Epilepsy and COVID 2021

Ignacio Valencia, MD1*, Anne T. Berg, PhD2,3, Lawrence J. Hirsch, MD4, Maria Raquel Lopez, MD5, Kara Melmed, MD6, Jillian L. Rosengard, MD7, William O. Tatum, IV DO8, and Barbara C. Jobst, MD9

1 Section of Neurology, Department of Pediatrics, Drexel University College of Medicine, St. Christopher’s Hospital for Children, Philadelphia, PA, USA
2 COMBINEDBrain, Brentwood, TN, USA
3 Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
4 Comprehensive Epilepsy Center, Department of Neurology, Yale University School of Medicine, New Haven CT, USA
5 Department of Neurology, Epilepsy Division University of Miami Miller School of Medicine, Miami, FL, USA
6 Departments of Neurology and Neurosurgery, Division of Neurocritical Care, NYU Langone Medical Center, New York, NY, USA
7 Saul R. Korey Department of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA
8 Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
9 Geisel School of Medicine at Dartmouth Health, Hanover, NH, USA
*Correspondence: Ignacio Valencia, MD, Section of Neurology, Department of Pediatrics, Drexel University College of Medicine, St. Christopher’s Hospital for Children, Philadelphia, PA 19134, USA. Email: Ignacio.valencia@towerhealth.org

Abstract
Coronavirus 19 (COVID-19) has infected over 400 million people worldwide. Although COVID-19 causes predominantly respiratory symptoms, it can affect other organs including the brain, producing neurological symptoms. People with epilepsy (PWE) have been particularly impacted during the pandemic with decreased access to care, increased stress, and worsening seizures in up to 22% of them probably due to multiple factors. COVID-19 vaccines were produced in a record short time and have yielded outstanding protection with very rare serious side effects. Studies have found that COVID-19 vaccination does not increase seizures in the majority of PWE. COVID-19 does not produce a pathognomonic EEG or seizure phenotype, but rather 1 that can be seen in other types of encephalopathy. COVID-19 infection and its complications can lead to seizures, status epilepticus and post-COVID inflammatory syndrome with potential multi-organ damage in people without pre-existing epilepsy. The lack of access to care during the pandemic has forced patients and doctors to rapidly implement telemedicine. The use of phone videos and smart telemedicine are helping to treat patients during this pandemic and are becoming standard of care. Investment in infrastructure is important to make sure patients can have access to care even during a pandemic.

Keywords
COVID, seizures, epilepsy, vaccine, telemedicine

Introduction
On 3/11/2020 the World Health Organization declared that the SARS-CoV-2 virus outbreak constituted a pandemic. COVID-19 caused devastation with human loss and suffering and disrupted clinical management and research of People with epilepsy (PWE) and forced reconceptualization and modification of global practice models.1 Although Coronavirus 19 (COVID-19 disease caused by SARS-CoV-2 virus) is a predominantly respiratory illness, it is...
now clear that it can be associated with a range of acute and prolonged neurological involvement in more than 30% of patients. For PWE, concerns about seizure control, stress, and access to care have been at the forefront.

This review is a report from the Hot Topics symposium delivered at the American Epilepsy Society Meeting in December 2021. It discusses the current status of the pandemic and its impact on PWE. Speakers covered patient perspectives during COVID, vaccine myths and the realities, emerging technologies that improve patients’ access to necessary care, and how to navigate these challenging times.

**The pandemic’s effect on PWE**

**Jillian L. Rosengard, MD**

The pandemic can affect PWE by direct effect of the viral infection on seizure control and by the consequences of broad societal changes related to the pandemic. Several studies, mostly cross-sectional questionnaires, found that 8.6–22.8% of PWE experienced worsened seizure control as a result of the pandemic’s broad societal impacts.3-6

A study during the initial surge in Spring of 20203 found that 17.5% of PWE who reported worsened seizure control during the pandemic’s first peak had significantly more seizures at baseline compared to their counterparts who remained stable or improved. This echoes findings from China and Italy, which also demonstrated that subjects who experienced increased seizures were significantly more likely to have poorly controlled seizures at baseline and require a greater number of antiseizure medications.4,5

The relationship between stress in general and seizure frequency has been studied extensively. Stress is the most common patient-reported seizure precipitant in many studies, and prospective seizure diary studies have demonstrated that patients have more frequent seizures during times of increased stress.7-9 Subjects with worsening seizures during the initial COVID-19 surge were also significantly more likely to report that stress was a typical seizure trigger and that they had increased stress related to the pandemic.3 Similarly, among the 8.6% of subjects who reported increased seizures in an early study from Wuhan, China, at least moderate worry about the impact of the pandemic on seizure-related issues was a risk factor for deterioration.4

