Hemiconvulsion-Hemiplegia-Epilepsy Syndrome in a Girl Presented with Complex Partial Seizures

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ABSTRACT

The mechanisms underlying the Hemiconvulsion-Hemiplegia-Epilepsy syndrome remains unclear. The current proposed pathogenic mechanism is a neuronal injury induced by venous thrombosis and/or hypoxia. Children develop hemispheric brain atrophy with contralateral hemiplegia, epilepsy, and a variable degree of cognitive deficit. We report a 33 months old female child a case of hemiconvulsion-hemiplegia-epilepsy syndrome with right hemisphere unilateral brain edema and left sided hemiplegia and aphasia who presented with left upper extremities complex partial seizures with generalization to tonic clonic seizures and developed status epilepticus that posed diagnostic and therapeutic challenges. Progressive atrophy of the right cerebral hemisphere was noted after 3 months of follow up. Hemiconvulsion-Hemiplegia-Epilepsy syndrome should be suspected in a child with unilateral cerebral hemisphere brain edema and hemiplegia with cognitive deficit following status epilepticus to provide patients and families with an accurate prognosis regarding the subsequent development of epilepsy.

KEY WORDS

Hemiconvulsion-Hemiplegia-Epilepsy syndrome, Hemispheric brain atrophy, Status epilepticus, Unilateral brain edema

INTRODUCTION

Hemiconvulsion-hemiplegia epilepsy 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.[1] They are characterized by the occurrence of refractory status epilepticus during or after fever without evidence of central nervous system infection. Status epilepticus is usually long and might persist for hours if not treated.[2] In the last 20 years, more than 50 patients have been reported.[3] We report a 33 months old female child a case of right hemisphere unilateral brain edema and left sided hemiplegia with aphasia who presented with complex partial seizures with generalization to tonic clonic seizures and developed status epilepticus that posed diagnostic and therapeutic challenges.

CASE REPORTS

A 33 month old developmentally normal female child presented with acute onset of involuntary clonic movement of body starting from left upper limb which gradually progressed to left lower limb and right side of body. The episode lasted for nearly 2 hours followed by loss of consciousness, frothing and urinary incontinence. Intravenous diazepam and phenytoin was given to control the seizures. There was no history of fever or trauma prior to the illness. She had similar episode 2 month back but recovered at home without any medical treatment. She was born to non-consanguineous parents at Patan hospital at 30 weeks of gestation and weighed 1200 gms. She was kept 57 days in neonatal intensive care soon after birth for prematurity and low birth weight (documents lost during earthquake).

On presentation she was febrile (40° C) and had respiratory rate of 60 per minute with crepitation over bilateral lung

field on chest auscultation. Bilateral pupils were equal and reactive to light. Cranial nerves were grossly intact, power and tones of both upper and lower limbs were normal. No signs of meningeal irritation were seen, and had no signs of papilledema. Routine hematological investigations and serum electrolytes were within normal range. Cerebrospinal fluid (CSF) analysis was done which was normal. On the 2nd day of admission, her mental status improved but she was noted to have a left facial droop and right sided lateral gaze was noticed. Weakness of left upper and lower limbs with power of 2/5 was present, power in the right extremities were normal. Left sided knee and ankle deep tendon reflex were brisk, plantar was up going on the left side and no spontaneous speech was observed. CT head (fig. 1) revealed diffuse hypo density in right cerebral hemisphere involving both grey and white matter suggestive of a right homogenous hemispheric edema without evidence of any thromboembolism, malformation, inflammatory process, infection, hematoma or evidence of any metabolic disease. On day 14 of admission, Electroencephalography (EEG) was done which showed right predominant periodic spikes and slow spikes over right central region suggestive of focal seizures.

