Mechanisms of SARS-CoV-2-induced Encephalopathy and Encephalitis in COVID-19 Cases

Neuroscience Insights
Volume 18: 1–8
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DOI: 10.1177/26331055231172522
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ABSTRACT: The SARS-CoV-2 virus caused an unprecedented pandemic around the globe, infecting 36.5 million people and causing the death of over 1 million in the United States of America alone. COVID-19 patients demonstrated respiratory symptoms, cardiovascular complications, and neurologic symptoms, which in most severe cases included encephalopathy and encephalitis. Hypoxia and the uncontrolled proliferation of cytokines are commonly recognized to cause encephalopathy, while the retrograde trans-synaptic spread of the virus is thought to cause encephalitis in SARS-CoV-2-induced pathogenesis. Although recent research revealed some mechanisms explaining the development of neurologic symptoms, it still remains unclear whether interactions between these mechanisms exist. This review focuses on the discussion and analysis of previously reported hypotheses of SARS-CoV-2-induced encephalopathy and encephalitis and looks into possible overlaps between the pathogenesis of both neurological outcomes of the disease. Promising therapeutic approaches to prevent and treat SARS-CoV-2-induced neurological complications are also covered. More studies are needed to further investigate the dominant mechanism of pathogenesis for developing more effective preventative measures in COVID-19 cases with the neurologic presentation.

KEYWORDS: SARS-CoV-2, COVID-19, encephalopathy, encephalitis, mechanisms, brain damage, neurologic complications

RECEIVED: December 27, 2022. **ACCEPTED:** April 12, 2023.

TYPE: Complications of COVID-19 on Brain Health - Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

The novel COVID-19 virus has rapidly spread throughout the globe, leading to an unprecedented pandemic. Creating a severe public health crisis, the SARS-CoV-2 virus has infected 36.5 million people and caused the death of over 1 million people in the USA since 8 October 2020.[1] This strain of Coronavirus falls under the betacoronavirus genera and has been known to develop within an animal reservoir. The SARS-CoV-2 virus represents one of the many strains of human Coronavirus that has crossed the animal-to-human barrier.[2] Human-to-human spread of the virus occurs through droplets, nosocomial infection, or direct contact. Consequently, the rapid spread of the SARS-CoV-2 virus has created problematic complications for numerous individuals over the past 2 years.

In a single-center case series of 138 hospitalized patients at Zhongnan Hospital of Wuhan University, SARS-CoV-2 symptoms included fever, cough, secondary infection, shortness of breath, muscle aches, and fatigue. While these symptoms could be managed in a hospital setting, the disease created severe cases of pneumonia that had to be managed by inpatient care. Tomographic scans of patients revealed patchy bilateral shadows in the lungs. Some patients needed to be transferred to the intensive care units (ICU) as the disease progressed to acute respiratory distress syndrome (ARDS), arrhythmia, and shock. It took 5 days for SARS-CoV-2 to cause dyspnea in the patients and 8 days for ARDS to develop.[3] Patients with respiratory distress could also begin experiencing coagulative dysfunctions and multiple organ failures in 1 week.[4] Clinical outcomes are considerably correlated with poor prognoses if patients present with comorbidities. Moreover, the mortality rates were higher in patients with pre-existed hypertension, diabetes, cardiovascular, and renal disease.

In addition to the commonly well-known symptoms, there is evidence of neurologic manifestations in COVID-19 patients. Since the beginning of the pandemic, many reported clinical cases acknowledged the development of neurological symptoms.[5] These symptoms were mild and/or severe, depending on the severity of the disease. Mild neurological symptoms included headaches, dizziness, attention and executive function deficits, memory, myalgia/fatigue, anosmia, and ageusia. Clinical presentation of COVID-induced severe damage to the brain is not limited to the aforementioned mild neurological manifestations but can additionally result in encephalopathy and encephalitis and spread to the brainstem and basal ganglia. Encephalopathy is characterized by any disease that alters the structure or function of the brain. The main symptom of encephalopathy is an altered mental state that entails fatigue, confusion, forgetfulness, and lack of concentration.[6] While encephalopathy refers to the altered mental state, COVID-induced encephalitis is characterized by the inflammation of the brain parenchyma and associated symptoms. Interestingly, angiotensin-converting enzyme 2 (ACE2) receptors found in

