Review paper

Neurological effects of SARS-CoV-2 infection and vaccines

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Abstract
After the first emergence of SARS-CoV virus, long before the emergence of SARS-CoV-2 (COVID-19, or the 'coronavirus'), the coronavirus' long term neurological sequalae has been a target of concern. Here, we explore the neuroinvasive mechanisms of SARS-CoV-2 in relation with the central nervous system as well as addressing the neurological complications associated with the virus and its vaccines. The virus invades host cells by engaging angiotensin-converting enzyme 2 (ACE2 or Ace2), which is widely expressed in neurons, however, could be expressed differently within the endothelial cells in the brain. The virus seems to invade the central nervous system (CNS) through the blood brain barrier, and most likely through the olfactory bulb as well. Within the CNS, the release of large amounts pro-inflammatory cytokines dubbed the 'cytokine storm' as well as viral replication within neurons lead to multiple short term and long-term neurological symptoms. These symptoms include headache, dizziness, cognitive impairments, ischemic stroke, and neuroinflammation as well as long term symptoms referred to as 'long covid'. We concluded that there is a lack of knowledge about the long-term prognosis of the viral infection as well as treatments and therapies for these neurological symptoms, which both can be targets of future research.

Keywords
SARS-CoV2, Coronavirus, Neurological sequalae, Blood brain barrier, Cytokine storm, Long Covid, ACE2, Olfactory bulb, Neurons, Vaccine

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Introduction

Since the first severe acute respiratory syndrome coronavirus (SARS-CoV or SARS) pandemic in 2002-2003, there have been reports of patients experiencing neurological symptoms and side effects from what seemed to only be a respiratory disease (1). These neurological effects have become much more prevalent with the widespread infection and pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19). Although the upper and lower respiratory tracts are the main sites of entry of SARS-CoV-2 into the body, the virus has been associated with involvement in multiple different organs such as the lung, liver, kidney, heart, and gastrointestinal, haematological, and nervous system (2). Survivors of the virus have also been reported with many long term physical and neurological complications (3). In this article, we review literature associated with SARS-CoV-2 caused neurological sequalae, the long-term complications of SARs-CoV-2 and the neurological side effects of SARS-CoV-2 vaccines. In addition, we also present the current research regarding treatments for the SARS-CoV-2 caused neurological sequalae and introduce future considerations.

Results

Neuroinvasive mechanisms of SARS-Cov-2

After the first emergence of SARS-CoV virus, long before the emergence of SARS-CoV-2, the coronavirus' long term neurological sequalae have been a target of concern (4). Studies have shown that SARS-CoV-1 and SARS-CoV-2 are similar in their binding to the ACE2 receptor, *via* the viral spike protein (5). The ACE2 receptor is a part of the Renin-angiotensin system, which regulates blood volume throughout the body (6, 7). ACE2 is expressed throughout the animal and human brain and body, such as the olfactory epitheliums, the brainstem as well as many neurons (8-10).

There is still debate about if SARS-CoV-2 can enter the brain. CSF analysis with RT-PCR for SARS-CoV-2 in critically ill patients failed to identify the virus. However, other analysis in patients, as well as autopsies have identified the virus within the CSF (11-14). Multiple literature sources have suggested that both SARS-CoV-2 and other similar coronaviruses primarily enter the brain by altering the blood brain barrier, and potentially through the olfactory nerve *via* trans-synaptic viral transfer.

Electron microscopy images have shown viral particles ingressing and egressing endothelial cell walls in an autopsy, with RT-PCR assays confirming COVID-19 presence in the observed brain tissue (14). Viral replication is delayed until the virus passes through the endothelial cells and reaches its target cells within the brain (3). A study of blood biomarkers of blood brain barrier disruption COVID-19 patients showed that levels of these biomarkers were similar, or higher than patients with amyotrophic lateral sclerosis, a neurological disease (15). This suggests that endothelial cells are a potential pathway for SARS-CoV-2 entry into the brain. However, there is still debate on the expression of ACE2 in endothelial cells, with one study concluding that ACE2 expression was very low in the endothelial cells of the human brain (8). Additionally, another study with 3 cell donors concluded that ACE2 expression was low in endothelial cells, and they were resistant to SARS-CoV-2 infection *in vitro* (16).

