

Child Neurology: Hemiconvulsion-hemiplegia-epilepsy syndrome

Jeffrey R. Tenney, MD,
PhD
Mark B. Schapiro, MD

Correspondence & reprint
requests to Dr. Tenney:
jeffrey.tenney@cchmc.org

ABSTRACT

Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is an uncommon outcome of prolonged focal status epilepticus in childhood. The prolonged focal motor seizure usually occurs during the course of a febrile illness and is followed by hemiplegia ipsilateral to the side of convulsions. This is accompanied by radiologic evidence of acute cytotoxic edema in the affected hemisphere followed by chronic atrophy. Intractable epilepsy may develop at a time remote from the initial presentation. The clinical features of HHE syndrome were first described more than 5 decades ago but its pathophysiology remains poorly understood and the long-term cognitive outcomes are unclear. Early recognition of the syndrome may help provide patients and families with an accurate prognosis regarding the subsequent development of epilepsy. *Neurology*® 2012;79:e1-e4

GLOSSARY

FIRES = fever-induced refractory epileptic encephalopathy in school-aged children; **HH** = hemiconvulsion-hemiplegia; **HHE** = hemiconvulsion-hemiplegia-epilepsy; **HHS** = hemiconvulsion-hemiplegia syndrome; **MR** = magnetic resonance; **NORSE** = new-onset refractory status epilepticus.

CLINICAL CASE, PART I A 21-month-old boy, former 25-week premature infant, with a history of bilateral grade III/IV intraventricular hemorrhages and hydrocephalus with ventriculo-peritoneal shunt, presented with a likely prolonged period of right-sided jerking. There was no prior history of seizures and his motor and language development was age-appropriate. His parents stated that he was in his usual state of health and acting normally on the day prior to presentation but he did have a tactile fever. He was last seen normal at midnight when he was checked on by his parents. His mother found him 6 hours later with right face, arm, and leg jerking but he had no impaired consciousness or eye deviation. During transport he had continuous right-sided jerking but was conscious and moving the left side normally. He was febrile upon arrival to the emergency room and he initially received IV lorazepam and IV valproic acid with no effect. At that point he developed gaze deviation to the right and mental status deterioration. He received IV fosphenytoin, was intubated, and was admitted to the intensive care unit. The right-sided face, arm, and leg jerking continued so a pentobarbital infusion was started. The total duration of the seizure was approximately 10 hours. The patient remained in a pentobarbital coma for 48 hours before it was weaned and levetiracetam was started as a maintenance antiepileptic medication. On hospital day 5 his mental status improved but he was noted to have a right facial droop, right visual field deficit, right hemiparesis, right hyperreflexia, and no spontaneous speech.

Differential diagnosis. Acute focal weakness following a seizure in a child has many serious etiologies that must be investigated (table). The evaluation is focused on excluding serious or treatable causes. Evaluation should begin with MRI and magnetic resonance (MR) angiography to exclude structural lesions such as neoplasms, intracerebral abscesses, acute disseminated encephalomyelitis, developmental brain malformations, or signs of trauma and vascular disorders such as ischemic or hemorrhagic infarctions. In the case presented it was also important to evaluate for ventriculo-peritoneal shunt malfunction causing increased intracranial pressure with fundoscopic examination, MRI, and shunt externalization, if needed. Other testing should include EEG, serum glucose, and CSF analysis.

CLINICAL CASE, PART II Following resolution of burst suppression the EEG became severely suppressed over the entire left hemisphere. MRI brain done on hospital day 5 showed restricted diffusion with apparent diffusion coefficient correlation throughout the left hemisphere (figure, A). This progressed over the next

From the Department of Neurology, Cincinnati Childrens Hospital Medical Center, Cincinnati, OH.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

Table Differential diagnosis of postictal focal weakness in childhood

Seizure with postictal paralysis
Stroke
Ischemic
Hemorrhagic
Neoplasm
Infectious
Encephalitis
Meningitis
Intracranial abscess
Acute disseminated encephalomyelitis
Metabolic
Hypoglycemia
Mitochondrial disorder (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes)
Developmental brain malformation
Trauma
Psychogenic

month to more pervasive signal abnormalities and volume loss of the entire left hemisphere that were likely consistent with diffuse cortical necrosis (figure, B). Routine electrolytes and CSF analysis at the time of presentation were within normal limits.

