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Neurological Implications of COVID-19: from Cognitive Decline to Blood Biomarkers

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Abstract

The COVID-19 pandemic has endured since 2019. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects a variety of organs, including the brain. Neurological complications after post-COVID-19 sequelae have been recognized in several reports. There is a plethora of evidence that COVID-19 sufferers have neurological, cognitive, and emotional problems. Among those infected with SARS-CoV-2, acute neurological symptoms like cognitive decline, neuroinflammation, cognitive decline, brain stroke, and loss of smell, are frequent direct outcomes. Three months after being infected with SARS-CoV-2, neurological abnormalities were recorded in up to 55% of COVID-19 patients in the hospital. The SARS-COV-2 virus' mutability and propensity for direct central nervous system (CNS) damage underscore the pressing need for technology to identify, manage, and treat brain injury in COVID-19 patients. This review explores the direct and indirect impacts of COVID-19 on the CNS and delves into the underlying causes and risk factors contributing to the deterioration of individuals' mental well-being and the COVID-19 pandemic. Furthermore, we also discussed the diagnostic blood biomarkers (BBs) for brain injury in patients with COVID-19.

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INTRODUCTION

The severe acute respiratory syndrome-related coronavirus SARS-CoV-2 has been formally named by the World Health Organization (WHO) as coronavirus 2019-nCoV. According to the most recent statistical data as of 22 March 2020, this disease has spread across international borders and into more than 150 nations, with more than 3,00,000 confirmed cases and 12,000 fatalities worldwide.[1] Although coronavirus can infect humans and animals, most coronaviruses discovered in bats appear to be immune to diseases brought on by coronaviruses.[2] According to a rigorous examination of their genetic makeup, these viruses possess a single-stranded positive-sense RNA genome surrounded by a membrane envelope. Additionally, it has genomic similarities with bat coronavirus (96%) and SARS-CoV (79.5%).[3,4] The glycoprotein spikes that are scattered across the virus's surface give it a crown-like appearance in the viral membrane.[5]

In the context of subsequent pathogenesis, the spike glycoprotein (S-protein) located on the virus's surface plays a pivotal role by recognizing the receptor necessary for membrane fusion.[6,7] This trimeric S-protein undergoes cleavage during infection, leading to the separation of its S1 and S2 subunits. Notably, the S1 subunits are released as part of the transition to the post-fusion conformation.[7,8] The S2 domain, on the other hand, assumes the responsibility of mediating the fusion with the host cell's membrane, whereas the S1 subunit houses the receptor binding domain (RBD), which possesses the capability to directly interact with the peptidase domain of the ACE-2 receptor.[9] It is essential for a viral infection that S1 binds to the ACE-2 receptor because this releases another cleavage site on the S2 subunits.[10-12]

Leukocyte integrins are membrane glycoprotein receptors that play a critical role in immunological and inflammatory responses via interactions between leukocytes and the extracellular matrix.[13–17] Patients that exhibit insufficient levels of leukocyte integrin receptors develop severe bacterial, viral, and fungal infections.[18] This review discusses the SARS-CoV-2 infection in people as it is currently

understood and provides evidence of COVID-19's connection with the neurological system.

COVID -19 AND LUNGS

SARS-CoV-2 initially binds to the ACE2 receptor located on the surfaces of type 2 alveolar cells, endothelial cells, and lung epithelial cells.[19] The primary S glycoprotein of the virus is facilitated in entering these host cells by the human type 2 transmembrane serine protease (TMPRSS2). Once inside a host cell's cytoplasm, the virus releases RNA that is then utilized by the host cell's machinery to replicate the virus. This replication process produces multiple copies of the virus, which subsequently spread to infect other host cells.

In response to the presence of viral antigens, certain cells in the human immune system become antigen-presenting cells. These cells process the viral antigens and present them in a way that attracts CD8+ cytotoxic T cells and natural killer (NK) cells. The innate and adaptive immune system releases pro-inflammatory cytokines and chemokines.

DOES THE VIRUS INVADE THE BRAIN?