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neurons and glial cells play an essential role in the physiology of the brain and are also believed to be a gateway for the SARS-CoV-2 virus to enter brain cells.[7] Based on structural analysis using magnetic resonance imaging (MRI), functional analysis using electroencephalography (EEG), and chemical analysis using lumbar punctures coupled with spinal fluid analysis for COVID-19 infection, some scientists believe that this ACE2-regulated pathway is responsible for the virus causing a series of reactions that harms neurons and brain tissue.[8]

Because 50% of hospitalized patients had symptoms of dizziness, altered mental status, ataxia, and cognitive dysfunction encephalopathy is recognized as the most common neurological symptom of COVID-19.[9] In addition, some post-COVID-19 autopsy reports found an association of neurological lesions in the brain's white matter with areas of hemorrhagic lesions and axonal damage. Interestingly, the cluster of white matter damage consisted of a perivascular acute disseminated encephalomyelitis (ADEM) appearance.[10]

There are several known COVID-19-related mechanisms of encephalopathy pathogenesis. The most commonly reported mechanisms are hypoxic and inflammatory cytokine-based hypotheses. Studies have shown that in the former mechanism, systemic hypoxia caused by COVID-19 infection can result in metabolic inadequacies that cause global brain dysfunction.[11] COVID-19 affects the standard functionality of the respiratory system by diminishing gas exchange in the lungs, which may lead to the development of a hypoxic state. Brain tissue needs oxygen to carry out normal metabolic functions. Without an adequate oxygen supply, glucose cannot be oxidized to generate ATP through the Krebs Cycle and Electron Transport Chain. In such a hypoxic state, the inability to maintain the energy demands leads to brain cell deficiency, starvation, and eventually death, causing COVID-19 encephalopathy.[12]

The second known mechanism of encephalopathy pathogenesis induced by COVID-19 infection is caused by the uncontrolled proliferation and secretion of cytokines. This can activate local and systemic cascade reactions to alter the integrity of the endothelial lining and disrupt the blood-brain barrier (BBB).[13] A recent longitudinal study of COVID patients focusing on serum cytokines expression discovered markedly increased levels of the pro-inflammatory cytokine interleukin (IL-6).[13] The S100 calcium-binding protein B (S100B), an astroglial marker, also had increased serum levels in these COVID-19 patients. The elevation of S100B levels indicates increased BBB permeability, while the increase of IL-6 was suggestive of cytokine release syndrome (CRS) in the brain.[13] As IL-6 crosses the BBB, it creates a positive feedback loop by activating neighboring immune cells to release additional cytokines: IL-6, IL-1β, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). The pro-inflammatory cytokines activate brain tissue-resident macrophages to create a secondary inflammatory state in the brain tissue. The additional inflammation propagates further release of cytokines to fuel this positive feedback loop.[13] Consequently, the reactive response involves monocytes and macrophages that cross the BBB to initiate reactive gliosis. As a result of this process, the creation of larger reactive glial cells in the brain leads to scarring and the development of encephalopathy.

Studies related to COVID-19-caused encephalitis proposed different mechanisms of development through the transsynaptic spread. It was reported that SARS-CoV-2 binds to the angiotensin-converting enzyme type 2 (ACE-II) receptor to invade neuronal cells.[14] After infection of neurons, the virus travels in a retrograde fashion to the central nervous system (CNS) via the axonal machinery. An example of this model can be explored through the olfactory system's neural connectivity with CNS.[14] As SARS-CoV-2 interferes with the sense of smell, the virus travels to the cribriform plate, anterior cranial fossa, and reaches the brain parenchyma. This direct gateway to the brain parenchyma may cause inflammation of the brain and initiate encephalitis. Additional reported mechanisms of COVID-19-related encephalitis include viral spread using host blood cells, cytokines storm, and molecular mimicry.[13-15]

While studies have detailed these neurological developments in COVID-19, we have yet to determine the interplay between encephalitis and encephalopathy in COVID patients. Do the pathological mechanisms between encephalitis and encephalopathy overlap? Or can these 2 conditions develop separately and independently?

COVID-19 Related Mechanisms of Encephalopathy Development

Hypoxia related encephalopathy

COVID-19 infection severely affects the respiratory tract, leading to hypoxia and subsequent brain injuries. The brain has a high oxygen demand and relies on an adequate oxygen supply for oxidative metabolism.[11] Oxygen dependence of the brain makes it vulnerable and prone to developing global dysfunctions in a hypoxic state.

