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Anticipated Long-Term Cognitive Impairment Following Covid-19 Recovery in Elderly Patients

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic was declared by the World Health Organization on 11th March 2020. The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing the disease was mainly associated with pulmonary manifestations. But according to the neuroinvasive properties of prior coronaviruses and the similarity of neuropsychological conditions, it appears that patients can develop injurious long-term cognitive events post-COVID-19 infection. Although geriatric patients with underlying comorbidities are highly susceptible to severe disease, most of them survive and recover from COVID-19. The survivors experienced long-lasting cognitive dysfunction that occurred after suffering from COVID-19 neuro infections. A comprehensive review of literature on peer-reviewed journals was conducted using a variety of keywords, including COVID-19, late consequences of COVID-19, cognitive impairment, neuroinvasion, and neurodegeneration. This review aimed at exploring the anticipated long-term cognitive impairment in geriatric patients following COVID-19 infection recovery, the neuroinvasive properties of prior Human Coronaviruses (HCoVs), and extensively researched disorders that share similar neurological mechanisms. Deeper insight into the full spectrum of these neurological disorders can result in improved clinical outcomes and better treatment algorithms. Consequently, this review summarizes only what is currently known about SARS-CoV-2-mediated neurological injury and establishes a framework for future and larger clinical studies to shed new light on the long-term cognitive impairment after overcoming the primary COVID-19 infection.

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Introduction

The recent Coronavirus Disease 2019 (COVID-19) epidemic triggered by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has rolled the world into disarray with its threateningly high frequency of transmissions resulting in more than 99 million confirmed cases and more than 2 million deaths globally by January 2021 [1]. It is the most enormous and dreadful pandemic since the 1918 pandemic of influenza [2]. It also has caused an unprecedented economic, sociodemographic, and health burden in many risk groups, including elderly patients.

These patients, who have preexisting clinical conditions, the so-called "chronic health conditions," such as diabetes, autoimmune diseases, and cancers, are more vulnerable to contract the disease and manifest acute respiratory, cardiopulmonary, renal, and other clinical symptoms with potential damaging long-term outcomes [3]. Moreover, it has been reported that SARS-CoV-2 RNA was detected in a Cerebrospinal Fluid (CSF) specimen of a patient infected with COVID-19; this suggests direct evidence to support the theory of SARS-CoV-2 neurotropic involvement in damaging the Central Nervous System (CNS), with a wide range of neurological manifestations, including headache, dizziness, hyposmia, and hypogeusia during illness. Furthermore, several COVID-19 cases have also presented as meningitis, acute necrotizing hemorrhagic encephalopathy, acute Guillain-Barré syndrome, and acute Cerebrovascular Disease (CVD) such as acute ischemic stroke, cerebral and subarachnoid hemorrhage, cerebral venous sinus thrombosis [4,5].

While the pulmonary, cardiovascular, and gastrointestinal complications of COVID-19 were well acknowledged, thus far, neurological complications have received less attention. Although these types of complications have been fairly detailed during previous epidemics, there is growing literature describing new challenges and subacute and long-term neurological impact on elderly patients with comorbid conditions. Therefore, in this review, published reports on patients infected with COVID-19 with various acute, subacute, and chronic neurological symptoms, with a focus on our current understanding of the pathophysiology of SARS-CoV-2 and how it impacts the CNS, will be summarized.

Methods

An extensive literature search was performed utilizing PubMed, Ovid Medline, and Google Scholar. In all electronic databases, the following search strategy was used for articles using the following keywords: "coronavirus", "SARS-CoV-2", "neurologic manifestations",, "cerebrovascular disease", "cognitive decline", "elderly," and "neuroinvasion". After an extensive and critical review, the literature search was restricted to studies published only in English, and a total of 74 articles were selected for inclusion.

Pathophysiology and mechanisms

For almost a year since the initial cases of COVID-19 infection emerged in Wuhan, all attention was predominantly on overseeing the acute manifestations; however, eventually, the long-term sequelae of SARS-CoV-2 infection recently gained emphasis.

