Long-Term COVID-19 Neurological Symptoms: A Review of Epidemiology, Pathophysiology, and Treatment

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Abstract

The World Health Organization (WHO) announced the discovery of a novel coronavirus, called COVID-19, in Wuhan, a central city in China, on January 10, 2020. Additionally, COVID-19 has been known to lead to many neurological dysfunctions including anosmia, dysgeusia, stroke, anxiety, depression, and memory loss/brain fog. Here we highlight neurological complications related to COVID-19 infection and cover epidemiology, current understood pathophysiology, and treatment options available.

Introduction

The World Health Organization (WHO) announced the discovery of a novel coronavirus, called COVID-19, in Wuhan, a central city in China, on January 10, 2020. This virus spread throughout the world and became a global pandemic. It is a very contagious and harmful virus that has similar symptoms to a cold, flu, or pneumonia but can lead to hospitalization and death. Schools were forced to convert to online learning in many areas which in the following years led to a shortage of teachers. Many people lost their jobs and homes, there was less social interaction as everyone was forced to stay home, and only go out wearing a mask. In the long run, this affected the mental and social well-being of individuals. As of December 2022, there have been 645 million cases and 6.6 million deaths.[40] In the United States, there are 4 approved vaccines which include Pfizer-BioNTech and Moderna COVID-19 which are mRNA vaccines.[38]There is also the Novavax COVID-19 which is a protein subunit vaccine. Lastly, there is Johnson & Johnson's Janssen, a viral vector vaccine that may be administered in certain circumstances. The Novavax vaccination was 100% effective against moderate and severe disease and 90% effective against lab-confirmed, symptomatic infection before the Omicron variant. By 14 days following immunization, the Johnson & Johnson vaccine had a 67% efficiency in avoiding moderate to severe/critical illness and a 66% efficiency by 28 days. 95% efficiency was displayed by Moderna. Pfizer-BioNTech also demonstrated 95% efficiency, however real-world effectiveness for adults demonstrates that the protection from the mRNA two-dose primary series wanes with time. [17] A booster dosage (for eligible individuals) restores the immune function to resilient levels. Risk factors for severe COVID-19 can include asthma, old age, obesity, diabetes, and people who are immunocompromised.[39] The percent range of asymptomatic infection is between 9-36%. More asymptomatic infections were seen in younger individuals. 50-70% of individuals have a cough and/or fever in COVID-19.[19]

Additionally, COVID-19 has been known to lead to many neurological dysfunctions including anosmia, dysgeusia, stroke, anxiety, depression, and memory loss/brain fog. This review paper will highlight neurological complications related to COVID-19 infection and will cover epidemiology, current understood pathophysiology, and treatment options available.

Anosmia and Dysgeusia

Anosmia and dysgeusia are very common acute COVID-19 symptoms affecting approximately 83% and 89% respectively. The majority of people regain their sense of taste and smell within six weeks. Paderno et. al. reported that 87% of patients with anosmia recovered and 82% with dysgeusia recovered. [29] Unfortunately, some people also have anosmia and dysgeusia as long-term lingering symptoms. 8-16% of people have anosmia and 6-14% have dysgeusia 3 months after the onset of COVID-19. [30] These symptoms occur for 3 months in most patients after which they regain their sense. But, in some patients, they persist even after 5 months after which they are less likely to recover. [30] Risk factors of anosmia and dysgeusia include current smokers, histories of allergies, particularly respiratory allergies, and hospitalization.[13] There are theories linking low zinc levels to anosmia and dysgeusia, however further clinical studies are needed to fully evaluate these theories. [18]

The mechanism behind anosmia and dysgeusia is still under investigation however several studies point to potential underlying pathophysiology. Based on an MRI study, COVID-19-infected patients showed a complete obstruction and edema of the olfactory clefts but recovered after a month shown through the improvement of their olfactory score. [10] Anosmia occurs due to nasal obstruction and rhinorrhea, cytokine storm, a substantial injury to olfactory receptor neurons, disability of the olfactory perception, and in some rare cases olfactory cleft syndrome.[4] Since the olfactory epithelium exhibits a notably high amount of ACE2 receptor expression, inflammation in this region may be one of the primary causes of anosmia. [28] Direct toxicity to taste buds or the olfactory epithelium, as well as peripheral neurotropism, are the most likely causes of transitory dysgeusia in COVID-19. Other elements, such as a flaw in the quantity and quality of saliva, pro-inflammatory cytokines, angiotensin II buildup, systemic illnesses, hypozincemia, and excessive chemical usage, may also contribute to dysgeusia.[27] Khani et. al. reported novel COVID-19 strains that engage with the ACE-2 (angiotensin-converting-enzyme) receptors found on taste buds and sustentacular cells directly harm the gustatory and olfactory systems. Other suggested processes include the virus's infiltration of the olfactory neurons and the subsequent local inflammation. Therefore, neuroprotective, anti-inflammatory, or depolarizing medications may be helpful for COVID-19 individuals who have lost their sense of smell or taste, but additional clinical trials are required.

