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Seizures in the Setting of COVID-19

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Key points
- Seizures and status epilepticus may occur in patients with COVID-19 infection.
- Acute symptomatic seizures generally occur because of acute brain injury related to systemic pro-inflammatory, hypercoagulable states, and severe metabolic derangements.
- People with epilepsy are not more susceptible to COVID-19 infection; however, they may be at higher risk for more severe COVID-19 infection.
- Clinicians should be aware of potential drug-drug interactions among treatments for COVID-19 and anti-seizure medications.
- COVID-19 pandemic globally affected people with epilepsy due to barriers to access care both routine as well as delaying surgical therapies for epilepsy.
- Implementation of telemedicine has been well received by both clinicians and people with epilepsy to reduce the barriers to healthcare that patients faced early in the pandemic.

Keywords COVID-19 · SARS-CoV-2 · Seizures · Status epilepticus · Epilepsy

Abstract

Purpose of review This review presents current available data relating to seizures in the context of COVID-19 infection from theorized pathophysiology to presentations and treatments. We also review the impact the COVID-19 pandemic has had on people with epilepsy (PWE) with special consideration of changes in healthcare access and COVID-19 vaccine.

Recent findings PWE are not more susceptible to contracting COVID-19 infection; however, recent data suggests PWE are a potential high-risk population for more severe symptoms and ICU admission. Given drug-drug interactions, caution should be advised when using certain treatments for COVID-19 (i.e., antiviral medications) and anti-seizure medications (ASM). COVID-19 vaccines appear to be safe for PWE.

Summary Acute symptomatic seizures and status epilepticus are an infrequent but severe acute neurological sequelae of COVID-19 infection in patients with and without epilepsy. The COVID-19 pandemic has had an enormous impact on PWE, resulting in changes to the

way we deliver healthcare, decreases in admissions to the epilepsy monitoring unit, and delays in surgical treatments for epilepsy. Further research is needed to better understand, if any, the long-term consequences of COVID-19 infection in PWE.

Introduction

Although coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a predominantly respiratory disease, neurologic complications are common. The mechanism in which neurologic symptoms occur in patients with COVID-19 is multifactorial and includes encephalopathy or acute neurologic injury due to severe systemic dysfunction (e.g., metabolic derangements and hypoxemia), immune dysfunction, autoimmunity, or an overall proinflammatory state [1, 2]. Cerebrovascular disease, including ischemic stroke, intracranial hemorrhage, and cerebral venous thrombosis, are infrequent complications of COVID-19 [3]. Seizures and status epilepticus may also occur as an uncommon neurologic sequela of acute COVID-19 infection [4]. Symptomatic seizures and status epilepticus often accompany associated entities such as meningoencephalitis, autoimmune encephalitis, and cerebrovascular disease in the context of acute COVID-19 infection and, however, may rarely be the first presenting symptom. Anti-seizure medications (ASM) remain the treatment of choice for seizures in the setting of COVID-19 infection; however, drug interactions and side effects much be taken into account when choosing an ASM. Additionally, despite the abundance of COVID-19-related research available, it remains unclear whether COVID-19 infection may worsen seizures in patients with epilepsy and how the pandemic has affected epilepsy care. The objective of this review is to understand the association between seizures, status epilepticus, and COVID-19 infection in patients with and without epilepsy.

Pathophysiology of seizures in COVID-19 infection

Proposed mechanisms for seizures associated with COVID-19 include direct entry to the central nervous system (CNS) or through innate and adaptive immunological responses that cross into the CNS via the blood brain barrier. Systemic etiologies related to hypoxemia, pro-thrombotic states (e.g., arterial or venous), immune dysfunction, and severe metabolic derangements related to COVID-19 can cause secondary CNS injury, lower the seizure threshold, and cause new-onset seizures.

COVID-19 infection causes ischemia by inducing a pro-thrombotic state via hypercoagulability and inflammation. Additionally, anoxia and hypoxemia in the context of severe pulmonary dysfunction may also cause ischemia to the brain with subsequent development of seizure [5]. In arterial or venous ischemic strokes, acute symptomatic seizures may result from the sudden disruption of the blood brain barrier, increasing extracellular glutamate concentrations, and/or impaired neuronal ion channel function due to decreased blood perfusion [6]. Longitudinal case series and retrospective reviews have described cases of new-onset seizure activity following acute infarction during COVID-19 [7, 8]. Moreover, epilepsy may be a late development after stroke (i.e., post-stroke epilepsy) due to chronic changes such as gliosis, chronic inflammation, abnormal neurogenesis, synaptogenesis, and loss of synaptic plasticity [9].