Neuropathological findings were reported from the postmortem evaluations performed on the brains of victims of COVID-19 or its complications. All patients had a positive nasopharyngeal swab test with reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays. Microscopic examination of the brain tissue revealed hypoxic injuries to the cerebrum and cerebellum. In addition, neuronal losses were seen in the cerebral cortex, hippocampus, and cerebellar Purkinje cells.[16] As a hypoxic mechanism of injury was established, the brain tissues were further tested for SARS-COV-2 proteins. Utilizing RT-PCR, the virus was detected at very low levels in some patients. These levels were not prominent enough to cause clinically significant symptoms as these patients did not suffer from encephalitis presentation.[16]

In another report of patient hospitalization and intubation due to a SARS-CoV-2-related hypoxic state, brain MRI scans 1 month after original hospitalization revealed diffusion restriction throughout the subcortical white matter.[17] Cerebrospinal

fluid (CSF) analysis was negative for SARS-CoV-2, and a repeat MRI 12 days after the first scan showed an exacerbation of the diffusion restriction. The normal CSF helps to rule out the possibility of viral encephalitis.[17] The hypoxia caused by encephalopathy was responsible for this neurological presentation due to the increased diffusion restriction. This MRI finding characterizes the consequence of oxygen-poor blood flow in the brain. The localized injury to the subcortical white matter deprived the affected brain tissue of oxygen and resulted in neurological presentation reported in this study.[17]

In another study, 41 SARS-CoV-2 patients who passed away with severe respiratory tract infections conducted autopsies. The report revealed that all patients suffered from hypoxia, and a large majority exhibited microglial activation.[18] This corresponded to areas of hypoxic damage in the brain, most prevalent in the lower brainstem. The medulla was also involved, as microglia cells were found in the inferior olivary nucleus and tegmental nuclei. While microglial cells can be found in viral encephalitis, no viral proteins were found within the brain.[18] The findings in these patients indicate that SARS-CoV-2-induced hypoxia creates encephalopathy through microglial activation. One possible mechanism occurs through the danger-associated molecular pattern, S100 calcium-binding protein.[19] One group of researchers discovered that this protein was increased in mouse microglial cells during hypoxic conditions.[19] S100 A8 phosphorylated extracellular signal-regulated Kinase (ERK) and c-JUN N-terminal kinase (JNK) in a chain reaction to activate TNF-α, IL-6, the nucleotide-binding oligomerization domain (NOD-), leucine-rich repeats (LRRs-), and the pyrin domain-containing protein 3 (NLRP3) inflammasome. The ERK and JNK are also correlated with neuronal cell diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's, and Alzheimer's.[19] Furthermore, the inflammasomes represent multi-protein complexes that initiate immune responses in stroke, meningitis, and Alzheimer's. Consequently, activation of these inflammatory molecules leads to neuronal cell death in an apoptotic manner within the brain.[19] The possibility of this mechanism occurring in SARS-CoV-2 patients is worth further investigation.

Post-mortem analyses with minimal invasive autopsy were completed on COVID-19 victims. Posterior reversible encephalopathy was detected on imaging.[20] The evaluated specimen was a part of the basal ganglia. This brain structure showed no evidence of encephalitis: no perivascular infiltrates, glial nodules, or cytopathic changes.[20] The changes in this patient correlated more with hypoxic injury, as seen in the clinical manifestation of the disease. Four episodes of cardiorespiratory arrest and prolonged mechanical ventilation characterize a hypoxic cause of death.[20] Wallerian degeneration (WaD) was found in this patient. This finding is commonly secondary to cerebral infarction and involves the descending damage of fiber tracts and their myelin sheaths. Furthermore, this degeneration is associated with ischemic lesions in other clinical studies.[21,22] The finding of WaD was supported by the Bielshowsky stain depicting axonal disruption and thickening.[20]

