

# Child Neurology: Hemiconvulsion-Hemiplegia-Epilepsy Syndrome in the Setting of COVID-19 Infection and Multisystem Inflammatory Syndrome

Paul Gong, MD, Cemal Karakas, MD, and Bethanie Morgan, MD

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## Correspondence

Dr. Gong  
paul.gong@louisville.edu

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## Abstract

Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is a rare pediatric epilepsy syndrome characterized by prolonged focal febrile convulsive status epilepticus with unilateral hemispheric cerebral edema, followed by the subsequent development of hemiplegia, global atrophy of the affected hemisphere, and epilepsy. The pathophysiology of HHE syndrome remains poorly understood though is clearly multifactorial. Factors thus far implicated are hyperthermia, proinflammatory state, and cytotoxic edema from prolonged ictal activity. Prognosis is variable, from the resolution of hemiplegia and seizures to permanent hemiparesis and refractory epilepsy. We describe a 2-year-old boy who presented with superrefractory focal status epilepticus in the setting of acute coronavirus infectious disease-2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C). He had right-sided hemiplegia on neurologic examination, and an MRI examination of the brain showed left cerebral hemispheric edema consistent with HHE syndrome. Our case represents the first report in the literature on HHE syndrome in the setting of acute COVID-19 and MIS-C.

## Case Report

### Clinical History

A 2-year-old boy was admitted to our hospital with convulsive status epilepticus (SE). His medical history included a previous complex febrile seizure (CFS), consisting of a febrile right focal motor seizure. Then, the EEG showed delta slowing in the left hemisphere with predominance in the posterior left temporal-parietal region intermixed with sharp waves. An MRI examination of the brain without contrast was normal. He was not started on antiseizure medications (ASMs) and was prescribed rectal diazepam as needed. He was otherwise healthy and met all developmental milestones. A family history was significant for seizures associated with an unspecified brain lesion in the mother. There were no further concerns for seizures until his presentation to our hospital 4 months after his CFS.

On admission to our hospital, his parents reported a right-sided predominant generalized tonic-clonic seizure at home. The time of seizure onset was unclear. His parents found him having a seizure after laying him down for a nap. They administered 7.5 mg of diazepam rectally, but his seizure persisted. He was taken to an outside facility and required intubation for airway protection due to ongoing SE. Multiple doses of 0.1 mg/kg of IV midazolam were necessary to abort the seizure. The duration of SE from the time noted by parents to cessation at the local hospital was approximately 1 hour. On neurologic examination, he had a left gaze preference, right facial weakness, and right-sided hemiplegia. He was subsequently transferred to the pediatric intensive care unit (PICU) in our hospital.

From the Division of Child Neurology (P.G., C.K., B.M.), Department of Neurology, University of Louisville; and Norton Children's Medical Group (C.K., B.M.), Louisville, KY. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

In the PICU, he had clinical and electrographic only seizures refractory to treatment. He received multiple ASM loading doses and required placement on continuous midazolam infusion for 10 days due to persistent seizures over multiple days. He also had a recurrence of SE when attempting to wean the infusion initially. He was treated with high-dose IV methylprednisolone due to findings of worsening cerebral edema and midline shift on repeat MRI of the brain. Seizure frequency decreased after treatment with methylprednisolone, but because the patient was also receiving multiple ASMs concurrently, the effect of methylprednisolone, if any, could not be determined. After weaning off continuous midazolam infusion, he was continued on multiple ASMs (Figure 1). The EEG initially showed focal seizures of the left hemisphere consisting of high-amplitude spike/polyspike and wave discharges. He then had seizures localized to the left posterior quadrant and right posterior quadrant. A sample of the EEG is provided in eFigure 1 ([links.lww.com/WNL/C271](https://links.lww.com/WNL/C271)). After resolution of seizures, the EEG showed decreased background amplitude and frequency of the left hemisphere when compared with that of the right, consisting of polymorphic 0.5–2 Hz delta activity.

### Laboratory Results

He was febrile to 103°F, so was tested for coronavirus infectious disease-2019 (COVID-19). PCR testing showed positive results. Inflammatory markers, including procalcitonin, beta natriuretic peptide, lactate dehydrogenase, ferritin, D-dimer, and C-reactive protein levels, were elevated.

