Role of SARS-CoV-2 Virus in Brain Cells: A Brief Review

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Abstract

SARS-CoV-2 virus—the virus causes COVID-19 infection—can via sundry mechanisms shrink the various areas of the brain. The published evidence to date indicates that the virus can enter the central nervous system (CNS) through sundry ways such as the olfactory nerve or hematogenous route. The virus can influence neurons and glial cells such as astrocytes, oligodendrocytes, and microglia, thereby impeding their normal functions. The results of such impediments are some adverse effects reported, namely agitation, altered consciousness, headaches, dizziness, brain fog, and mental disorders. It also can induce neurodegenerative disorders via triggering demyelination and other risk factors. To lessen the time of recovery or treat COVID-19 infection, many drugs have been investigated thus far. Of these, Paxlovid has been approved by FDA. It reduces not only the chance of hospitalization or death from a coronavirus infection but also the risk of long-term sickness. Herein several mechanisms by which SARS-CoV-2 virus affects the brain cells, neurons and glial cells, will be discussed.

Keywords: SARS-CoV-2; COVID-19; Infection; Central Nervous System; Neuron

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Introduction

The coronavirus disease 2019 (COVID-19), which has affected million people worldwide and has posed a serious health threat on a global scale, is caused by the positive-sense, enveloped, single-stranded RNA virus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). The published evidence indicates that the virus can enter the central nervous system (CNS) through the olfactory nerve, most likely using axonal transport and transsynaptic transport. In addition, the hematogenous pathway and other ways have been identified as other ways by which the virus might enter the brain (2-4).

The effects of COVID-19 on the brain are becoming more obvious. According to recent research, the coronavirus may attack specific brain cells directly, decrease blood supply to brain tissue, or cause the creation of immune chemicals that can damage brain cells. Former studies also reported the complications including agitation, impaired consciousness, headache, and dizziness stemmed from COVID-19 infection (5). Thereafter recovery, alas, suffering from few adverse effects of this infection have also been shown, namely fatigue, anxiety, depression, and insomnia (6). Accordingly, impediment to memory, concentration, or attention has been reported over the acute phase, accounting for a third of participants (7).

Of note, COVID-19, in accordance with a study carried out in Oxford University, gives rise to shrinking the brain and diminishing grey matter in the areas controlling memory. By comparison with uninfected participants in this study, patients irrespective of afflicting with mild or sever COVID-19 have been shown to have noticeably impair episodic memory – which can be durable up to 6 months thereafter infection, and not to be able to sustain attention over time – being durable up to 9 months thenceforth infection. Not understanding the mechanisms that cause these cognitive impediment notwithstanding, these adverse events were pointed out hopefully to return predominantly to normal in most COVID-19 patients by 6-9 months after infection (8).

General SARS-CoV-2 Pathophysiology Mechanism

SARS-CoV-2's pathophysiology can be summarized as follows: Coughing and sneezing can spread the SARS-CoV-2 virus to other people. Following this, the virus enters the lungs via the respiratory tract and assaults alveolar epithelial type 2 (AT2) cells, which are also in charge of creating the surfactant that lowers the surface tension in alveoli and lowers the pressure that is collapsing. According to reports, the angiotensin converting enzyme 2 (ACE2) receptors on AT2 cells are engaged by the SARS-CoV-2 spike proteins (9, 10). The virus uses the ribosome of the host cell to produce polyproteins after entering the host cell and releasing its positive sense ssRNA. The ssRNA can also replicate its RNA using RNA dependent RNA polymerases. The cell packaging structure can be used to deliver synthesized spike proteins to vesicle carriers. The produced polyproteins of SARS-CoV-2 are broken down by proteinases in the cytoplasm (11).

Cytokine Storm

Further, in order to activate macrophages, the virus releases certain inflammatory mediators that cause the production of cytokines (IL-1, IL-6, and TNF) (12) and chemokines (CCL2 and CXCL10) into the bloodstream. Thus, plasma will leak into the interstitial spaces of the alveolar cells, noticeably lowering the amounts of surfactant in AT2, and compressing alveoli cells. The implications of releasing such molecules are to promote both vasodilation and capillary permeability (13-17). Alveolar collapse and reduced gas exchange are the final results of the cascade processes. Inflammatory cytokine (cytokine storm) production is also visible simultaneously (18); inflammatory mediators increase the production and recruitment of neutrophils and macrophages, which produce and utilize IL-21, IL-22, and IL-17 (13). All of these phases result in coughing, hypoxemia, and breathing difficulties in the later stages of the illness.