The olfactory mucosa of the nose is known to be penetrated by SARS-CoV-2, which results in loss of smell.[20] The virus could potentially access the brain through several routes, such as passing from the cribriform plate via the olfactory tract[20] or utilizing the vagal or trigeminal pathways. However, it's important to note that there is currently insufficient evidence to firmly establish these pathways as confirmed routes of viral entry into the brain. As inflammatory cytokines cause BBB instability, SARS-CoV-2 may be able to cross the blood-brain barrier (BBB) or enter brain tissue through monocytes.[21] Circumventricular organs (CVOs), midline structures positioned around the third and fourth ventricles, could potentially act as entry points for the virus to infiltrate brain tissue. These specialized structures monitor the content of both blood and cerebrospinal fluid through fenestrated capillaries that lack the tight junctional proteins typically found in the blood-brain barrier (BBB). This unique feature could make CVOs more permeable and susceptible to viral infiltration. Reverse transcription-quantitative real-time polymerase chain reaction (RT-qPCR) was used to detect viral RNA in the medulla and cerebellum, both of which are in proximity to the postrema—a circumventricular organ responsible for regulating emetic responses to toxins. However, attempts to employ in situ hybridization for detection were unsuccessful. Notably, unlike neurons or glia, the presence of the SARS-CoV-2 protein has been exclusively observed in the vascular endothelium within the brain.[20]

Therefore, viral RNA found in the leptomeninges and Virchow-Robin spaces may be a result of vascular contamination. A comprehensive histopathological examination of the entire human brain revealed the presence of microglial nodules and the phagocytosis of neurons, a condition known as neuronophagia. These pathological features were predominantly observed in the brainstem and were also found, although less frequently, in the cortex and limbic structures. Importantly, no correlation was found between these observations and the level of viral mRNA in the same patients.[22] While circumventricular organ (CVO) involvement and viral invasion of the brainstem may be linked to symptoms like ageusia, nausea, and vomiting, it is more likely that other short- and long-term neurological symptoms are primarily caused by neuroinflammation and damage due to hypoxia. Anxiety and persistent autonomic anomalies may be explained by brain stem involvement.

NEUROTOXICITY CAUSED BY MICROGLIA ACTIVATION AND CYTOKINES

Patients experiencing severe COVID-19 infections have been characterized by a pronounced cytokine storm, marked by significantly elevated serum levels of pro-inflammatory cytokines, including interleukin 1 (IL-1), tumor necrosis factor (TNF)-α, IL-6, and IL-10. Damage caused by cytokines increases the BBB permeability that allows the penetration of TNF-α.[21] Cytokines cause microglia and astrocytes to become active after crossing the BBB.[23] Activated microglia release inflammatory mediators like quinolinic acid, glutamate, complement proteins, ILs, and TNF-α in addition to phagocytosing injured cells.[24] With increased quinolinic acid, glutamate levels rise and NMDA receptors are upregulated, which may affect learning, memory, neuroplasticity, hallucinations, and nightmares. NPs are region- and neurotransmitter-specific as a result of excitotoxicity and neuronal death.

MECHANISM UNDERLYING CEREBROVASCULAR DAMAGE

While it is likely that most patients who suffer a stroke during COVID-19 have preexisting cardiovascular and cerebrovascular conditions that are exacerbated or triggered, after a cerebrovascular injury.

Investigations have been made into the etiologies of ischemic and hemorrhagic stroke in the presence of COVID-19 infection. In a series of clinical cases involving six consecutive patients in Europe, it was observed that five out of these six patients, who had experienced acute ischemic stroke characterized by significant artery blockage, tested positive for lupus anticoagulant. It's worth noting that among these patients, one exhibited low titer IgG and IgM antibodies, while another had medium titer IgM anticardiolipin antibodies.[25] Another European study demonstrated that all positive blood samples also had a longer activated partial thromboplastin time (aPTT), ninety-one percent of patients infected with SARS-CoV-2 tested positive for lupus anticoagulant. In comparison to the control group, this group had a significantly higher percentage of lupus anticoagulant-positive investigations.[26] Upon entry of the SARS-CoV-2 virus into the body, it triggers the production of angiotensin II. This,

in turn, activates macrophages, prompting them to release pro-inflammatory cytokines. These cytokines, in a cascading effect, activate tissue factors. The tissue factor then initiates an extrinsic coagulation pathway, leading to the deposition of fibrin and the formation of blood clots. These clots are secreted from endothelial cells and macrophages. This process leads to the extensive development of small vessel platelet-fibrin thrombosis, affecting venules, arterioles, and capillaries throughout the body. Furthermore, it results in the conspicuous presence of intravascular megakaryocytes, a unique and notable characteristic associated with COVID-19 infection.[28]

