

Convulsive Status Epilepticus in a Child With Controlled Epilepsy and Concurrent COVID-19 Infection: A Case Report and a Quick Review

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ABSTRACT: The current unprecedented COVID-19 pandemic has been another step toward learning about the unique interaction between viral infections and human nervous system. Very few scientific papers explored neuroinvasive and neurotropic potentials of the SARS-CoV-2 virus in children. We report a child with convulsive status epilepticus and confirmed COVID-19 infection. Brief review of current available literature was discussed.

KEYWORDS: SARS-CoV-2, COVID-19, status epilepticus

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Background

There has been a rapid increase in the number of confirmed cases of SARS-CoV-2 virus, the cause of COVID-19 infection. More than 11 million cases globally and 2.9 million cases in the United States were infected. Children account for approximately 3% of the patients' cohort.¹ There are some published reports describing neurological complications of SARS-CoV-2 infection supporting both its neuro-invasive and neurotropic potential. However, there are limited data to draw final conclusions in the pediatric age group in particular.² Although it is believed that various neurological disorders possibly constitute a higher risk for severe COVID-19 disease such as demyelinating and neuromuscular disorders, studies on epilepsy as an independent risk factor had conflicting results.³ Conclusive evidence that COVID-19 infection directly generates cortical excitability is lacking, but the other associated features of COVID-19 such as high fever, hypoxic insult due to severe respiratory compromise, and multi-organ dysfunction are likely to contribute considerably to seizure pathogenesis in rapidly developing, more vulnerable pediatric brains. We report an 8-year-old child with preexisting, well-controlled epilepsy who developed a breakthrough, unusually prolonged seizure (convulsive status epilepticus) in the context of positive COVID-19 infection.

Case Summary

Our patient is an 8-year-old boy with a partial deletion of the short arm of chromosome 4 (4p16.3), motor and expressive language delays, swallowing dysfunction, and epilepsy since the age of 6 months. His initial seizures were in the form of left sided gaze deviation, head turning to the left, body posturing, and clonic rhythmic left lower extremity shaking progressing

to bilateral tonic clonic seizures, typically for a total duration of less than 1 minute. Clinical seizures were associated with ictal epileptiform activity in the right hemisphere. Thus, he was diagnosed with focal epilepsy with focal to bilateral tonic-clonic seizures of genetic etiology. Prior to this presentation, his seizures had been completely controlled for more than 3 years with levetiracetam at dose of 30 mg/kg/day, divided over 2 times per day, without any breakthrough activity. He had no prodromal symptoms with no fever, respiratory symptoms, or recent change in overall health. He did not have medication compliance concerns or recent medication changes.

He then presented with a sudden unprovoked seizure comprising eye rolling then left sided eye gazing, drooling, and loss of responsiveness, followed quickly by body tonic posturing and bilateral rhythmic clonic shaking of all extremities. Emergency medical service were called. The episode was estimated to last for 20 to 25 minutes without gaining of consciousness. Thus he was thought to have an episode that was consistent with diagnosis of convulsive status epilepticus. His prolonged seizure was managed with an abortive dose of benzodiazepine (2 mg of Lorazepam which was corresponding to 0.1 mg/kg). He then had a loading dose of levetiracetam of 750 mg, which was corresponding to 40/kg). His seizure resolved while getting the Levetiracetam loading. He was then transferred to be closely observed in the pediatric intensive care unit. Further work up included a complete blood count revealed mild leukocytosis with relative neutrophilia. Serum chemistry profile results were normal, and blood and urine cultures were negative. Electroencephalogram study demonstrated a generalized background slowing and intermittent bilateral multifocal epileptiform discharges without evidence of nonconvulsive status epilepticus (Figure 1). Levetiracetam