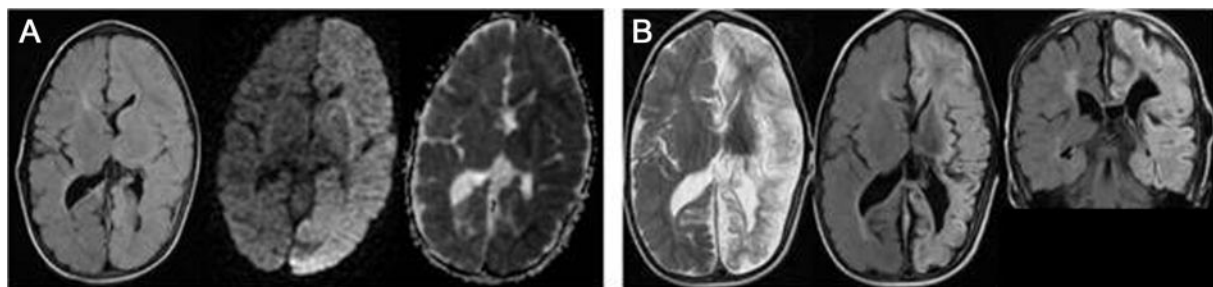
At the last follow-up (16 months posthospitalization) the patient remained seizure-free on levetiracetam. The presenting symptoms, hospital course, and imaging were most consistent with hemiconvulsion-hemiplegia (HH) syndrome since he has not developed subsequent epilepsy. His motor functioning improved with weekly physical therapy/occupational therapy and he was taking some steps independently. He continued to have limited use of the right upper extremity, especially with fine motor movements of the hand. Speech progressed well and

he was speaking in sentences, counting, and identifying some letters.

DISCUSSION Epidemiology. HHE syndrome was first reported by Gastaut and colleagues¹ approximately 50 years ago. The specific incidence is unknown but it has been reported that it is declining in developed countries.^{2,3} This could be due to improved and more rapid treatment of status epilepticus as well as the wider availability of rectal and IV benzodiazepines. A decrease in the incidence of febrile status epilepticus due to increased rates of childhood immunizations is another possible explanation.

Clinical characteristics. The first report in the English literature of HHE syndrome (1960) described the clinical, electrographic, radiologic, and pathologic features of 150 children identified with the syndrome.¹ Children are usually less than 4 years of age at the time of presentation and a concurrent febrile illness should be present. The initial stage is referred to as HH syndrome (HHS) since epilepsy has not yet developed. HHS is characterized by prolonged (hours), unilateral, and clonic convulsions that are often initially unrecognized and many times the child is found having the convulsions in his or her bed.⁴ The hemiconvulsion has the following characteristics that have been described by Chauvel and Dravet⁴: 1) duration of hours and at times more than 24 hours, 2) variable location of the jerking, with a possibility of contralateral seizures if it is prolonged, 3) inconstancy of impairment of consciousness, 4) variable onset with possible head/eye deviation, unilateral jerking, or bilateral jerks evolving to unilateral jerks, and 5) the possibility of severe autonomic symptoms such as hypersalivation, respiratory disorders, and cyanosis. HHE syndrome can be divided into 2 groups based on known etiologies. Idiopathic HHE syndrome is only associated with fever and pre-

Figure MRI brain



MRI brain done on hospital day 5 shows fluid-attenuated inversion recovery (FLAIR) (left), diffusion-weighted imaging (middle), and apparent diffusion coefficient (right) signal abnormalities throughout the left hemisphere (A). These abnormalities are not consistent with any vascular territories. This progressed over the next month to more pervasive signal abnormalities and volume loss of the entire left hemisphere that were likely consistent with diffuse cortical necrosis as seen on the T2-weighted (left) and FLAIR axial (middle) and coronal (right) images (B).

sumed extracranial infection while the symptomatic type is associated with fever as well as some identified, predisposing factor (head trauma, intracranial infection, or cerebral vascular disease).

