Neurocognitive Rehabilitation in COVID-19 Patients: A Clinical Review

Ryan Mathern, MD, Pooja Senthil, BSc, Nguyen Vu, MD, and Thanigaiarsu Thiyagarajan, MD

Abstract: COVID-19 has affected many people all around the world for more than two years now have suffered many long-term consequences which is commonly referred to as long-haulers. Despite multiorgan complaints in long haulers, symptoms related to cognitive functions commonly referred as brain fog are seen in the high risk covid patients with age more than 50, women more than men, obesity, asthma and those who experienced more than five symptoms during the first week of covid illness. Long term isolation has certainly contributed to high level of anxiety and stress calling for an empathetic response to this group of covid patients as there is no specific test to detect long haulers and no specific cognitive rehabilitation techniques available as of today.

Key Words: coronavirus disease 2019 (COVID-19), Patient Reported Outcomes Measurement Information System (PROMIS), postacute sequelae of SARS-CoV-2 (PASC), severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)

Patients recovering from cerebrovascular accidents and brain injuries are common in the neurocognitive rehabilitation domain. The coronavirus disease 2019 (COVID-19) pandemic has brought a new patient population to the forefront, however, in people with neuropsychiatric sequelae following a confirmed diagnosis of COVID-19. In fact, 1 in 3 people who have had COVID-19 have a neurological or psychiatric condition diagnosed within 6 months of infection.[1] The viral infection often leads to different neurologic complications as part of what has been called long COVID or postacute sequelae of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. One of the neurologic complications is cognitive impairment, with deficits ranging from mild to severe. This can be debilitating in terms of the physical and mental well-being of COVID-19 patients. Furthermore, cognitive deficits are some of the most persistent long-term symptoms that people experience after initial infection. Given the size of the global pandemic, the chronicity of the disease, and its many consequences, health and social systems will continue to feel substantial effects of the disease. This article focuses on neurocognitive rehabilitation in the COVID-19 patient population, which has become imperative to the success of their overall recovery. To continue to care for the neurologic complications of COVID-19 patients, it is important to use all primary and secondary care services, especially those that specialize in neurocognitive rehabilitation.[2]

Mechanism/Pathophysiology of Neurological Damage by COVID-19

To date, no definitive mechanism of neurological insult has been identified by those studying COVID-19. Among the different possible mechanisms reported, the first involves direct infection through the angiotensin-converting enzyme 2 (ACE2) receptor expressed on both astrocytes (Fig. 1) and neurons (Fig. 2). COVID-19 has been shown to bind to ACE2 through the receptor-binding gene region of its Spike protein. Neurons appear to be more susceptible than astrocytes, as shown by their high pattern of resistance to the virus.[3] The second proposed mechanism is via an inflammatory cascade triggered by the virus that results in a central nervous system vasculitis or that an autoimmune

Key Points

- One in three people who have had coronavirus disease 2019 (COVID-19) have a neurological or psychiatric condition diagnosed within 6 months of infection, which often leads to different neurocognitive complications diagnosed as long COVID or postacute sequelae of severe acute respiratory syndrome-coronavirus-2 infection.
- Brain fog accounts for 81% of different neurological symptoms experienced by long COVID patients. The high rate of encephalopathy in hospitalized COVID-19 patients leads one to question whether brain fog, with or without fatigue, may represent a mild form of post-COVID-19 encephalopathy.
- There is an urgent need for further research to identify the exact mechanism of neurological insult to not only explain why patients have neurological symptoms but also to help create more targeted treatment in the management of neurocognitive complications from COVID-19.

From the Department of Physical Medicine and Rehabilitation, Atrium Health, Carolinas Rehabilitation, Charlotte, North Carolina, the Department of Life Sciences, McMaster University, Hamilton, Ontario, Canada, and the Department of Hospital Medicine, Atrium Health, Carolinas Medical Center, Charlotte, North Carolina.

Correspondence to Dr Thanigaiarsu Thiyagarajan, Department of Hospital Medicine, Atrium Health, Carolinas Medical Center, 1000 Blythe Blvd, Charlotte, NC 28203. E-mail: thanigaiarsu.thiyagarajan@atriumhealth.org.