COVID-19 AND CNS

SARS-CoV-2 infiltrates the Central Nervous System (CNS) shortly after infection, and this is subsequently followed by an immune evasion mechanism. After entering the central nervous system (CNS), the virus disseminates throughout the brain and neuron that leads to neurological dysfunctions. According to preliminary research from Wuhan, a staggering 36.4% of people with COVID-19 had neurological symptoms.[29] In patients with more severe SARS-CoV-2 infections, there have been observed associations with a heightened risk of experiencing acute cerebrovascular conditions (such as strokes) as well as a decrease in levels of consciousness. The most common neurological symptoms observed in individuals with SARS-CoV-2 infections include headaches, myalgia (muscle pain), and disturbances in taste and smell, specifically anosmia (loss of smell) and ageusia (loss of taste).[30] Recent meta-analyses, which compiled data from larger sample sizes, have confirmed the prevalence of these symptoms.[31]

Less frequently reported neurological signs and symptoms associated with SARS-CoV-2 infections include nausea, dizziness, and decreased consciousness. In several accounts, sporadic but difficult-to-define encephalitis and stroke were also mentioned.[31,32] Dizziness, nausea, and reduced consciousness were less frequent symptoms. Some reports also indicated sporadically, but hard to define, encephalitis and stroke.[31,32] Hypoxic ischemia, which can be brought on by both encephalitis and stroke can harm the brain permanently if blood flow is not restored. There have also been reports of systemic hypoxia primarily caused by Acute Respiratory Distress Syndrome (ARDS), along with localized CNS hypoxia.[33] Some patients, however, experience quiet hypoxia, also known as joyful hypoxia, which is characterized by the absence of dyspnea and the patients' unawareness of their dangerously low oxygen levels.[34] The "respiratory drive" may be disrupted in the medulla oblongata, resulting in feedforward neurodegeneration and silent hypoxia. Hypoxia is exacerbated by respiratory drive loss, further impairing it.[35] The upregulation of ACE2 expression in ischemic brains, which enhances susceptibility to CNS infection, is likely exacerbating this reinforcing cycle.[36] In a study of 18 COVID-19 patients, one postmortem report showed acute hypoxic insult to the cerebellum and brainstem. They also reported the death of neurons in Purkinje cells, hippocampal region and cortex.[37] Even among individuals who recover from SARS-CoV-2 infection, a significant portion is likely to experience similar adverse effects. Multiple neurological side effects of SARS-CoV-2 may last for a long time; these are increasingly referred to as "Long COVID," and include conditions like sleep disorder, headache, cognition, hyposmia etc. Some claim that the SARS-CoV-2 vaccines that are currently available can lessen or eliminate Long COVID symptoms such as exhaustion, dyspnea, and insomnia, providing additional optimism for the vaccination period.[38] To advance the development of effective treatments for long-term COVID, it is imperative that future research explores the potential involvement of neuroinvasion, hypoxia-induced brain injury, and the neuro-immune response in the development and persistence of this condition.

The previous report suggests that SARS-CoV-2 could enter the CNS in addition to hypoxic environments. Matscheke *et al*., 2020 showed the infiltration of viral into the CNS with a notable emphasis on the frontal lobe. Additionally, they observed a higher concentration of viral RNA copies, as well as increased production of spike and nucleocapsid proteins in the medulla oblongata, highlighting the significance of this region.[39] This seminal work tracked the transmission of SARS-CoV-2 using post-mortem samples. In more recent work, human brain organoids were used to investigate SARS-ability CoV-2's to infect CNS tissue.[40] They showed that SARS-CoV-2 might cause considerable neuronal loss and infect the human brain via ACE2. In COVID-19 patients who suffered from severe neurological symptoms, it was shown that the CSF contained anti-viral antibodies. Astrogliosis was found in 86% of patients, regardless of viral invasion.

Furthermore, the cerebellum and brainstem, specifically the medulla oblongata, exhibited marked signs of microgliosis and infiltration by cytotoxic T-lymphocytes, with a predominant focus on perivascular regions. Additionally, in a significant proportion of patients (79%), there was a notable presence of macrophages in perivascular and meningeal areas, along with cytotoxic T lymphocytes in the meninges.

