**Hemiconvulsion—hemiplegia—epilepsy syndrome: Current understandings**

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**Abstract**

Hemiconvulsion—Hemiplegia (HH) syndrome is an uncommon consequence of prolonged focal febrile convulsive seizures in infancy and early childhood. It is characterized by the occurrence of prolonged clonic seizures with unilateral predominance occurring in a child and followed by the development of hemiplegia. Neuroradiological studies showed unilateral edematous swelling of the epileptic hemisphere at the time of initial status epilepticus (SE). This acute phase is followed by characteristic cerebral hemiatrophy with subsequent appearance of epilepsy, so called Hemiconvulsion—Hemiplegia—Epilepsy (HHE) syndrome. The etiologies and the underlying mechanisms remain to be understood. Using a review of the literature, we summarized the data of the last 20 years. It appears that idiopathic HH/HHE syndrome is the most common reported form. The basic science data suggest that immature brain is relatively resistant to SE-induced cell injury. Several factors might contribute to the pathogenesis of HH/HHE syndrome: 1. prolonged febrile seizure in which inflammation may worsen the level of cell injury; 2. inflammation and prolonged ictal activity that act on blood—brain-barrier permeability; 3. predisposing factors facilitating prolonged seizure such as genetic factors or focal epileptogenic lesion. However, these factors cannot explain the elective involvement of an entire hemisphere. We draw new hypothesis that may explain the involvement of one hemisphere such as maturation of brain structure such as corpus callosum or genetic factors (CACNA1A gene) that are specifically discussed. An early diagnosis and a better understanding of the underlying mechanisms of HHE are needed to improve the outcome of this condition.

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1. Introduction

Hemiconvulsion–Hemiplegia (HH) syndrome is an uncommon consequence of prolonged focal febrile convulsive seizures in infancy and early childhood. It was first described by Gastaut et al. It is characterized by the occurrence of prolonged clonic seizures with unilateral predominance occurring in the course of a febrile illness in a child usually younger than 4 years, and followed by the development of hemiplegia. Neuroradiological studies showed unilateral edematous swelling of the epileptic hemisphere at the time of initial SE. This acute phase is followed by characteristic global edematous swelling of the epileptic hemisphere at the time of hemiplegia. The diagnosis of HH syndrome should be discussed each time that a persistent flaccid hemiplegia is observed after a prolonged febrile seizure in a child. The early seizure is most often a prolonged clonic convulsion, usually with marked unilateral predominance. In addition to the hemiplegia, other post-ictal neurologic deficits can be observed such as motor aphasia. It is not uncommon that the prolonged convulsions were unnoticed by the caregivers due to nighttime or sleep time of the child leading to a prolonged duration of status epilepticus (SE).

During the acute period, edema of the affected hemisphere can be severe resulting in life-threatening such as temporal lobe herniation. Imaging should be performed as early as possible to confirm the diagnosis. As described below, MRI study with the clinical evaluation permits to diagnose HH syndrome.

After a free interval of variable duration, spontaneous recurrent seizures appear. 85% of the patients that have epilepsy started within 3 years of the initial HH phase (average interval of 1–2 years). The seizures are often complex partial seizures originating from the temporal lobe. In a study of 37 patients, it has been shown using stereo-EEG recordings in adults that most of the patients exhibit several types of seizures from different area. Interictal-EEG recordings showed more frequently multifocal spikes and sharp-waves. Long-term cognitive outcome following HHE syndrome has been poorly studied. Most of the patients have severe intellectual disability. Surgical treatment can be discussed with an improvement more than half of the patients. Exclusive temporal lobe involvement seems to be a very good predictor of seizure freedom after surgery.

2. Diagnosis

The mechanisms underlying the HH/HHE syndrome are unclear. Until recently, the proposed pathogenic mechanism was a neuronal injury induced by venous thrombosis and/or excitotoxicity. Previous abnormalities of the brain were also suggested as underlying mechanism. We have recently reported the neuropathological data of a patient with acute HH syndrome showing cytotoxic edema without any evidence of malformation, inflammatory response or infectious disease. We found axonal damages in the thalamus of the epileptic hemisphere illustrating the involvement of the whole hemisphere in this condition.

Here, we have reviewed the available data of the last 20 years using a Pubmed search from January 1st 1990 to August 1st, 2011 (using two keywords: “hemiconvulsion” and “hemiplegia”). We briefly summarize the electroclinical data and the neuro-imaging findings of the HH/HHE syndrome. We focus our analysis on the possible causes of the acute phase of HH/HHE syndrome suggesting new pathophysiological hypothesis.