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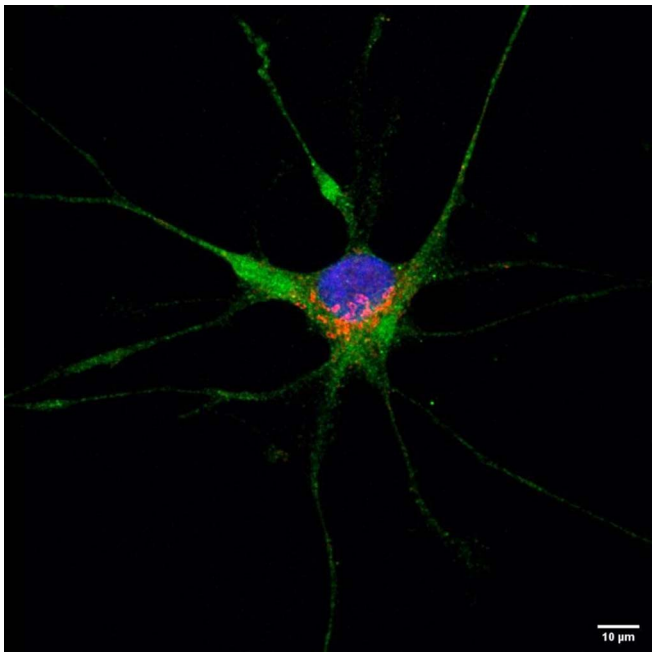

Fig. 1. A single astrocyte displaying expression of the SARS-CoV-2 receptor protein ACE2 (red). ACE2, angiotensin-converting enzyme; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2. From SciTechDaily[3] with permission.

response occurs that mistakenly attacks the various cells of the brain instead of the virus itself. There is an urgent need for further research to identify the exact mechanism of neurological insult to not only explain why patients have neurological symptoms that range from mild to severe but also to help create more targeted treatments in the management of neurocognitive complications from COVID-19.

Clinical Course and Presentations

As the COVID-19 pandemic continued into 2021, it was becoming increasingly clear that some patients had long-term neurological symptoms after the initial COVID infection. This long-lasting condition is now known as long COVID, or postacute sequelae of SARS-CoV-2 infection, which comprises a combination of neurologic, pulmonary, cardiac, and gastrointestinal symptomatology. COVID-19 patients with underlying comorbidities, including hypertension, diabetes mellitus, and advanced age, as well as those with intensive care unit stays, often have a more severe COVID-19 disease course and are more prone to significant neurological manifestations.[4,5]

Neurological symptoms are among the most common lingering effects in patients diagnosed as having COVID-19. In a study of 100 nonhospitalized patients who presented to a neuro-post-COVID clinic at Northwestern University, 50 SARS-CoV-2–positive patients were evaluated at approximately 4.72 months postsymptom onset and 50 SARS-CoV-2–negative patients were evaluated at 5.82 months postsymptom onset.[6] The patients were noted to have different neurological symptoms, including "brain fog" (81%), headache (68%), numbness/tingling (60%), dysgeusia (distortion of the sense of taste; 59%), anosmia (loss or impairment of the sense of smell; 55%), myalgias (muscle pain; 55%), and fatigue (85%). Overall, the study found that 85% of patients had multiple neurologic symptoms.[6] The research team found that brain fog had similarities to those symptoms described by patients with posttraumatic brain injuries, those receiving chemotherapy, and those with chronic fatigue syndrome.[7–11]

Taquet et al found that 20% of COVID-19 survivors were diagnosed as having a psychiatric disorder within 3 months of infection.[2] The most common psychiatric diagnoses were anxiety disorders, occurring in 17% of the patients, mood disorders in 14% of the patients, substance misuse disorders in 7% of the patients, and insomnia in 5% of the patients. It is interesting to note that these disorders did not appear to be related to how mild or severe a patient's COVID-19 infection had been. This study included 236,379 patients with COVID-19 from the US TrinetX electronic health records network comparing similar respiratory diseases, such as influenza and upper respiratory tract infections; COVID-19 survivors were more likely to have conditions such as anxiety and mood disorders diagnosed.[2]

Contrary to the psychiatric conditions mentioned above, the severity of COVID-19 infection does appear to play a role in the development of neurological sequelae. It has been found that 1 in 3 people who have had COVID-19 have a neurological or psychiatric condition diagnosed within 6 months of infection, and nearly half of the people who had been admitted to intensive care units (46%) had a neuropsychiatric condition diagnosed