Furthermore, there is evidence showing that ACE2 is not the only host receptor for SARS-CoV-2. A study using x-ray crystallography and biochemical approaches showed that SARS-CoV-2 was able to bind to the

neuropilin-1 receptor, with its presence increasing SARS-CoV-2 infectivity. Neuropilin-1 is highly expressed within the olfactory and respiratory endothelium, with the highest expression in endothelial cells. Furthermore, using cell culture methods, the same study showed that blocking this interaction reduced viral infection *in vivo* (17).

Immune cells serve as another potential pathway for SARS-CoV-2 to enter the brain. The virus binds to the ACE2 receptor on the surface of macrophages, entering their cytoplasm. The virus does not replicate inside the host macrophage, using it as a "trojan horse" to migrate to different areas of the body, and potentially the CNS. This requires immune cells that expresses ACE2, such as lymphocytes, granulocytes, and monocytes, and conditions in which the virus does not replicate inside these immune cells (3).

Previous studies on SARS-Cov in mice showed that the virus primarily entered the brain *via* the olfactory bulb, which resulted in rapid trans neuronal spread to connected areas of the brain. (4, 18). ACE2 has also been shown to be expressed more in the olfactory than in other cortexes (8). Sustentacular cells and stem cells in the olfactory epithelial all highly express ACE2, which may have a role in the binding of SARS-CoV-2 to the olfactory bulb, followed by transport into the brain (3). Studies have also reported CoV particles together with SARS-CoV-2 RNA in the olfactory mucosa in patients infected with the virus (19). Figure 1 shows the various mechanims by which the virus can cause neuroinvasion.

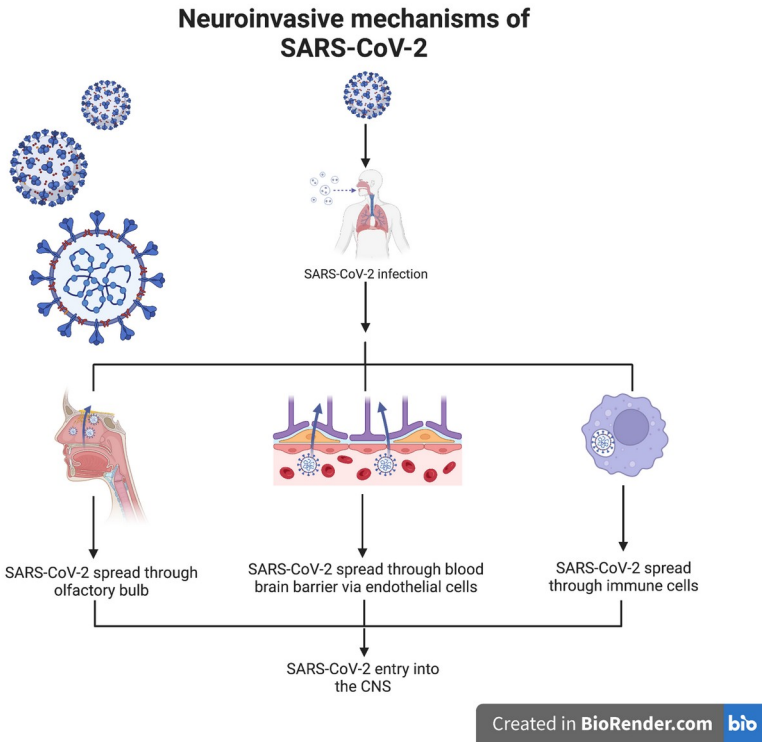

Figure 1. Mechanisms by which SARS-CoV-2 may cause Neuroinvasion

SARS-CoV-2 caused neurological sequalae

Regardless of how SARS-CoV-2 enters the CNS, it causes widespread damage to the brain, resulting in a multitude of short and long-term complications. A study of 54 patients in a single medical facililty comparing COVID-19 patients admitted into ICU with other non-COVID-19 ICU patients showed that overall, patients with COVID-19 admitted into ICU had a 2-fold higher risk of developing neurological complications than non-COVID-19 ICU patients admitted for acute respiratory distress syndrome (20). Furthermore, one in three patients admitted into ICU developed neurological complications, which according to a prospective clinical evaluation of 1800 patients over 2 years, resulted in a 2.5 fold longer ICU stay time, and a twofold increase in ICU stay times (20, 21).