Unilateral hemispheric swelling occurs during the time of convulsive status epilepticus. The earliest changes seen are edema of the subcortical white matter in the affected hemisphere.⁵ This is followed by the development of global cerebral hemiatrophy over weeks to months.⁶ An important distinguishing feature from stroke is that these abnormalities are independent of any vascular territory. In addition, in HHE syndrome the MRI often shows prominent diffusion restriction within the internal capsule, basal ganglia, and portions of the thalamus initially, as it did in this case. MR angiography in this case was normal and is consistent with data from larger case series of HHE syndrome that have shown normal vascular imaging.⁷ The radiologic abnormalities correspond with clinical changes such as hemiplegia, visual field deficit, or aphasia.

Pathogenesis. The etiology of HHE syndrome remains unclear, but it is likely the result of multiple factors. Radiologic findings indicate that there is a relationship between a sequence of events including early repetitive seizures, brain edema, cortical and subcortical atrophy, and chronic epilepsy in many of the cases.⁴ It is clear from pathologic examinations that the hemispheric swelling is related to cytotoxic edema.⁸ Other reported pathologic features are spongiosis and disruption of the normal cellular architecture. It has been proposed that these changes could be related to the primary, presumed viral, infection with resultant inflammatory cytokine damage.² There has also been speculation that the syndrome is directly related to the prolonged ictal activity. The young age seen at the time of onset is possibly related to the propensity of the immature brain to develop unilateral ictal discharges. This prolonged, unilateral ictal activity could cause excessive neuronal excitation via *N*-methyl-D-aspartic acid (NMDA) glutamate receptors. This could lead to a cascade of increased intracellular calcium causing cytotoxic edema and eventual necrosis and apoptosis. Most likely is that there is a synergistic relationship between inflammation and seizures that potentiates status epilepticus and cellular damage. It has been proposed that HHE syndrome, along with fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) and new-onset refractory status epilepticus (NORSE), may be part of the same spectrum of inflammatory mediated encephalopathy and status epilepticus syndromes with the difference in clinical expression related to the stage of brain maturation.⁹ There are no known underlying genetic factors associated in children with HHE syndrome; however, a re-

cent report has linked it with CACNA1A mutation and possible cerebral vasospasm.¹⁰

Much of the data related to the pathogenesis of HHE syndrome support the existence of a “febrile idiopathic HHE syndrome” that shares some commonalities with simple febrile seizures. However, the relative rarity of HHE syndrome has caused some authors to question this connection and raise the possibility that children who develop HHE syndrome may have a preexisting cerebral lesion which transforms what would have been a simple febrile seizure into focal status epilepticus.⁴

Treatment and prognosis. Treatment for HHE syndrome during the early acute phase of the illness is mainly supportive and in the short term most children do well once the initial status epilepticus is controlled. However, it has been proposed, based on radiologic and pathologic findings, that the use of anti-edema agents and NMDA-type glutamate receptor antagonists during the acute period could help to stop neuronal injury.²

After some variable period (months to years) of seizure freedom, approximately two-thirds of patients will develop epilepsy that is in many cases intractable.¹¹ Making a distinction between idiopathic and symptomatic types of HHE is important because the 2 types differ in long-term prognosis.¹² Patients with the idiopathic type tend to develop temporal lobe epilepsy whereas those in the symptomatic group have an earlier onset of epilepsy and it is a symptomatic generalized type. No guidelines exist as to whether children with HHE syndrome should be on chronic anticonvulsant medication to prevent the remote seizures. There is evidence that surgical treatment of delayed intractable epilepsy in HHE syndrome is beneficial.¹²

The motor deficits associated with HHE syndrome have a variable course with some patients having persistent hemiplegia and others with complete resolution.¹ Physical and occupational therapy can be useful in the acute and chronic periods of the syndrome in order to maximize motor function. Long-term cognitive and language outcomes associated with HHE syndrome are poorly understood. Chauvel and Dravet have reported mental retardation as a feature in one-third of the patients with intractable epilepsy referred for epilepsy surgery, but a more recent study demonstrated that outcome can vary depending on which hemisphere is affected and mental retardation is not universal.^{4,13} Patients with retained language in the affected hemisphere tended to have a better cognitive outcome.

Based on this literature, the prognosis for our patient can be made. His focal status epilepticus seemed to be related to a prolonged febrile seizure as in many of the idiopathic cases. However, he had preexisting

neuronal injury which places him in the symptomatic HH category making early, symptomatic generalized epilepsy more likely. Long-term language outcome may be dependent upon whether the functional cortex was reorganized following cerebral injury. Future fMRI for language function could help to establish the prognosis in this regard more accurately.