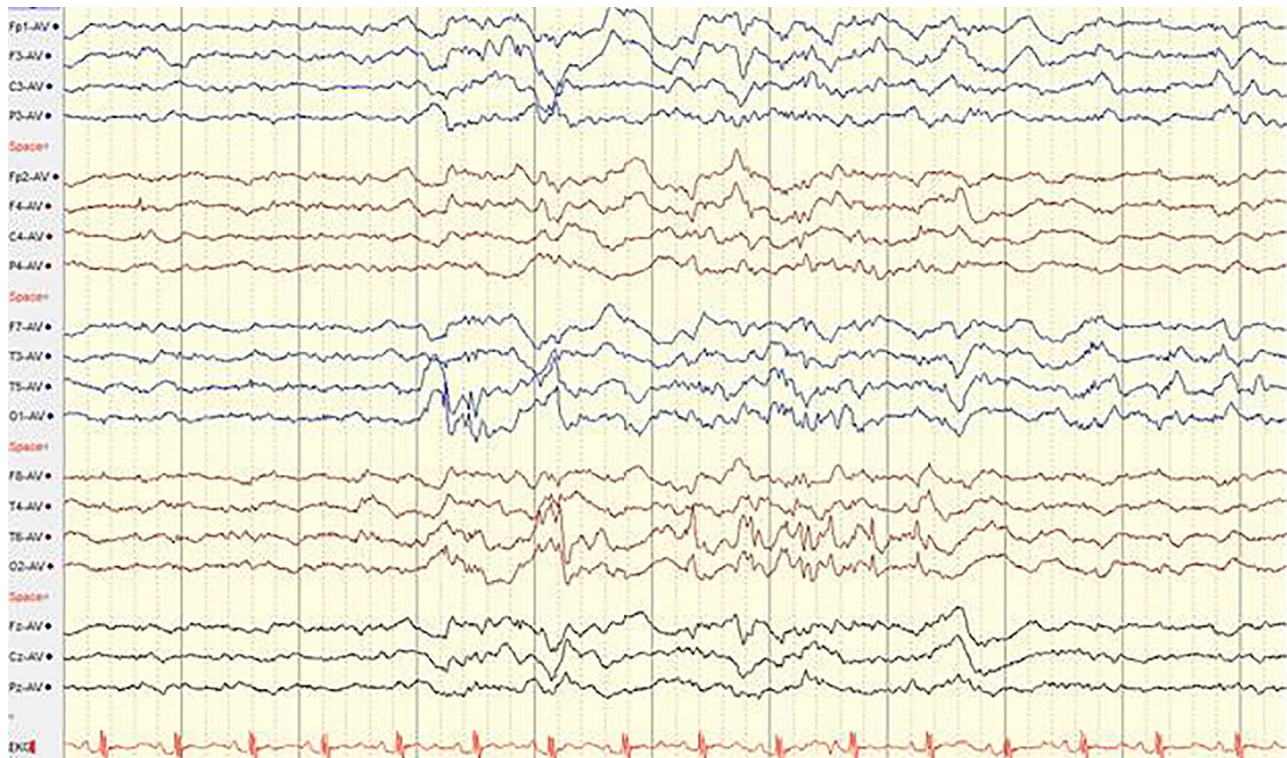


Figure 1. Inter-ictal EEG demonstrating: 1. Independent, bi-posterior irregular spike and wave activity in brief bursts. 2. Diffuse background slowing and moderate disorganization for age. 3. No clinical or electrographic seizures identified.

level drawn prior to loading was found to be sub-therapeutic ($10\ \mu\text{g/ml}$, with reference range of $12\text{--}46\ \mu\text{g/ml}$). COVID-19 screening was positive for SARS-CoV-2 by polymerase chain reaction (PCR) from nasopharyngeal swab specimen. Subsequently, the patient had a largely uncomplicated hospital course. He was discharged next day from the hospital with an adjusted dose of levetiracetam to $40\ \text{mg/kg/day}$ divided twice a day and no specific need for respiratory or systemic support measures. No neuroimaging or cerebrospinal fluid analysis studies were obtained. It was concluded the patient trigger of status epilepticus is possibly partially attributed to his concurrent COVID-19 infection.

Discussion

Many neurological disorders, including, but not limited to, multiple sclerosis, large-vessel stroke, Parkinson's disease, dementia, motor neuron disease, and neuromuscular disorders, are considered high risk factors for severe COVID-19 complications. However, substantial evidence that epilepsy by itself constitutes an independent risk factor for COVID-19 infection complications is currently lacking. A knowledge gap persists in our understanding of the exact pathogenic mechanisms of COVID-19 infection and especially potential neurological sequelae in the pediatric age group. Available data suggest that children tend to have a milder phenotype of COVID-19 infections in general.⁴ However, given the variable presentation of COVID-19, it is plausible that children may not present with typical respiratory symptoms similar to those of adults.⁴ Among the non-respiratory clinical presentations, many patients have

reported both peripheral and central nervous system symptoms, but with seizures being relatively rare.⁵ A rising number of reports have described acute viral encephalitis, infectious toxic encephalopathy, acute ataxia, worsening headaches, and acute cerebrovascular accidents to be the most prevalent acute neurological complications of COVID-19 infection.⁶ Possible nervous system mechanisms of dysfunction include direct brain invasion, hematogenous spread, neuroal migration, secondary hypoxic brain injury, angiotensin converting enzyme dysfunction, autoimmune mediated neurotoxicity, and inflammatory cascade pathways activation.⁶

Few reports of patients with COVID-19 infection presenting with status epilepticus were recently published, almost exclusively in adult population. Moriguchi et al⁷ reported a 24-year old young man who presented with acute SARS-CoV-2 viral encephalitis proven by CSF viral PCR and acute prolonged symptomatic seizures. Sohal and Mossammat⁸ reported a 72-year old patient who developed recurrent tonic seizures on his third day of admission with acute COVID-19 infection. Vollono et al⁹ reported a 78-year old man with pre-existing symptomatic epilepsy secondary to prior HSV encephalitis, who presented with right facial twitching consistent focal status epilepticus needing multiple rounds of anti-seizure medications, who ultimately tested positive for SARS-CoV-2. Somani et al¹⁰ has reported 2 adult patients (49 years and 73 years old) who presented with acute COVID-19 infection and concurrent convulsive status epilepticus without prior history of epilepsy. There was another recent report of a 64-year old who developed non convulsive focal status epilepticus along

with acute respiratory and psychotic symptoms who was found to have acute COVID-19 infection.¹¹ To date, we are only aware of one 11-year-old child who presented with acute SARS-CoV-2 encephalitis and convulsive status epilepticus.¹² However, that patient did have other systemic symptoms including pyrexia, in contrast with our patient.