Alternatively, acute symptomatic seizures can be attributed to secondary manifestations of a pronounced neuroinflammatory state due to systemic infection with COVID-19. The release of pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin 6 (IL-6) and IL-1B, prostaglandin E2, and free radicals can lower the seizure threshold via multiple mechanisms and include increased permeability of the blood brain barrier, neurotoxicity through increased levels of excitatory neurotransmitters such as glutamate, decreased levels of inhibitory neurotransmitters such as GABA, and ion channel dysfunction [6]. It is these proposed pathologic mechanisms, in additional to traditional risk factors such as hypertension and kidney disease, which may underlie the several cases of reversible posterior leukoencephalopathy syndrome (RPLS) reported in the literature in the context of COVID-19 infection [10, 11]. A 2021 case series described eight COVID-19 patients with evidence of RPLS, seven of whom presented with acute symptomatic seizures [11].

The adaptive immune response against SARS-CoV-2 can generate post-viral autoimmune encephalitis. Although the majority of case reports described antibody-negative limbic encephalitis, there are reports demonstrating the presence of antibodies against neuronal antigens with known associations to autoimmune encephalitis, such as NMDAR and CASPR-2 [12•, 13]. In some cases, the presenting symptom did include new-onset refractory status epilepticus [14].

Finally, direct infection of the CNS by SARS-CoV-2 can occur; however, this is an uncommon finding in patients presenting with seizures. Experts hypothesize direct invasion of the CNS in the form of viral meningoencephalitis which may occur via hematogenous spread, direct orbitofrontal invasion through the olfactory bulb and cribriform plate via ACE-2 receptors, or via retrograde movement along peripheral nerve fibers [15]. Patients presenting with COVID-19 infection and seizures may also commonly have negative work-up for any CNS involvement [16]. A 2021 review of CSF analyses of COVID-19 patients with acute seizures detected viral RNA in only 13% of CSF samples [12•]. In this same group, intrathecal-produced antibodies to SARS-CoV-2 were detected in only 8%. These studies suggest that direct CNS infection by SARS-CoV-2 is infrequent in patients presenting with seizure and COVID-19.

Acute symptomatic seizures and status epilepticus as a symptom of Covid-19

The incidence of neurologic manifestations is high in patients with COVID-19 infection and more frequently seen in those requiring hospitalization. Acute symptomatic seizures and status epilepticus are a rare but important neurologic symptom frequently reported in association with SARS-CoV-2 infection and carry a risk of mortality [17–19]. In a retrospective multicenter study of 509 patients, the most frequent neurologic symptoms were myalgias, headaches, encephalopathy, dizziness, dysgeusia, and anosmia [1]. In this same study, seizures occurred in only four patients (0.8%) at any time during COVID-19 infection in this study. In a single center retrospective review of 439 cases of COVID-19 infection, 19 patients (4.3%) presented with

acute symptomatic seizures [8]. A majority of these cases (14/19 patients) were associated with primary pathology commonly associated with seizures: COVID-19-related ischemic stroke (3 patients), hemorrhagic stroke (2 patients), and encephalitis (6 patients). Alternatively, a retrospective multicenter study of 304 patients without a prior history of epilepsy reported no cases of acute symptomatic seizures or status epilepticus [20]. In a systematic literature review of 175 patients with seizures, status epilepticus, and/or cortical myoclonus associated with concomitant COVID-19 infection, most patients had "good outcomes" (66.3%) defined as discharge without severe deficits and/or return to near baseline [21]. The most common underlying diagnoses were encephalitis (autoimmune or infectious), infarct, and intracerebral hemorrhage. Severe COVID-19 was associated with more myoclonus, poor outcome, and mortality ($p < 0.001$), with a trend towards more EEG abnormalities ($p = 0.066$).