Brain cell damage caused by the SARS-CoV-2 virus: Mechanisms

To entry into cells, the virus binds via its S1 spike protein to angiotensin converting enzyme 2 (ACE2) (19, 20). In human, the ACE2 RNA expression, even though shown chiefly in lung tissues (21), heart, gastrointestinal (GI) system, and kidney (22), has been detected in both brain tissues and cerebrospinal fluid (CSF) (23, 24); thus, the nervous system – both the neurons and glial cells of the brain – can be damaged by COVID-19 infection (25). Incidentally, a blood circulatory pathway has been proposed by which this virus—SARS-CoV-2—directly infects the CNS (26), thereby escalating the permeability of the blood brain barrier (BBB). Explicitly, BBB is vital to maintain CNS homeostasis and to prevent the neurons against the penetration of pathogens, such as bacteria and viruses (27).

The exact pathophysiological mechanisms the SARS-CoV-2 virus leads to the neurological adverse symptoms is still not clear. However, some neurotoxic mechanisms rooted from COVID-19 infection have been stated, most noticeable of which will be cited as follows:

1. The virus is neurotropic and enters into both neurons and glial cells. Also, the virus reaches indirectly the CNS via the BBB and/or directly through olfactory receptors neuron situated in axons thereof, thus neuronal dysfunction and damage – neuro invasion (28-32).
2. The virus affects cerebral blood vessels and causes coagulopathy (33-35).
3. The virus can cause a huge releasing proinflammatory cytokines so-called "cytokine storm" and peripheral organs dysfunction relating to the brain (36, 37). All these mechanisms have remarkable role to play in the cognitive impairment etiology in COVID-19 survivors (38). (Figure 1.)

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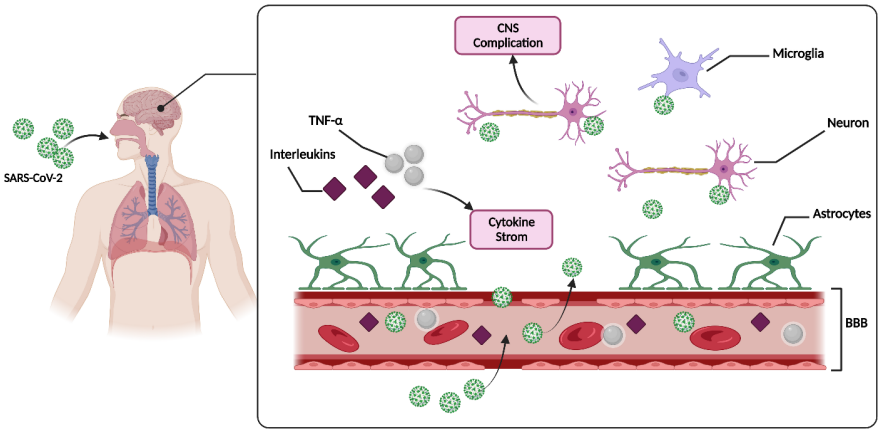

Figure 1.: The mechanism of COVID-19 infection and pathway for CNS invasion and associated CNS complications. The COVID-19 can enter the CNS through the olfactory, neuronal, and BBB pathways. The main way that the CNS is harmed is by cytokine storm syndrome, which not only harms neurons but also messes with the BBB's normal functioning.

As per the available information and the authors' perspective, the virus can enter the central nervous system (CNS) through the olfactory nerve, most likely using transsynaptic and likely axonal transport. In addition, the hematogenous route has been identified as the second way the virus might enter the brain. (2-4).

According to fierce evidence, damaging the zones of the brain relating to memory by SARS-CoV-2 virus gives rise to elevating in proinflammatory cytokines such as IL-6, TNFα (39), and IL-1β (40). The implication of this event is to inactivate the synthesis of all forms of nitric oxide synthases (NOSs), which in turn gives rise to reducing the generation of NO that acts as one of the key mediators of local inflammation (41-43). Noteworthy, hippocampus zone that has a unique role in memory is shrunk as a result of exceed release of cytokines, culminating in hippocampal atrophy (44).

In addition, ACE2 acting as the host receptor of SARS-CoV-2 virus (45, 46) can regulate normal brain function through provoking brain-derived neurotrophic factor (BDNF) activity (47). BDNF has remarkable role to attenuate neuronal inflammation (48) and microglial activation (49); thus, the low levels of BDNF, influenced by COVID-19 infection, are relevant to cognitive impairment (49-51).

Both IL-6 and TNFα, furthermore, pass the BBB and then activate microglia (52). These activation leads to releasing IL-1β, the receptors for which are specifically concentrated in the postsynaptic sections of hippocampal neurons (53). This event makes the hippocampus susceptible to IL-1β, which has been shown to interfere with LTP and memory (54).

SARS-CoV-2 Virus Impact on Oligodendrocytes

Increasing evidence indicates that SARS-CoV-2 virus infection is a definite risk factor for demyelination in both the peripheral and central nervous systems. This notion is supported by the description of a COVID-19 patient who was hospitalized for interstitial pneumonia and seizures and then described by Zanin et al. Damage to the demyelin sheath was detected recently, according to a brain MRI. However, high-dose steroid therapy triggered repair in the neurological and respiratory systems. They suggested that a SARS-CoV-2-induced delayed immune response was what led to the degeneration of the myelin sheath (55).