3. Neuro-imaging data

There are now several reports of patients with longitudinal MRI investigations. Patients observed in our institution showed similar findings. Early MRI demonstrates diffuse signal anomalies confined to one hemisphere (Fig. 1):
Hypersignal on T2 sequence and diffusion imaging (DWI) involving the whole pathologic hemisphere, within some cases, mass effect on contralateral hemisphere. As a result of mass effect also, ipsilateral temporal lobe herniation has been reported in few patients.\textsuperscript{10,13} Hypersignal on diffusion imaging (DWI) is also noted on early MRI reflecting a restricted diffusion due to cytotoxic edema; consequently, ADC (apparent diffusion coefficient) is decreased, resulting in hypointensity on ADC map (Fig. 1D). This reduced ADC involved the entire affected hemisphere with predominance in the subcortical white matter. All these anomalies affect only one hemisphere. It is not uncommon to observe a diaschisis with contralateral cerebellar hemisphere atrophy as a sequellae.\textsuperscript{9}

There is currently no patient that has been reported to have abnormal angio-MRI study (Table 1). On day 8–15, cytotoxic edema decrease, with pseudo-normalization of the ADC maps, but hypersignal due at this stage, to gliosis, with ongoing loss of volume is visible on T2 images. One month after the HH syndrome, the evolution is characterized by a cerebral atrophy of the initially involved hemisphere.

Initially, proton Magnetic Resonance Spectroscopy (1H-MRS) shows a reduction in the concentration of the neuronal marker N-acetyl aspartate [NAA] and a mild increase of lactate.\textsuperscript{17} Evolution in the first two weeks shows stability or a slight increase of NAA level,\textsuperscript{11,17} that remain stable one month after the event.\textsuperscript{17}

If the temporal modifications of the MRI in HHE patients seem now well known, these data do not provide any convincing explanation about the mechanisms which determine the early and diffuse involvement of the white matter and the unilaterality of the damage observed in HH/HHE syndrome.

4. EEG findings

An EEG recording is important at the acute phase of HH syndrome to exclude an ongoing subtitle status epilepticus.

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**Fig. 1** – Imaging studies at acute phase of HH syndrome in a 18-month-old boy. A: CT-Scan Day1 after admission: hypodensity of the left hemisphere sparing the thalamus and left basal ganglia, without mass effect. B–D: MRI study on day 3 after admission (B) T1-Weighted, (C) T2-weighted, (D) ADC map of the diffusion-weighted sequence. Brain MRI shows abnormalities throughout the left hemisphere involving both gray and white matter: loss of differentiation between gray and subcortical white matter on T1; hypersignal of the whole hemisphere on T2. ADC map demonstrates hypointensity of the left hemisphere sparing only the thalamus and basal ganglia, with subcortical white matter predominance, due to cytotoxic edema.
However, the diagnosis of HHE does not require EEG to be confirmed. At the late stage of HHE syndrome, EEG recording would permit to identify epileptogenic area of the atrophic hemisphere that may need surgical management in case of pharmacoresistance. At the acute stage of HH syndrome, the ictal discharge is characterized by rhythmic (2–3/see) slow waves that are usually bilateral with higher amplitude on the affected hemisphere associated with spikes, sharp-waves and episodic fast activity (10/see). It is very common that the discharge may change in shape and frequency. The use of polygraphic recording (EMG–EEG) does not permit to correlate clinical symptoms to EEG abnormalities.

After the prolonged seizure, slow waves and spikes are followed by delta slowing with higher amplitude on the affected hemisphere. These abnormalities contrast with the recording of the unaffected hemisphere that usually show slow waves associated with reappearing physiological rythms.

5. **Neuropathology**

Few pathologic data are available. Two papers by Mori et al. are the first studies reporting the pathological findings of HHE syndrome. The post-mortem specimens reported by Mori showed diffuse cortical scarring in the laminae. Only one patient had malformation (polymicrogyria in the left sylvian fissure). 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.

We recently reported the neuropathological study of an acute HH syndrome. We did not find any underlying conditions. Moreover, we did not observe any cell death as a result of prolonged SE. Anti-neurofilament immunostaining was very useful to determine the existence of axonal damage in the thalamus of the epileptic hemisphere in our patient.