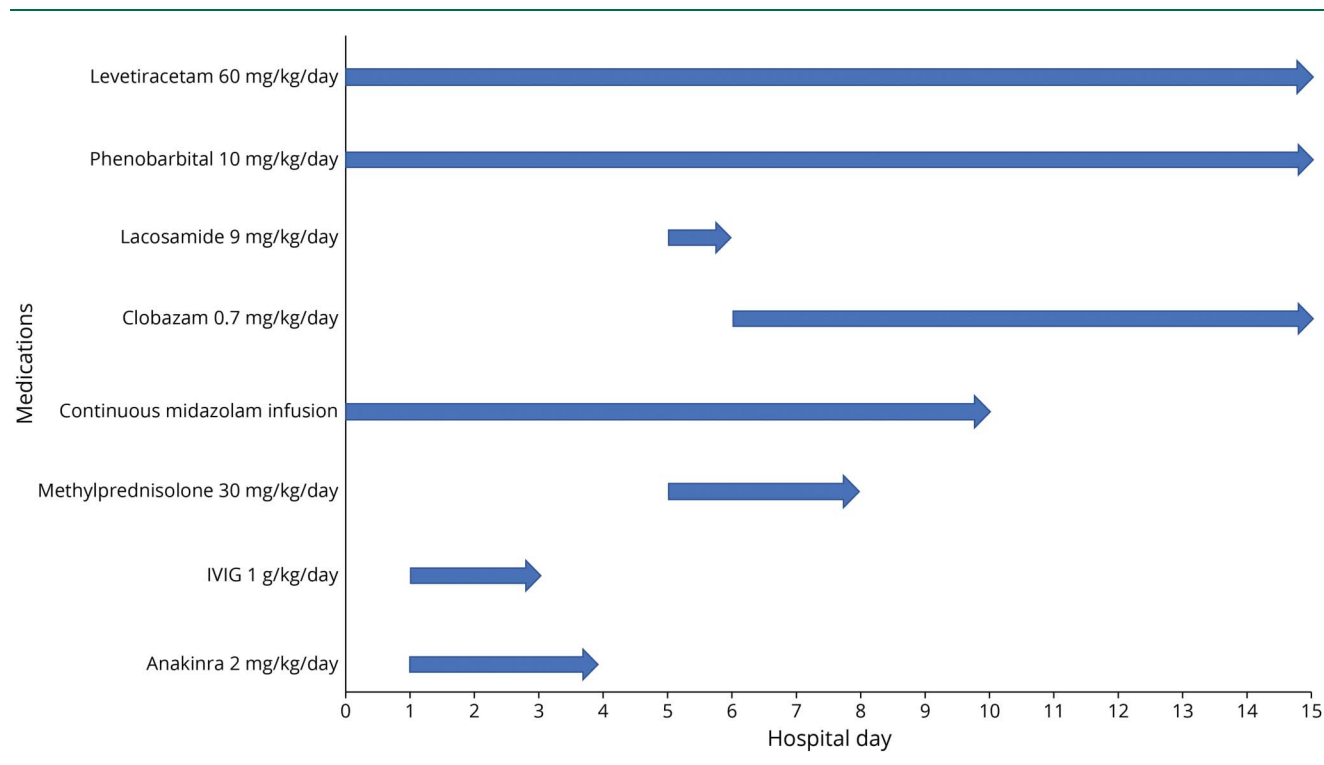
He had elevated transaminases, which gradually normalized, and elevated blood urea nitrogen, concerning for acute kidney injury, which improved over time. Given multiorgan dysfunction with elevated inflammatory markers, his presentation was consistent with multisystem inflammatory syndrome in children (MIS-C). He was treated for MIS-C with IV methylprednisolone, IV immunoglobulin, and anakinra (Figure 1).

Testing for other intercurrent infections showed negative results for pathogens on blood, urine, and CSF cultures. CSF pathogen panel also showed negative results. Additional information about the panel is listed in eTable 1 ([links.lww.com/WNL/C271](https://links.lww.com/WNL/C271)). CSF studies showed no pleocytosis and normal glucose and protein levels. CSF COVID-19 PCR was not tested. An epilepsy gene panel was inconclusive, revealing 3 heterozygous variants of uncertain significance in *CNTN2* (c.1315C>G [p.Pro439Ala], associated with autosomal recessive disease [ARD]), *EHMT1* (c.818A>G [p.Gln273Arg], associated with ARD), and *RELN* (c.10131C>G [p.His3377Gln], associated with ARD) genes. Additional information is listed in eTable 2 in the Supplement. A comparative genomic hybridization analysis showed negative results.

### Neuroimaging Results

3T MRIs of the brain without contrast on hospital day 2, day 5, and day 12 revealed edema in the left cerebral hemisphere, left basal ganglia, left thalamus, left amygdala/hippocampus, and the left subcortical white matter with

**Figure 1** Timeline for Medications Administered During Hospitalization



associated restricted diffusion (Figure 2). Magnetic resonance angiography (MRA) of the brain was normal.

