



# Idiopathic Hemiconvulsion Hemiplegia Epilepsy in an Eight-Year-Old Boy! Is It the Time to Revisit the HHE Definition?

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Int J Ep

## Abstract

Idiopathic hemiconvulsion hemiplegia epilepsy (IHHE) syndrome is characterized by the combination of unilateral convulsive status epilepticus, mainly clonic, followed by transient or permanent ipsilateral hemiplegia. It occurs in infants during the course of a nonspecific febrile illness, mainly in the first 2 years of life and in any case before the age of 4 years. Most studies have mentioned that disease occurs in children younger than 4 years. The exact cause of unilateral involvement is not clear. Occurrence of this condition beyond 4 years of age has rarely been described. We report here a previously healthy 8-year-old boy who presented with right hemiclonic seizures for almost 2 weeks occurring along with nonspecific viral illness. He had residual right hemiparesis and his magnetic resonance imaging (MRI) of the brain showed left hemispheric cortical edema with diffusion restriction. The workup for neuroinfections, mitochondriopathy, and MR angiography was negative. The child improved with injection methyl prednisolone pulse therapy along with multiple intravenous and oral antiseizure medications. This case report suggests that IHHE can also occur beyond 4 years of age, and there is a need to revise the diagnostic criteria of IHHE.

## Keywords

- ▶ hemi-convulsion hemiplegia epilepsy
- ▶ focal status epilepticus
- ▶ hemiplegia

## Introduction

Hemiconvulsion hemiplegia (HH) syndrome is a rare clinico-radiological condition that is associated with prolonged focal febrile convulsive seizures in infancy and early childhood (<4 years).<sup>1</sup> It is associated with high-grade fever at the time of onset of refractory status epilepticus, and unilaterally abnormal acute imaging, followed by hemiparesis lasting at least 24 hours, and excluding definite infectious encephalitis. Neuroimaging studies showed unilateral edematous swelling of the epileptic hemisphere at presentation. This is then followed by cerebral hemiatrophy with subsequent development of epilepsy. This evolution that

happens over a period of 1 to 3 years is called as hemiconvulsion hemiplegia epilepsy (HHE) syndrome. The seizures that occur tend to originate in the temporal lobe. We here report the case of a child who developed idiopathic HHE (IHHE) at the age of 8 years and discuss some novel insights into the disease.

## Case Report

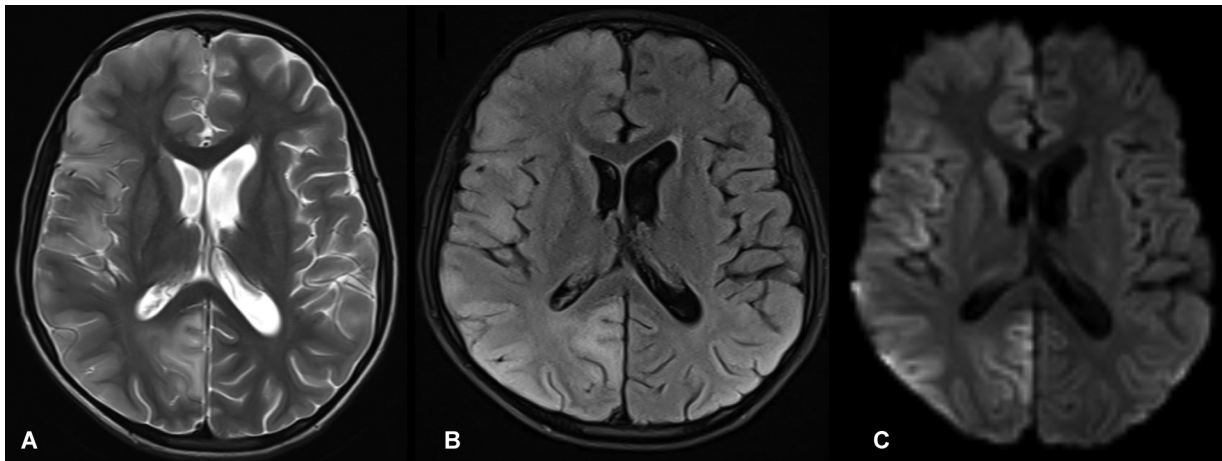
An 8-year-old boy, previously normal, presented with fever, cough, and cold for 4 to 5 days. From the third day onward, he developed recurrent episode of seizures (clonic type) occurring for few minutes to few hours in the left upper and

DOI <https://doi.org/10.1055/s-0044-1787988>.  
ISSN 2213-6320.