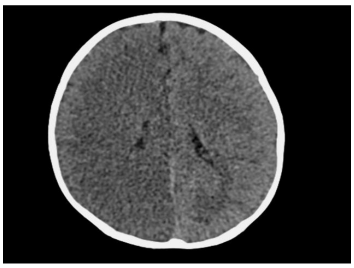

Figure 1. CT scan of brain during acute illness, Right hemisphere cerebral edema

We kept in mind the possibility of thromboembolisms, infection, vasculitis, hypercougulopathy, hemoglobinopathy, autoimmune disorders, endocrine disorders, mitochondrial disorders and metabolic disease. We tried to further investigate and workup with the facilities which were available in our hospital. Bilateral carotid Doppler showed no thrombosis, echocardiography and electrocardiography showed no cardiac defects, blood analysis for lipid profile, liver, renal, and thyroid function test were within normal limits. Blood counts, arterial blood gas analysis, serum lactate, antinuclear antibodies, rheumatic tests were normal. Sickle solubility test and antibodies for VDRL and HIV were negative. A hypercoagulability study to evaluate for pro-coagulant states could not be performed due to its unavailability in our hospital. Child improved symptomatically with phenytoin and mannitol. Child was discharged after 14 days of hospital stay with low dose aspirin and continued with oral antiepileptic (Sodium valproate) and physiotherapy.

On 3 months follow up (36 months of age), she was seizure free, hypotonia resulted in left sided spastic hemiparesis with involvement of the flexor muscles of the arm, forearm and hand as well as left equinovarus was noted; CT scan (Fig. 2) done on follow up showed right cerebral hemi atrophy. She consequently received rehabilitation treatment, which improved her spasticity and gait, however she had slurred speech. Visual field deficit could not be tested due to her young age. Consequent follow up demonstrated improvement in hemiparesis.

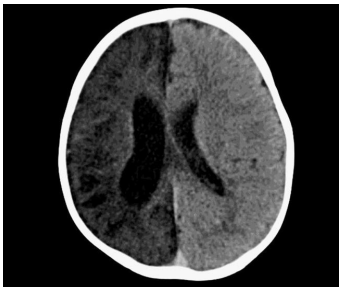

Figure 2. CT scan of brain after 3 months follow up, Right cerebral hemisphere atrophy

The presenting symptoms, hospital course and CT scan during the acute illness and at 3 months follow up were most consistent with a diagnosis of hemiconvulsion-hemiplegia-epilepsy syndrome. Her motor function improved with weekly physical and occupational therapy and she was taking some steps independently. She continued to have limited use of the left upper extremity, especially with fine motor movements of the hand. Speech progressed well and on 6 months follow up she was speaking in sentences, counting, and identifying some letters. According to father significant improvement in the desire to communicate and in eating behavior was noted, her language and speech improved. Although behavior was assessed by parental report rather than standardized questionnaire, significant improvement in quality of life was noticed, although the limited use of her left upper extremity still persist.

DISCUSSION

Hemiconvulsion–hemiplegia (HH) syndrome is characterized by the emergence of hemiplegia after a prolonged unilateral convulsion, and successive atrophy of the contralateral cerebral hemisphere. The term hemiconvulsion–hemiplegia–epilepsy (HHE) syndrome is applied when epilepsy with complex partial seizures newly emerges as a sequela of HH syndrome.[4]

HHE syndrome is a sequel to prolonged status epilepticus, which was first recognized by Gastaut, in 1960.[1] Since then, it has been well known to pediatricians. It is characterized by the appearance of clonic epileptic seizures of long duration affecting one side of the body in the course of a febrile illness in children under 4 years. Subsequently, a hemiplegia of varying intensity is developed, which can be permanent.

The incidence of these syndromes has declined dramatically in the industrialized countries over the past 30 years, probably due to more effective management of

status epilepticus.[3,5] A decrease in the incidence of febrile status epilepticus due to increased rates of childhood immunizations is another possible explanation. However, they are recognized worldwide and were both included in the last proposition for classification of the International League Against Epilepsy (ILAE).[6] This sequence is stereotyped and HH syndrome with or without epilepsy has been introduced as an epileptic syndrome in the first ILAE classification of epilepsies and was included among epilepsy syndromes and epilepsies in the recent report of the ILAE Taskforce on Classification and Terminology.[6]

HH syndrome is followed by epilepsy, leading to the onset of HHE syndrome by the appearance of partial seizures in 56%-70% of cases.[7] After a free interval of variable duration, spontaneous recurrent seizures appear. The seizures are often complex partial seizures originating from the temporal lobe.[3] However, since our patient was under 3 years of age at the end of follow-up, she might be in a 'silent period' preceding temporal lobe epilepsy.

