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Review

SARS-CoV-2 infection and seizures: the perfect storm

Carolyn Tsai[1], Susan E. Wilson[1], Clio Rubinos[1,*]

[1]Department of Neurology, University of North Carolina, Chapel Hill, NC 27599-7025, USA
*Correspondence: crubinos@unc.edu (Clio Rubinos)

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Abstract

Seizures have been increasingly identified as a neurologic manifestation of coronavirus disease 2019 (COVID-19) infection. They may be symptomatic due to systemic infections, as a result of direct central nervous system (CNS) invasion, or occur in response to inflammatory reactions to the virus. It is possible that proinflammatory molecules released in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to hyperexcitability and epileptogenesis, similar to infections caused by other neurotrophic viruses. Cerebral spinal fluid (CSF) in patients with COVID-19 and seizures is negative for SARS-CoV-2 (PCR) in the majority of patients, but has been found to be positive for proinflammatory molecules like IL-6, IL-8, and anti-neuronal autoantibodies. Electroencephalogram (EEG) in COVID-19 patients are nonspecific. However, in the encephalopathic and critically ill subpopulation, EEG is essential in detecting nonconvulsive seizures and status epilepticus which is associated with increased overall mortality in COVID-19 patients. Thus, as encephalopathy is often the only CNS symptom evidenced in patients with nonconvulsive seizures, more judicious use of continuous EEG in encephalopathic COVID-19 patients should be considered. This would facilitate earlier detection and treatment of seizures in this population, which would ultimately improve outcomes. Further research into the onset and potential for development of seizures and epilepsy in patients with COVID-19 is needed.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Seizures; Status epilepticus; EEG

1. Introduction — SARS-CoV-2 and other coronaviruses

In December 2019 a new strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, China [1]. This new virus caused coronavirus disease 2019 (COVID-19), which has been associated with a wide spectrum of symptoms, ranging from mild upper respiratory tract infection to life-threatening pneumonia and acute respiratory distress syndrome [2]. In March 2021, the World Health Organization declared the coronavirus outbreak a pandemic, and as of October 2021, there have been over 200 million identified cases worldwide, resulting in over 4 million deaths [3].

SARS-CoV-2 is part of the coronavirus family, Coronaviridae. Like other coronaviruses, it is a positive single-stranded RNA virus of zoonotic origins; however, it is a strain with the capabilities to infect humans and can be categorized along with severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) [4]. The virus internalizes into host cells by binding its spike protein to angiotensin-converting enzyme 2 (ACE2) receptors [1,2,4]. In addition to being found in the nasal and oral mucosa, lung, gastrointestinal organs, and kidney, ACE2 receptors are found in astrocytes, oligodendrocytes, and neurons, and are widely expressed throughout the brain, in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb [1]. Therefore, SARS-CoV-2 has the potential to infect the brain via the olfactory epithelium, cribiform plate, vagus nerve, blood brain barrier, or cerebrospinal fluid.

The most common symptoms of COVID-19 are those associated with pneumonia; however, as the virus has become more widespread, central nervous system (CNS) manifestations were increasingly identified. In Wuhan, a study of 214 COVID-19 patients showed that 36.4% developed neurologic manifestations [5]. CNS manifestations of COVID-19 noted in the literature include headache, dizziness, ataxia, impaired consciousness and encephalopathy, agitation, delirium, hypogeusia and hyposmia, seizures, meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, neuroleptic malignant syndrome, ischemic and hemorrhagic stroke, and neurogenic respiratory failure [1]. In this review, we will discuss the link between SARS-CoV-2 infection and seizures, as well as explore current literature regarding incidence of seizures, cerebrospinal fluid (CSF) abnormalities, and electroencephalographic (EEG) findings in patients with COVID-19.

2. Routes of SARS-CoV-2 CNS invasion

COVID-19 is theorized to potentially affect the central nervous system through multiple mechanisms, including direct neuronal invasion, immune-mediated damage, or a combination of both [6,7]. Direct neuronal invasion mechanisms require crossing of the blood-brain barrier (BBB).