The last available data are from a surgical biopsy of the right temporal cortex of a patient that had decompressive craniectomy. The examination showed some granular cells within a diffuse spongiosis and edema without cell necrosis. Both pathological and angio-MRI studies did not provide any evidence of the involvement of thrombosis or vascular abnormalities. The most recent data did not report a high level of cell injury. These studies did not find any evidence for an underlying condition of the epileptic hemisphere such as pathological findings suggesting encephalitis or cortical and/or hippocampal dysplasia.

6. **Etiologies**

The HH/HHE syndromes have been described to result of multiple etiologies but in many patients no cause is obvious. Hyperthermia is most often present during the acute phase of initial SE, suggesting that HH/HHE syndrome may be a severe variant of complicated febrile convulsions. Most of the recent available data report idiopathic HH/HHE syndrome. In the last 20 years, more than 50 patients have been reported in Table 1. Salih et al. reported the initial presentation and the long-term outcome of 6 HHE patients. Their data suggest that all of them were idiopathic. More recently, a retrospective case series reported 8 patients. However, most of the patient (n = 6/8) was diagnosed at the late HHE stage excluding any investigation regarding the etiology. One of the two patients that have been observed since the HH phase experienced measles at time of initial SE onset and MRI studies revealed a temporal lobe tuberculoma that might have lowered the seizure threshold. The details of the etiology and standard investigations of the other patients are reported in the Table 1. Fourteen of 15 have had typical idiopathic HH/HHE
syndrome. Looking at the available data, it is obvious that the seizure threshold in some patients may have been lowered by a preexisting condition but we did not find any direct etiology such as homolateral epileptogenic brain abnormalities or thrombosis (Table 1). A patient has been reported to have HHE syndrome as a presenting feature of L-2-hydroxy-glutaric aciduria. The authors reported a full recovery of the left hemiplegia within the first 24 h and the MRI study did not reveal edema restricted to one hemisphere.21 The diagnosis of HH syndrome in this patient seems unlikely.

Until recently, the proposed etiologies were venous thrombosis, metabolic disease, focal brain abnormalities leading to a prolonged focal status epilepticus inducing the hemispheric cytotoxic edema.5 The recent data don’t support that these etiologies are frequent in HH/HHE syndrome (see Table 1).

In the last years, typical idiopathic HH/HHE syndrome has been mostly reported (Table 1). In one third of the reported cases, precipitating factors have been reported such as contralateral cortical dysplasia (n = 1), coagulation disorders without proved thrombosis (n = 2), viral infection (n = 1) and SCN1A gene mutation (n = 1). The most frequent findings in the recent years have been the identifications of coagulation disorders (3/20): protein S deficiency (n = 1),22 factor V Leiden mutation (n = 1) and homozygous for the MTHFR C677T mutant gene (n = 1).7 These findings increase the likelihood of thrombosis as the cause and allows for consideration of anti-coagulation to prevent recurrence or progression. However, only one of the three patients exhibited abnormal MRI-angiography showing a paucity of distal vessels in left middle cerebral artery on late MRI study showing hemispheric brain atrophy.22 In our previous report,6 we did not find any thrombosis as well as in our most recent patients (unshown data). Venous thrombosis should be always discussed appropriately.

Finally, it has been suggested that HH syndrome may represent a variant of the dual pathology that may be observed in prolonged febrile seizure followed by hippocampal sclerosis. In case of mesial temporal sclerosis, cortical lesions such as neuronal migration disorders, low-grade tumors, or gliotic lesions have been frequently observed. These lesions may represent a common pathogenic mechanism, which could explain the predisposition to prolonged febrile seizures and the development of mesial temporal sclerosis due to a dual pathology (combination of developmental abnormalities and prolonged febrile seizure).23 In the recent years, only one patient has been reported to have a contralateral focal cortical dysplasia.15 We cannot exclude that such epileptogenic lesion can be undetected by the MRI.24 However, none of neuropathological data have demonstrated such abnormalities.6,18,19 The collection of neuropathological data are needed to investigate the presence of cortical or hippocampal dysplasia.