Mechanisms of SARS-CoV-2 neurological sequelae

There are two main pathways which SARS-CoV-2 utilises to cause CNS damage: Pro-Inflammatory Cytokines and the "Cytokine Storm" and direct neuronal damage (Figure 2).

The release of an excessive amount of pro-inflammatory cytokines by the immune system increases vascular permeability, abnormal blood coagulation, and results in multiple-organ failure. This may explain the widespread organ damage found in many patients infected with the SARS-CoV-2 virus. These cytokines may also increase microvascular permeability in the CNS, facilitating further entry of SARS-CoV-2 through the blood brain barrier and into the brain (22).

The SARS-CoV-2 RNA genome and all sub-genomic RNAs can integrate into the host cell's mitochondria by transcription of its RNA into the mitochondria, leading to virus replication (23). Eventually, the infected cells may undergo necrosis, apoptosis, or cellular senescence (3, 23). Despite necrosis and apoptosis seeming to help slow the infection by destroying the cells, collateral CNS damage results, as does the promotion of inflammation and further spread of the virus (24).

Symptoms of SARS-CoV-2 neurological damage

The propagation of SARS-Cov-2 throughout the central nervous system can cause a wide variety of symptoms, with the some notable ones being headache, dizziness, cognitive impairments, mental disorder, acute cerebrovascular disease, epilepsy, ischemic stroke, and neuroinflammation (25). A retrospective observational study of the MRI's of 37 patients with SARS-Cov-2 neurological involvement found abnormalities in the medial temporal lobe, white matter hyperintense lesions, and excessive white matter microhemorrhages (26).

Cerebrovascular disease was one of the many symptoms experienced by patients with severe SARS-CoV-2 infections. A study of 1683 patients in a Spanish hospital found that 1.4% developed cerebrovascular disease, of which 73.9% underwent ischemic stroke, and 21.7% experienced haemorrhagic stroke (27). Other cohort studies for Ischemic stroke reported similar findings regarding these symptoms' presentation (28).

Long term neurological complications from SARS-CoV-2

There is growing concern regarding the long-term effects on CNS function caused by the SARS-CoV-2 virus. A study of patients with multiple sclerosis had 57% reporting a worsening of the disease after COVID-19 infection, and 20% developing new symptoms of multiple sclerosis (29). Another study found that SARS-CoV-2 shares many differentially expressed genes as well as

signaling pathways with multiple neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (30).

It is estimated that 31%-69% of COVID-19 survivors will experience long COVID symptoms after recovery from the initial infection (31). An assessment of 179 patients with symptoms of long COVID determined the most prevalent symptoms: fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnoea (21%), anxiety (27%), chest pain, and arthralgia (18%) (32). Studies have proposed that these disorders are caused by CNS dysfunction in response to neuroinflammation caused by COVID-19 (31). Furthermore, a study of 24 patients with long COVID experiencing neurological symptoms found a significant loss in cortical grey matter in all patients (33). Regarding vaccines, studies and surveys of individuals from various cohorts found that being vaccinated prior to contracting acute COVID-19 led to a decreased likelihood of experiencing long COVID symptoms (34).

Neurological damage and side effects caused by SARS-CoV-2 vaccines

There are a few different types of vaccines for SARS-CoV-2, with the most notable ones being inactivated and live-attenuated vaccines, which presents an inactive or weakened version of the virus to the body, and RNA vaccines, which presents the mRNA for the SARS-CoV-2 spike protein to the cell (35, 36). A review of multiple sclerosis patients who have had a SARS-CoV-2 vaccine concluded that RNA, DNA, and inactivated vaccines are likely safe for multiple sclerosis patients, with live-attenuated vaccines to be avoided if possible (37). A study of patients in the UK who had Acute inflammatory CNS diseases after being administered the ChAdOx1S (AstraZeneca) or BNT162b2 (Pfizer) SARS-CoV-2 vaccines hypothesised that ChAdOx1S vaccination could be more likely to trigger autoimmune CNS disease than BNT162b2(38). With the exception of one patient who died, all other patients within the study were assessed as having "good" or "moderate" outcomes after a median follow up time of 322 days, with none of the symptoms being debilitating. It is also important to note that these studies only involved a small percentage of patients who developed neurological symptoms, and due to their small cohort sizes, these studies stated that conclusive evidence could not be provided.