In distinction to the common pulmonary symptoms, COVID-19 patients also reported cognitive impairment during and after the disease [6]. While it is rumored to have separate pathophysiology than the encephalopathy of a noninfectious origin [7], speculative evidence necessary to accurately evaluate the causatives of cognitive impairments is lacking. Many hypotheses have been formulated to justify the effects of the virus on the nervous system, such as disseminated systemic inflammation, viral neurotropism along with the psychological distress brought by the global prevalence of this fatal disease [8-12]. These sequelae comprise cognitive impairment post-COVID-19 and have been associated with mechanical ventilation use to improve the conditions of those with severe forms of infection [13]. Furthermore, the enormous psychosocial tension due to the surging number of cases every day, spiraling mortality, and worldwide lockdowns [14-16] may have played role in the neurological consequences of the disease [8].

A study was conducted in 2020 using the information and knowledge of the other coronaviruses that caused neurological symptoms and an attempt was made to quantify the late cognitive sequelae of COVID-19 [17].

These coronaviruses are enveloped RNA submicroscopic infectious agents widely spread among individuals, other mammals, and birds; these coronaviruses cause respiratory, renal, enteric, hepatic, and neurological illnesses [18]. These viruses have an astounding capacity to adapt and withstand the adaptive immunity acquired naturally through the host's defense system or artificially through medication or vaccines.

The SARS-CoV-2 virus belongs to Coronaviridae. It is a single-stranded RNA virus, identified by the presence of the spike (S) glycoprotein, which aids entry into cells. The virus is mainly transmitted through respiratory droplets. It invades the respiratory system by attaching to angiotensin-converting enzyme 2 (ACE2) receptors present on epithelial cells. The virus has a varied incubation period and ranges from three to seven days [19]; it mainly targets the respiratory system by inducing pathological changes, such as alveolar destruction, interstitial fibrosis, hyaline membrane formation, and immune infiltration [20]. The complications arising from COVID-19 infection are perceived to be due to the cytokine storm [21,22]. Several mechanisms have been suggested to explain the direct invasion of SARS-CoV-2 into the nervous system. These include the retrograde entry via the olfactory nerve, transsynaptic transfer across infected neurons, leukocyte migration across the Blood-Brain Barrier (BBB), and the infection of the vascular endothelium [22].

During normal aging, the slow deterioration of the BBB might be a risk factor for viral neurotrophic potential in older adults [23]. Once the virus enters the CNS, coronaviruses can cause demyelination, neurodegeneration, and cellular senescence, which are all acute pathologies that have long-term outcomes. The entire genome of Human Coronaviruses (HCoVs), including the S glycoprotein, is set to modulate pathogenesis, and the S protein is essential for HCoVs to reach the brain [24]. HCoV-OC43 can cause mild upper respiratory tract infections, but it also exhibits neuroinvasive properties. Murine models showed that HCoV-OC43 is capable of entering the CNS intranasally, quickly spreads to the rest of the CNS via the olfactory bulb, and infects neurons, causing encephalitis [25]. This infection culminates in considerable neuronal destruction and even mortality without significant inflammatory infiltration. In humans, it is responsible for lasting infections in neural cell lines and can induce neuronal destruction, which seems to be the result of a direct virus rather than an immune-mediated injury [22].

Coronaviruses can infect both neural and non-neural cells in the CNS (brain and spinal cord), and the Peripheral Nervous Sys-

tem (PNS), which express the entry protein ACE2. Like other viruses, SARS-CoV-2 enter cells and replicate. Olfactory cell invasion is responsible for anosmia, the loss of smell that is common in infected people. A mode of retrograde transport from the nasal mucosa to the brain has been described for SARS-CoV-1 [26-28]. Patients with COVID-19 may experience an ageusia sensation as a result of the virus spreading from the gustatory receptor cells of the tongue to the nucleus solitarius of the medulla. Genetically, SARS-CoV-2, like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), exhibits similar neurotropic and neurovirulent properties [29] and can infect the CNS. These viruses use the S proteins to bind to the ACE2 receptor of their host, after which they use the transmembrane protease serine 2 to prime the S [22]. The expression of ACE2 also occurs in both neurons and glia [30], indicating that the brain is likely a target of SARS-CoV-2.