A study performed in February, 2020 in China demonstrated that PWE had significantly higher rates of severe psychological distress (33% vs 4% of healthy controls, using the 6-item Kessler Psychological Distress Scale), with drug-resistant epilepsy being an independent predictive factor.10 The recent ILAE special report on epilepsy care during the COVID-19 pandemic was distributed in May through September 2020 and offered in 11 languages provided a global perspective later in the pandemic.6 More than 57% of respondents met criteria for severe psychological distress. Although exact comparisons are unavailable, this is more than 4 times as high as the 14% reported in a National Health Interview Survey of adults with active epilepsy that was conducted in 2010-2017.6,11

Lastly, limited access to epilepsy care was significantly associated with seizure worsening across studies. Specific barriers included trouble reaching the neurologist and difficulty obtaining anti-seizure medications, which were reported by 19-40% of patients across studies.3,5,6 In a survey of the American Epilepsy Society membership, respondents (79% of whom were physicians and 80% from US) identified many pandemic-related potential barriers to care, particularly financial stressors, healthcare closures/restrictions in elective care, and fear related to the pandemic.12 However, less than 10% of respondents selected lack of access to anti-seizure medications as an obstacle, suggesting a disconnect between providers’ perceptions and our patients’ experiences.

In conclusion, factors consistently associated with increased seizures during the pandemic are poorly controlled seizures at baseline, increased stress, and impeded access to care. As this pandemic is ongoing, we should proactively ask our patients with epilepsy about their stress related to the pandemic and recommend treatment and self-management tools accordingly. Though barriers to care have hopefully been alleviated by the advent of telehealth and lifted restrictions, new variants could intensify this problem again.

**Vaccination controversies and COVID**

**Anne T. Berg, PhD**

Vaccinations have been controversial since they were first introduced over 2 centuries ago; they remain so. This is despite the overwhelming evidence regarding the safety of modern vaccines and their effectiveness - measurable on the population level - in preventing illnesses, their consequences, and mortality. COVID-19 vaccinations were produced and given emergency approval in an astonishingly short time. Their safety has been demonstrated in surveillance studies that include millions of individuals.13-15 The largest and most consistent signals for vaccine-related serious adverse events (SAE) have been for thromboembolism (estimated to affect 7/1 000 000 vaccinated people13) and myocarditis or pericarditis primarily in young males and particularly after a second dose.13-15 The estimates of excess cases in this highest risk situation run from about 20 to 150 per million vaccine doses. Cases were almost all, of mild to moderate severity, although 1 death from fulminate myocarditis was reported out of over 10, 000, 000 people vaccinated across 3 studies. The protection conferred by vaccination is not absolute; people may still be infected, and our understanding is evolving as new strains appear. The severity of the disease, however, appears to be much less in vaccinated individuals. By comparison the risks associated with an active COVID infection include serious illness requiring hospitalization, ICU admission, a large range of autoimmune manifestations, and death. CDC estimates through early January, 2022 are that approximately 2500 deaths per 1 000 000 US residents (infected or not) have been attributed to COVID since the start of the pandemic.16 This is more than an order of magnitude greater than the highest estimates of SAEs
(specifically, myocarditis in young males) from vaccination. For survivors, the long-term consequences of COVID infections are just becoming evident as data come in. Neurological manifestations occur in up to a third of patients 6-months after discharge for COVID hospitalization. Long-term autoimmune disorders, including diabetes, Kawasaki-like disease, and others are now being studied as potential consequences of infection. These are most common in younger individuals who have generally been thought to be at lower risk of severe disease from COVID; the lesser severity of acute disease may be counterbalanced by longer-term complications.

For PWE, there are further considerations. On average, there is a somewhat higher burden of medical morbidities in PWE that may place them at greater risk of serious disease if infected. This is something to address on an individual level, but as a general concern, it needs consideration. In children with pre-existing neurological conditions, including epilepsy, COVID infections may be associated with a greater likelihood of ICU admission; of those admitted, pre-existing neurological conditions are associated with a greater likelihood intubation, additional neurological complications, and death. Medications used to treat COVID infections and antiseizure medications may interfere with each other thus posing special pharmacologic considerations for such patients. The longer-term residua of COVID infections include depression, anxiety, and memory complaints, concerns that are already more prevalent in PWE than in the general population.

For some individual patients with rare, severe forms of epilepsy, such as Dravet syndrome, a history of severe seizures following vaccination may alter the risk-benefit equation. The same, however, is true of natural illness. On balance, patients with Dravet syndrome do not have a worrisome response to vaccination. Larger studies have found no evidence suggesting worsening of seizures after vaccination.

People with epilepsy have a greater risk of harm than the general population if infected by SARS-CoV-2 and thus an even greater incentive to avoid infection. Vaccines are effective in preventing and modifying severity of COVID-19 disease and should, as a general policy, be recommended for PWE unless there are specific considerations that modify the risk-benefit analysis for a given individual.