### Follow-up

On a follow-up examination on hospital day 5, gaze preference and facial droop had resolved. The patient had gradual improvement in right-sided motor strength throughout the admission. After transferring out of the PICU on hospital day 17, the patient did not have any further breakthrough seizures. He continued to have improved but persistent right-sided hemiparesis and right-sided spasticity on discharge to acute inpatient rehabilitation on hospital day 32. No further neuroimaging was performed after discharge from the hospital.

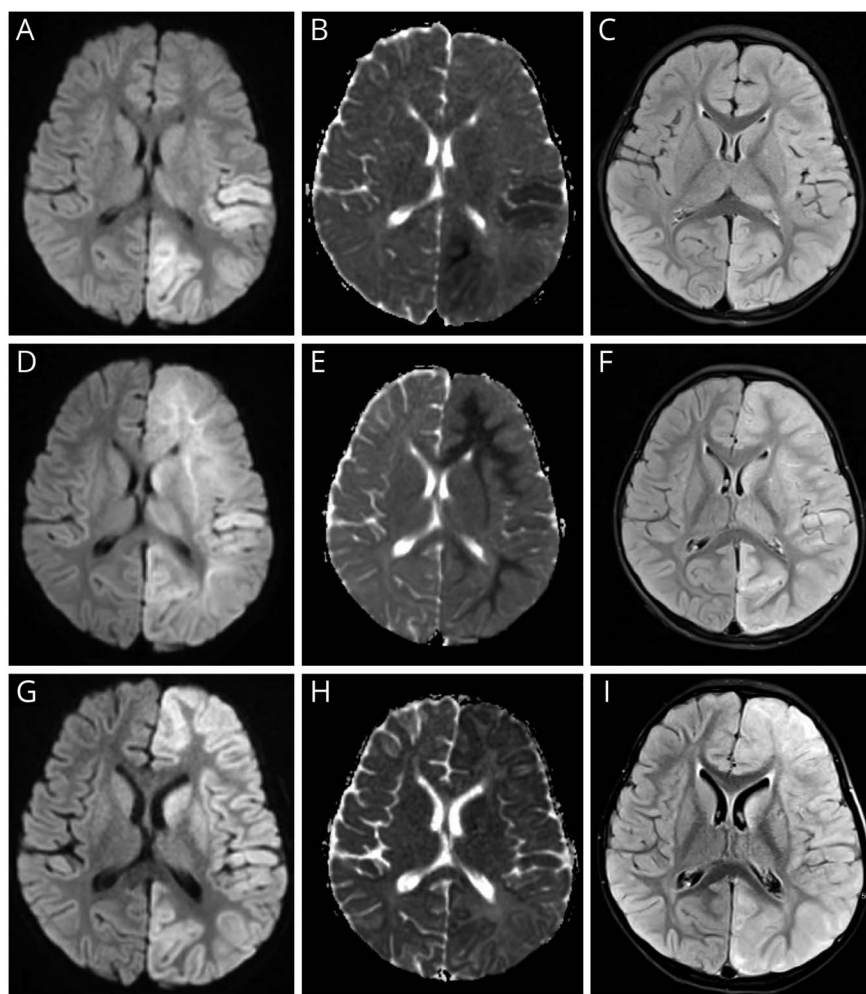
At the 6-month outpatient follow-up visit, the patient had only 1 focal seizure with altered awareness since discharge. He was maintained on levetiracetam, phenobarbital, and clobazam. He was placed on baclofen for right-sided spasticity and referred for outpatient physical and occupational therapies.

## Discussion

Our patient had superrefractory focal febrile SE in the setting of acute, symptomatic COVID-19 and MIS-C. His overall presentation was consistent with hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome.

Although first described by Gastaut and colleagues more than 6 decades ago,<sup>1</sup> the pathophysiology of HHE syndrome remains unclear. Fever and prolonged focal convulsive seizures in children younger than 4 years are typical of the clinical presentation.<sup>2</sup> Children subsequently develop hemiplegia, global atrophy of the affected hemisphere, and epilepsy.<sup>2</sup> Of patients who develop epilepsy, 85% do so within the first 3 years after presentation.<sup>2</sup> Unilateral edematous hemispheric swelling, independent of any vascular territory, is seen during initial SE, and prominent diffusion restriction of the basal ganglia, internal capsule, and thalamus is also seen.<sup>2</sup> Etiology is divided into idiopathic or those associated with an identified predisposing factor.<sup>3</sup> There are case reports of HHE syndrome associated with

