A Systematic Review on Temporal Lobe Epilepsy Patients with Corona Virus Infection

Pugazhandhi Bakthavatchalam¹, Fouad Saleih R.AL-Suede²,³, Sudarshan S.¹*

Abstract
Objective: To systematically review the neurological symptoms and complications in temporal lobe epilepsy patients with Coronavirus infected patients. Methods: A systematic review of clinical studies on cases with neurological symptoms linked to COVID-19 and other coronaviruses was conducted. Following the PRISMA guidelines, a search for related scientific publications was performed in the following electronic databases: PubMed, Scopus, and Embase. The keywords used were “coronavirus” or “Sars-CoV-2” or “COVID-19” and “neurologic manifestations” or “neurological symptoms” or “meningitis” or “encephalitis” or “encephalopathy.”

Results: A total of 43 articles varying from case reports to case series, cohort studies, and systematic reviews were examined on SARS-CoV-2 and other human coronavirus infections with clinical symptoms in the central nervous system. Hyposmia, headaches, weakness, and altered awareness were among the most commonly reported symptoms. COVID-19 has been linked to encephalitis, demyelination, neuropathy, and stroke. Infection via the cribriform plate of the ethmoidal bone and olfactory bulb, as well as trans- synaptic transmission, are some of the proposed mechanisms. Invasion of the medullary cardiorespiratory center by SARS-CoV-2 may have a role in the refractory respiratory failure seen in corona virus-infected patients who are critically ill. Conclusion: Coronaviruses have a high potential to damage the central nervous system and can cause a variety of neurological symptoms, from moderate to severe. cephalalgia, lightheadedness, and altered level of consciousness were the most common neurological functional and structural signs discovered.

Key Words: COVID-19, SARS-CoV-2HCoVSARS, MERS-CoV, SARS-CoV, Neurological manifestation, Encephalopathy

Introduction
The World Health Organization (WHO) proclaimed the coronavirus (CoV) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection a pandemic on March 11, 2020 (Montalvan, Lee, Bueso, De Toledo, & Rivas, 2020). It has spread significantly around the world since its finding in Wuhan, China, with more than 4,000,000 cases confirmed to date (Perlman, 2020; Velavan & Meyer, 2020; Wang, Horby, Hayden, & Gao, 2020). Since December 12, 2019, the infection has been reported in Wuhan, Hubei Province, China, with a probable link to Huanan Seafood Wholesale Market located in Jianghan District (Huang et al., 2020). The World Health Organization has classified the virus as Coronavirus Disease 2019 (COVID-19) (WHO). As of August 16, 2020, COVID-19 had infected 216 countries, resulting in 3,012,000 confirmed cases and 81,000 deaths (Organization, 2020). SARS-CoV-2 causes symptoms that aren’t just restricted to the respiratory tract; it also affects the nerve system. The most common symptoms described were dizziness, headache, and loss of taste and smell (Mao et al., 2020). Dyspepsia, vomiting, myody-
were included for the systematic review, all of which involved following exclusion and full-text eligibility. A total of 43 studies were included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the studies included. The research’s level of proof and quality were also scrutinized. The publications were included in the analysis based on the PRISMA () protocol’s requirements as represented in Figure 1 (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

For this review, only articles written in English were considered. To ensure that the literature was covered, the investigators of our study carefully reviewed the references in the included research. To determine eligibility and inclusion, all the investigators of this study separately surveyed the titles and completed abstract reports against the established search paradigms. Discussions were used to address disagreements over the inclusion of articles. From all of the studies included, the authors gathered the following information: investigator, year of the study, age of the patients, the onset of coronavirus symptom and status epilepticus interval, neuropathological symptoms, diagnostic assays, treatments, and shortcomings. The research’s level of proof and quality were also scrutinized. The publications were included in the analysis based on the WHO suggested standard parameters like laboratory findings, clinical symptoms, and epidemiological history. Only reports with confirmed cases of coronavirus-2 were included in this study. We compiled tables of clinical investigations for COVID-19s along with symptoms engaging the central nervous system with onset of seizures, including case series, original publications, multicentre and prospective studies.