Although the investigations were conducted post-mortem, the data obtained from these studies offer crucial insights into the neuropathology associated with SARS-CoV-2. These findings suggest that the virus may have a particularly effective route of neuroinvasion, possibly utilizing cranial nerves IX (vagus nerve) and X (glossopharyngeal nerve) to access the medulla oblongata. This highlights the significance of understanding the potential neurological impact of SARS-CoV-2 and the pathways it may exploit to reach the central nervous system.[39]

Additionally, there is supporting evidence from experiments involving transgenic mouse models expressing human ACE2, which suggests the possibility that previous variants of SARS-CoV (SARS coronavirus) could enter and

spread within the central nervous system by utilizing the olfactory bulb as a potential pathway.[40,41] These findings underscore the need for a comprehensive understanding of how coronaviruses, including SARS-CoV-2, may affect the central nervous system and the various routes they might employ for neuroinvasion.

While it might seem logical to assume that anosmia (loss of smell) is a prevalent symptom in human SARS-CoV-2 infections, it's crucial to take into account the substantial neuroanatomical differences between rodents and humans, especially regarding the structure of the olfactory bulb. Consequently, the results obtained from studies in rodents may not be readily applicable to human cases.

Notably, in individuals who had died from SARS-CoV-2 infection, the olfactory mucosa was identified as a site with substantial viral presence. However, within the central nervous system, the primary site of infection appeared to be the medulla oblongata, rather than the olfactory bulb.[42] Interestingly, while SARS-CoV-2 has been sporadically detected in cerebrospinal fluid (CSF), it is typically not found in patients presenting with neurological problems. This observation lends support to the theory that neuroinvasion by SARS-CoV-2 occurs via cranial nerves through retrograde transport.[43]

COVID-19 AND NEUROINFLAMMATION

The SARS-CoV-2 infection continues to pose a concern on a global scale, particularly for aged people. With respect to elder dementia patients, the death rate for COVID-19 is nearly twofold.[44] Additionally, the infection may lead to pneumonia and an unchecked cytokine storm that mainly involves IL6, IL1, and TNF, which can manifest as a number of symptoms including encephalopathy.[45] Mild symptoms like dizziness, fatigue, and psychomotor slowness may be present in the "sick behavior," a non-specific cytokine-induced syndrome prevalent in many infectious-inflammatory disorders as a result of the activation of innate immunity.[46] Conversely, a particular underlying encephalitis may be the source of severe signs like disorientation, agitation, delirium, and seizures. Delirium was discovered to often emerge over the clinical course of COVID-19 in dementia patients, but in some instances, it constituted the disease's initial symptom and signaled a worse prognosis.[47] Immune responses of the CNS may be the source of neurological symptoms. SARS-CoV-2 may enter the CNS via one of three different pathways:[44] the trans-synaptic route, which travels through the brainstem's cranial nerves or the brain's olfactory bulbs to the basal frontal lobes;[45] the endothelial-astrocytic route, which penetrates the BBB. Although viral localization in a few brain neurons was observed in earlier investigations on SARS-CoV-1 pathogenesis, the topographical distribution was not defined.[48] Nevertheless, despite these considerations, there is currently no definitive evidence supporting the neurotropic capabilities of SARS-CoV-2. Notably, the human brain typically expresses low levels of ACE-2 and TMPRSS2, which are the crucial factors enabling the virus to enter cells.[49,50] Immunohistochemical labelling has revealed the existence of limited viral proteins, primarily confined to isolated neurons and endothelial cells within the medulla oblongata of the central nervous system (CNS), despite the detection of viral RNA in approximately half of the patients.[51] Furthermore, there is no connection between protein or RNA of COVID-19 virus in the brain and the degree of neuropathological alterations.[51]

Brain from varied spectrum of COVID-19 patients who underwent postmortem examinations that revealed a wide variety of neuropathological alterations of varying degrees of severity. These were particularly prominent in older patients who displayed substantial neurological problems.[52,53] The COVID-19 clinical course has a significant impact on neuropathological changes (e.g., the presence of critical illness, hypoxia, and sepsis). Apart from neuronal death due to hypoxia events and brain edema congestion, the neuropathological picture looks inconsistent, displaying a range of abnormalities mostly consisting of two categories of pathologies[44] that is vascular injuries and inflammatory processes.[51-63]

Both types of diseases have been described by numerous authors, and almost all articles documenting inflammatory alterations have shown a certain level of activation of microglial, frequently linked to microglial nodules. Especially in older individuals or those with dementia, the hyperactive immune system, specifically involving the brain's innate immune system (microglia), seems to play a significant role in the development of neurological impairment. The precise mechanisms underlying these neuropathological changes are still unknown, as was recently brought up, and learning more about the precise role played by SARS-CoV-2 will likely have significant clinical implications,[64] especially in older people whose brain pathology can be affected by several other concurrent conditions, such as vascular comorbidities and pre-existing neuro-degenerative processes that cause inflammation.