Is there a specific EEG signature of COVID-19?

Lawrence J. Hirsch, MD

There are multiple published series of EEG findings in patients with COVID-19; these findings include diffuse slowing in the majority of patients and epileptiform changes in up to half of patients undergoing prolonged EEG recordings. Epileptiform patterns are often frontally predominant (not specific to COVID), and not uncommonly in the form of generalized periodic discharges (also non-specific). Periodic discharges were seen even in patients with no other explanation for them (pure “COVID-19 related encephalopathy”). Electrographic seizures are less common (10% with prolonged EEG recordings), but certainly not rare. Focal findings are usually explained by strokes or pre-existing abnormalities. Given that seizures and periodic discharges are at least as common in non-COVID patients with sepsis-associated encephalopathy (electrographic seizures in 11% and periodic discharges in 25% in a prospective series of 100 patients) it is difficult to argue that COVID-19 itself commonly causes these findings; it is usually simply the critical illness, possibly related to cytokines and neuroinflammation.

Electrographic seizures are independent predictors of inhospital mortality in COVID-19 patients, and epileptiform abnormalities are strong predictors of a prolonged hospital stay. An alpha coma EEG pattern appears to be over-represented, seen in 5 of 19 patients with severe COVID-19 in one series, perhaps related to brainstem involvement.

In summary, epileptiform discharges and electrographic seizures are common in patients with severe COVID-19, as is true in all forms of severe infectious illness with encephalopathy. Alpha coma may be more common in the setting of severe COVID-19. However, there is no known specific EEG signature of COVID-19. Seizures and epileptiform discharges are independent predictors of longer hospital stays and mortality in patients with COVID-19.

Post-COVID Inflammatory Syndrome with Refractory Status Epilepticus

Kara Melmed, MD

Features relevant to COVID-19 such as high fevers, hypoxia, metabolic derangements and stroke increase the risk of seizures and status epilepticus. Treatment should follow standard regimens, taking into account possible drug-to-drug interactions between antiviral treatments and anti-seizure medications as well as the respiratory depressive effects of benzodiazepines in patients already susceptible to hypoxia. A subset of patients with COVID-19 experience status epilepticus without apparent provocation. It typically has a delayed onset from recovery from the acute COVID-19 infection, results in more severe status epilepticus and exhibits a worse response to treatment. Plausible mechanisms that might contribute to delayed status epilepticus include viral invasion of the central nervous system (CNS), a coincidental presentation, or a third underlying condition that could explain both, such as a SARS-CoV-2-induced systemic inflammatory response. The direct viral invasion theory is less supported. In a systematic review of CSF results in published cases of COVID-19 who had seizures, only 13% of patients had a positive CSF SARS-CoV-2 PCR and only 2 patients had evidence of intrathecal antibody synthesis. SARS-CoV-2-induced systemic inflammatory response, or post-COVID syndrome encompasses symptoms related to residual inflammation, organ damage, and the sequelae of prolonged ventilation and/or hospitalization. In some patients, however, immune dysregulation, allows an influx of pathogenic inflammatory cells and ultimately results in elevated levels of
cytokines. This “cytokine storm” and the prolonged inflammation has a key role in the pathogenesis of post-COVID syndrome.

Neurologic examples of post–COVID-19 inflammatory syndromes include Guillain-Barre syndrome, acute disseminated encephalomyelitis, and multisystem inflammatory syndrome (MIS). MIS among adults (MIS-A) results from low antibody levels resulting in prolonged infection, abnormal immune responses resulting in increased inflammation and the added hyperinflammation due to age-induced imbalances between antiviral and proinflammatory responses.37 Incidence of MIS-A is unknown; it is difficult to distinguish from biphasic acute COVID-19 and post-infectious sequelae. In 1 systemic review of 221 patients with MIS-A most patients were young, male, and either non-Hispanic Black or Hispanic persons.36 The majority had symptomatic illness and recovery prior to presentation with fever, hypotension, or cardiac dysfunction, and almost all had elevated markers of coagulopathy and/or inflammation such as D-dimer and lymphopenia. Patients with MIS-A were critically ill and while most required ICU care, only 7% died.

There are many case reports of patients with delayed presentation of seizures in patients with post-COVID syndrome/MIS-A. In patients with delayed neurological complications, many have elevated serum inflammatory markers and CSF protein, IgG, IgG synthesis rate, IgG index, albumin, and albumin index.38 One case report described a patient who exhibited refractory status epilepticus as a result of a delayed and poorly regulated immune response and eventually responded to immunotherapy.39

Though the epidemiology, range of presentations, pathophysiology, and ideal treatment of postinfectious inflammatory response to COVID-19 remains unknown, patients with MIS have been shown to respond to IVIG and pulse dose steroids and 1 might consider similar treatment in patients with ongoing seizures following COVID-19 infection.