Results
We received a total of 290 abstracts using our search method. Following exclusion and full-text eligibility. A total of 43 studies were included for the systematic review, all of which involved epileptic symptoms as a new-onset condition caused by coronavirus-2 infection. Case reports accounted for 31 of the studies, whereas case series accounted for eight and multicentre cross-sectional studies accounted for four. The collected investigations are summarised in Tables 1 and 2. (Atere et al., 2020; De Stefano, Nencha, De Stefano, Mégevand, & Seeck, 2020; Dixon et al., 2020; Elgamsy et al., 2020; Farhadian et al., 2020; Fasano, Cavallieri, Canali, & Valzania, 2020; Galanopoulou et al., 2020; Garazzino et al., 2020; Hepburn et al., 2020; Lyons et al., 2020; Mao et al., 2020; Morassi et al., 2020; Moriguchi et al., 2020; Pinna et al., 2020; Sohal & Mossammat, 2020; Somani, Pati, Gaston, Chitlangia, & Agnihotri, 2020; Zanin et al., 2020).

All studies were evaluated using the usual temporal lobe epilepsy diagnostic (e.g., Radiological imaging techniques and laboratory tests). CSF-PCR was also done to evaluate the neuroinvasion of SARS-CoV-2 for intervention planning of anti-epileptic drug administration. In addition, we explored a few significant studies in detail to gain more understanding about the mode of action and entry of SARS-CoV-2 into the central nervous system.

Discussion
Several studies have previously shown a link between CoVs and CNS illnesses such as Acute Disseminated Encephalomyelitis and encephalomyelitis disseminata. However, it is known that the virus causes encephalomyelitis, which has a fatality rate of roughly 29%, with nearly half of those who recover having a considerable risk of neuropathological abnormalities. Ecological intervention, heredity, and immune-mediated processes are all factors that influence the outcome of CoV infection (Yogarajan R et al., 2022). The inflammatory response is mediated by cytokines, which are a well-known mediator (Bell, Taub, & Perry, 1996; Organization, 2020). Cluster headaches and aberrant psychological processes were common in 97 MERS-CoV patients, according to a study(Saad et al., 2014). SARS-CoV-2 has a high degree of similarity with other coronavirus strains, and the present epidemic has left neurologists and medical practitioners grappling with difficult issues in dealing with neural system involvement (Ramesh T V et al., 2022). An enhanced research study could provide insight on the types of epileptic seizures that can be used to detect severe acute respiratory coronavirus infection, allowing physicians to better understand the fundamental pathophysiology and start treating patients sooner.

Epileptic seizures and their clinical manifestations: Prevalence and treatment
In our research, we found that the symptoms of epileptic seizures and temporal lobe epilepsy are closely connected. Articles, on the other hand, are in short supply. The first case of epileptic seizure in a COVID-19 patient was reported by Takeshi Moriguchi et al.
(Moriguchi et al., 2020). In the past, coronavirus infections have been related to epileptic seizures. According to a study by Saad M., 12 patients (14.6%) developed epileptic seizures after contracting the Middle East respiratory syndrome (MERS)-CoV virus (Saad et al., 2014). The time gap between infection and the onset of initial symptoms is usually 5-10 days, although in exceptional cases it can be up to 15 days. (Table-1).

Outcome measures were lacking at the time of study due to the patients’ hospitalization, according to the researchers (Galanoopoulou et al., 2020; Mao et al., 2020; Pinna et al., 2020).

Status epilepticus, tonic colonic movements, and convulsions were the most prevalent clinical presentations of epileptic seizures among COVID-19 patients. According to a study, epileptic seizures occurred in 38 (69.0 percent) of COVID-19 patients in the United States. The investigators documented heterotopia, grand mal seizure-like phenomena such as stiffness, abnormal involuntary movement in epilepsy, and new encephalopathy development (Sasi Kumar S et al., 2022). As a result of damage caused to the central nervous system, alterations in processes of metabolism, asphyxia, and multiple organ dysfunction syndromes, COVID-19 infection can produce these symptoms (Brownyn Lok et al., 2019). The scientists related SARS-CoV-2 entry via the nasopharyngeal mucosa or the olfactory nerve to the emergence of frontal sharp waves as epileptic discharge, implying a frontal epileptogenic abnormality (Galanoopoulou et al., 2020). According to Mao et al, 14.8 percent of individuals with severe COVID-19 illness showed signs of encephalopathy (Mao et al., 2020).

The most commonly prescribed epileptic seizure medications are lorazepam and levetiracetam (Dixon et al., 2020; Elgamasy et al., 2020; Lyons et al., 2020; Morassi et al., 2020; Moriguchi et al., 2020; Sohal & Mossammat, 2020; Somani et al., 2020; Zanin et al., 2020). Other medications prescribed include lacosamide, phenytoin, midazolam[15, 17], valproate[20], magnesium, lacosamide, and cllobazam (Elgamasy et al., 2020).