Potential treatments for SARS-CoV-2 related neurological complications

There are new treatments in development to combat the neurological complications caused by SARS-CoV-2. OP-101 is a hydroxyl-polyamidoamine dendrimer–N-acetylcysteine conjugate that specifically targets activated macrophages, which are an implicated cause of the hyperinflammation that is triggered by SARS-CoV-2. The treatment attenuated inflammation, neurological injury markers, and generally improve overall patient outcomes in a recent phase 2a clinical trial involving 24 patients with severe COVID-19 (39). However, there was one notable outlier during the clinical trial, who had significantly elevated levels of C-reactive protein after receiving the treatment, and another patient, who died.

Due to the long-term pathology of SARS-CoV-2 being mostly unknown, it is challenging to prescribe very specific drugs or treatments for "long COVID". It has been shown that antiviral drugs used in the treatment of acute COVID-19, specifically Paxilovid, a combination of nirmatrelvir and ritonavir can significantly reduce the risk of developing long COVID when administered in the acute phase and is promising in the treatment of long-COVID. However, the use

of Paxilovid and other antiviral drugs in reducing the neurological symptoms of long COVID have yet to be addressed (34).

Multiple studies have been performed regarding the risk factors of "long covid": the variant of SARS-CoV-2 infection, pre-existing conditions such as asthma and type 2 diabetes, and advanced age (40-42). It was advised to monitor these risk factors during the acute stage of SARS-CoV-2 infection in order to prepare long term treatments for the patient (31).
Additionally, another study of 167 patients also identified a correlation between genetic variations in antioxidant enzymes and long COVID manifestations (43).

Discussion

Neuroinvasive mechanisms of SARS-Cov-2
There is still debate as to the exact neuroinvasive mechanisms of SARS-CoV-2, with many theories proposed, but inconclusive evidence to prove them. A recent example is an article that examined the spatial and cell type distributions of the ACE2 receptor in both human and mouse brains (8). The ACE2 receptor is a part of the Renin-angiotensin system, which regulates blood volume and systematic vascular resistance and the general consensus is that it is expressed on alveolar epithelial cells and capillary endothelial cells, as well as throughout the brain (7). However, this was contradicted by the article, which described "low expression of ACE2 in the endothelial cells and the pericytes from the human brain". Ten publicly available brain transcriptome databases were used for the data, which varied widely in terms of subject age, as well as having a low number of cell nuclei, which were obtained from unspecified areas of the brain. This sample heterogeneity may have impacted the reliability of the results. From their results, the authors arrived at two main conclusions as follows: 1. blood vessels may not be the main source of ACE2 expressed endothelial cells in mice; 2. the heterogeneity of ACE2 or ACE2 distribution in the subtypes of the endothelial cells or pericytes may exist in both the human and mouse brains. The first conclusion is unlikely to be true, as ACE2 is a key part of the Renin-angiotensin system, as described above. The second conclusion is more likely. This was also supported by an *in vitro* study in which SARS-CoV-2 was unable to infect endothelial cells, which also were shown to have low levels of ACE2. This study also supported the second conclusion, as the endothelial cells were only obtained in small amounts, and only from three donors. However, due to multiple lines of evidence regarding the presence of ACE2 expression in the brain and endothelial cells, as well as the previously mentioned observations of viral particles entering and exiting the cells themselves, endothelial cell ingress most likely remains a key mechanism for the neuro-invasive mechanisms of SARS-CoV-2 (9, 10). This indicates the need for further research into the spatial and cell type distributions of ACE2 in the human brain and the differences between human and animal models, as it seems to be a vital mechanism of SARS-CoV-2 pathogenesis.

Previous studies on SARS-Cov in mice reported that the virus primary entered the brain *via* the olfactory bulb, and resulted in rapid trans neuronal spread to connected areas of the brain (4, 18). Furthermore, studies have shown that ACE2 was expressed to a larger extent in the olfactory, rather than in other cortexes, as well as being expressed in most neurons (3, 8). This line of reasoning provided indirect evidence that SARS-CoV-2 is able to replicate these expression patterns. Recently, a study found the presence of intact CoV particles together with SARS-CoV-2 RNA in the olfactory mucosa, providing

evidence that the olfactory bulb is an area of entry for SARS-CoV-2 into the brain (19). Unlike other mechanisms of SARS-CoV-2 neuroinvasive mechanisms, there does not appear to be much evidence against this infection pathway, further reinforcing the previous conclusion.