**Phone videos provide an emergency solution for diagnosing seizures during COVID**

M. Raquel Lopez, MD, FAES.

Video-EEG monitoring is the gold standard to obtain a definitive diagnosis of epileptic and non-epileptic events. During the current COVID-19 pandemic, access to all EEG services for PWE was highly limited. The use of home videos has been suggested in the past40 and recently their use provided Class II evidence for diagnostic value in PWE and higher sensitivity to predict nonepileptic seizures.41

Smartphone videos are convenient, cost effective and easy to upload into the electronic medical record. The overall video diagnostic accuracy ranges between 88%42,43 to 100%44 compared to history and physical examination alone.45 Semiology features such as motor findings increase accuracy in the diagnosis of seizures,43,46-48 and convulsive events are especially useful to increase predictability and accuracy.41

Smartphone videos have limitations. The family may feel overwhelmed, seizures may be short, onset of the seizure may not be captured and there may be inadequate resolution. However, the literature supports their use as a powerful extension of the history,44 and helping in the classification of seizure type.40,49 It is time to implement them as a health tool to triage care, facilitate diagnosis and provide expert opinion at lower cost.

**“Smart” Tele-Epilepsy: Living in the New Age**

William O. Tatum IV, DO, FAES

Catapulted into action by COVID-19, the face of health care delivery was changed forever. Epilepsy management became a particular challenge and forced new ways to care for patients. Connectivity with cyberspace for virtual consultation, conferences, and education increased to expedite care and increase access. In addition, it improved health outcomes, reduced patient travel, limited missed workdays, and saved costs of overnight lodging. Access to video EEG monitoring worsened beyond pre-existing limitations during COVID-19 as monitoring units went on lock-down world-wide. The age of technology flourished with texting, tweeting, surfing the web, and online shopping during social distancing. Broad band mobile devices, networks and wearables collecting near real-time high-resolution large datasets helped to remotely monitor behavior. Smartphones became the new tele-tool.50 Quality issues of interpretation proved operational and user dependent despite high technology. Personal electronic devices became “digital hypodermic needles” and are products engineered to be addictive. Use of home video game became a prescription product for children 8 to 12 years old. Health care professionals believe data that patients collect using personal electronic devices and smartphone applications impacts clinical practice. Seizure detection devices now include EEG, heart rate, electrodermal activity, motion detection, and electromyography employing miniaturized computer microprocessors with wearables proven effective for accurate detection of convulsive seizures.51 Patient-specific digital phenotypes and ictal time-evolution patterns are identifiable for focal seizures. Reproducible patterns of evolution resulted in high-performance algorithms and potentially more precise and customizable ways to optimize focal seizure detection.

Groups are evaluating wearable devices in treatment of depression, epilepsy, and other neurological diseases. Others are in search of non-invasive wearable biosensors to forecast seizure probability.52 “Smart tele-treatment” continues with deep brain stimulation and responsive neurostimulation and multi-modal brain monitoring combining detection and treatment. Smart seizure monitoring with new sub-scalp EEG recording devices and audio visual systems based on artificial intelligence are emerging that promise high sensitivity detection with minimal false positive detection. The ability to classify EEG and seizures using software algorithms and supervised machine learning is complete with cloud storage of data for remote access. Future implications for epilepsy populations vulnerability to sudden unexplained death in epilepsy remains to be seen. For people diagnosed with functional seizures video telehealth cognitive behavioral therapy and tele-neuropsychology have gained evidentiary support.
Despite advances, Americans are now less happy by 2018 standards than a decade prior. To move forward post-pandemic, we will need to ensure adequate resources are available to provide public health support of billing and infrastructure to ensure the new age of smart tele-epilepsy is fully incorporated into best practices for patients.

Conclusions

There is no doubt that the COVID-19 pandemic has changed the lives of PWE and the way we practice medicine. Mankind has always found its way through different world-crisis, including the much larger Spanish flu pandemic from 1918. Through resiliency, creativity, collaboration, and leadership we make changes and adapt to new circumstances. We learn from our current experiences, making progress and scientific advance along the way. It makes us better equipped to react quickly in case of a new event of this type. The development of new technologies will help us care for patients, even through difficult times.

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ORCID iDs

Ignacio Valencia https://orcid.org/0000-0003-2385-4933
Lawrence J. Hirsch https://orcid.org/0000-0002-6333-832X
Maria Raquel Lopez https://orcid.org/0000-0003-2421-5682
William O. Tatumb https://orcid.org/0000-0002-4536-3791
Barbara C. Jobst https://orcid.org/0000-0001-9243-2238

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