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

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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 and 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, pro-inflammatory 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 super-refractory 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 neurological examination, and an MRI 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.
1. Case Report

1.1 Clinical History

A 2-year-old boy was admitted to our hospital with convulsive status epilepticus (SE). His past medical history included a prior complex febrile seizure (CFS), consisting of a febrile right focal motor seizure. At that time, EEG showed delta slowing in the left hemisphere with predominance in the posterior left temporal-parietal region intermixed with sharp waves. MRI of the brain without contrast was normal. He was not started on anti-seizure medications (ASMs) and was prescribed rectal diazepam as needed. He was otherwise healthy and met all developmental milestones. 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 four months after his CFS.

On admission to our hospital, 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 diazepam 7.5 mg rectally, but his seizure persisted. He was taken to an outside facility and required intubation for airway protection due to ongoing SE. Multiple IV midazolam 0.1 mg/kg doses were necessary to abort the seizure. The duration of SE from the time noted by parents to cessation at the local hospital was about one hour. On neurological 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.
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 following treatment with methylprednisolone, but since 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). 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 in the Supplement. After resolution of seizures, EEG showed decreased background amplitude and frequency of the left hemisphere compared to the right, consisting of polymorphic 0.5 to 2 Hz delta activity.

1.2 Laboratory results

He was febrile to 103F, so was tested for Coronavirus Infectious Disease-2019 (COVID-19). This was positive on PCR testing. Inflammatory markers, including procalcitonin, beta natriuretic peptide, lactate dehydrogenase, ferritin, D-dimer, and C-reactive protein, were elevated. He had elevated transaminases, which gradually normalized, and had 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 was negative for pathogens on blood, urine, and CSF cultures. CSF pathogen panel was also negative. Additional information about the panel is listed in eTable 1 in the Supplement. 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. Comparative genomic hybridization analysis was negative.

1.3 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 associated restricted diffusion (Figure 2). Magnetic Resonance Angiography (MRA) of the brain was normal.

1.4. Follow up

On 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 upon discharge to acute inpatient rehabilitation on hospital day-32. No further neuroimaging was done after discharge from the hospital.
At the 6-month outpatient follow-up visit, the patient had only one 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 therapy.

2. Discussion

Our patient had super-refractory 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.

Though first described by Gastaut and colleagues over six decades ago, the pathophysiology of HHE syndrome remains unclear. Fever and prolonged focal convulsive seizures in children under four years of age are typical of the clinical presentation. Children subsequently develop hemiplegia, global atrophy of the affected hemisphere, and epilepsy. Of patients who develop epilepsy, 85% do so within the first 3 years after presentation. Unilateral edematous hemispheric swelling, independent of any vascular territory, is seen at the time of initial SE, as well as prominent diffusion restriction of the basal ganglia, internal capsule, and thalamus. Etiology is divided into idiopathic or those associated with an identified predisposing factor. There are case reports of HHE syndrome associated with genetic mutations, e.g., CACNA1A and SCN1A, and with structural brain abnormalities, such as focal cortical dysplasia. Our patient had negative genetic testing. His initial MRI of the brain at 2 years of age was normal though given it was done 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. Febrile seizures are defined as seizures occurring in childhood (typically six months to five years of age) associated with a febrile illness and no other acute CNS infection or acute metabolic derangements. CFSs are seizures having a focal onset, occurring more than once during the same febrile illness, or lasting longer than 10-15 minutes.

Certain neurotropic viruses, such as HHV-6 and HHV-7, have been postulated as causative agents in CFS and SE. Both were negative in our patient. It is unclear at this time whether or not 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. Given the known association of COVID-19 with a hypercoagulable state and development of thrombotic complications, it is possible acute coagulopathy also contributed to the development of HHE syndrome in our patient, though MRA of the brain was normal.

The literature regarding the diverse neurological complications of acute and post-acute COVID-19 infection continues to grow. Several neurological complications of COVID-19, such as Guillain-Barré syndrome, arterial ischemic stroke, cranial neuropathies, meningoencephalitis, and epilepsy, have been reported. Acute encephalitis with focal neurological signs, seizures, and EEG abnormalities has also been described in association with MIS-C. 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.
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 if 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. HHE syndrome may represent a severe form of CFS, and since our patient had a prior CFS and prior focal abnormalities on EEG, it is possible he had a predisposing epileptic focus on the affected side, despite prior 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.

3. 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, infections with SARS-Cov-2 may also contribute as an etiological 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 neurological outcomes.

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References


Figure 1.
Timeline for medications administered during hospitalization

- Levetiracetam 60 mg/kg/day
- Phenobarbital 10 mg/kg/day
- Lacosamide 9 mg/kg/day
- Clobazam 0.7 mg/kg/day
- Continuous midazolam infusion
- Methylprednisolone 30 mg/kg/day
- IVIG 1 g/kg/day
- Anakinra 2 mg/kg/day
Figure 2: 3T MRI of the brain on hospital day 2

(A) restricted diffusion in the left occipital and parietal lobe on DWI; (C) associated decreased signal in the left occipital and parietal lobe on ADC; and (C) T2 prolongation and gyral swelling involving the left occipital and parietal cortex.

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 of the diffusely throughout the left cerebral hemisphere.