Cytokine related encephalopathy

A longitudinal study at the Strasbourg University Hospital was conducted with COVID-19 patients who presented with severe neurological manifestations such as confusion, tremor, cerebellar ataxia, agitation, impaired consciousness, etc.[13] Laboratory marker assessments were measured to observe cytokine release syndrome (CRS) of IL-6, C-reactive protein, ferritin, and lactate dehydrogenase.[13] The peak in these CRS serum markers developed simultaneously with neurological manifestations in more than half of the patients. In addition, the BBB permeability was increased as the S100B protein was elevated during CRS. The Reverse Transcription PCR assays did not detect any presence of SARS-CoV-2 in the CSF for all study subjects.[13] These results indicate that the above symptoms were independent of viral encephalitis for the neurological symptoms in these patients. Rather, the encephalopathy was a result of CRS from COVID-19 infection. The increased level of IL-6 crosses the BBB to trigger a positive feedback loop of pro-inflammatory cytokines. These cytokines create a secondary inflammatory state where macrophages initiate reactive gliosis. The development of glial cells in the brain ultimately leads to scarring and encephalopathy. Because COVID-19 encephalopathy showed improvement after steroid and intravenous immune globulin treatment,[23,24] this study implemented a similar treatment that successfully mitigated the effects of CRS encephalopathy.[13] Further investigation of this CRS treatment is warranted.

In another clinical case, a 67-year-old man was admitted with COVID-19 and readmitted later with a case of acute encephalopathy. The patient was admitted with COVID-19-like symptoms of cough, fever, nasal congestion, and sore throat,[25] but was not in a hypoxic state like in previously reported studies. Nasopharyngeal PCR was positive for SARS-CoV-2, and the patient was treated until day 9 when he was discharged with improvements. Two days after discharge, the patient returned with symptoms of confusion, emesis, and anorexia without hypoxia. Physical examination revealed postural and action tremors. Furthermore, brain MRI depicted scattered peri-ventricle deep and sub-cortical white matter ischemia. CSF did not indicate any presence of SARS-CoV-2; therefore, encephalitis was not diagnosed in this patient. C-reactive protein (CRP) levels increased to 10.7 mg/dl compared with readings from previous 0.55 mg/dl measurements.[25] The findings in this report present a notable encephalopathy without presentation or evidence of hypoxia and encephalitis. The onset of encephalopathy correlated with the increased levels of the inflammatory marker CRP, and thus the encephalopathy in this patient was a response of profound inflammatory reaction driven by innate immunity. Through this mechanism, the cytokine storm, also called cytokine-associated toxicity, is likely the reason for the development of encephalopathy. This occurs when inflammation triggers the release of IL-6 as a part of a systemic response. As discussed earlier, IL-6

can cross the BBB to trigger a positive feedback loop of pro-inflammatory cytokines.[13] Consequently, macrophages cause reactive gliosis and brain scarring. This report illustrated cytokine-related encephalopathy, which can have a delayed onset and clinical presentation. Future COVID-19 patients discharged from the hospital, even without hypoxia, should be closely followed up for this reason. If more cases result in encephalopathy after hospital discharge, then it is possible that cytokine-related encephalopathy occurs in a delayed manner.

Although cytokine levels are increased in patients diagnosed with COVID-19, the virus interferes with interferon production.[26] Interferon type 1 (IFN-I) is a cytokine created during infection. Pathogen Recognition Receptors (PRR) such as toll-like receptor 7 (TLR7), retinoic acid-inducible gene 1 (RIG-1), and melanoma differentiation-associated protein 5 (MDA5) recognize a virus' RNA and activate interferon-regulatory factor (IRF) proteins to create IFN-I. This cytokine serves to combat infection through its antiviral properties, as IFN-I turns on genes that restrict certain viral replication steps.[27] It has been reported that IFN-α and IFN-γ inhibit SARS-CoV replication.[27,28] Furthermore, the delayed release of IFN-I led to hyperinflammatory states with great recruitment of macrophages and monocytes through the human angiotensin-converting enzyme type 2 (ACE-2) receptor. In addition, the postmortem lung samples of COVID-19 patients had undetectable levels of IFN-I and IFN-III.[26] As IFN-I levels are unfavorably inhibited in lung tissue, does this pathophysiology of COVID-19 translate to human brain tissue?