Several studies have suggested that human herpes virus (HHV)-6 may be a common etiologic agent in febrile seizures. If it is true that HHV-6B and HHV-7 primary infection coincides with the peak incidence of FS, the available data did not permit to determine the role of these viruses in FS occurrence.25 It may be related to the fever induced by the primoinfection or HHV-6 CNS invasion.26 In case of HH syndrome, only one patient has been reported with HHV-7 primoinfection.27 In this patient a PCR analysis was positive in the plasma while it was negative in CSF. The patient had a seroconversion for HHV-7 shown by a raise of anti-HHV-7 antibodies in plasma. Kawada et al. excluded a CNS invasion but they suggest a possible endothelial involvement leading to vascular disorder explaining the hemispheric involvement.27 Regarding the available data (Table 1), it is difficult to conclude on the involvement of HHV-6 and/or HHV-7 in HH/HHE syndrome pathogenesis. CSF analyses are frequently reported as normal. However, negative PCR result in CSF cannot exclude meningitis or meningoencephalitis. 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.28 Further investigations such as PCR from brain tissue as well as pathological investigations (immunostaining and electronic microscopy) are needed to investigate adequately this hypothesis.

7. Pathophysiological hypothesis (Fig. 2)

The pathophysiological mechanisms of HH/HHE syndrome remain unclear. Several factors might contribute to the pathogenesis of HH/HHE syndrome:

1. Seizure of long duration that may pass unnoticed leading to impairment of neuronal energy metabolism and excitotoxic cell injury.
2. Prolonged febrile seizure in whom inflammation may worsen the level of cell injury
3. Inflammation and prolonged ictal activity that act on blood–brain-barrier permeability
4. Predisposing factors facilitating prolonged seizure such as genetic factors and/or focal epileptogenic lesion.

The most surprising findings in HH syndrome is the evident involvement of one hemisphere. Here, we discuss the pathophysiological hypothesis of 1. the occurrence of cytotoxic edema, 2. restricted to one hemisphere. We suggest new hypothesis based on the current knowledge.

7.1. Occurrence of cytotoxic edema

First of all, it may be suggested that the hemispheric edema is a direct result of the focal febrile seizures. The question remains why we see so many children with prolonged and/or focal febrile convulsions who do not suffer similar consequences.

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 (see above).

In experimental studies, it has been shown that SE in immature brain result in moderate cell injury level.29,30 The immaturity of the brain structure cannot be taken into an account to explain a particular sensibility to brain injury. If long lasting SE in immature brain cannot explain such a level
of injury, it has been described that inflammation and hyperthermia may worsen acute consequence of SE.\textsuperscript{31–33} These factors may contribute to cell injury but it can explain the pathophysiology of HH syndrome. Moreover, hyperthermia and inflammation are also observed in prolonged FS.

It is now well established that prolonged SE act on Blood–Brain-Barrier (BBB). It is likely that the combination of inflammation and SE increase the leakage of the barrier. But it has not yet been proved in human. In experimental studies, it has been shown that prolonged SE induced by lithium–pilocarpine model was responsible of BBB leakage. These phenomena were observed in all adult animal, in 2/3 of P21 rats and none of P9 rats.\textsuperscript{34,35}

As described here, there are several hypotheses explaining a high level of cerebral injury leading to edema (Fig. 2). But none of them can explain why the edema is restricted to one hemisphere.

7.2. **Edema restricted to one hemisphere**

There is currently no explanation of the unilateral involvement of acute edema in HH syndrome. This acute phase is the start of definitive consequences observed in this disease such as hemiplegia and brain atrophy with epilepsy. There is currently no way to reverse these phenomena. A better understanding is necessary to improve our management of the patients. Here, we discuss new hypotheses.

- Regional maturation of brain structures across the development

A focal lesion or a restriction of the diffusion of the epileptic discharge to one hemisphere can be suggested. Bahi-Buisson et al. have suggested that the kinetics of regional cortical maturation could be involved.\textsuperscript{12} The major commissure connecting the cerebral hemispheres is the corpus callosum (CC). Its implication may be suggested. The CC changes structurally throughout life, but most dramatically during childhood and adolescence. During the first 10 years of life, the connections between the two cerebral hemispheres mature gradually. This coincides with improvement in interhemispheric integration during childhood, as has been shown behaviorally in many transfer tasks. It is possible that this developmental profile of CC play a role in bilateral synchronization of seizure discharge. Data are needed to confirm this hypothesis.