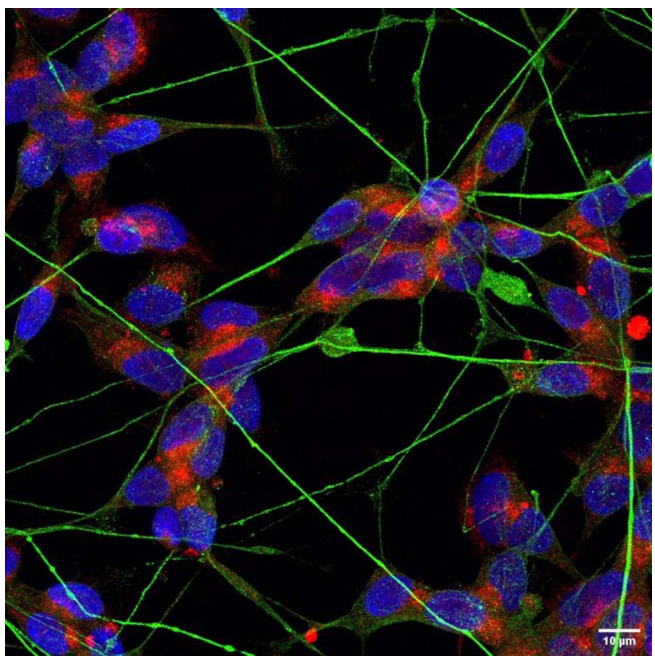

Fig. 2. A group of neurons (blue) and the dendrites that connect them (green). The ACE2 receptor (red) is present in the neuronal main body. ACE2, angiotensin-converting enzyme. Image by Mohammad Islam and Robert Dayton, CCDS Virus Complications Core, Louisiana State University Health Sciences Center, New Orleans.

Table 1. Incidence of neuropsychiatric conditions of 236,379 patients with COVID-19 from the US TrinetX electronic health records network

Neurologic condition	Nonhospitalized patients, %	Patients admitted to ICU, %	Patients who had encephalopathy, %
Brain hemorrhage	0.3	2.7	3.6
Ischemic CVA	1.3	6.9	9.4
Psychotic disorder	0.9	2.8	7
Dementia	2.66	—	4.72

COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident; ICU, intensive care unit.

within 6 months. This number rose to 62% of patients when that team examined a new diagnosis of delirium or encephalopathy during a hospitalization.[2] After adjusting for underlying health characteristics such as age, sex, ethnicity, and existing conditions, patients were found to be at a 44% greater risk of neurological and mental health diagnosis after COVID-19 than after the flu and a 16% greater risk after COVID-19 than with other respiratory tract infections. This was further supported by a hazard ratio of 2.33 when comparing COVID-19 with influenza.[1] The rate of individual conditions also increased with the severity of COVID-19, as shown in the incidence data in Table 1 extracted from the US TrinetX electronic health records network.

It is alarming to see an increased incidence of cerebrovascular events, particularly ischemic stroke, presenting with a focal motor, sensory, or speech disturbance. Almost 1 in 9 patients with the dual diagnosis of COVID-19 and stroke seems to be encephalopathic, as noted in Table 1. Acute encephalopathy is a relatively common presenting symptom of severe COVID-19 disease.[4,12] The high rate of encephalopathy in hospitalized COVID-19 patients leads one to question whether brain fog, with or without fatigue, may represent a mild form of post-COVID-19 encephalopathy.[13] In looking at the exact etiology of this increase in cerebrovascular events, some studies revealed a questionable association of lupus anticoagulants and ischemic thrombosis causing acute cerebrovascular accident in COVID-19 patients, with a prevalence of 45% to 91% for lupus anticoagulants in their study.[14,15] Because the clinical significance is not yet known, these laboratory values should not be routinely checked in COVID-19 patients without a thrombosis. Similarly, it is unclear whether elevated D-dimer levels in a COVID-19-associated coagulopathy are directly associated with either arterial or venous ischemic stroke. Other neurological complications such as seizures, postinfectious demyelination, and encephalitis, and neuromuscular disorders such as critical illness polyneuropathy, critical illness myopathy, acute inflammatory demyelinating polyneuropathy, and cranial neuropathies (particularly olfactory neuropathy) have been reported as well.

Role of Focused Neurocognitive Rehabilitation

Patients have reported that their neurocognitive abnormalities, especially the short-term memory loss and attention-related cognitive dysfunction, have led to significant impacts on their activities of daily living, often preventing them from returning to work entirely. Servick found that of 57 recovering COVID-19 patients referred for neuropsychological evaluation before hospital discharge, 81% had memory impairment.[16] Most patients surveyed experienced problems with attention and executive function, which includes skills such as planning, organization, and multitasking.