How the virus crosses the BBB is unknown, although it is theorized that it could enter via either of two pathways: retrograde axonal transport in the cribriform plate or systemic viremia [1,8]. The first route is supported by evidence that 33.9 to 68% of patients with COVID-19 have olfactory dysfunction [9]. However, a study of anosmic COVID-19 patients demonstrated that only 3 out of 51 patients (6%) with altered olfactory or gustatory functions had positive SARS-CoV-2 PCR in CSF, suggesting that altered olfactory or gustatory function is unlikely to be related to systemic viral neuroinvasion [10]. The second route, occurring after dissemination of SARS-CoV-2 into the circulatory system, leads to the virus crossing the BBB either through direct invasion or migration through endothelial cells of CNS blood vessels, through tight junctions between endothelial cells, or through a "Trojan horse" strategy, where viruses are engulfed by neutrophils or macrophages crossing the BBB [8].

Immune-mediated mechanisms do not require the virus to cross the BBB. Instead, the neuronal damage is done by the body's own immune cells. Infection of cells with SARS-CoV-2 leads to increased production of cytokines, known as "cytokine storm". Several studies have reported that cytokines such as TNF-α, IFN-γ, IL-6, IL-8, IL-2, IL-4, and IL-10 are widely produced in COVID-19 patients, and that higher levels are associated with more severe disease [11]. Furthermore, elevated levels of IL-6 and IL-8, cytokines that increase BBB permeability, have been found in CSF of COVID-19 patients with neurological symptoms [12]. With this disruption of the BBB, immune cells can cross into the CNS and attack neurons [13]. Thus, even if SARS-CoV-2 itself may not be crossing into the CNS to cause direct neuronal damage, it has been hypothesized that the "cytokine storm" it triggers may result in a neuroinflammatory process that can provoke normal network breakdown and trigger network reorganization predisposing the subject to seizures, and in some cases, development of epilepsy. Although this has not yet been demonstrated in the literature, future studies are needed to support this hypothesis.

3. Seizures and epilepsy in viral infection

Several neurotrophic viruses that cause encephalitis, such as human herpesvirus 6, herpes simplex virus, Eastern equine encephalitis virus, and Japanese encephalitis virus, are not only known to cause acute symptomatic seizures, but also lead to the development of epilepsy in up to 20% of patients [14,15]. Respiratory viruses such as metapneumovirus and respiratory syncytial viruses are associated with neurological complications, with the most frequently reported including encephalitis, seizures, and status epilepticus in patients with severe respiratory illness [16–19]. The common mechanism underlying seizures in these viral infections is the induction of an inflammatory cascade that leads to the release of cytokines [20,21]. These cytokines induce neuronal hyperexcitability through activation of glutamate receptors, such as N-methyl-D-aspartate receptors, which lead to acute symptomatic seizures [15]. The persistent hyperexcitability and the neuronal cell death from the infection itself are thought to cause structural damage, which eventually leads to the development of epilepsy [22]. This has been demonstrated in mouse models of viral infection with Theiler's murine encephalomyelitis virus [23]. Proinflammatory cytokines TNF-α and IL-6, and C3 of the complement system — all parts of the innate immune response to viral infection — were found to play a role in the development of acute seizures. Additionally, mice that had acute seizures were noted to have decreased seizure thresholds when tested two months post infection by trans-corneal electrical stimulation, and 65% of the infected mice were noted to have spontaneous epileptic seizures at seven months post infection [23]. Furthermore, upregulation of pro-inflammatory cytokine IL-1β has been linked to seizures and some forms of epilepsy [24,25]. Additionally, IL-1β was shown to be upregulated and present in significantly higher levels in patients with COVID-19 requiring ICU admission [26]. It has been theorized that cytokine IL-1β plays a role in development of neurological complications of COVID-19 [27]. Although there are no current studies investigating the role of IL-1β in association with COVID-19 and development of epilepsy, given the evidence, it is possible IL-1β could play a role in epileptogenesis after COVID-19.