Pathophysiology of convulsive status epilepticus in the context of acute COVID-19 infection is likely complex and multifactorial. Viral meningoencephalitis infection is one of the most common etiologies for symptomatic acute status epilepticus worldwide with seizure burden being parallel to the degree of brain infection and inflammation.¹³ SARS-CoV-2 has been isolated in CSF of some patients suggestive a potential causative relationship with concomitant meningoencephalitis and associated seizures in both adults and children.^{8,11} An obvious limitation to our reported case is unavailability of CSF evaluation during this presentation. Status epilepticus is also a known possible clinical manifestation of autoimmune encephalopathy disorders with several reports of such phenomena among children and adults who were recently infected with COVID-19 infection.¹⁴ Zanin et al¹⁵ reported a 54 years woman who had status epilepticus and was found to have acute demyelinating encephalomyelitis following an acute COVID-19 infection. Our patient did not have any evolving neurological exam findings to suspect a demyelinating disorder. Nevertheless, and given the lack of an updated neuroimaging, we cannot completely rule out such possibility and constitutes another limitation to our study conclusions. Breakthrough seizures including status epilepticus are observed in some fever sensitive pediatric epilepsy syndromes during acute viral infections such as Dravet syndrome and febrile infection related epilepsy syndrome (FIRES). In a series of 168 children who were hospitalized in Italy for acute COVID-19 infection, 5 children had breakthrough seizures, and out of them 4 children had preexisting epilepsy syndrome.¹⁶ Although our reported patient has an established and likely genetic epilepsy diagnosis, he was not diagnosed with a particular epilepsy syndrome. Neurovascular injury is a postulated as a potential neurological implication of COVID-19 infection and is likely contributing to pathogenesis of status epilepticus in some patients, particularly in adults.¹⁷ Endothelial cells infection, monocyte activation, secondary lymphohistiocytosis, secondary plaques destabilization, and end organ vasculitis are among the possibly involved mechanisms of injury in this context.¹⁸ As stated, our patient did not undergo an updated brain MRI for evaluation of secondary neurovascular injury.

Several metabolic derangements can take place due to both direct and indirect COVID-19 infection. There have been multiple studies of documented multi-organ dysfunction in the setting of acute COVID-19 infection. Hepatic and metabolic dysfunction can alter pharmacokinetics of circulating anti-seizure medications, and thus serve as a potential provoking factor for status epilepticus in susceptible patients. Our reported patient was not noted to have major electrolyte derangements. It is unknown yet

if anti-seizure medications do elevate the risk for controlled or uncontrolled epilepsy patients to have a clinically distinct SARS-CoV-2 infection phenotype. However high dose corticosteroids and other immunomodulatory drugs which are occasionally used for their anti-seizure benefits can result in more severe COVID-19 infection phenotype.¹⁹ Severe or disseminated COVID-19 might then act as a further trigger for worsening or prolonged seizures. Clinicians must also remain aware that there are potential drug-to-drug interactions between some anti-seizure medications and anti-microbial treatments occasionally used off label in management of COVID-19.²⁰ Lastly, it is non debatable that the whole health system has undergone a major shift since the COVID-19 pandemic. Decreased access to primary and specialized care due to patients fears or cancellation of appointments, reduced diagnostic test openings, and delays in dispensing medications have been some of the real life challenges. In fact, possibility of jeopardized epilepsy care quality amid the COVID-19 pandemic and the potential end result of worsening seizure control in some patients is a matter of ongoing discussion.^{21,22} It is unknown if those logistic barriers may contribute to increased incidences of uncontrolled or prolonged seizures in pediatric epilepsy population.

Conclusion

An association between epilepsy and novel SARS-CoV-2 infection might exist, although it is not currently well understood. Our reported patient's status epilepticus might have been precipitated by the concurrent SARS-CoV-2 infection. However with limitations of sub-therapeutic anti-seizure medication level and absence of fever or respiratory symptoms present a challenge in arriving confidently at that conclusion. Nevertheless, we believe our reported patient is a useful addition to the library of potential neurological manifestations of the current COVID-19 pandemic. We posit that SARS-CoV-2 testing be considered in pediatric patients with status epilepticus during the pandemic, given its heterogeneous presentation and lack of respiratory symptoms in several patients. Reports such as ours will be central to improving the understanding of the complex relationship between infectious diseases and neurological dysfunction.

Author Contributions

AMK: Substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SH: Substantial contributions to the drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work

are appropriately investigated and resolved. GK: Substantial contributions to the drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SF: Substantial contributions to the drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent

A parent consented to study publication, provided that name, address, and personal identification info are not publicly published.

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