Corticosteroids have been studied the most among the various drugs mentioned in COVID-19. It should be understood, though, that using systemic corticosteroids to treat SARS-CoV-2-mediated olfactory and gustatory dysfunctions may carry extra hazards and may slow the body's ability to rid itself of the virus. Singh et. al. reported that the utilization of steroids like fluticasone nasal spray and triamcinolone medicine assists in recovery within a week for anosmia and dysgeusia. [33] Olfactory exercises, intranasal or oral corticosteroids, and intranasal sodium citrate are all possible treatments. Tissue engineering and stem cell therapy are two of the innovative therapeutic approaches that are now being researched and developed.[28] One technique for assisting olfactory sense recovery is smell training, which utilizes eucalyptus, lemon, rose, and clove essential oils. Even though evidence shows that they enhance recovery, there are superior compounds for expediting recovery. Numerous phytochemicals have bioactive qualities that have anti-viral and anti-inflammatory impacts. [21] Given that the neuronal pathway plays a role in COVID-19-induced anosmia and/or ageusia,

neuroprotective medications like intranasal vitamin A, intranasal insulin, omega-3, statins, minocycline, and melatonin may be able to help patients with persistent anosmia by encouraging the regeneration of the olfactory receptor neurons.[18]

Arterial Ischemic Stroke

Stroke was shown to be a rare but potentially fatal COVID-19 consequence, involving 1-3% of hospitalized patients and up to 6% of those in the intensive care unit (ICU). Males account for roughly 62% of those that develop strokes during COVID-19 since they are more likely to experience severe COVID-19 symptoms during ICU admission. Rarely was a stroke the initial symptom; instead, most instances showed up within 21 days from COVID-19 onset after respiratory symptoms.[35] In a study of COVID-19 patients with arterial ischemic stroke (AIS), Beyrouti et. al. revealed that the AIS developed 8 to 24 days after the onset of COVID-19 symptoms. These patients had significantly higher levels of lactate dehydrogenase (LDH), fibrinogen, D-dimer, and C-reactive protein in their laboratory tests.[3]

Although the pathophysiology and ideal management of ischemic stroke linked with COVID-19 are still unknown, recent statistics suggest cytokine storm-induced endotheliopathy and coagulopathy as potential targetable mechanisms. [35] Systemic hypercoagulability brought on by COVID-19 results in high levels of D-dimer, fibrinogen, low platelet count, and prolonged coagulation time which are triggers for ischemic strokes. Some studies have therefore hypothesized that COVID-19 causes ischemic stroke by encouraging a hypercoagulable state in affected patients. Patients with severe COVID-19 are more likely to have an arterial ischemic stroke(AIS). [37] Li et al reported COVID-19 in the cerebrospinal fluid (CSF) of patients, alluding to the possibility that this particular virus can cross the blood-brain barrier (BBB) and impair brain tissue. [23] Of note, Oxley et al. found cases of secondary AIS in young COVID-19 patients, some of whom did not have stroke risk factors or elevated levels of D-dimer and fibrinogen.

The majority of individuals had significant vascular risk factors already present, including hypertension and diabetes mellitus. Race and ethnicity are critical risk factors for COVID-19 strokes. This is a result of the prevalence of cardiovascular risk factors in some particular ethnic groups. In one study of 7868 individuals hospitalized with COVID-19, Black patients had the highest rates of obesity, hypertension, and diabetes. Due to these variables, individuals with COVID-19-related stroke are more likely to be from one ethnic group than another. In a recent research of 83 instances, 47% of the patients were Black, 28% Hispanic, and 16% White. In cases of young individuals with stroke, it is often seen that they have large-vessel occlusion. These risk factors are seen more as triggers than independent causes. [35]

According to studies, heparin anticoagulant medication can significantly lower mortality rates of hospitalized COVID-19 patients. Standard anticoagulation therapies like tissue plasminogen activators, thrombolytics, statins, aspirin, and clopidogrel can reduce hypercoagulability in patients with AIS and can be used for COVID positive patients. Prophylactic anticoagulation is advised for patients with D-dimer levels below 1,000 (ng/ml), according to Ouderk et al. Therapeutic anticoagulation is advised for patients whose D-dimer levels are >1,000 (ng/ml) and who also experience progressive D-dimer level increases.