Mehta et al. discovered demyelinating lesions linked to neurological impairment in a COVID-19 case in a different study. The patient's brain and spine MRIs revealed multiple demyelinating lesions that had recently developed but were not enhancing. They postulated that glial cell activation and subsequent demyelination during SARS-CoV-2 infection would be due to the pro-inflammatory environment caused by the cytokine storm (56). Likewise, encephalomyelitis was reported by Zoghi et al. in a male patient, age 21, who had upper

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respiratory symptoms two weeks before to this presentation and intermittent vomiting for four days. Brain MRI revealed bilateral posterior internal capsule lesions extending to the ventral part of the pons as well as a marbled splenium hyperintensity pattern. A substantial transverse myelitis was discovered throughout their research using thoracic and cervical MRI (57).

Gilles et al. reported a 54-year-old woman who had been exposed to SARS-CoV-2 and had brain lesions that indicated acute demyelination. The pallidum and supratentorial white matter on both sides of the patient's brain were afflicted by hypodense lesions, according to the patient's brain CT scan. Confined diffusion lesions were seen on an MRI of the brain, but there was no bleeding or amplification. Unaffected areas included the striatum, posterior fossa, and thalamus. A follow-up MRI revealed no new abnormalities, and the spinal cord MRI was normal (58). Furthermore, two other studies (59, 60) presented demyelination in patients afflicted with COVID-19; MRI in both studies presented that the corpus callosum and the pericallosal white matter were where the majority of the myelin destruction foci and a concentric demyelination pattern and the presence of hemosiderin deposits together. Given such evidence, SARS-CoV-2 virus is able to cause demyelination in sundry ways.

SARS-CoV-2 Virus Impact on Astrocytes

SARS-CoV-2 targets astrocytes as its primary target in the brain. It has been proven that SARS-CoV-2 preferentially infects astrocytes over neurons in primary and organoid cortical cultures, causing astrocyte reactivation and non-cell-autonomous neuronal death. Furthermore, it is found that basigin (BSG) also known as extracellular matrix metalloproteinase inducer (EMMPRIN) or cluster of differentiation 147 (CD147) and dipeptidyl-peptidase 4 (DPP4) are significant SARS-CoV-2 infection-related molecular actors in cortical astrocytes (61).

As per a study carried out by Andrews et al., infected astrocytes exhibit heightened reactivity and cellular stress (62). In addition, SARS-CoV-2-infected cultures show non-cell autonomous inflammatory effects such as an increase in reactive microglia and a general loss of neurons due to apoptosis. According to research, astrocytes may have a significant supporting function in the regulation of brain energy, metabolism, and the microenvironment (63). It is interesting to note that BSG/CD147 is important for the astrocyte metabolic pathways that support the energy requirements of neurons (64).

Kriegstein et al. also showed in a preprint published that SARS-CoV-2 preferentially infects astrocytes over other types of brain cells, leading to fatigue, depression and "brain fog". The virus was introduced to brain organoids, which are tiny, lab-grown structures that resemble the brain. Over all other cells present, astrocytes were almost completely infected by SARS-CoV-2 (65).

Therefore, by inducing inflammation and aberrant brain energy metabolism, SARS-CoV-2 infection in astrocytes may indirectly result in neuronal death.

SARS-CoV-2 Virus Impact on Microglia

Microglia, which resemble macrophages and seem to be CNS immune cells, play a crucial role in preserving brain homeostasis and in the quick response to damage and inflammation (66). Microglia can be activated in response to immunological stimuli, thereby shifting from ramified to amoeboid phenotype and secreting TNF-α, IL-1, and IL-6 (67). Activated microglia are included in both the neurotoxic M1 phenotype, which contributes to neuroinflammation, and the neuroprotective M2 phenotype. Based on an increasing number of studies, the neurological system may suffer irreparable harm from dysregulation and overactivation of microglia (66, 68-70).

A patient may be more likely to experience neurological and mental issues if their microglia are activated even after they have fully recovered clinically from the infection (71). Furthermore, poor or aberrant microglial function may substantially impair cognitive abilities like judgment, decision-making, learning, and memory. Accordingly, proinflammatory activation brought on by SARS-CoV-2 infection of microglia may significantly affect the short-, moderate-, or long-term neurological and psychiatric effects of infection with SARS-CoV-2 (72).