Much like those who have experienced cerebrovascular accidents or traumatic brain injuries, patients diagnosed as having COVID-19 can undergo cognitive screening assessments like the Patient-Reported Outcomes Measurement Information

Table 2. PROMIS health-related quality of life domains for adult patients

	Physical health	Mental health	Social health
PROMIS profile domains	Physical function Pain intensity Pain interference Fatigue Sleep disturbance	Depression Anxiety	Ability to participate in social roles and activities
PROMIS additional domains	Pain behavior Pain quality Sleep-related impairment Sexual function and satisfaction Gastrointestinal symptoms Dyspnea Itch	Anger Cognitive function, Alcohol use, consequences, and expectancies Smoking Substance abuse Life satisfaction Meaning and purpose Positive affect Psychosocial illness impact Self-efficacy for managing chronic conditions	Satisfaction with social roles and activities Social support Social isolation Companionship
PROMIS global health	Global physical health	Global mental health	

PROMIS, Patient Reported Outcomes Measurement Information System.

System (PROMIS) quality of life and National Institutes of Health Toolbox cognition assessments to confirm deviation from premorbid baseline functions and to identify target areas for treatment. PROMIS is a set of person-centered health measures that evaluates and monitors health-related quality of life, which is defined as "the extent to which one's usual or expected physical, mental, and social wellbeing is affected by medical condition or its treatment."[17] PROMIS presents a new set of multidimensional health-related quality of life instruments that combine features of physical, mental, and social health developed using rigorous qualitative and quantitative methods (Table 2).

Neurocognitive rehabilitation programs use a multidisciplinary team, which includes physiatrists, neuropsychologists, and speech-language therapists who can help COVID-19 patients with seizures, ataxia, and olfactory impairment and patients with brain fog symptoms. The approach uses both established and new innovative strategies and techniques to address functional deficits throughout a patient's recovery. Although it is important to understand that no neurological condition acts or behaves the same, attention process training, compensatory strategies, errorless learning training for memory deficits, pragmatic language skills for cognitive-communication disorder, meta-cognitive strategy, and problem-solving training for executive disorders are the mainstays of therapy for cognitive deficits in people with traumatic brain injuries and play a role in cognitive rehabilitation following COVID-19.

By including a rehabilitation-driven mindset in a COVID-19 hospitalization stay, the identification of both physical and cognitive deficits can be done quickly in such a way that targeted treatment plans can be implemented early during an acute care stay. Furthermore, this will provide a "link" in patients' acute care stay to that of their recovery period, allowing for a smooth transfer to an inpatient or outpatient rehabilitation setting, where dedicated rehabilitation of functional deficits can continue. With this approach, the entirety of the postinfectious symptomatology can be addressed to allow for maximization of neurological and physical recovery as well as a safe return home.[18] Long COVID patients at home will benefit from mindfulness-based cognitive therapy using different strategies that include (1) prescribing memory-strengthening homework to address lack of concentration, inability to remember common words, and trouble recalling the events from the previous day, such as taking notes, using a planner to record information, and dividing a task into smaller increments to prevent brain fatigue, which are common strategies that can be used with pacing, endurance, and memory[19]; (2) teaching patients about real-life memory loss scenarios; and (3) creating a behavior plan to prevent relapse, which includes a list of daily activities and a letter that the patient addresses to him-/herself explaining the importance of staying mentally active, reducing self-criticism, and giving oneself credit for successes.

Much like other research regarding the COVID-19 pandemic, dedicated studies regarding the specific treatment of neurocognitive complications are developing at a rapid pace. A consensus statement regarding rehabilitation was published by Barker-Davies et al that discussed a litany of topics ranging from cardiopulmonary rehabilitation to that of managing the neuropsychiatric effects of COVID-19.[20] Elsewhere, Taub and Uswatte are attempting to validate traditional neurocognitive rehabilitation methodologies, such as constraint-induced cognitive therapy, with ongoing clinical trials.[21] Technologies such as virtual reality and interactive digital platforms[16] are being trialed by teams headed by van Goor and Jackson, respectively, as the rehabilitation world works to identify the optimal treatment regimen for this new and challenging diagnosis.

Conclusions

There is a great need for a dedicated neurocognitive rehabilitation for long COVID patients following an infection with COVID-19. With symptoms that are at times severe and the recovery course often prolonged, neurocognitive rehabilitation is uniquely positioned to provide an intervention in the acute, subacute, and chronic stages of neuropsychological recovery. The National Institutes of Health has launched a database, NeuroCOVID, which will serve as a hub for connecting scientists and clinicians who are researching the prevention, management, and treatment of neuropsychological complications associated with COVID-19. With further research and focus on this matter, the healthcare community at large will benefit from focused innovative treatment strategies and rehabilitation techniques to manage the neurocognitive sequelae of COVID-19 for patients to regain quality of life and return to being active members of their communities. Once we have a good medical understanding of long COVID, we need a comprehensive national plan to build the necessary infrastructure to provide equitable access to care for all long COVID patients.

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