Neurovascular coupling in limbic and associated cortices, as well as decreased cerebral blood flow with aging is now considered a hallmark sign of vascular cognitive impairment in older adults [31]. SARS-CoV-2 has shown a capability to infect endothelial cells that express ACE2, potentially leading to a further deterioration of this fundamental structure. As a result of this hypoperfusion, neuronal networks would be deprived of important energy substrates, accelerating cognitive decline in the elderly. A SARS-CoV-2 infection may adversely affect the differentiation of oligodendrocyte progenitors which also express ACE2 [32], resulting in chronic demyelinating conditions. The invasion of hematopoietic cells (e.g., dendritic cells, monocytes, or macrophages) by SARS-CoV induces a low-level expression of antiviral cytokines, such as Interferon (IFN)-αβ, and the overexpression of pro-inflammatory cytokines, such as Tumor Necrosis Factor (TNF) and interleukin-6 (IL-6), as well as inflammatory chemokines, such as CCL2, CCL3, CCL5, and CXCL10 [33]. A cytokine storm has been frequently associated with a COVID-19 infection [34]. As a pro-inflammatory mediator, IL-6 may be involved in the activation of immune cells in the brain and the injury of the brain tissue. However, a relevant question is whether this molecular storm has a subacute and long-term effect on the CNS. The inability of blood to clot in a pro-thrombotic situation marked by an inflammation-related "cytokine storm" can damage multiple organs, including the CNS [35]. In addition, patients infected with COVID-19 and who have a preexisting CVD can develop significant hypoxia, leading to tissue death [36]. Moreover, infection, inflammation, and hypercoagulable states can further worsen the danger of ischemic stroke, especially among elderly patients [37].

Furthermore, chronic neuroinflammation is linked to the development of some neurodegenerative diseases in elderly patients, such as multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's (PD), Alzheimer's (AD), and Huntington's diseases [38]. Research has shown that in AD under the presence of pro-inflammatory cytokines (mainly IL-1 or IL-6), the microglia lose their capacity to engulf the αβ protein, and the number of microglia increases in cortical layers, influenced by the deposition of amyloid plaques in patients with AD [39,40]. Moreover, several postmortem studies have confirmed that inflammatory mediators are usually present in the CSF of patients with PD, as well as in their brains [41,42]. A similar pattern of pro-inflammatory mediators, such as CXCL13, TNF, IFN-γ, CXCL12, IL-6, IL-8, and IL-10, has been observed in the CSF of patients with multiple sclerosis, accompanied by significant damage to the gray matter at diagnosis.

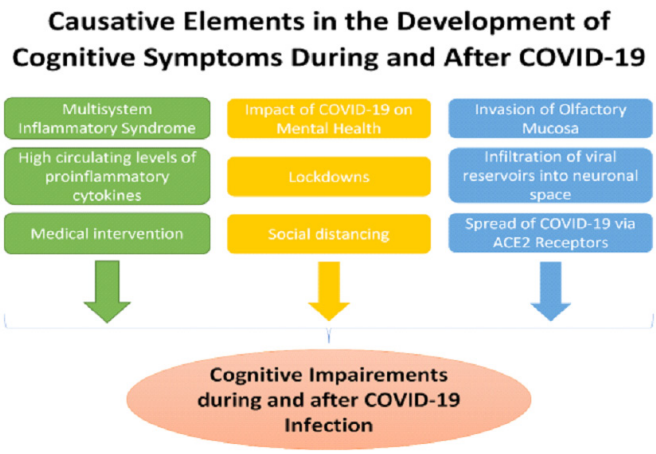

Figure 1: Causative elements in the development of cognitive symptoms during and after COVID-19.