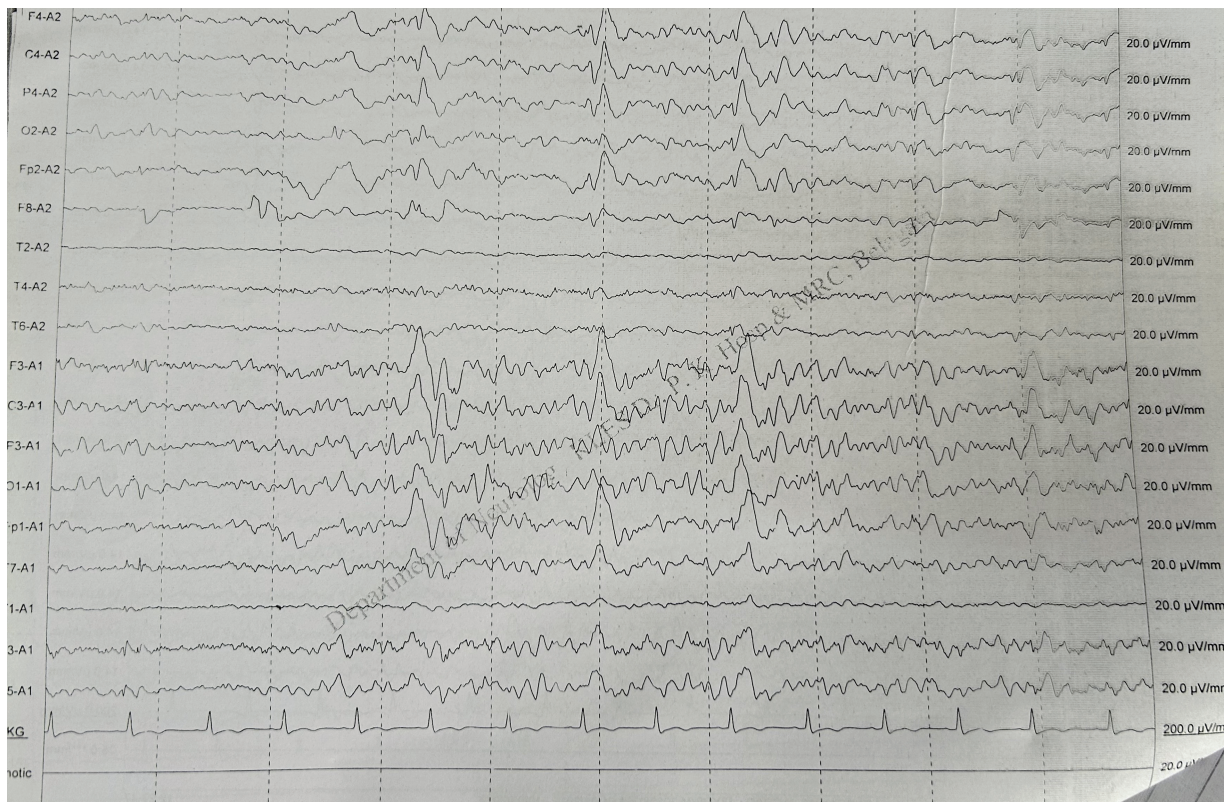
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lower limbs along with altered sensorium. The seizures persisted despite use of intravenous (i.v.) phenytoin, valproate, levetiracetam, lacosamide, and oral topiramate with perampanel. Seizure persisted for 2 weeks and was referred to us. The child had right hemiparesis in between seizures and there were no meningeal signs. Magnetic resonance imaging (MRI) done on day 15 showed cerebral edema in the entire left cerebral hemisphere with diffusion restriction in the affected areas suggestive of the HHE syndrome