Targeting cytokines in COVID-19 patients has become an unavoidable trend because of their critical involvement in causing tissue damage and a hypercoagulable state. These therapies are still being researched and need to be further improved to increase the efficiency in reducing mortality rates and hypercoagulability.[37]

Anxiety and Depression

According to the COVID-19 Mental Disorders Collaborators, in 2020 the pandemic caused a 27.6% increase in cases of major depressive disorders and a 25.6% increase in cases of anxiety disorders worldwide.[8] Deng et al. found 45% depression and 47% anxiety in 31 studies.[9] Anxiety and depression are introduced during COVID-19 and are established post-COVID-19. The odds of depression and anxiety are elongated by COVID-19. Schou et al. reported decreased anxiety at the 1 to 3 months follow up however, it was significantly higher in survivors of COVID-19 compared to non-COVID-19 patients. Additionally, Mazza et al. discovered that at the 3-month follow-up, depression symptoms persisted whereas anxiety had reduced at this point.[32]

The increased cytokine levels seen in COVID-19 patients have been directly linked to lung inflammation and malfunction as well as the emergence of psychiatric disorders, both peripherally and centrally. This connection has already been made in the context of acute COVID-19 patients, where it was discovered that participants who had depression and/or anxiety symptoms tended to have higher levels of the cytokines, specifically interleukin (IL-1β), than COVID-19 patients who did not show depression/anxiety symptoms. It was also revealed that although women had lower levels of inflammatory markers at baseline, they still experienced anxiety and depression. Therefore further research into the role of inflammatory cytokines and depression/anxiety needs to be conducted in the context of COVID-19 and other diseases. At follow-up, baseline systemic immune-inflammation index (SII) values were positively correlated with depression and anxiety scores.[32] It has been demonstrated that the SII, a composite indicator incorporating platelet, neutrophil, and lymphocyte counts, is a significant prognostic predictor for a number of diseases. This implies that the severity of the depression psychopathology at the three-month follow-up can be predicted by the systemic inflammatory response at admission. Similar to other diseases, the authors also reported that female sex and prior psychiatric history were indicators of depression and anxiety. COVID-19 can damage endothelial cells by entering through ACE2 receptors, causing inflammation, thrombi, and brain trauma. Additionally, systemic inflammation results in a reduction in neurotrophic factors as well as the formation of reactive microglia, which raises glutamate levels as well as N-methyl-d-aspartate (NMDA) leading to excitotoxicity. The emergence of anxiety and depression is presumably accompanied by this increased inflammatory response. [32]

Risk factors of anxiety and depression in COVID-19 include isolation, quarantine, previous definitive psychiatric diagnosis/disease, hospitalization in the ICU, use of mechanical ventilation, requiring stay in the ICU, pregnancy, etc. This is rarely seen as a severe symptom and is treatable by seeing a psychiatrist or therapist. They would be treated as normal depression and anxiety patients.[9]

Memory Loss/Brain Fog

Cognitive dysfunction and memory loss have been reported in up to 70% of Long COVID-19 patients. Guo et. al. revealed that 77.8% of participants had trouble focusing, 69% had brain fog, 67.5% had forgetfulness, 59.5% had trouble identifying words, and 43.7% had semantic disfluency (speaking or typing an incorrect word). Guo et al. conducted a study and discovered that the presence of neurological symptoms resembling chronic fatigue during the first three weeks substantially predicted the presence of cognitive symptoms later in the future illness. Patients who reported neurological symptoms performed poorly in terms of executive function, memory, and attention, indicating some correlation between symptomatology and the degree of cognitive loss. [15] In COVID-19 patients who were not hospitalized, Graham et al. documented neurological symptoms that persisted for at least 6 weeks following system onset.[14] Seven out of ten individuals with acute COVID-19 infection experience persistent cognitive symptoms for months after the infection, including memory loss, concentration problems, and brain fog. [25]