Status epilepticus (SE) is a rarer yet more severe neurologic complication of COVID-19 infection requiring sedating anti-seizure medications and anesthetics but also requiring hospitalization and diagnostic investigations such as continuous EEG. In a systematic review and meta-analysis of 47 cases of SE associated with COVID-19, patients that developed SE most frequently had respiratory and/or gastrointestinal COVID-19 symptoms and were hospitalized [19]. No clear etiology was found for status epilepticus in 55.3% of the patients, with 17/47 patients meeting the diagnostic criteria for new-onset refractory status epilepticus (NORSE). Abnormal neuroimaging was reported in 42.6% of patients receiving brain magnetic resonance imaging (MRI) with lesions suggestive of acute inflammation (17%) and PRLS (8.5%) being the most common etiology. Patients had motor onset status epilepticus more often than non-motor onset (non-convulsive status epilepticus). First line anti-seizure medications (ASM) most frequently used were lorazepam and levetiracetam. Benzodiazepines, which are typically first-line treatment for SE, were started less often than levetiracetam due to concerns for respiratory depressive effects. Second line ASM usage included levetiracetam, valproic acid, phenytoin, and lacosamide. Midazolam and propofol were the most commonly used anesthetic treatments for refractory SE. Some patients received further treatment with intravenous steroids (14.9%) and intravenous immunoglobulins (IVIg) (10.6%). In patients with reported treatment outcomes (53.2%), the majority of cases (96%) had the favorable outcome after SE cessation.

Children are less likely to have symptomatic disease than adults are when contracting COVID-19 [22•]. Symptoms are generally milder and most commonly include fever and mild respiratory symptoms. In a retrospective review of 175 children with COVID-19, 11 patients presented with seizures of which five met criteria for status epilepticus [23]. Unlike in adults, seizures could be the first or main manifestation of acute COVID-19 in children. Seizures and SE were typically easily controlled, and the patients made full recoveries in this cohort.

Electroencephalography (EEG) findings in COVID-19 patients

In a meta-analysis of 12 studies of EEG findings in patients with COVID-19 infection, abnormal background activity and generalized slowing were the most frequently reported findings in 96.1% and 92.3% of patients, respectively [24]. Interictal epileptiform discharges (IEDs) were present in 20.3% of cases. IEDs were more common in patients with a prior history of epilepsy compared to those without a history of epilepsy. EEG recorded seizure in 2.1% of patients and only 0.8% were in status epilepticus at some point during EEG monitoring. In a more recent retrospective multicenter study of 4100 patients hospitalized with COVID-19, EEG was utilized in 110 patients (2.68%) [17]. Seizures were recorded in 13 patients with focal-onset and generalized clinical seizures more common than electrographic seizures. Background slowing was the most common interictal EEG finding in 91% of patients monitored followed by focal slowing/attenuation (27%), rhythmic and/or periodic discharges (24%), and sporadic epileptiform discharges (14%). Of the rhythmic or periodic patterns, generalized periodic discharges (GPDs) with triphasic morphology (21%) appeared most frequently followed by generalized rhythmic delta activity (GRDA) (18%), and GPD without triphasic morphology (9%). Lateralized or bilateral-independent patterns were noted in 5% of patients. The presence of seizures, status epilepticus, and interictal epileptiform discharges was not significantly associated with patient outcomes in this study.

In the previously mentioned meta-analysis of status epilepticus patients, EEG data was available in 33/47 patients [19]. The authors reported IEDs in 24 patients, the most common finding being GPDs in 5 patients, lateralized periodic discharges (LPDs) with or without fast activity in 4 patients, GRDA in two patients, and bilateral independent lateralized periodic discharges (BiLPDs) in two patients.

It is important to note that early in the pandemic, as a precaution to limit the potential exposure of COVID-19 to hospital staff (i.e., EEG technologists), the use of continuous video EEG was potentially underutilized or reserved for when clinical suspicion for seizures was high. This may underestimate incidence of both SE, particularly nonconvulsive SE or subtle clinical SE, and seizures. The use of portable point-of-care limited-lead EEG devices such as the FDA-approved Ceribell (8-channel EEG) has been investigated to address this diagnostic barrier. One study showed Ceribell allowed for earlier diagnosis of SE and non-SE conditions with reduction in workforce demands given ease of placement and design that allowed for easy disinfection [25].