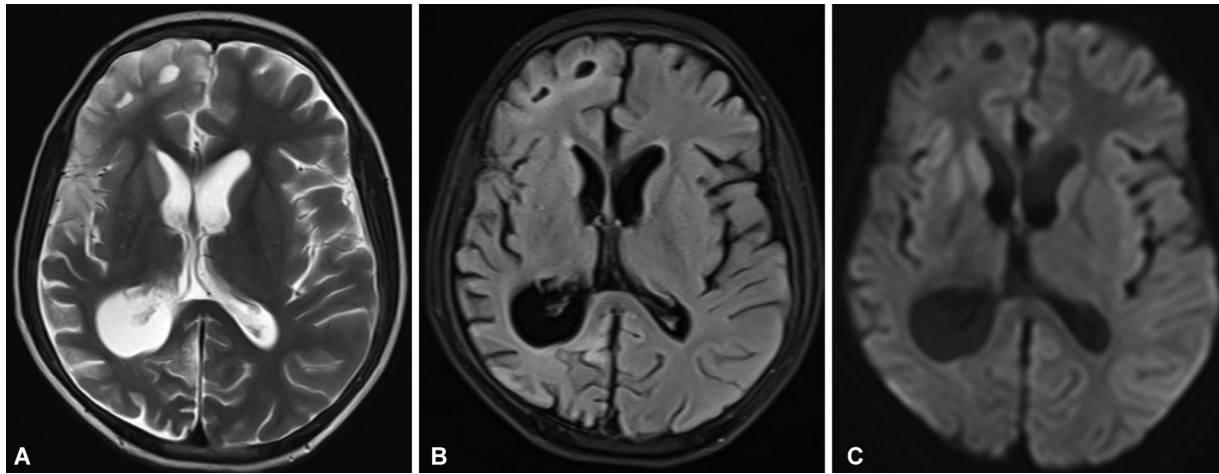
(►Fig. 1). Lumbar puncture cerebrospinal fluid examination was normal and serum myelin oligodendrocyte glycoprotein antibody was negative. Electroencephalogram showed short-interval generalized periodic epileptiform discharges throughout the record (►Fig. 2). Pulse methylprednisolone therapy was initiated along with midazolam drip and other antiseizure medications. The seizures subsided after 1 week and the child was discharged after 3 weeks of hospital stay. Later after 3 months, the child presented with recurrent left



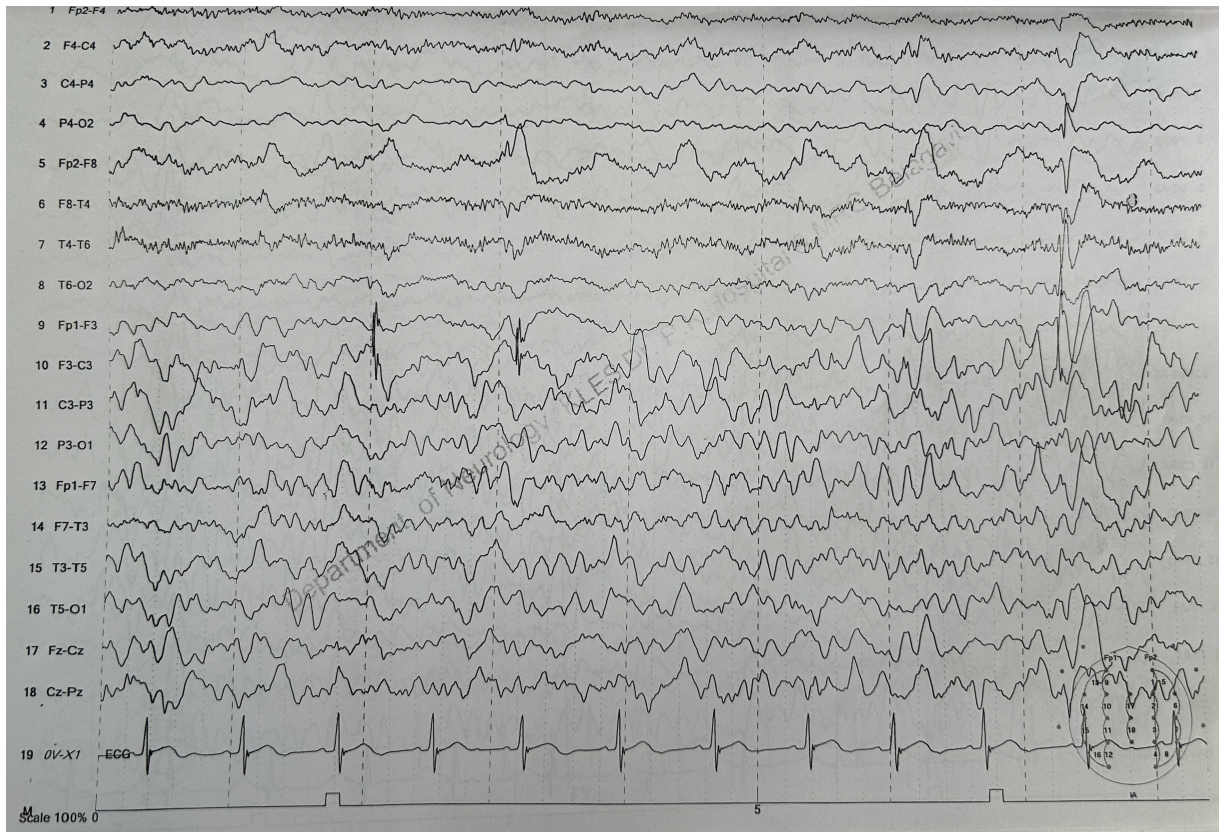
**Fig. 1** Cross-sectional images of the magnetic resonance imaging (MRI) of the brain (A, T2-weighted image; B, fluid-attenuated inversion recovery [FLAIR], and C, diffusion-weighted imaging [DWI]) on day 15 of illness show right hemispheric edema with signal hyperintensities and diffusion restriction in the same areas. There is compression on the lateral ventricle on the right side. Changes are more pronounced in the cortex than in the white matter.