An Oxford University study has discovered that COVID-19 can cause brain shrinkage by diminishing grey matter in the areas that control emotion and memory.[5] In the orbitofrontal cortex and parahippocampal gyrus, regions connected to the sense of smell, COVID-19 caused a higher loss of gray matter thickness. It also caused a greater reduction in whole-brain volume and an increase in cerebrospinal fluid volume. Additionally, there has been a generalized loss in the capacity for complicated activities, which on brain scans was linked to atrophy in the crus II region of the cerebellum, a region linked to cognition. [1] The exact mechanisms producing these cognitive deficiencies require more research, however, they most likely involve one or more of the following. They may be brought on by immunological response, neuroinflammation, or even a direct viral invasion of brain cells. Normally, the parasympathetic (PNS) and sympathetic (SNS) nerve systems collaborate to enable your body to react quickly to environmental changes. Long-term COVID-19, however, upsets this equilibrium and results in symptoms like inability to exercise, headaches, blood pressure changes, urine incontinence, heart palpitations, breathing difficulties, brain fog, and memory issues. Even while it is unclear how exactly autonomic nerve system (ANS) dysfunction in long COVID-19 patients results in memory loss, certain research indicates that the ANS is crucial for memory consolidation during sleep and for enhancing working memory. [26]

A neurovascular coupling malfunction can happen after a COVID infection, in which case several brain regions struggle to carry out their activities because they no longer obtain the resources they require. Patients may experience different sorts of physical and cognitive impairments depending on which areas are impacted. Forgetfulness and a decrease in executive function, for instance, are influenced by vascular abnormalities in the hippocampus. Due to this, different types of memories may be challenging for patients to process and retrieve. When a patient has COVID-19, their bodies launch an immunological reaction that draws immune cells to the location of the viral attack to combat the invasive virus. This is a common reaction; in most people, so the immune system settles down after a few days. Unfortunately, this reaction could spiral out of control and cause a hyperinflammatory reaction throughout the body. There is some indication from the evidence that this excessive response may be the cause of working memory and consolidation memory issues in patients with protracted COVID-19. [2] Long COVID-19 can lead to sleep disturbances in some patients, which can

result in memory problems. Memory consolidation is hampered by poor sleep as it throws off sleep cycles. Additionally, studies have shown that those who lack sleep are more prone to creating false memories and have weaker working and visual-spatial memory. [24] [31] Your brain may indicate increased sympathetic nervous system activity when you concentrate, which causes a temporary increase in breathing rates. Under normal conditions, the parasympathetic nervous system restores regular breathing rates. However, the sympathetic branch may continue to predominate in patients with protracted COVID-19. When it comes to cognitive function, poorer performance in memory and attention are linked to, both increased sympathetic activity and decreased parasympathetic activity. [25] [12]

In order to improve memory issues, you can undergo a series of multidisciplinary cognitive therapies. Some therapies, such as cognitive, sensorimotor, neuromuscular, and visual therapy, to name a few, are combined with aerobic exercise. Combining these treatments will aid in your body's recovery from COVID-19's residual effects. By facilitating the flow of oxygen to the brain, diaphragmatic breathing can also enhance focus and memory. A deep inhalation via the nose while concentrating on using the diaphragm is followed by a gradual exhalation while practicing the diaphragmatic breathing technique. The body can slow its breathing down and activate the parasympathetic nervous system by breathing more effectively. Some home remedies for memory loss are to include physical exercise in your daily routine, challenge your brain with logic puzzles or strategy board games, socialize frequently, get enough sleep, lower your stress levels, have your vitamin levels checked, identify and treat other health issues, follow a healthy diet, and get enough sleep. [25]

Conclusion

Long-term neurological symptoms of COVID-19 include anosmia and dysgeusia, anxiety and depression, stroke, and memory loss. These symptoms occur in almost 20% of COVID-19 patients and can last for over 6 months after the infection has been cleared. While the pathophysiology of these symptoms is still under active investigation, potential mechanisms of these long symptoms include damage to ACE2 receptors in the olfactory epithelium causing anosmia, peripheral neurotropism leading to dysgeusia, cytokine storm-induced endotheliopathy and coagulopathy as potential targetable pathways for ischemic stroke, and memory loss secondary to COVID-19 induced brain atrophy and inflammation. Anxiety and depression may occur through direct and indirect consequences of COVID-19 including social isolation during periods of quarantine. There are few established treatments for these long-term neurological side effects of COVID-19, namely high-risk patients should be placed on prophylactic heparin during the course of the disease.

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