A case study followed a 39-year-old man who spent several days in the ICU for COVID-19 infection. Prolonged intubation was required as the patient had severe respiratory failure. During the first 2 weeks of treatment, 3 doses of IFN-β 1b were administered. Following 63 days in the ICU and correction of metabolism, sedation was discontinued, and the patient had encephalopathy for the next 3 weeks. The patient was moved to a rehabilitation hospital; a neuropsychological assessment revealed impairments in processing speed, working memory, visuospatial abilities, etc. The patient improved these measurable cognitive deficits following early treatment.[29] Because COVID-19 inhibits IFN levels, the supplementation of IFN-β aims to trigger an antiviral response, as investigated in other COVID-19 cases.[30] Despite the patient's recovery, this treatment failed to prevent the patient's encephalopathy. Even though the IFN-I level executes its anti-viral function in the lungs, this case suggests that this mechanism does not carry over to the brain.[27]

In another study, patients with COVID-19 and neurologic symptoms indicative of encephalopathy were assessed for CSF biomarkers of intrathecal inflammation.[31] In the absence of BBB disruption and CSF pleocytosis, neurofilament light chain (Nfl) was elevated in the CSF of 2 patients.[31] The presence of this biomarker suggests a case of axonal injury. Nfl represents a neuronal cytoplasmic protein that is found in myelinated axons. The levels rise in CSF in proportion to the extent of axonal damage in several neurological disorders: inflammatory, neurodegenerative, traumatic, and cerebrovascular diseases.[32] The cause of this injury was not traced, although the study suspects that this could have resulted from hypoxia.[31]

COVID-19 Related Mechanism of Encephalitis Development

Direct invasion encephalitis

Encephalitis is defined as inflammation of the brain that can be present with various symptoms but is most commonly present with headache, vomiting, and fever. The pathogenesis of neurological symptoms may occur via the ACE-2 receptor.[7] COVID's spike protein S1 binds to the patient's ACE-2 receptor on the capillary endothelium. This allows the virus to enter the BBB and access the brain tissue.[7] Subsequently, the inflammation of the brain leads to a demyelination process that creates the patient's neurological symptoms of headache and vomiting. The pro-inflammatory state causes vasodilation of the brain, which can be seen on CT scans. The virus isolation may allow a definitive diagnosis of encephalitis. Moreover, patients should be immediately monitored for a potential case of delayed encephalitis. Thus, a 47-year-old patient presented with a fever, cough, and fatigue. He received a positive RT-PCR for SARS-CoV-2 but remained home for 15 days with 2 nasopharyngeal swabs negative for SARS-CoV-2 on day 20.[33] The patient did not present any symptoms on day 20. The fever reappeared on day 41 with symptoms of vomiting and severe headache.[33] CT was ordered, and vasogenic edema was present in the right temporal, frontal, and parietal lobes with extension to the capsular region. Blood tests displayed increased C-reactive protein, white blood cells, and neutrophils. One day later, the patient's brain edema worsened, which led to generalized seizures.[33] This clinical presentation of encephalitis highlights a direct invasion mechanism of the virus, slow development, and reappearing symptoms is a well-reported case of COVID-19 causing delayed encephalitis. The lumbar puncture to detect the presence of COVID-19 in CSF is a recommended diagnostic approach.

Another case involved a 52-year-old male with no fever, respiratory symptoms, or positive COVID test.[34] He was admitted with a 6-day history of gait instability. The patient's orientation fluctuated, and the patient became severely agitated on day 7. The MRI of the brain stem revealed brain stem encephalitis, and the patient tested positive for SARS-CoV-2 on the 17th day. A retrospective analysis of this patient's CSF hospital admission samples discovered the presence of SARS-CoV-2 RNA. In addition, the anti-amphiphysin antibody was detected in the patient's serum. This antibody is an onconeural antibody that is found in paraneoplastic encephalitis.[35] As COVID-19 encephalitis manages to launch responses against this antigen, the brain parenchyma becomes vulnerable to direct invasion of the virus. This fits into the postulated theory

of either trans-synaptic propagation or hematogenous invasion.[34] Despite the findings of this case study, the presence of SARS-CoV-2 in CSF has been rare in other cases. As a result, the direct invasion of COVID via CSF is possible but not common pathogenesis.