**Fig. 2** Electroencephalogram at presentation showing short interval generalized periodic epileptiform discharges.



**Fig. 3** Cross-sectional images of the magnetic resonance imaging (MRI) of the brain (A, T2-weighted image; B, fluid-attenuated inversion recovery [FLAIR], and C, diffusion-weighted imaging [DWI]) 6 months after onset of seizures show right hemispheric atrophy with ventricular dilatation and white matter hyperintensities in the subcortical region. Few cysts are seen in the frontal white matter and hyperintensities are also noted in the caudate and putamen on the right side. There is no diffusion restriction now.



**Fig. 4** EEG at 6 months follow-up showing asymmetric background activity and generalized sharp waves.

focal motor seizures that persisted with four antiseizure medications and was advised functional hemispherotomy. A repeat MRI after 6 months showed right cerebral atrophy with underlying white matter hyperintensities with cysts and ventriculomegaly (►Fig. 3). This was suggestive of HHE. Repeat electroencephalogram (EEG) after 6 months showed asymmetric background activity and generalized sharp waves (►Fig. 4).

## Discussion

The prolonged clonic seizures in HHE have a unilateral predominance that is followed by the development of hemiplegia. In order to differentiate this condition from the more common unilateral deficit (Todd's paralysis) after a "complex" febrile seizure, a minimum duration of hemiplegia of 1 week is required.

HHE has been reported mainly in children younger than 2 years but never in children older than 4 years. Even the recent International League Against Epilepsy (ILAE) definition has mentioned the age limit of 4 years for IHHE and onset after 6 years of age as an exclusionary criterion.<sup>2</sup> The ILAE mandatory criteria mention that an HHE diagnosis requires a history of both acute stage and chronic stage disease. The acute stage consists of episodes of febrile, hemiclonic status epilepticus, which is immediately followed by permanent hemiparesis, and the chronic stage consists of unilateral focal motor or focal to bilateral tonic-clonic seizures appearing after a variable time (usually <3 years after initial status epilepticus). However, the exact reasons for the age predilection have not been mentioned. There have been some case reports of similar entity like our case even in children older than 4 years and even in adults as well.<sup>3</sup> Even in one of the large series of HHE by Albakaye et al, there were seven cases with seizures starting at the age of  $\geq 6$  years.<sup>4</sup> Thus, the age factor in the definition of IHHE needs to be removed.