**Possible Epileptic seizure Mechanism in SARS-CoV-2 Patients**

SARS-CoV-2 can infect the central nervous system in a variety of ways. One of the main targets of the SARS-CoV-2 virus is the Angiotensin-converting-enzyme-2 (ACE-2) receptor cells (De Stefano et al., 2020; Farhadian et al., 2020; Lyons et al., 2020; Morassi et al., 2020; Moriguchi et al., 2020; Sohal & Mossammat, 2020). ACE-2 receptors can be located on a variety of cells throughout the body, including cardio-respiratory neurons in the brainstem, glial cells, basal ganglia, motor cortex, raphe, and endothelial cells. SARS-CoV-2 can infect blood-brain barrier endothelial cells, which then cluster in ACE 2 heavy brain regions, resulting in direct infection with neurological effects (Libbey et al., 2008; Singhi, 2011). The olfactory nerve, which enters the Central nervous system through the nasal passage, is thought to provide a second route for SARS-CoV-2 to enter the brain (De Stefano et al., 2020). Within seven days of infection, SARS-CoV-2 has been found to enter the CSF and brain via the olfactory nerve, causing inflammation and demyelinating reactions, as well as the risk of epileptic seizures. When SARS-CoV-2 overloads ACE-2 receptors, ACE-2 expression is downregulated (Dorandeu, Barbier, Dhote, Testylier, & Carpentier, 2013; McDonough Jr & Shih, 1997). As ACE-2 receptors are eliminated, the renin-angiotensin system becomes dysfunctional, resulting in increased angiotensin II production. Overproduction of angiotensin II sets off a cascade of events that culminate in severe acute lung injury, vasoconstriction, and oxidative processes that promote brain deterioration, potentially leading to neurological problems (Atere et al., 2020; Hepburn et al., 2020; Somani et al., 2020). COVID-19 has been linked to the development of pneumonia and life-threatening ischemia. Hypoxia can aggravate intrapartum asphyxia, leading to epileptic seizures. Ischemic brain injury produces hypoperfusion of cerebral tissue, which can lead to epileptic seizures. (Atere et al., 2020; Zanin et al., 2020). COVID-19’s effects on people with temporal lobe epilepsy are still unknown. Because patients with uncontrollable epileptic seizures have a higher risk of death from temporal lobe epilepsy, maintaining temporal lobe epilepsy management with Antiepileptic drugs is crucial. Illness, pyrexia, lack of sleep, and metabolic acidosis can all provoke epileptic seizures, which aren't always associated with COVID-19. Drug-drug interactions between AEDs and anti-COVID medication should be examined because several medicines are being studied for the treatment of COVID-19 (Dixon et al., 2020).

**Neuroinvasion triggered by SARS-CoV-2:**

Viral transmissions to the Central nervous system are aided by the BBB and its altered functional implications. SARS-CoV-2 can reach the Central Nervous System in two ways: through the bloodstream and the nervous system. The virus enters the Blood-brain barrier through the specialized brain microvascular endothelial cells (BMECs) directly or via the paracellular route, which uses infected cells from the vascular endothelium as a vehicle (Bohmwald, Galvez, Rios, & Kalergis, 2018). The hematological invasion could also be caused by circulating lymphocytes (Moriguchi et al., 2020). According to Tohidpour et al., 2017, the COVID virus can penetrate the BBB directly and cause meningeal inflammation (Tohidpour et al., 2017). The astrocytes’ end-feet cover cerebral blood arteries structurally (Verkrhatsky & Nedergaard, 2018).