SARS-CoV-2 caused neurological sequalae

The previously mentioned study comparing COVID-19 patients admitted into the ICU with other non-COVID-19 ICU patients showed that overall, patients with COVID-19 admitted into ICU had a two-fold higher risk of developing neurological complications than non-COVID-19 ICU patients admitted for acute respiratory distress syndrome (20). The study also found that one in three patients admitted with non-neurological pathology into ICU developed neurological complications, which resulted in a 2.5 fold longer ICU stay time, and a twofold increase in ICU stay times (20, 21). However, it should be noted that this study only observed a small cohort of 54 patients in a single medical facility. This could result in bias due to differences between the facilities themselves, or the patients vising these facilities. Whilst this result does lend credibility to the proposition that SARS-CoV-2 ICU patients have a higher risk of developing neurological complications, as it is a single centre study, the exact percentage of patients who developed neurological complications could differ in other medical facilities.

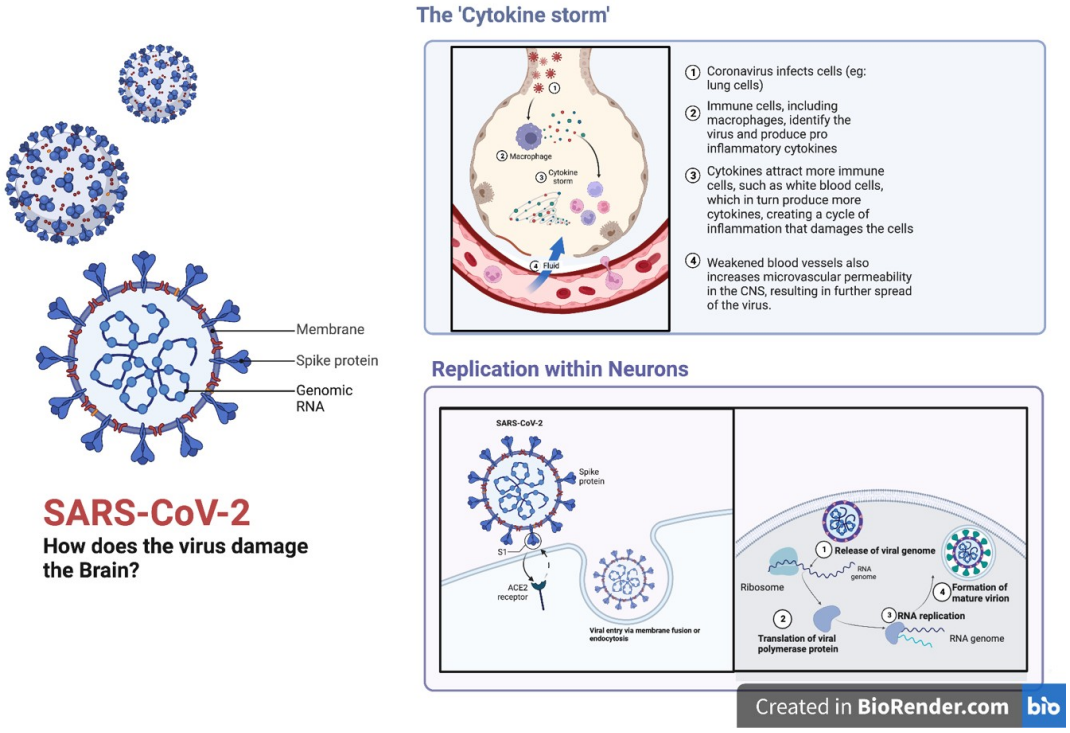

Figure 2. Damage to the brain caused by the SARS-CoV-2 virus

Long term neurological complications from SARS-CoV-2

As previously mentioned, a study of multiple sclerosis patients found that 57% of the cohort reported worsening symptoms (29). However, the study used a self-reporting email questionnaire, which could be impacted more by subjective biases experienced by the patient. However, this error was most likely offset by the large cohort size of 404 patients. Thus, the study found that most multiple sclerosis patients experienced a worsening of symptoms following SARS-CoV-2 infection, but it was unable to reliably conclude as to what extent these symptoms worsened. This conclusion could also be extrapolated to include all patients with neurodegenerative diseases, however due to the lack of knowledge on the relationship between neurodegenerative diseases, this additional conclusion can only be tentative. MRI scans could reliably show the extent of adverse effects caused by SARS-CoV-2 to these patients but would be too costly for such a large number cohort.

