

As a consequence of infection, the elderly population with concurrent dementia develop a more serious version of the disease. Dramatic, severe signs and symptoms may develop in said patient with AD, whom are very likely to forget the common practices of avoiding COVID-19 infection, like social distancing, repeated handwashing, and donning personal protective equipment such as face masks or shields[45].

There is also evidence of rapid dementia worsening post-COVID-19 infection. Reasons include virus penetration into the brain and subsequent neuronal damage, accompanied delirium with confusion, and loss of ability as a symptom of COVID-19. These worsen dementia, with brain fog as well as invasive ventilation or ICU, further worsening confusion.

The Alzheimer's Society UK also noted how people with dementia in a care home were at a bigger risk of getting infected partly due to the already compromised age-related immune system and likelihood of living with others in close proximity. These increase the chance of contagion spread among residents and care workers[46].

Strict measures for reducing the risk of infection include regular reminders for basic hygiene in everyday practices, installing alert signals in public washrooms, encouraging handwashing with soap for 20 s, and to apply face coverings were proposed for AD patients by The Centre for Disease Control of the USA[47].

Hypotheses concerning that of two common drugs, Amantadine and Memantine, used to prevent tremor and treat AD, may play a protective function against SARS-CoV-2[45]. As NMDA antagonists, excess cellular calcium inhibition prevents neurotoxicity, thus deterring viral replication, reducing the chance of acute respiratory distress development.

MRI brain abnormalities after prolonged COVID-19 infection

The novel COVID-19 exhibits an infective process mainly affecting the respiratory system; however, recent evidence shows that it has neurological involvement[48]. Brain MRI imaging performed on patients infected with SARS-CoV-2 showed microscopic haemorrhages, infarctions, and even intra-axial instability irregularities[48]. Changes in the cortex and the microstructure of white matter were documented in patients 3 months post-COVID-19 infection[49]. In addition, the frontal and parietal lobes of the cerebral hemispheres demonstrated multiple subcortical white matter lesions in a study conducted by Linköping University, 4 months post-hospital discharge for COVID-19[49]. Moreover, PubMed and Embase databases were used to conduct secondary analyses via systematic review to identify brain MRI investigations in SARS-CoV-2- infected patients and posterior reversible encephalopathy syndrome. Such research found that approximately a quarter of patients had superimposed foci with limited spread as well as half of patients showing areas of haemorrhage on top of findings for posterior reversible encephalopathy syndrome[50]. Regarding MRI abnormalities, a systematic review of a total of 27 types of research reporting abnormalities in neuroimaging findings in patients infected with SARS-CoV-2, demonstrated the implication of the olfactory system, disruptions affecting four olfactory structures as well as the insula, corpus callosum and cingulate cortex[51].

Association of cognitive dysfunction with other symptoms of COVID-19 infection

COVID-19 infection affects several organ systems in the human body, including the respiratory tract, gastrointestinal organs, cardiovascular system, and neurological system, both peripheral and central components[42]. COVID-19 impairs cognitive function by affecting several domains, including problem-solving, attention, working memory, and executive functioning[7,52,]64–66.

A study addressing neurocognitive deficits caused by COVID-19 infection divides neurological changes into three stages: the first occurring when the brain is unaffected by the cytokine storm, the second when the cytokine storm causes blood vessel inflammation, and the third when the cytokine storm damages the BBB[53,54].

There appears to be no cognitive impairment during the initial phase; nonetheless, COVID-19 symptoms that emerge include nausea, vomiting, sore throat, fever, anosmia, and ageusia, the last two indicating peripheral nervous system damage[53].

Conversely, neurological impairment develops in the second phase, resulting in partial hemiplegia, aphasia, brain fog, pain, blurry vision, and ataxia[42,53]. Working memory, attention deficit, and cerebellar dysfunction are all symptoms of cognitive impairment during this period[42]. During this phase, COVID-19 symptoms include fatigue, bodily aches or discomfort, headache, insomnia, depression, and/or anxiety[42].