Nonspecific neurological complications

Several clinical studies have shown that patients with confirmed COVID-19 diagnoses were more likely to suffer from nonspecific neurological complications. These nonspecific neurological symptoms include fatigue, headache, altered mental health status, dizziness, depressed level of consciousness, ageusia, anosmia, and myalgia [41-44]. A retrospective study published by Mao et al. showed that 36.4% of the patients experienced neurological manifestations, notably more common CNS- than PNS-related events. Likewise, patients with severe symptoms of COVID-19 were more likely to have neurological manifestations compared with those with mild symptoms. Approximately 24.8% of patients presented with CNS manifestations, such as headaches, confusion, dizziness, acute CVD, ataxia, and seizures. PNS symptoms, which include issues with taste, smell, and vision, were evaluated in 8.9% of the patients, whereas musculoskeletal symptoms were observed in 10.7% [41]. Nonspecific neurological complications were also described in a meta-analysis published by Wang et al., who reported that olfactory (35.7%-85.6%) and gustatory (33.3%-88.8%) disorders are common neurological manifestations of COVID-19 [45]. Another study published by Lechien et al. showed that 85.6% of the patients suffered from olfactory dysfunction and 88% from gustatory dysfunction [44]. It was found that there is a relationship between olfactory dysfunction and fever and gustatory symptoms, but not with rhinorrhea or nasal dysfunction [46].

In another large prospective study on mild COVID-19, the same group found that females and younger patients reported a loss of smell more frequently [44]. It is interesting to note that headaches can occur without fever, such as migraine, tension-type headache, or cluster headache [47,48]. Patients with severe COVID-19 may display these nonspecific neurological signs because of the neurotoxic effects of hypoxia and the cytokine storm this disease produces. It is important, though, to distinguish several of these indications from delirium, and other secondary causes (such as metabolic, gastrointestinal, renal, and hematological complications) must also be eliminated, particularly in elderly patients with inherited comorbidities. Some patients with respiratory failure had developed non-specific neurological symptoms, which supports the hypothesis that the CNS manifestations of SARS-CoV-2 may contribute to respiratory failure. In addition, patients with non-specific neurological symptoms have shown higher levels of leukopenia, thrombocytopenia, and blood urea nitrogen [41]. According to these data,

some of these findings may be prognostic indicators of severity for neurological complications. The predictive potential of non-specific neurological symptoms needs to be further explored in future prospective studies so that specific neurological symptoms can be identified promptly for patients with COVID-19 at risk of more severe sequelae.

Specific neurological complications

Several neurological complications described in patients infected with severe COVID-19 were independently reported by several studies, suggesting a potential real association with the pathogenesis of COVID-19 infection.

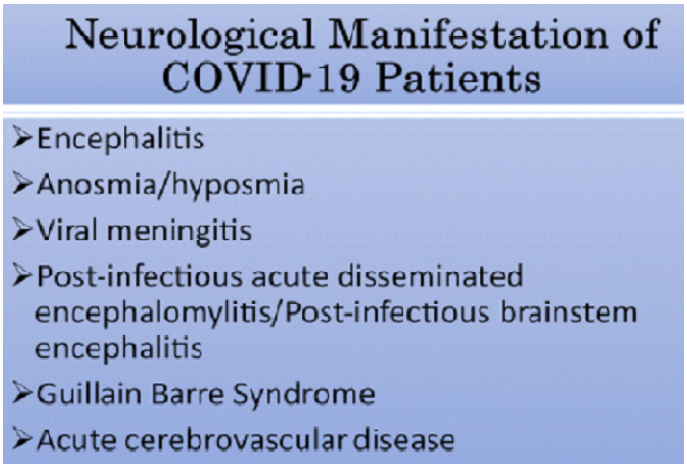

Figure 2: Neurological manifestation of patients with COVID-19.

Little is known about the potential duration and long-term persistence of SARS-CoV-2 in the CNS. For example, HCoV-OC43 RNA was present in the CNS of a murine model of coronavirus-induced encephalitis for more than a year post-inoculation [49]. Taken together, inflammation of the brain, along with extended hypoxia, may promote both acute and chronic neuropsychiatric developments and cognitive impairments.