Anti-NMDA encephalitis

Glutamate is an amino acid recognized as the primary excitatory CNS neurotransmitter. Glutamate works through ionotropic receptors such as the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor has been most frequently affected in CNS diseases and is extensively studied. Low stimulation of the NMDA receptors can interfere with memory function and cause severe neurotoxicity via disruption of neuronal cytoskeletons. These abnormal structures occur throughout the brain and are responsible for memory function within hippocampal pathways. Downstream effects include the excessive release of acetylcholine and glutamate.[15] These excitatory neurotransmitters overstimulate postsynaptic neurons and result in cognitive and behavioral imbalances.[15] In some cases of COVID-19 encephalitis, antibodies against the NMDA receptor have been found.[36] A clinical case of an 18-year-old female patient admitted to the hospital with generalized tonic-clonic seizures followed by aggravated respiratory symptoms.[36] No other neurological symptoms were presented upon the neurological exam. As the patient lost consciousness, she was admitted to the ICU, and a lumbar puncture was performed. CSF PCR after 3 days revealed the weak presence of COVID-19. Furthermore, an indirect immunofluorescence test returned positive for the NMDAR antibody in the CSF. After 2 weeks, the patient eventually improved consciousness and respiratory symptoms with treatment. The patient had mild respiratory symptoms without the need for ventilation.[36]

The SARS-CoV-2 virus in CSF confirms encephalitis as the culprit for neurological symptoms. This case interestingly depicts how COVID-19 encephalitis can present with neurological problems before exacerbating respiratory symptoms. COVID-19 encephalitis works in this manner via the NMDA antibodies.[36] While it is unclear how COVID-19 produces these antibodies, the CSF findings show a clear correlation. NMDA receptors serve as the receptor for the excitatory neurotransmitter glutamate. The antibody for NMDA will prevent glutamate from binding to its receptor. As a result, this will create problematic neurological issues. In this case, the manifested neurological symptoms included altered consciousness and generalized tonic-clonic seizures.[36]

Another report supporting COVID-19-associated anti-NMDA antibody pathogenesis of encephalitis was documented in a 7-year-old boy with a 4-day history of unsteady gait.[37] A neurological exam revealed ataxia, wide-based gait, and deep tendon reflexes that could not be evoked. CSF analysis was normal and did not display a presence of SARS-CoV-2. On the third day of hospitalization, the patient received a positive COVID test from a throat swab despite no respiratory symptoms. The patient's neurological symptoms worsened on the eighth day with the appearance of choreiform movements, tongue protrusion, agitation, catatonia, bruxism, and lip-smacking. Following the worsening state, a test for anti-NMDAR IgG was positive in the CSF. Given these symptoms, autoimmune encephalitis was considered. The lymphopenia led to prompt treatment with pulse steroid treatment, which improved reported neurological symptoms.[37]

The mechanism of how the presence of NMDA antibodies can elicit encephalitis in COVID-19 patients was evident in many recent reports. While some patients had neurological symptoms followed by a respiratory presentation, others developed only neurological symptoms without respiratory system distress. The absence of respiratory symptoms is paradoxical, given the positive COVID test from the throat swab.[37] A similar clinical presentation has been seen in many reports.[38,39] Monti et al reported the absence of respiratory symptoms with anti-NMDA antibodies positive COVID-19 RT-PCR and status epilepticus.[38] Panariello et al characterized no respiratory symptoms but acute psychosis in the COVID-19 patient with NMDA antibodies.[39] The variety of clinical presentations can be explained by the presence of NR1-a subunit of the NMDA receptor. This subunit is the target of autoantibodies and is found in the hippocampus, neocortex, and cerebellum.[40,41] Thus, when COVID-19 patients have a neurological presentation of disease without respiratory symptoms, anti-NMDA encephalitis should be considered. The detection of anti-NMDA in CSF should be promptly done, and non-contraindicated steroid treatment started to reverse symptoms.

T cell encephalitis

To compare and properly differentiate between COVID-19 viral encephalitis and encephalopathy, single-cell sequencing is used to identify cell profiles in the CSF. This can help to understand the etiology of neurological pathology and the potential link to COVID-19 infection. Most SARS-COV-2 cases had undetectable levels of the virus in CSF, suggesting an indirect mechanism causing neurological symptoms. The recent use of single-cell RNA sequencing studies has depicted immune dysregulation in the blood with a severity-specific pattern of clonally expanded cytotoxic (CD8+) T cells in pulmonary COVID-19.[42,43] Whether these changes occur in CSF encephalitis patients is unknown. Heming et al created an atlas of CSF leukocytes in COVID patients with neurological symptoms.[44] The CSF analysis revealed that viral encephalitis (VE) patients had higher CSF leukocyte counts and protein concentrations than other patients. The CSF of VE patients featured an increase in regulatory T cells (Treg) and plasma clusters as well.[44]