The early seizure is a prolonged clonic convulsion, usually with marked unilateral predominance. Post-ictal neurologic deficits include hemiparesis, intellectual deterioration, and epileptic seizures. During the acute period, edema of the affected hemisphere is so severe as to be apparent on CT in many cases. SPECT shows hyper-perfusion of the cortical lesion. At the subacute stage (1 week to 1 month after onset), there is progressive atrophy and hypo-perfusion.[8] In addition to the hemiplegia, other post-ictal neurologic deficits can be observed such as motor aphasia.[9] In our case the post ictal phase was associated with hemiplegia and aphasia. It is not uncommon that the prolonged convulsions were unnoticed by the caregivers due to night time or sleep time of the child leading to a prolonged duration of status epilepticus.[10] Our case had a similar episode 2 month back (31 months of age) but recovered at home without any medical treatment. During the acute period, edema of the affected hemisphere can be severe resulting in life-threatening condition such as temporal lobe herniation.[11]

However, many cases are idiopathic and occur in apparently healthy infants who exhibit neither clinical nor imaging evidence of pre-existing brain lesion. Moreover, CSF comprises neither pleocytosis nor electrophoresis of CSF proteins shows oligoclonal bands, polymerase chain reaction (PCR) is negative excluding an infection of the central nervous system (CNS).[2] Similarly, in our case there was no imaging evidence of pre-existing brain lesions and laboratory investigations also didn't show any evidence of CNS infections. CSF analyses are frequently reported as normal. However, negative PCR result in CSF cannot exclude meningitis or menigoencephalitis. In a large series of 662 patients, mostly immunocompetent, detection of HHV-6 and EBV by CSF PCR did not correlate clinically in several individuals with the presence of a CNS infection.[3] Further investigations such as PCR from brain tissue as well as pathological investigations (immunostaining and electronic microscopy) are needed to investigate adequately.

After some variable period (months to years) of seizure freedom, approximately two-thirds of patients will develop epilepsy that is in many cases intractable.[7] 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. Long-term cognitive and language outcome following HHE syndrome has been poorly studied. Most of the patients have severe intellectual disability.[13]

Until recently, the proposed etiologies were venous thrombosis, metabolic disease, and focal brain abnormalities leading to a prolonged focal status epilepticus inducing the hemispheric cytotoxic edema.[3] The recent data don't support that these etiologies are frequent in HH and HHE syndrome. The mechanisms underlying the HHE are unclear. The current proposed pathogenic mechanism is a neuronal injury induced by venous thrombosis and/or excitotoxicity.[14] The most frequent findings in the recent years have been the identifications of coagulation disorders, protein S deficiency, factor V Leiden mutation and homozygous for the MTHFRC677T mutant gene.[9,15] These findings increase the likelihood of thrombosis as the cause and allows for consideration of anti-coagulation to prevent recurrence or progression. Unfortunately, we could not evaluate for pro-coagulant states in our case, which may have been a major limitation of our case study. This syndrome has been associated with hypercoagulability, such as factor V Leiden or protein S deficiency.[9,15] However, the ischemic theory would not explain the general atrophy of the hemisphere in the absence of evident ischemic lesions or the absence of arterial obstruction in the angio-MRI.[16] Hemiplegia in HHE syndrome differs from postictal or Todd paralysis in that it lasts for longer than 7 days. The degree of hemiparesis correlates with the degree of brain atrophy seen in the MRI.[10] We excluded in our patient an underlying condition such as thrombosis, brain malformation or cortical dysplasia.