There are many suggested mechanisms through which COVID-19 induces seizures [28]. It is possible that SARS-CoV-2 may mimic other viruses in its activation of the innate immune system, which contributes to seizures and eventually development of epilepsy. This proposal is supported by case reports of patients with COVID-19 developing immune-mediated encephalitis without evidence of SARS-CoV-2 infection in CSF but with higher cytokine levels in CSF than in serum [29–32]. Given the presence of proinflammatory cytokines in the CSF of patients with COVID-19, SARS-CoV-2 infection has the potential of triggering development of epileptogenesis in the same way other neurotrophic and respiratory viruses do.

4. COVID-19 and seizure incidence

The incidence of seizures in adult patients with COVID-19 varies throughout the literature [33–40]. Early reports demonstrated the prevalence of seizures among hospitalized cohorts with COVID-19 infection ranged between 0.1%–7.9% [5,41,42]. Larger studies such as the Global Consortium Study of Neurologic Dysfunction in COVID-19 and the European Academy of Neurology Neuro-COVID Registry noted a higher incidence of 10% and 8%, respectively [43]. Most of the reported cases were based on clinical seizure activity, since the use of EEG in COVID-19 patients has been limited by resources and concerns regarding contamination of equipment, leading to underdiagnosis of subclinical or electrographic seizures [44].

The incidence of seizures in pediatric patients with COVID-19 has been reported to be around 0.1% [45]. Unlike in adults, seizures in pediatric patients were recognized as the presenting symptom of COVID-19 infection, without concurrent fever or respiratory disease [45]. However, most patients had a prior history of neurological disorders, including epilepsy. Similarly, case reports indicated that COVID-19 may potentiate seizures in children with pre-existing epilepsy [46]. More research into the pediatric COVID-19 population is needed to elucidate early seizure symptomatology.

The etiology of seizures in reported cases of patients with seizures related to COVID-19 infection is often multifactorial. Many patients had comorbidities such as diabetes and kidney disease, aplastic anemia [47], multiorgan failure, acute cerebrovascular events [48,49], electrolyte derangements, hypoxia, history of well-controlled epilepsy [50], history of structural brain injuries [38,51], and acute cerebral edema [35], or received medications that contributed to worsening of critical illness and development of acute symptomatic seizures [52]. We should highlight that a complete seizure workup was not completed in many of these patients [34]. It is possible that COVID-19 infection or post-infection inflammation potentially lowers seizure threshold in patients with pre-existing epilepsy. One example could be the case of a 69-year-old woman that went into status epilepticus after recovery from COVID-19 infection. She was likely suffering from forgetfulness prior to SARS-CoV-2 infection, possibly due to temporal lobe seizures, since outpatient workup showed hippocampal atrophy on MRI [51].

However, there are also reports of adult patients without any history of epilepsy risk factors, normal brain MRI and CSF studies, who present with COVID-19 infection and generalized tonic-clonic seizures [44,53,54]. New onset focal motor seizures and focal status epilepticus were described in two patients with severe COVID-19 infection and encephalopathy, who otherwise had no history of seizures, no seizure risk factors, and no previous history of any neurological diseases [36,39]. Nonconvulsive seizures were noted after COVID-19 infection in a patient without any history of seizures and without brain lesions on MRI [37]. Many patients with severe systemic COVID-19 have changes in their mental status [55,56]. Changes in mental status could be a result of nonconvulsive status epilepticus (NCSE). Proper diagnosis in these cases requires prolonged continuous electroencephalogram (cEEG) monitoring [52]. However, due to disruption of EEG use during the COVID-19 pandemic associated with the risk of cross-contamination, cEEG was not as widely used for these patients [57,58]. Thus, in spite of the fact that there are few case reports of nonconvulsive seizures and NCSE in patients with COVID-19 infection, the actual occurrence of this condition is likely higher than reported, especially in critically ill patients which are known to have a higher incidence of nonconvulsive seizures and NCSE [59–61].