Treg brain cells are important for the remodeling and homeostasis of tissue. Ito et al induced strokes in mice to study the purpose of Treg cells in brain injury.[45] Amphiregulin (AREG) is an epidermal growth factor (EGFR) ligand produced by Treg

tissue to maintain muscle regeneration and suppress tissue fibrosis.[46] In Treg-depleted mice, supplementation of AREG minimized neurotoxic astrocyte gene expression, astrogliosis, and apoptosis of neurons. This indicates that AREG is an important Treg mediator that prevents inflammatory damage to the brain. Moreover, the upregulation of IL-6 in Treg-depleted mice led to astrogliosis and brain injury. This suggests that Treg cells target IL-6 during inflammatory states[45] and can be used as a target to decrease the negative effects and complications in COVID-19-induced encephalitis.

Cytokine related encephalitis

Edén et al investigated whether CSF SARS-CoV-2 antigens were associated with CNS inflammation.[47] CSF nucleocapsid antigen was detected in a hospital-based cross-sectional study of COVID patients. Compared to healthy controls, the patients had increased CSF B2-microglobulin, IL-2, IL-10, and TNF-α.[47] Viral RNA of SARS-CoV-2 was not detected in these patients. Despite this, the ability to detect biomarkers in the CSF indicates that COVID is capable of eliciting a CNS response without invading the CNS. These inflammatory mediators travel throughout the CNS to result in inflammatory damage and encephalitis. This mechanism of encephalitis via biomarkers and cytokines is supported by other laboratory findings. The pro-inflammatory molecules such as C-reactive protein, D-dimer, and IL-6 are found to be elevated in CSF analysis[48-50] in response to COVID-19 infection.

A study was conducted to determine whether SARS-CoV-2 encephalitis is a cytokine release syndrome. A full screening protocol for COVID encephalitis (COV-Enc) patients was followed.[51] For that, COVID-positive patients greater than 18 years of age must have been admitted with altered mental status for at least 24 hours. The patients needed 2 or more of these requirements: seizures of no preexisting origin, new neurologic findings, CSF white blood cells count ⩾5/cubic mm^3, abnormal neuroimaging of brain parenchyma, or electroencephalography (EEG) indicative of encephalitis.[51] With this screening, 13 cases of SARS-CoV-2 encephalitis were reviewed. EEG was abnormal, with focal epileptic alterations observed in 3 patients, while generalized slow waves were prominent for frontal derivations in 10 patients. RT-PCR was negative for the presence of COVID in the CSF of all patients. The CSF analysis did show increased levels of Nfl and glial markers in encephalitis patients. In addition, IL-1B, IL-6, IL-8, and TNF-α were elevated in the CSF of COV-Enc patients compared to healthy control patients. IL-8 level was increased in the CSF of all COV-Enc cases.[52] The results of this study indicate that COVID-19 encephalitis is directly related to cytokine increases and associated with a prominent immune response. The diverse presence of elevated inflammatory markers in the CSF suggests the contribution of a cytokine-release syndrome/cytokine storm as the primary mechanism in developing COVID-19-induced encephalitis. Moreover, the presence of Nfl in the CSF indicates that encephalitis leads to neuronal damage. Inflammatory mediators in these patients cross the BBB to create an inflammatory state in the brain.[53] The increased presence of glial cells suggests a compensatory mechanism to support and protect damaged brain cells.[54]

Discussion

When COVID-19 produces severe respiratory symptoms, hypoxic encephalopathy represents the responsible mechanism of neurological symptoms. All cases of hypoxic patients had some alterations to brain structure. In the 59-year-old male, diffusion restriction through the subcortical white matter was seen on MRI.[17] The postmortem brains of deceased COVID patients had neuronal losses in the cerebral cortex, hippocampus, and cerebellar Purkinje cells.[16] Another study showed microglial activation in the medulla, inferior olivary nucleus, and tegmental nuclei.[18] The microglial activation may occur through the S100 calcium-binding protein, leading to the activation of inflammatory apoptotic molecules in the brain. Finally, post-mortem analysis of a patient with posterior reversible encephalopathy discovered Wallerian degeneration. This finding indicated the presence of cerebral infarction involving fiber tracts and their myelin sheaths.[22] All of these reported brain alterations were a result of hypoxia. Furthermore, some cases from above were reported without signs of encephalitis. Thus, RT-PCR detected low levels of SARS-CoV-2 in post-mortem brains, and negative in CSF analyses.[17] In addition, the patient with posterior reversible encephalopathy did not have any proof of encephalitis: no perivascular infiltrates, glial nodules, or cytopathic changes.[20] As a result, hypoxia-related neuropathological lesions of the brains observed in COVID-19 patients were not associated with encephalitis.