The pathogenesis is believed to be an interplay among genetic predisposition; viral infection or toxin exposure; excitotoxicity due to prolonged ictal activity; and contributory systemic factors such as cytokine excess, hypoxia, ischemia, and fever.[8] In status epilepticus, neuronal injury is mediated by excess excitation via activation of the N-methyl-D-aspartate subtype of glutamate receptors and consequent elevated intracellular calcium that causes acute necrosis and delayed apoptotic cell death.[14] In experimental studies, it has been shown that status epilepticus in immature brain result in moderate cell injury, it has been described that inflammation and hyperthermia may worsen acute consequence of status epilepticus.[3]

Mori et al. was the first to report the pathological findings of HHE syndrome. He reported the studies of two brains from infants who died several days after hemiconvulsions and/or generalized status epilepticus. In these two patients, CSF was normal and the histological examination did not reveal any inflammatory process or vascular lesions. Diffuse laminar necrosis and edema in cortical layers 3 and 5 extending throughout the hemisphere and including hippocampus were the main histological features.[3]

The pathogenesis of HHE syndrome is controversial. Some authors suggest that a primary viral infection could cause, directly or through pro-inflammatory cytokines, a cerebrovascular disorder, which would in turn cause hemiconvulsion, hemiplegia, and cytotoxic edema.[17] Other authors believe that the injury is a direct result of prolonged seizure activity. The most convincing hypothesis is that the repeated crises may cause a brain lesion by altering neuronal energy metabolism.[10] Several factors may contribute to the pathogenesis of the syndrome, such as the beginning of the crises in the first year of life, possible unnoticed long-term seizures, alteration of neuronal energy metabolism, genetic factors that may predispose towards prolonged febrile seizures and systemic factors such as hypoxia, hypoglycemia, low blood pressure and hyperthermia.[18]

After the prolonged seizure, slow waves and spikes are followed by delta slowing with higher amplitude on the affected hemisphere.[11] Short period of suppression activity may be observed.[14] These abnormalities contrast with the recording of the unaffected hemisphere that usually show slow waves associated with reappearing physiological rythms.[3] Interictal-EEG recordings show more frequently multifocal spikes and sharp-waves.[3] In our patient EEG showed right predominant periodic spikes and slow spikes over right central region.

Neuro-radiological studies show unilateral edematous swelling of the epileptic hemisphere at the time of initial status, followed by characteristic global cerebral hemi-atrophy independent of any vascular territory with subsequent appearance of epilepsy.[14] Unilaterality could result from early age of occurrence of the status epilepticus before interhemispheric connections, mainly the corpus callosum, have become myelinated.[19] MRI scans show, in the early stages, hyper-intensities located throughout the cerebral hemisphere on T2 sequences and diffusion with a decreased apparent diffusion coefficient, which would indicate that the underlying lesion is a cytotoxic edema.[18] After a period of several days, these changes disappear and brain atrophy becomes evident, uniformly affecting an entire hemisphere, both cortical and subcortical, with dilatation of the ventricular system.[20] Swelling and cerebral atrophy was strictly unilateral in our patients. This pattern makes it possible to differentiate HHE syndrome from focal atrophies that appear in perinatal lesions with a vascular origin.[21] The occurrence of edema is frequent in venous thrombosis. However, the hypothesis of venous thrombosis appears unlikely. Despite coagulation disorders have been observed in several patients, there is no evidence for an involvement of thrombosis in both MRI angiography and neuropathological studies.[3]

No guidelines exist as to whether children with HHE syndrome should be on chronic anticonvulsant medication to prevent the remote seizures. However, there is evidence that surgical treatment of delayed intractable epilepsy in HHE syndrome is beneficial and exclusive temporal lobe involvement seems to be a very good predictor of seizure freedom after surgery.[12]

In HH syndrome, it seems that the brain injury is the result of cytotoxic edema caused by a prolonged focal seizure. An early diagnosis and a better understanding of the underlying mechanisms of HHE are needed to improve the outcome of this condition. All of these factors influence quality of life and the burden of illness for the child and his or her family. Early recognition of the syndrome may help provide patients and families with an accurate prognosis regarding the subsequent development of epilepsy.

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