5. CSF findings in patients with COVID-19 and seizures

In the literature, the incidence of patients with COVID-19, seizures, and CSF PCR positive for SARS-CoV-2 is low. Japan reported one of the first cases regarding the association between COVID-19 and seizures. A previously healthy 24-year-old man without a history of mesial temporal sclerosis presented with an one-minute generalized seizure. The patient's CSF was positive for SARS-CoV-2 via PCR, and MRI showed fluid-attenuated inversion recovery signal in the right mesial temporal lobe [40]. This case suggested the possibility of direct viral neuroinvasion leading to encephalitis, as well as subsequent structural changes leading to epilepsy.

A systematic review of 69 patients with seizures in the setting of COVID-19 who underwent CSF testing showed that only 13% had positive CSF SARS-CoV-2 PCR [62]. Hence detection of SARS-CoV-2 in CSF of patients with seizures is uncommon, and seizures in patients with COVID-19 are unlikely to be due to direct viral invasion of the brain [62]. This may lend additional support to the theory that seizures and epileptogenesis in patients with COVID-19 may occur because of neuroinflammatory reactions to the virus rather than direct CNS invasion. One study examining 11 critically ill COVID-19 patients with neurologic symptoms reported that all developed anti-neuronal autoantibodies in serum or CSF [63]. While only 1 of 11 patients had epileptic seizures, 6 of 11 had myoclonus, implying that through molecular mimicry, autoantibodies which were created in response to COVID-19 infections have the potential to cause neurological symptoms of hyperexcitability, such as seizures [63].

6. EEG findings in patients with COVID-19

The EEG findings in patients with COVID-19 range from single case reports to larger studies [6,37,44,64]. A systematic review of EEG findings in 617 patients with COVID-19 from 84 reports showed that the most common background abnormalities were diffuse slowing (68.6%) followed by focal slowing (17%) [65]. Periodic and rhythmic patterns were seen in 14.3% of the patients, and epileptiform discharges, indicating underlying cortical irritability with predisposition to seizures, were also commonly seen (13%) [65]. In addition, the systematic review reported 12 patients with seizures (1.9%) and 22 cases of status epilepticus (3.6%), however, the authors didn't specify the incidence of convulsive versus nonconvulsive electrographic seizures [65].

Despite the underuse of cEEG during the pandemic, the incidence of NCSE in the critically ill COVID-19 patient has been reported to be up to 5.6% [6,44,66]. In one large multicenter retrospective study of patients with COVID-19 who underwent cEEG, 19 of 197 patients

(9.6%) were found to have nonconvulsive seizures, with 11 (5.6%) diagnosed with NCSE [44]. Epileptiform abnormalities were seen in 96 of 197 (48.75%) patients monitored with cEEG. Another retrospective study of 111 patients hospitalized in a New York hospital with confirmed COVID-19 infection monitored on cEEG reported that epileptogenic findings (epileptiform discharges, periodic discharges, or seizures) were found in 30 of 100 (30%) non-post cardiac arrest patients [6]. Seizures were recorded on EEG in 7 (7%) non-post-cardiac arrest patients and one had NCSE (1%).

Although no head-to-head studies exist comparing the incidence of EEG abnormalities in COVID-19 patients with non-COVID hospitalized patients, a systematic retrospective study indicates that the incidence may be comparable [67]. cEEG is broadly used in various intensive care units (ICU), and several studies demonstrated higher incidence of seizures in specific populations. A study of 570 patients in the neuroscience ICU monitored with cEEG indicated 110 (19%) had electrographic seizures, with 101 of 110 (92%) exclusively nonconvulsive [68]. A similar study of 154 patients in the surgical ICU found that 24 (16%) had nonconvulsive seizures and 45 (29%) had periodic epileptiform discharges [69]. Among patients in the medical ICU, a study of 201 patients noted 21 (10%) had epileptic seizures and 34 (17%) had periodic epileptiform discharges [60]. These studies indicate that the incidence of seizures in the critically ill population (10–19%) is slightly higher than that reported in the COVID-19 patient population (5.5%) [60,65,68,69]. However, given that the use of cEEG on encephalopathic COVID-19 patients was limited during the pandemic, it is possible that the currently reported incidence of seizures in COVID-19 patients is grossly underreported.