The primary neurologic pathway for SARS-CoV-2 transmission to the CNS is retrograde axonal nerve fiber transport through specific nerve fibers. In viral transmission, the olfactory epithelium and nerve fibers are critical (Swanson II & McGavern, 2015). Other CoVs have been revealed to have a clathrin-dependent
endocytotic/exocytotic mechanism that allows for trans-synaptic viral transmission. Even though Severe acute respiratory Syndrome Coronavirus, except for one case study, enters the brain via the BBB (Moriguchi et al., 2020). All SARS-CoV-2 PCR testing in Cerebro Spinal Fluid were confirmed to be negative during our investigation (Atere et al., 2020; De Stefano et al., 2020; Dixon et al., 2020; Elgamasy et al., 2020; Farhadian et al., 2020; Fasano et al., 2020; Galanopoulou et al., 2020; Garazzino et al., 2020; Hepburn et al., 2020; Lyons et al., 2020; Mao et al., 2020; Morassi et al., 2020; Pinna et al., 2020; Sohal & Mossammat, 2020; Somani et al., 2020; Zanin et al., 2020). Infections in the early stages may prevent viral entry into the CNS, although this could lead to neural inflammatory diseases. As a result, COVID-19 therapy should concentrate on lowering inflammation in the host. Farhadian et al. discovered increased Monocyte Chemoattractant Protein-1 (MCP-1) in CSF, a key chemokine that indicates the deployment of an infiltrate that could lead to inflammation into the brain tissue (Farhadian et al., 2020).

**Conclusion:**
Several case reports have revealed a probable link between SARS-CoV-2 viral infection and neurologic symptoms during the current worldwide COVID-19 pandemic, comparable to CNS findings reported during and after earlier SARS and MERS epidemics. Knowing these patterns can help doctors investigate COVID-19 infection when they encounter unexplained neurologic symptoms, which is especially important now that the COVID-19 pandemic is in full swing. Due to the scarcity of information on this subject, more research is needed, especially studies on long-term neurologic repercussions. Coronavirus is an infection that can affect the central and peripheral nervous systems, among other organs. Coronavirus causes the same pathological changes in persons of all ages; the most common symptoms are neuralgia (28%), lightheadedness (22.3%), and syncope (16.4 percent). The new study should concentrate on neuropathological abnormalities that can harm the clinical characteristics of patients. Furthermore, we discovered that coronavirus infection caused the expression of numerous cytokines as well as putative immune system damage in the Central Nervous System, highlighting the virus’s neurotropic effects. Patients with this condition may experience a variety of symptoms, including neurological indications. Some people may just have neurological symptoms, with no signs or symptoms of the flu. Previous research in Corona patients revealed signs of encephalitis, multiple sclerosis, brain bleeding, and, most significantly, respiratory failure. In the case of COVID-19, more animal and human investigations are needed to back up these findings.

In addition to recent experimental models demonstrating neuroinvasion, a significant amount of studies of COVID-19 various neurodegenerative problems supports the possibility that SARS-CoV-2 is a novel neuropathogenic that is still underdiagnosed. It’s unknown how it causes acute and chronic neurologic problems, or whether the medullary cardiorespiratory center’s likely targeting contributes to the unfavorable effects. Researchers will learn more about COVID-19’s neurologic symptoms to better comprehend the virus, control its transmission, and treat COVID-19 patients.

**Abbreviations**
- acute necrotizing encephalopathy (ANE)
- acute respiratory distress syndrome (ARDS)
- blood-brain barrier (BBB)
- brain microvascular endothelial cells (BMECs)
- CD8 (cluster of differentiation 8)
- Central nervous system (CNS)
- Cerebrospinal fluid (CSF)
- Computed Tomography (CT)
- Coronavirus disease 2019 (COVID-19)
- Magnetic Resonance Imaging (MRI)
- Middle East respiratory syndrome coronavirus (MERS-CoV)
- monocyte Chemoattractant Protein-1 (MCP-1)
- N-methyl-D-aspartate receptor (NMDA)
- novel coronavirus (2019-nCoV)
- polymerase chain reaction (PCR)
- porcine haemagglutinating encephalomyelitis (HEV67)
- Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
- status epilepticus (SE)
- Tick-borne encephalitis virus (TBEV)
- Zika virus (ZIKV)

**Author Contributions**
PM wrote manuscript, conducted the survey, research and FSRS surveyed and Sudarshan survey the literature.

**Acknowledgment**
All author are grateful to the Manipal university support. No targeted funding was reported.

**Competing financial interests**
Authors declare no competing interest.

**Supplementary Information**
None

**References**


https://doi.org/10.25163/angiotherapy.6122191290707122


Yogarajan R1, Jayakumari S2, Sumathi K3 and Mohan Kumar P R*4…(2022). A Case of Uncontrolled Asthma. ournal of Angiotherapy 6(1).

Yogarajan R1, Jayakumari S2, Sumathi K3 and Mohan Kumar P R*4…(2022). A Case of Focal Epilepsy Associated with SARS.