FUTURE PERSPECTIVES HHE syndrome is a rare but serious disorder in the pediatric population. It can greatly impact the quality of life for patients and their families. Health care dollars spent on patients with this disorder could be substantial given the remote development of medically intractable epilepsy and possibly lifelong hemiplegia.

HHE syndrome should be preventable by continued advances related to the rapid resolution of seizures. The severe impairments associated with HHE syndrome makes it imperative that continued research into the pathophysiology and treatment of the disorder is performed. It would be reasonable to pursue research related to preventing cytotoxic damage acutely with the use of NMDA antagonists or aggressive, early treatment of cerebral edema.

AUTHOR CONTRIBUTIONS

J. Tenney qualifies as an author based on the following contributions: drafting/revising the manuscript for content and analysis/interpretation of diagnostic testing. M. Schapiro qualifies as an author based on the following contributions: drafting/revising the manuscript for content and analysis/interpretation of diagnostic testing.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Gastaut H, Poirier F, Payan H, et al. H.H.E. syndrome: hemiconvulsions, hemiplegia, epilepsy. *Epilepsia* 1960;1:418–447.

2. Auvin S, Devisme L, Maurage C, et al. Neuropathological and MRI findings in an acute presentation of hemiconvulsion-hemiplegia: a report with pathophysiological implications. *Seizure* 2007;16:371–376.
3. Salih M, Kabiraj M, Al-Jarallah A, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome: a clinical, electroencephalographic and neuroradiological study. *Childs Nerv Syst* 1997;13:257–263.
4. Chauvel P, Dravet C. The HHE syndrome. In: Roger J, Bureau M, Dravet C, et al, eds. *Epileptic Syndromes in Infancy, Childhood, and Adolescence*. Montrouge: John Libbey Eurotext; 2005:277–293.
5. Toldo I, Calderone M, Boniver C, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome: Early magnetic resonance imaging studies and neuroradiological follow-up. *Brain Dev* 2007;29:109–111.
6. Sankhyan N, Sharma S, Kamate M, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome: sequential MRI follow-up. *Neurology* 2008;9:e28.
7. Aicardi J, Amsli J, Chevrie J. Acute hemiplegia in infancy and childhood. *Dev Med Child Neurol* 1969;11:162–173.
8. Freeman J, Coleman L, Smith L, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome: characteristic early magnetic resonance imaging findings. *J Child Neurol* 2002;17:10–16.
9. Nabbout R, Vezzani A, Dulac O, et al. Acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol* 2011;10:99–108.
10. Yamazaki S, Ikeno K, Abe T, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome associated with *CACNA1A* S218L mutation. *Pediatric Neurol* 2011;45:193–196.
11. Aicardi J, Amsli J, Chevrie J. Acute hemiplegia in infancy and childhood. *Dev Med Child Neurol* 1969;11:162–173.
12. Kim D, Kim K, Chu K, et al. Surgical treatment of delayed epilepsy in hemiconvulsion-hemiplegia-epilepsy syndrome. *Neurology* 2008;70:2116–2122.
13. Mirsattari S, Wilde N, Pigott S. Long-term cognitive outcome of hemiconvulsion-hemiplegia-epilepsy syndrome affecting the left cerebral hemisphere. *Epilepsy Behav* 2008;13:678–680.

Neurology[®]

Child Neurology: Hemiconvulsion-hemiplegia-epilepsy syndrome

Jeffrey R. Tenney and Mark B. Schapiro

Neurology 2012;79:e1-e4

DOI 10.1212/WNL.0b013e31825dce5f

This information is current as of July 2, 2012

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/79/1/e1.full
References	This article cites 12 articles, 1 of which you can access for free at: http://n.neurology.org/content/79/1/e1.full#ref-list-1
Citations	This article has been cited by 2 HighWire-hosted articles: http://n.neurology.org/content/79/1/e1.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Developmental disorders http://n.neurology.org/cgi/collection/developmental_disorders Status epilepticus http://n.neurology.org/cgi/collection/status_epilepticus Viral infections http://n.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