In COVID-19 patients, studies reported EEG abnormalities over frontal areas such as bifrontal slowing, frontal intermittent rhythmic delta activity, and periodic discharges, which could support a hypothesis that there could be an EEG biomarker for detection of COVID-19 neuroinvasion via the nasal mucosa [66,70–73]. Similarly, several studies that reported seizures revealed a frontal onset or status epilepticus over frontal regions [37,64,73,74]. In fact, almost 50% of all reported focal slowing and status epilepticus cases arose from the frontal regions [65]. These frontal EEG abnormalities may indicate an acute neurological process associated with SARS-CoV-2 infection, similar to Herpes simplex encephalitis, which demonstrates anatomo-electrophysiological correlation with temporal/frontal EEG abnormalities. Frontal EEG findings in combination with the commonly reported symptom of anosmia and frontal lobe hypometabolism seen on brain imaging, may support the hypothesis of SARS-CoV-2 neuroinvasion through the olfactory pathway [70,75]. However, since this hypothesis is not supported by CSF SARS-CoV-2 findings, it is possible other undiscovered mechanisms lead to frontal lobe hypometabolism and frontal EEG findings in COVID-19 patients. Future investigations into this area are needed.

The incidence of electrographic seizures has been shown to be associated with increased overall mortality in patients with COVID-19 [44]. This finding correlates with previous studies showing an association between the incidence of electrographic seizures and NCSE with worse outcomes in the critically ill patient population [44,66]. For this reason, the American Clinical Neurophysiology Society (ACNS) consensus guidelines recommend that cEEG be used to identify nonconvulsive seizures and NCSE in critically ill patients with fluctuating mental status or unexplained alteration of mental status without known acute brain injury [76]. As electrographic seizures most commonly occur in severe systemic disease, their presence could be a marker of severe COVID-19 [44]. Overall, while most EEG findings have been nonspecific, nonconvulsive seizures, NCSE, and epileptiform abnormalities were not uncommon in encephalopathic COVID-19 patients. Thus, cEEG should be considered in encephalopathic COVID-19 patients to guide the delivery of tailored treatment strategies and decrease morbidity and mortality [77].

7. Conclusions

Similar to other neurotrophic and respiratory viruses, SARS-CoV-2 can induce damage to the CNS through either direct neuro invasion or immune-mediated mechanisms, or a combination of both. Given the increasing incidence of SARS-CoV-2 variants despite the availability of multiple vaccines, it is likely that the incidence of COVID-19 will continue to increase, and with it, the incidence of seizures. The incidence of seizures may be currently underreported due to the limited availability of cEEG due to contamination concerns. Despite the underuse of cEEG in COVID-19 patients, multicenter studies indicate that the incidence of NCSE is not minimal, and a low threshold for cEEG monitoring in the encephalopathic COVID-19 patient population should be maintained. The chronic effects of COVID-19 infection are still unknown. Given that the immune reaction it induces bears some similarity to that of other epilepsy-related neurotrophic viruses, the possibility to generate epileptogenesis exists. Thus, further aggressive identification with early application of cEEG for encephalopathic patients with COVID-19 and long-term investigation into the population of patients with COVID-19 and seizures is necessary.

Abbreviations

CNS, central nervous system; CSF, cerebral spinal fluid; EEG, electroencephalogram; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, caused coronavirus disease 2019; ACE, angiotensin-converting enzyme 2; cEEG, continuous Electroencephalogram; NCSE, nonconvulsive status epilepticus.

Author contributions

CT and CR contributed to the drafting, editing, and proofreading of this paper. SW contributed to proofreading of this paper.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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