**Figure 2** 3T MRIs of the Brain During Hospitalization



3T MRI of the brain on hospital day 2. (A) Restricted diffusion in the left occipital and parietal lobes on DWI; (B) associated decreased signal in the left occipital and parietal lobes on ADC; and (C) T2 prolongation and gyral swelling involving the left occipital and parietal cortices. 3T MRI of the brain on hospital day 5: (D) diffuse edema with restricted diffusion in the left subcortical white matter on DWI; (E) associated decreased signal in the left subcortical white matter on ADC; and (F) T2 prolongation and gyral swelling throughout the left cerebral hemisphere with left to right midline shift. 3T MRI of the brain on hospital day 12: (G) restricted diffusion diffusely throughout the left cerebral hemisphere on DWI; (H) associated decreased signal diffusely throughout the left cerebral hemisphere on ADC; and (I) T2 prolongation and gyral swelling diffusely throughout the left cerebral hemisphere. ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging.

pathogenic genetic variants, for example, CACNA1A<sup>4</sup> and SCN1A,<sup>5</sup> and with structural brain abnormalities, such as focal cortical dysplasia.<sup>6</sup> Our patient had negative genetic testing. His initial MRI of the brain at 2 years of age was normal though, given it was performed without contrast and was not an epilepsy protocol study, underlying focal structural abnormalities cannot be ruled out.

Hyperthermia is a salient feature of HHE clinical presentation, and it has been hypothesized that HHE syndrome represents a severe form of CFS.<sup>2</sup> Febrile seizures are defined as seizures occurring in childhood (typically from 6 months to 5 years of age) associated with a febrile illness and no other acute CNS infection or acute metabolic derangements.<sup>7</sup> CFSs are seizures having a focal onset, occurring more than once during the same febrile illness or lasting longer than 10–15 minutes.<sup>7</sup>

Certain neurotropic viruses, such as human herpesvirus (HHV)-6 and HHV-7, have been postulated as causative agents in CFS and SE.<sup>2</sup> Both were negative in our patient. It is unclear at this time whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has neurotropic properties akin to HHV-6 or HHV-7.

There have been case reports of HHE syndrome associated with coagulation disorders such as protein S deficiency and factor V Leiden mutation.<sup>2</sup> Given the known association of COVID-19 with a hypercoagulable state and development of thrombotic complications,<sup>8</sup> it is possible acute coagulopathy also contributed to the development of HHE syndrome in our patient, although MRA of the brain was normal.

The literature regarding the diverse neurologic complications of acute and postacute COVID-19 infection continues to grow.<sup>9</sup> Several neurologic complications of COVID-19, such as Guillain-Barré syndrome, arterial ischemic stroke, cranial neuropathies, meningoencephalitis, and epilepsy, have been reported.<sup>9</sup> Acute encephalitis with focal neurologic signs, seizures, and EEG abnormalities has also been described in association with MIS-C.<sup>10</sup> A recent case report described a pediatric patient with MIS-C who presented with febrile SE and whose clinical picture was suggestive of febrile infection-related SE.<sup>11</sup>

Given the high prevalence of COVID-19 and the poor understanding of the pathophysiology of HHE syndrome, our case ultimately describes an association of HHE syndrome with COVID-19. Thus, a limitation of the study is that it cannot prove the causative role of COVID-19 in the development of HHE syndrome. It is unclear whether the virus SARS-CoV-2 itself or the secondary immune dysregulation of MIS-C had any causative effect on the development of HHE syndrome in our patient. The HHE syndrome may represent a severe form of CFS, and because

our patient had a previous CFS and previous focal abnormalities on EEG, it is possible he had a predisposing epileptic focus on the affected side despite previous negative MRI of the brain. This may explain the laterality of the seizures in the setting of high fevers triggered by acute COVID-19 and MIS-C and the subsequent unilateral edema of the epileptic hemisphere.

## Conclusion

Our patient represents the first report of HHE syndrome associated with COVID-19 and MIS-C. As the literature has shown an association of HHE syndrome with acute febrile illnesses,<sup>2</sup> infections with SARS-CoV-2 may also contribute as an etiologic trigger for the syndrome. Given the growing literature on neurologic conditions associated with COVID-19, our case adds to the list of possible associations and should prompt clinicians to consider COVID-19 and MIS-C when investigating future cases of HHE syndrome. More research is necessary to improve our understanding of the syndrome, improve recognition of the entity, develop effective treatment strategies for those patients affected, and optimize neurologic outcomes.

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## Disclosure

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## Appendix Authors

Name	Location	Contribution
<b>Paul Gong, MD</b>	Division of Child Neurology, Department of Neurology, University of Louisville, KY	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Cemal Karakas, MD</b>	Division of Child Neurology, Department of Neurology, University of Louisville; Norton Children's Medical Group, Louisville, KY	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
<b>Bethanie Morgan, MD</b>	Division of Child Neurology, Department of Neurology, University of Louisville; Norton Children's Medical Group, Louisville, KY	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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