BLOOD BIOMARKER IN COVID-19 BRAIN INJURY

Blood-based tests utilizing well-validated proteins known to signify cell death, acute brain injury, and neurodegeneration can be employed to study central nervous system (CNS) damage and cellular demise after viral infections. Including Caenorhabditis elegans, rats, and humans, these proteins are largely conserved across species and are measured by blood tests to determine the processes of CNS cell damage and death. Increased levels of neurofilament light polypeptide (NfL), glial fibrillary acidic protein (GFAP), tau, and various inflammatory markers were seen in the CSF and/or plasma of COVID-19 patients in recent observational research and a few case reports.[65-69] Analysis of the brain through post-mortem examination in a COVID-19 patient revealed elevated GFAP staining.[70] Studies have also revealed elevated levels of BBs

in the cerebrospinal fluid (CSF) of patients with tuberculous meningitis (GFAP, S100 calcium-binding protein [S100B], and neuron-specific enolase [NSE]),[71-73] HIV patients[74] (NfL, GFAP, and S100B),[73-78] and cerebral malaria (S100B, NSE, tau proteins, and inflammatory protein markers).[79-84] Following various acute injury scenarios, protein markers indicating CNS damage have also been detected.[85–88] After variety of brain injuries in both animals and humans, several biomarker was found to be elevated such as ubiquitin C-terminal hydrolase L1 (UCH-L1), and GFAP. The American Heart Association (AHA) guidelines, as outlined in their latest report,[89] have recommended elevated levels of NSE, S100B, and GFAP as indicators for predicting an unfavorable neurological prognosis.[90] UCH-L1 and GFAP were found to be the best BB predictors of the outcome as early as 24 hours following cardiac arrest, according to a recent analysis of 717 patients.[91] It was advised to use BBs in conjunction with other diagnostic techniques. Children receiving extracorporeal membrane oxygenation (ECMO) can also be monitored for GFAP plasma concentrations and other brain damage biomarkers such as S100B and NSE.[92] It's interesting to note that serial examinations of serum S100B samples from adult ECMO patients with cerebral lesions showed significant increases in biomarker levels and rising trajectory.[93] Serial NSE levels following cardiac resuscitation in patients on ECMO were linked to neurological outcomes.[94] NSE and S100B were found to be increased in the blood of an adult patient with accidental hypothermia and also associated with mortality and poor neurological outcome.[95]

Patients with AD also have BB changes. Serum GFAP levels are elevated in AD and are associated with cognitive deterioration.[96] Serum NfL temporal patterns have been linked to the cognitive deterioration[97] and can potentially predict clinical progression in presymptomatic AD.[98] The extent of brain injury levels in COVID-19 patients remains uncertain. Recent data, however, has demonstrated that protein biomarker assays can identify even low levels of UCH-L1, GFAP and S100B, increased after sports concussions that are not connected to CNS pathology visible on computed tomography (CT) scans.[99] The potential of BBs for the treatment of brain damage has not yet been completely realized. The research served as the basis for the FDA's rapid approval of the GFAP and UCH-L1 measurements for the acute diagnosis of traumatic brain injury (TBI) not correlated with CT abnormalities, in contrast to cases of mild TBI accompanied by CT abnormalities. This authorization was provided through the FDA's Breakthrough Devices Program.[100–102]

CONCLUSIONS

In this comprehensive review, we aimed to shed light on the neurological complications arising from COVID-19 infections. Commonly reported symptoms such as headaches and loss of smell have become increasingly recognized as part of the typical early signs of a COVID-19 infection. While these symptoms affect only a minority of patients, it is crucial to consider the significant impact of cerebrovascular issues in these individuals. Severe and longstanding infections often lead to encephalopathy, and there is evidence to suggest that COVID-19 may lower the threshold for experiencing seizures. Our understanding of the pathobiology of SARS-CoV-2 infection in the CNS and its neurological consequences is still in its infancy.

The COVID-19 pandemic carries substantial risks for both immediate and long-term neurological complications, as well as a potential heightened susceptibility to neurodegenerative disorders. Big dataset analytics combined with the deployment of brain injury-specific BBs may offer quick and affordable solutions to this medical need, which is becoming more and more urgent.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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