Furthermore, the third phase of the disease is the most severe, with neurological effects presenting as encephalitis, coma, seizures, and delirium[53]. Motor functions, attention, memory, language or speech, and executive functioning are the cognitive aspects compromised during this period[42,53]. COVID-19 manifestations include chest discomfort, confusion, dyspnoea or laboured breathing, and changes in blood pressure and heart rate[42,53]. The figure below summarizes the association of cognitive dysfunction with other symptoms of COVID-19 (Fig. 1).

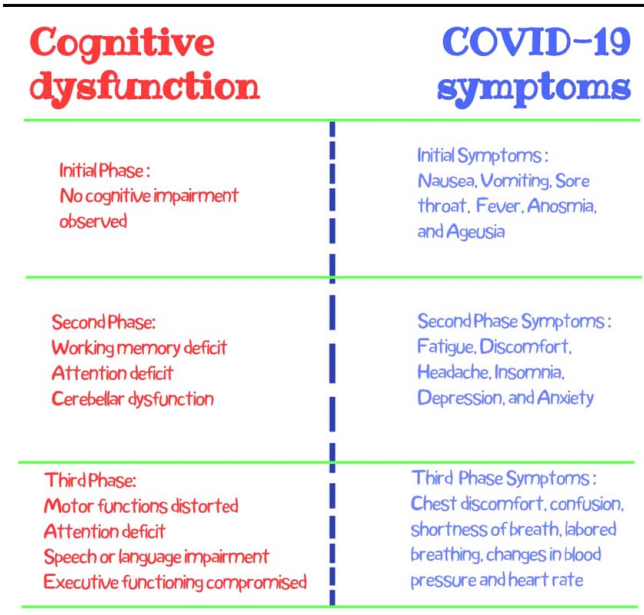

Figure 1. The association between cognitive dysfunction and other COVID-19 symptoms.

Prevention of cognitive dysfunction and delirium in patients infected with COVID-19

Multiple cognitive complications have been found linked with the severity of SARS-CoV-2 infection, leading to COVID-19. Of recent, emergence of various evidence indicates SARS-CoV-2 as a cause of a plethora of neurological complications, including delirium among others[54]. In most cases, elderly patients with MCI or dementia have a higher tendency to possess neuropsychiatric symptoms including delirium[55]. It is difficult to implement delirium prevention while patients are subjected to social isolation, therefore their prevention needs connective majors and strategies when applied to COVID-19 patients.

Neuropsychiatric symptoms become severe upon hospitalization due to COVID-19 infection. Extreme attention necessitates prevention of delirium in cognitive dysfunction patients suffering from COVID-19 infection. These include both cognitive and motor training as essential tools use in the management of psychiatric symptoms[56]. Home therapeutic management can be employed using telecommunication tools, comprising phone or video with speech and occupational therapy[57]. Concerning patients admitted to ICU, the prevention of delirium requires rigorous training for ICU physicians[55]. ICU-related delirium risks can be prevented by using standard guidelines that help in accessing and managing pain, as well as avoiding other activities such as constipation and excessive urinary retention as well as adequate oxygenation[58]. This can be followed by a frequent pain assessment via critical care pain observation or behavioural pain scales tools[59]. Withdrawal of unnecessary psychoactive medications as well as the prohibition of long-time use of sedatives or stay in ICU is highly recommended for delirium management[58].

Conversely, non-pharmacological intervention can also be employed for adequate prevention and management by showing affected individuals a warm attitude as well as a constant reminder of the current location and date[58]. Attachment items of patients such as radio and calendar should be allowed for the patient to access. Proper communication between patients admitted to ICU and their families through video calls should be allowed to mitigate delirium and patients' distress[59]. Concerning non-ICU patients, NICE[60] provide a guideline which describes four basic strategies for delirium prevention, including sleep, cognition, nutrition, and functionality. Such measures involve out-of-bed transition to a chair and encouraging mobility (Fig. 2).