Several studies have shown a critical role of inflammation in the pathological process of cognitive impairment [50]. Direct CNS infection, together with the common systemic inflammation of COVID-19, compromises the BBB and triggers a massive neuroinflammatory response exhibited by reactive astrogliosis and microglia activation. This data supports the fact that neuroinflammation plays a role in the neurodegenerative phase of this disease [51], and it is critical for the pathophysiology of sudden onset neurological conditions. The lower efficiency and responsiveness of innate immunity contribute to the vulnerability of elderly patients to infection [52]. In addition, several studies have indicated that proinflammatory growth fosters the development of age-related illnesses, demonstrating a relationship between immunosenescence and its contribution to neuroinflammation, as well as the subsequent development of neurodegenerative pathology. Therefore, the abnormal misfolding and aggregation of proteins in patients who survive and recover from their acute SARS-CoV-2 infection can theoretically lead to brain degeneration decades later [53]. The cytokine storm and the resultant cerebral insults may lead to brain dysfunction in the long term. Viral entry may also create a cytotoxic insult and initiate apoptotic pathways or generate an excitatory-inhibitory imbalance, which plays a role in several neurodegenerative diseases, including AD and PD. A slow infiltration throughout the CNS may precipitate underlying pathologies associated with age-related neurodegenerative disorders months or years following an acute viral infection [54].

Acute CVD, typically presenting as an ischemic stroke but occasionally as intracerebral hemorrhage, has emerged as the major clinical feature of severe COVID-19 infection. The result will be lasting brain damage and an increased risk of stroke and vascular cognitive impairment. Additionally, patients who recovered from COVID-19 showed signs of microstructural damage and disruption of functional brain integrity at three months follow-up, suggesting the possibility of long-term neurological consequences in patients with severe COVID-19. Several metabolic abnormalities affecting patients with COVID-19 may also increase the risk of developing AD. There are several comorbidities and risk factors shared by dementia and COVID-19, including an overactive renin-angiotensin system, cerebrovascular dysfunction, and neuroinflammation. In vascular dementia, the defining pathological process is ischemic brain damage, and strokes rank among the top risk factors for dementia [55]. Cognitive impairment or dementia can also result from thromboembolic occlusion of cerebral blood vessels. About 20% of dementia cases resulting from strokes are due to infarction caused by thromboembolism in major cerebral arteries [56]. There is a risk of dementia in patients with severe COVID-19 when there is acute large cerebral vascular occlusion with hypercoagulability. Small vessel disease is the leading cause of vascular cognitive impairment, accounting for about 20% of all strokes and 80% of stroke-related dementia cases [56]. A hypercoagulable state and disseminated intravascular coagulation are more common in individuals with severe COVID-19, resulting in decreased perfusion through small intracerebral vessels than through larger ones. The integrity of cerebral white matter is critical for maintaining cognitive function, and it is particularly vulnerable to changes in cerebral blood flow. One of the consequences of white matter damage is cognitive impairment in patients with severe COVID-19 [57], and this damage is present in up to two-thirds of patients with AD [58].

CNS manifestations acknowledged before the COVID-19 pandemic are distinct [24]. The neurological manifestations of COVID-19 disease can be largely divided into acute, subacute, and chronic events. Neuropsychiatric symptoms, including impaired consciousness/delirium, headache, dizziness, confusion, amnesia, cognitive impairment, agitation, insomnia, anxiety/depression, loss of taste, loss of smell, and neuralgia, are most commonly reported. For example, the neuropsychological profile is well established for anoxic brain injury [59-61], causing moderate-to-severe anterograde amnesia in half of all cases. Executive dysfunction is also commonly noted, with patients exhibiting significantly impaired planning, abstraction, and increased distractibility. The long-term prognosis for people suffering from Acute Respiratory Distress Syndrome (ARDS) is usually poor [62]. Patients manifest long-term consequences, and often suffer cognitive, psychological, neuromuscular, and pulmonary impairments, along with long-term healthcare utilization and reduced quality of life post-hospitalization. According to an ARDS Cognitive Outcomes Study [63,64], 55% of patients had cognitive impairments along with concomitant functional impairments [65], which often lasted months after discharge from the hospital. The risk factors for prolonged cognitive impairments include several Intensive Care Unit (ICU) hospitalizations [66], length of delirium [67,68], exposure to severe hypotension [66], the experience of hypoxemia [64,66], and the experience of acute stress while hospitalized [69].