**Neuroimaging:** During the early phase of HHE, T2 hyperintensities and restriction on diffusion-weighted imaging (DWI) are seen in the whole pathological hemisphere. Rarely there can be mass effect on contralateral hemisphere. Restriction on DWI is noted early in the disease reflecting cytotoxic edema; consequently, apparent diffusion coefficient (ADC) decreases, resulting in hypointensity on the ADC map. This reduced ADC involved the entire affected hemisphere with a predominance in the subcortical white matter. Rarely, a diaschisis with contralateral cerebellar hemisphere atrophy as a sequela is seen. On days 8 to 15, cytotoxic edema decreases, with pseudonormalization of the ADC maps, but hypersignal due, at this stage, to gliosis with ongoing loss of volume is visible on T2 images as was seen in our case (**→ Fig. 1**). After a month, the evolution is characterized by a cerebral atrophy of the initially involved hemisphere.<sup>1</sup> Magnetic resonance angiography is usually normal in HHE as some cases of the moyamoya disease can have similar initial presentation, but the angiography there would clinch the diagnosis and the clinical course is characterized by recurrent bilateral strokes. Magnetic resonance spectroscopy to look for lactate peak may help differentiate other differentials like polymerase gamma-related mitochondriopathy.

Although this entity has been described five decades ago, the etiologies and the underlying mechanisms remain to be understood.<sup>5</sup> Among the proposed mechanisms, neuronal injuries induced by venous thrombosis and/or excitotoxicity are believed to be the most common mechanisms. Many studies on MRI and at autopsy have not found any thromboses. The underlying brain pathologies were also thought to contribute; however, there are many children who are normal prior to the onset of seizures. Thus, the contribution of the underlying abnormality in causation of HHE is doubtful. Neuropathological studies have revealed cytotoxic edema without any evidence of malformation, inflammatory response, infectious disease or thromboses. Diffuse laminar necrosis and edema in cortical layers 3 and 5 extending throughout the hemisphere and including the hippocampus are the main histological features. A few have even shown

axonal pathologies in the thalamus of the epileptic hemisphere suggesting the involvement of the entire hemisphere in HHE. These features suggest that HHE is a unilateral manifestation of the cytokine storm occurring in the brain. The clinical and radiological manifestations of HHE do resemble those of acute encephalopathy with biphasic seizures and restricted diffusion (AESD) or acute leukoencephalopathy with restricted diffusion (ALERD). So, is HHE a unilateral manifestation of AESD/ALERD? This aspect needs some more studies. There are some case reports supporting this aspect.<sup>6,7</sup> This would also encourage the use of drugs that have been found to be useful in the treatment of AESD/ALERD to treat HHE cases like cyclosporine, dextromethorphan, anakinra, or tocilizumab. As of now, there is no specific treatment for HHE, except for empirical use of steroids (pulse therapy or oral steroids). These measures could help minimize the sequelae like hemiatrophy and associated drug refractory epilepsy that mostly needs surgical intervention like hemispherotomy.

The reason for exclusive involvement of only one cerebral hemisphere is also not clear. Whether it is due to some specific mutation in the glial cells and astrocytes of one hemisphere only (due to post-zygotic somatic mutation) predisposing them to develop unilateral edema secondary to some viral infection needs to be ascertained in future studies. Recently children with mutations in the *CACNA1A* gene have been associated with features resembling HHE.<sup>8</sup> This gene is associated with familial hemiplegic migraine, and there have been reports of children developing an attack of hemiplegic migraine after minor trauma and having seizures with changes of HHE after a week of headache onset.<sup>9</sup> Further studies are needed to ascertain whether this is the cause in all the children with HHE or whether there are other channelopathies that predispose them to developing HHE.

To conclude, HHE needs to be revisited with the recent developments in its understanding. Age should not be a criterion in the definition, and studies looking into the genetic aspect and inflammatory mechanisms of the disease are needed. Similarly, treatment trials including anti-inflammatory drugs need to be conducted.

#### Author Contributions

M.K. diagnosed the patient and was involved in the management of patients. He will act as the guarantor of the study. V.H. read the MRI images. The final manuscript was approved by all the authors.

#### Funding

None.

#### Conflict of Interest

None declared.

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