Future recommendations

The authors believe it is paramount to expand our current knowledge of the underlying mechanisms concerning neurocognitive disability post-COVID-19. Endeavors to develop relevant neurocognitive assessment models with various tools depending on the vulnerability of patients is of utmost importance. Recommendations include scheduled follow-up visits with psychological support and support group to aid patient recovery.

Conclusion

It has been emphasized that the importance of periodic long-term neurocognitive assessments after recovery from COVID-19 infection is crucial. Since cognitive impairment may negatively

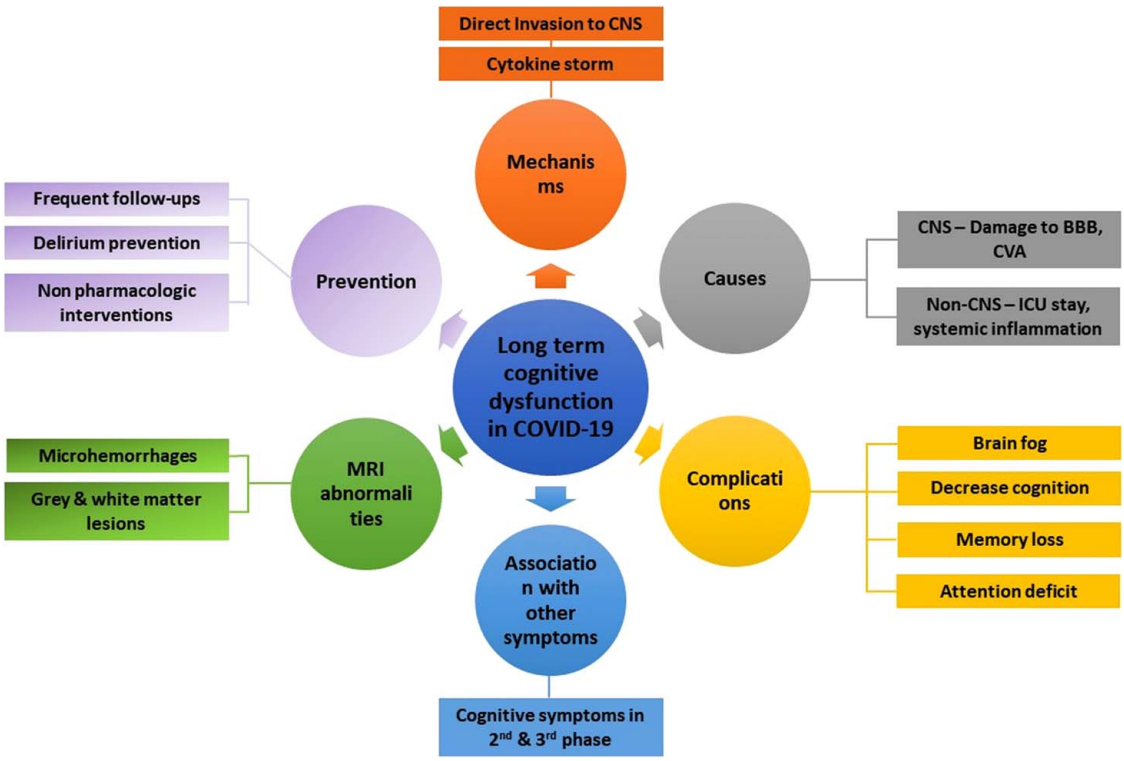

Figure 2. Summarizing long-term cognitive dysfunction after the COVID-19 pandemic. BBB, blood-brain barrier; CNS, central nervous system.

impact social and occupational performance, early intervention may improve affected patient's quality of life. To conclude, the need for comprehensive interdisciplinary approaches is reiterated to assessing and managing the short and long-term effects of cognitive dysfunction post-COVID-19. This review of the COVID-19 pandemic has elucidated a new global challenge which is affecting individuals' quality of life by inducing long-term impaired cognitive function.

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