In a meta-analysis study, an extensive evaluation of patients with SARS and MERS showed similar neurological complications, including insomnia (41.9%), confusion (27.9%), anxiety

(35.7%), depression (32.6%), and impaired memory (34.1%), among patients in the acute stage of illness, whereas depression (10.5%), post-traumatic stress (32.2%), anxiety (12.3%), insomnia (12.1%), memory impairment (18.9%), and irritability (12.8%) were observed in infected patients post-recovery [70]. These findings suggest that both SARS and MERS leave behind residual symptoms after remission and are responsible for COVID long-hauler symptoms. In addition, following the two outbreaks in 2002 and 2012 caused by SARS-CoV-1 and MERS, respectively, 20% of the recovered patients reported ongoing memory impairment [70].

Another French study revealed that patients infected with COVID and admitted to the ICU had neurological features [71]. Similarly, patients infected with COVID-19 in the Chinese city of Wuhan showed varying neurological symptoms, such as lost sense of smell and taste, seizures, neuropathic pain, and strokes [41]. Worth noting is the fact that these symptoms tended to be more frequent among elderly patients (mean age = 59.2 years), those with severe infections, and individuals with underlying health conditions. Given the potential for organ failure in multisystem inflammatory syndrome in children, secondary neurological and neurocognitive outcomes, for example, neurological injury secondary to cerebrovascular changes or metabolic encephalopathy, are possible [72]. Postinfectious autoimmune responses may also incite immune-mediated neuronal damage in pediatric and adult-aged populations. Age-related loss of proteostasis has been strongly correlated with more severe consequences of SARS-CoV-2 infection in older adults. Losing the ability to properly activate stress response mechanisms in elderly patients can lead to severe phenotypes, including a decrease of protein solubility and accumulation of aggregates, such as those characteristics of various age-associated neurodegenerative disorders, including PD. Another study found significant mechanistic overlap between AD and COVID-19, centered on neuroinflammation and microvascular injury, as well as significantly altered expression of several AD markers (CXCL10, TNFRSF1B, SPP1, TGFB1, GSTM3, and NKTR) in patients infected with severe COVID-19 [73].

Conclusion

Millions of people have been infected by SARS-CoV-2 and billions of lives have been disrupted. Once this viral outbreak is managed, our healthcare system could face an increased volume of patients and their associated comorbid neurological issues. Cognitive impairment poses a significant health burden and drives up healthcare costs. The onset of the disability is associated with worsened mortality and substantial increases in medical expenses over subsequent years. Growing evidence demonstrated that COVID-19 infection results in neurological degeneration in high numbers of relevant patients. While these complications acutely arise during sickness, little is known about their lasting effects on the brain. Insight about the enduring impact of neurological disease in individuals affected by COVID-19 is constantly changing, and clinicians ought to continue monitoring patients closely over the long term to understand them. Better detection of neurological deficits may lead to improved clinical outcomes and better treatment regimens. Additional laboratory and clinical data, such as testing of the CSF, brain imaging, and testing of CNS tissue, can help to uncover the pathophysiology of and treat CNS injury. Additionally, post-recovery neurological assessments will provide insight into how COVID-19 manifests in the CNS and how it may cause enduring neurological symptoms. Nevertheless, it is imperative to assess both the short- and long-term impacts of the intervention to improve the lives of severely infected survivors. Moreover during recovery, psychological evaluation has to be prioritized, especially for people showing signs of cognitive decline and impairment. It is thus imperative to elucidate the pathogenesis of neurological disturbances in COVID-19, some of which have probably been hidden and whose prevalence may be greatly underestimated. Understanding the long-term consequences of the disease (including the possibility of dementia in some cases) and determining ways to prevent or minimize brain damage is crucial.

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