Epilepsy as risk factor for COVID-19—incidence, morbidity, mortality

In 2020, the International League Against Epilepsy (ILAE) informed that persons with epilepsy (PWE) were not likely to be more susceptible to contract COVID-19 nor were they inclined to suffer through more severe manifestations of SARS-CoV-2 infection than the general population [26•]. Within this consensus statement, if PWE were exposed to SARS-CoV-2, it was unlikely that the frequency of seizures increased. However, recent data suggest PWE are a potential high-risk population for more severe symptoms:

In a Korean population-based cohort study of 212,678 participants who underwent a COVID-19 test, having epilepsy was not associated with increased susceptibility to COVID-19 infection [27•]. However, patients with COVID-19 with epilepsy were at higher risk for severe complications including intensive care unit admission, mechanical ventilation, and death than patients with COVID-19 without epilepsy. Mortality alone was not significantly different between patients with or without epilepsy.

A systematic review and meta-analysis of over 67,000 patients found that epilepsy as a comorbidity was associated with an enhanced risk of severe COVID-19 infection and increased mortality from COVID-19 [28•]. The authors reported COVID-19 disease severity association was further affected by gender and pre-existing neurodegenerative disease. They posited that the association between epilepsy and severity of COVID-19 infection/mortality lies within a neuroinflammatory process, which can be pro-epileptogenic and may lead to status epilepticus, psychological stress, drug-drug interactions, relation of seizures to hypoxemia, and barriers to healthcare in the setting of societal pandemic measures (e.g., lockdowns).

Treatment of COVID-19 in PWE

Management of COVID-19 in PWE may be more complicated than in other individuals. Some ASMs taken by PWE may interact with drugs commonly used to treat COVID-19—particularly those that alter hepatic enzyme metabolism. Jain et al. provide a comprehensive resource, which summarizes evidenced based and hypothetical drug-drug interaction risk among anti-seizure medications and current treatments for COVID-19 infection [29••]. The clinician should also be aware that patients with concomitant cardiac, hepatic, or renal disease, which may be secondary to COVID-19 infection, might also require adjustment to ASM dosage.

Paxlovid, a combination of nirmatrelvir and ritonavir, received an Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for the treatment of mild-to-moderate COVID-19 infections in adult and certain pediatric patients who are at high risk of progression to severe COVID-19. Per the American Epilepsy Society (AES) official guidelines, concomitant

use of Paxlovid with ASMs that are strong inducers of CYP3A4 isozyme (e.g., carbamazepine, phenobarbital, phenytoin, and primidone) is contraindicated as these ASMs could cause loss of virologic response and development of resistance [30]. Conversely, Paxlovid may increase the plasma concentrations of many ASMs via inhibition of the CYP3A4 isozyme; these ASMs include cannabidiol, carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, everolimus, felbamate, lacosamide, midazolam, oxcarbazepine, perampanel, stiripentol, tiagabine, and zonisamide. The treating physician should be aware of potential toxicity associated with these medications.

In severe COVID-19 patients who require extracorporeal membrane oxygenation (ECMO), ECMO may affect the pharmacokinetics of highly protein-bound ASM [31]. ECMO circuits may initially sequester these drugs, while later releasing the drug into the circulation resulting in an unpredictable effect.

Vaccines have been shown to have a good safety profile and low risk of worsening epilepsy among PWE [32–34]. Despite this, a recent meta-analysis of the literature showed a considerable proportion of PWE and caregivers (26.1–89.3%) unwilling to receive COVID-19 vaccination during the height of the pandemic [34]. Increase in post-vaccination seizures is rare. There have been isolated case reports of encephalitis with seizures or status epilepticus, which were possibly associated to COVID-19 vaccination [35, 36].

Changes in epilepsy care as a result of the pandemic

PWE experienced barriers to care during the height of the COVID-19 pandemic. In a survey of AES-associated providers, they identified financial stressors and barriers to healthcare including access to transport, technology to facilitate telehealth, and ability to obtain anti-seizure medications [37]. In a multinational survey of pediatric neurologists, COVID-19 led to 91.5% of providers reporting changes to outpatient care, 90.6% with reduced access to electroencephalography (EEG), 37.4% with altered management of infantile spasms, 92.3% with restrictions in ketogenic diet initiation, 93.4% with closed or severely limited epilepsy monitoring units, and 91.3% with canceled or limited epilepsy surgery [38]. In a European survey, most EMUs had restricted access or closed for planned admissions [39].

In the USA, a comparison of data reported in 2019 and 2020 from all 260 level 3 and 4 National Association of Epilepsy Centers (NAEC) demonstrated EMU admissions declined 23% (largest median reduction in level 3 centers, adult centers) (see Fig. 1) [40••, 41]. Survey responders attributed reduction to re-assigning EMU beds, restrictions on elective admissions, reduced staffing, and patient reluctance. Treatment surgeries declined by 5.7%, the largest reductions seen in VNS implantations and temporal lobectomies.