Long covid is another growing concern for many, as an estimated that 31%-69% of COVID-19 survivors will experience long COVID symptoms after recovery from the initial infection (31). According to the WHO, there were over 750 million cumulative cases of COVID-19 as of February 2022, which according to the estimates above, could mean cumulative long covid cases of 225 million to 517 million worldwide. This presents a significant challenge to the health system, as these symptoms can last from weeks to months, and ultimately impose a burden on the effectiveness of the health system as well as human society as a whole (31). Therefore, further studies are necessary to search for potential treatments, as well as the prognosis of SARS-CoV-2 infection in the long term.

Neurological damage caused by SARS-CoV-2 vaccines

There is little evidence regarding the neurological effects caused by SARS-Cov-2 vaccines, with only a small number of cases being reported in the UK after mass SARS-CoV-2 vaccinations (38). Furthermore, those neurological long-term symptoms that were observed were neither severe nor debilitating (38). The small percentage of patients who developed these symptoms indicated that the risk of developing neurological side effects were extremely low, and that the benefits of receiving a SARS-CoV-2 vaccine outweighed the risks in most scenarios. The previously mentioned study of SARS-CoV-2 vaccines in multiple sclerosis only recommended avoiding live attenuated vaccines due to a guideline imposed by the American Academy of Neurology after conducting a systematic review of randomized controlled trials, cohort studies, and case-control studies published from 1990 to March 2018 (44). The guideline did not include any data on SARS-CoV-2 vaccines specifically. Furthermore, it was shown that vaccination reduces the likelihood of developing long COVID symptoms. This, combined with the previous studies on multiple sclerosis patients infected with COVID-19, suggested that in cases with higher risk of COVID-19 infection, it was most likely safer for patients with neurodegenerative disease to be administered the live attenuated vaccine (29). However, these neurological side effects resulting from SARS-CoV-2 cannot simply be dismissed, and future observation and research could provide further insight into the cause of these side effects.

Potential treatments for SARS-CoV-2 related neurological complications

There has not been much research into potential treatments for SARS-CoV-2 related neurological complications. The aforementioned phase 2a trial for OP-101,

while resulting in good outcomes for the patients who received the treatment, was not conclusive (39). There were only 24 patients in the trial, and due to an outlier, future trials involving more patients are needed to conclusively show the treatment's effectiveness and safety, as well as observe any potential side effects of this treatment.

With the knowledge of the multiple different receptors of SARS-CoV-2, future treatments regarding blocking these receptors could be possible. However, due to the fact that this has only been documented *in vitro*, as well as there being multiple different receptors for SARS-CoV-2, this potential treatment pathway alone may not be clinically effective. Rather, a combination of this potential treatment, in conjunction with others such as the previously mentioned OP-101, and antiviral drugs could help significantly reduce viral load during the acute phase of SARS-CoV-2 infection, and also potentially reduce neurological symptoms.

Other than studies into the risk factors and prevention of long covid, there have not been many effective treatments for it as well as its neurological complications. Histamine antagonists have been used to relieve long COVID associated symptoms, however there is a need for clinical trials to formally investigate their safety as a treatment for long covid (31).

Regarding the correlation of certain genetic variations of antioxidant enzymes being associated with an increased or decreased risk of developing long COVID manifestations, while this article does provide insight into further research on potential treatments, it alone does not provide much benefit in terms of potential therapies or treatments (43). Perhaps a combination of this article and the previously identified studies on the risk factors of long COVID, in conjunction with a large sample of clinical records and other statistics, could prove helpful in pre-emptively identifying those within the previously infected population that are most at risk of these long-term manifestations of COVID-19.

There is a lack of effective and safe treatments for SARS-CoV-2 related neurological complications, representing an area for future research.

Conclusion.

In conclusion, this literature review provided an update on the current knowledge of SARS-CoV-2 neuroinvasive mechanisms within the central nervous system, its long term sequelae, effects of vaccines, as well as potential treatments for the neurological symptoms caused by the virus. While the current knowledge regarding the neuroinvasive mechanisms of SARS-CoV-2 is substantial and mostly conclusive, this review highlighted a significant need for identifying previously infected patients who are most at risk for long-covid; for research into the long-term prognosis of SARS-CoV-2, as well as potential treatments for the virus' neurological sequelae.

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