Even though encephalopathy and encephalitis do not overlap in COVID-induced hypoxic states, they have multiple evidence of similar cytokine release mechanisms.[13,18,31,52,54] In encephalopathy, cytokine release of IL-6, C-reactive protein, ferritin, and lactate dehydrogenase led to neurological manifestations via inflammation. IL-6 crosses the BBB and triggers a positive feedback loop of pro-inflammatory molecules.[13] The secondary inflammatory state ultimately altered brain structure through reactive gliosis. In COVID-19 encephalitis, CSF analysis revealed increased IL-6, IL-8, and TNF-a.[52] Like encephalopathy, these inflammatory molecules cross the BBB and lead to neurological symptoms. Nfl was also elevated in the CSF of patients with encephalitis and encephalopathy, suggesting axonal injury from inflammation.[31,52] Finally, glial cells were elevated to protect the damaged brain cells in encephalopathy and encephalitis.[13,18,52,54] As a result of this overlapping mechanism, the inhibition of cytokine storms in COVID-19 patients may conveniently stop the development of both encephalopathy and encephalitis.

COVID-19 encephalitis seems to have mechanisms that are distinct from encephalopathy. Through direct invasion, COVID's spike protein S1 binds to ACE-2 receptors on capillary endothelium.[7] Access to the brain via antibodies against amphiphysin also causes inflammation and a demyelination process of brain neurons. While encephalitis can directly access the brain parenchyma, other cases have shown non-invasive mechanisms.[15,36,45,46] Thus, encephalitis in an 18-year-old female and a 7-year-old male revealed how COVID creates antibodies against the excitatory neurotransmitter glutamate. The presence of NMDA antibodies in the CSF indicates the ability of COVID to suppress excitatory impulses.[15,36] As a result, the patients will present with neurological symptoms ranging from altered consciousness to seizures. NMDA antibodies in COVID-19 encephalitis patients interestingly create neurological symptoms free of respiratory symptoms. Aside from anti-NMDA, COVID-19 also increases the amount of Treg cells in the CSF. These Treg cells protect the brain from inflammatory damage and potentiate neurological recovery.[45,46] Moreover, Treg cells bind to IL-6 to suppress the transition from acute to chronic inflammation.[45] Future studies should focus on the effects of suppressed NMDA antibodies and increase the presence of Treg cells to potentially reverse the negative outcomes of COVID-19 encephalitis. Also, it would be beneficial to the biomedical field to evaluate the potential development if any, SARS-CoV-2-induced encephalopathy and encephalitis in the vaccinated population.

Summary

COVID-19 has unexpectedly led to the development of neurological symptoms during the pandemic spread around the globe. Neurological symptoms include headache, dizziness, attention and executive function deficits, memory, myalgia/fatigue, anosmia, and ageusia. Encephalopathy is a disease state that alters the structure or function of the brain. Encephalitis is characterized by the inflammation of the brain parenchyma and leads to associated symptoms. The pathological mechanisms between encephalitis and encephalopathy do overlap. COVID-19-induced encephalopathy shares a common mechanism with COVID-19-induced encephalitis by engagement of cytokines storm mechanism of development. It seems that 2 conditions can also develop independently of each other without overlaps. Thus, encephalopathy predominantly alters the brain's structure via a hypoxic mechanism. But encephalitis can develop via direct invasion, NMDA antibodies, and Treg inflammatory mechanisms. More studies are needed to further understand the dominant mechanism of pathogenesis in COVID-19 patients to develop more effective approaches to treat and prevent the development of neurological manifestations and complications.

Author Contributions

JHH contributed to the development of the conceptual framework for the review, and critically reviewed and revised the manuscript. AV and DN conducted the initial literature review, synthesized and analyzed the data, and drafted the manuscript. DN and MS contributed to the literature review, provided additional analysis and interpretation of the data, and assisted in the drafting and editing of the manuscript. All authors read and approved the final version of the manuscript for publication.

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