Due to the pandemic, utilization and access of medical services evolved for PWE and those seeking care for seizures. An analysis of the Center for Disease Control (CDC) data of epilepsy and seizure-related ED visits before and during the pandemic found visits abruptly decreased during the early pandemic period [42]. By the end of 2020, seizure-related ED visits returned to almost pre-pandemic levels for all persons except children under 9 years

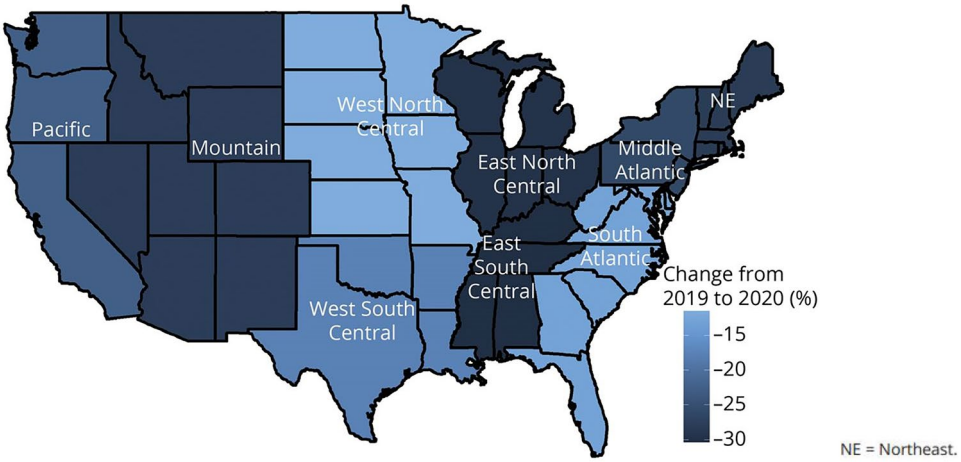

Figure 1 Changes in aggregate admissions by US Census Division from 2019 to 2020. COVID-19 pandemic led to detrimental effects with delay in video EEG admissions with subsequent delay in adjustment of medications and delay in surgical interventions. Reprinted with permission from Ahrens et al. Neurology [40••].

old. By mid-2021, this group also returned to baseline. The authors postulated that the decrease in ED visits may have been related to fear of exposure to COVID-19 infection, adherence to mitigation measures in avoiding public settings, or increased access to telehealth.

In the setting of both safety precautions and prioritization of management of patients with COVID-19 infection, the implementation of telemedicine provided a way to increase access to clinical care for PWE with positive effect. In a tertiary care center in India for children with epilepsy, 96% of caregivers surveyed were satisfied with quality of telemedicine consultations in place of typical outpatient epilepsy visits [43]. Another survey of perceptions of telehealth visits found 66% of patients and 67% of providers would use a telehealth visit in the future if given the option [44]. Furthermore, a level 4 epilepsy center surveyed their epilepsy patients and found that the degree of satisfaction tended to increase with greater distance patient lived from the clinic [45]. In this study, 89% of patients reported a preference for continuing telemedicine if their epilepsy symptoms remained stable, while only 44.4% chose telemedicine should their symptoms worsen. Economically, visits made via telemedicine saved patients an estimated US $30 per visit.

Conclusion

New onset seizures and status epilepticus are a potential acute manifestation of COVID-19 infection. Acute symptomatic seizures are generally secondary to acute brain injury related to systemic pro-inflammatory state, toxic-metabolic derangements, and ischemia secondary to hypercoagulable state. Status epilepticus is a rare but severe neurological sequelae of COVID-19 infection, which is associated with increased morbidity and mortality. People with epilepsy are not at higher risk to contract COVID-19; however, the pandemic negatively

affected this population due to barriers to receiving healthcare such as epilepsy monitoring unit admissions, outpatient care, and delays in surgical therapies for epilepsy. We advise special consideration when treating COVID-19 in the epilepsy population due to potential drug-drug interactions.

Compliance with Ethical Standards

Conflict of Interest
Brigitte Reina, Michael L. Fitzpatrick, and George W. Culler declare that they have no potential conflicts of interest. Barbara C. Jobst has no conflicts of interest related to the topic discussed in this review.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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