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There is evidence that SARS-CoV-2 can infect a human microglial cell line directly. The RNA-seq research findings showed that a viral infection resulted in ER stress, immunological reactions, and apoptosis in the late phase. Additionally, SARS-CoV-2 infection caused human microglia to undergo apoptosis by activating both intrinsic and extrinsic pathways. In short, in lung tissues and cell lines, SARS-CoV-2 has been demonstrated to induce intrinsic and extrinsic apoptosis (73). In a preprint study also transgenic mice were found to have microglia that were infected with SARS-CoV-2, which resulted in the ongoing death of microglia and the release of pro-inflammatory cytokines (74).

Long Covid and Brain Fog

In recent times, the term "Long COVID" has been used to state affliction in either persons who have recovered from COVID-19 but still have lasting infection impacts or those who have had the common symptoms for far longer than would be expected to. The most prevalent symptoms reported among these persons has been cognitive symptoms such as concentration difficulties (75), as well as forgetfulness, disorientation, and struggling to find the right words, colloquially referred to as brain fog (76-78).

Likewise, focusing on the neuropsychiatric effects of the SARS-COV 2 infection, longitudinal epidemiology research has revealed a wide range of long-term effects in patients who survived the COVID-19 pandemic. This research shows that almost 80% of subjects discharged from hospitals complained of at least one of the following symptoms, such as fatigue, myalgia, dizziness, muscle weakness, headache, sleep disturbances, cognitive impairment, and brain fog (79-81).

Brain fog can cause confusion, forgetfulness, and a loss of focus and mental clarity. This can be exacerbated by overwork, inadequate sleep, stress, and excessive internet use. High levels of cellular inflammation and changes in the hormones that regulate your mood, energy, and focus are known to have a role in brain fog. The hormone levels are out of balance, which throws off the entire system. Additionally, brain fog syndrome may lead to the development of additional conditions like obesity, irregular menstruation, and diabetes mellitus (82).

Paxlovid as an Effective Drug Approved by FDA for COVID-19

It is interesting that Pfizer Inc. reported that paxlovid (PF-07321332; ritonavir), an oral antiviral drug, has been shown to drastically lower hospital admissions, which account for 89% of covid-19 patients, particularly those who are at high risk of developing serious disease. Additionally, following randomization, patients receiving paxlovid treatment were admitted to the hospital up until day 28; among those who received treatment after the onset of symptoms throughout a three-day period, there were no fatalities. The SARS-CoV-2-3 CL protease, required for coronavirus replication, is inhibited by the medication PF-07321332 (paxlovid; ritonavir). During a stage known as proteolysis, Paxlovid (PF-07321332; ritonavir) can also halt viral replication before viral RNA replication. According to www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate, Pfizer Inc. now intends to submit the data as soon as feasible to the U.S. FDA as part of its ongoing rolling submission (83, 84).

According to a large new study (85), those who took the antiviral medication Paxlovid shortly after contracting the coronavirus were less likely to continue to experience long-lasting COVID-19 months later. The results imply that Paxlovid not only lowers the chance of being hospitalized or dying from a coronavirus infection, but it also lowers the likelihood of long-term symptoms for those who are medically eligible for the antiviral, such as older adults or people with specific health issues. The results are extremely provocative and point to the urgent need for additional research on antiviral medicines and their impact on extended COVID-19. It was also found that the treatment with Paxlovid within 5 days of a positive SARS-CoV-2 test was associated with a lower risk of PASC regardless of vaccination status and history of prior infection in individuals with SARS-CoV-2 infection who had at least one risk factor for progression to severe COVID-19 infection.

Conclusion

The SARS-CoV-2 virus, which is the cause of COVID-19 infection, has the ability to reduce several parts of

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the brain. Axonal and transsynaptic transport are most likely used by the virus to reach the CNS through the olfactory nerve. The second way the virus might enter the brain is the hematogenous route. According to prior study, COVID-19 infection can negatively affect glial cells, which leads to negative side effects such agitation, altered consciousness, headaches, and dizziness, or even mental and neurodegenerative disorders.

Paxlovid has been approved by FDA in the treatment of COVID-19 infection. The findings suggest that Paxlovid diminishes not only the risk of hospitalization or death from a coronavirus infection but also the risk of long-term illness.

Abbreviations

COVID-19 : Coronavirus Disease 2019; **CNS** : Central Nervous System; **AT2** : Alveolar Epithelial Type 2; **ACE2** : Angiotensin Converting Enzyme 2; **GI** : Gastrointestinal;**CSF** : Cerebrospinal Fluid; **BBB** : Blood Brain Barrier;**BDNF:** Brain-derived Neurotrophic Factor; **BSG** : Basigin;**EMMPRIN** : Extracellular Matrix Metalloproteinase Inducer;**CD147:** Cluster of Differentiation 147; **DPP4:**Dipeptidyl-peptidase 4; **CAM:** Cell Adhesion Molecules;**COPD** : Chronic Obstructive Pulmonary Disease.

Declarations section:

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