- Focal CNS infection by neurotrophic virus

The existence of a preexisting cerebral lesion modifying the cortical excitability has been suggested a long time ago. In HH syndrome, Gastaut has originally described ipsilateral structural abnormalities such as neonatal hypoxic–ischemic lesions and neuronal migration disorders.\textsuperscript{1} In the recent year, it appears that reported the HH syndromes are mostly idiopathic. This modification may be explained by the dramatic decrease of incidence of this condition. However, CNS viral infection may act as a focal trigger. As discussed above, HHV-6 and HHV-7 are neurotrophic virus. Moreover, several reports suggest that HHV-6 and HHV-7 infection may be associated with prolonged febrile seizures and status epilepticus.\textsuperscript{36,37} It is

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Fig. 2 — Current understanding of the pathophysiological mechanisms involved in HH/HHE syndrome.
still unclear if these virus by inducing fever act as a precipitating factor or if they cause both fever and focal invasion of the brain inducing in some case focal brain lesion leading to the occurrence of unilateral edema.

• CACNA1A gene hypothesis

Recently, a patient with HHE syndrome occurring during a B19 parvovirus infection has been reported with a heterozygous S218L mutation in CACNA1A gene. The genetic study of CACNA1A gene has been performed in this patient because of history of cerebellar ataxia and episodic unconsciousness with vomiting.38 The CACNA1A gene encodes the main subunit (1A) of the neuronal P/Q type voltage-gated calcium-ion channel.39 In humans, mutations in CACNA1A have been described in familial hemiplegic migraine (OMIM #141499) but also in epilepsy.40–44 In case of hemiplegic migraine, some reports may give us an insight of the occurrence of localized brain edema. Chabriat et al. first described a young woman with hemiplegic migraine (HM) due to CACNA1A gene mutation that had reversible reduction of water diffusivity in the brain during a prolonged attack of hemiplegic migraine.44 The diffusion changes were observed in the contralateral hemisphere 3 and 5 weeks after the onset of hemiplegia. These results suggest the occurrence of hemispheric cytotoxic edema during severe attacks of hemiplegic aura. The reduction of water mobility measured in the abnormal region strongly suggests the shrinkage of the extracellular space and the accumulation of intracellular water.45

One particular type of CACNA1A mutation, the S218L mutation, was found in patients who suffered from particularly severe attacks of HM which were triggered by trivial head trauma and were associated with often fatal excessive cerebral edema. Stam et al. found a de novo mutation in two patients with early seizures and cerebral edema after trivial head trauma.46 In these two patients, the edema was restricted to one hemisphere. Malpas T et al. reported a 5-year-old girl with severe HM induced by minor head trauma. She has a de novo mutation in CACNA1A (p. Arg1349Gln). She had a right-sided focal seizure on day 8, and on day 10 following the injury MRI demonstrated marked enlargement of the left cerebral hemisphere with generalized sulcal effacement and significant mass effect.47

Moreover, the role of other genes polymorphisms may be discussed. The ideal gene candidates should be genes that regulated both inflammation and edema. Bradykinin pathways should be investigated because bradykinin receptors are over-expressed in epileptic tissue.48 Moreover, it has been shown in a model of focal brain injury that the inhibition of bradykinin receptor leads to a lower level of BBB leakage and a lower level of injury.49

The Fig. 2 summarizes the different pathway that may be involved in hemispheric brain edema. The pathogenesis seems related to interplay among consequences of prolonged seizure activity, inflammation and hyperthermia. The involvement of genetic predisposition and viral infection are strongly suggested. But it remains to be proved in larger series.

The hemispheric brain atrophy is the result of the cytotoxic edema. The early decrease of NAA in MRI spectroscopy suggests the occurrence of an early neuronal involvement. Both hyperthermia and inflammation probably worsen the level of cell injury. Neuropathological data and MRI data have shown that the brain injury is not restricted to cortical and subcortical area. We found axonal damage in thalamus of the epileptic hemisphere.6 All these process lead to hemispheric atrophy.

8. Conclusion

IN the HH/HHE syndrome, early edema of the entire epileptic hemisphere is the initiation of a cascade that is not totally understood. The previous hypothesis of undiagnosed thrombosis seems to be currently excluded even if it is important to rule out this hypothesis in clinical practice. Moreover, experimental data do not suggest a particular vulnerability to cell injury during brain development. Prolonged seizure activity, hyperthermia, inflammation and blood brain barrier damage probably contribute to the pathogenesis of HH/HHE syndrome. Since these factors are also combined in prolonged febrile seizures, we think that additional factor(s) lead to HH/HHE pathogenesis. Regarding to the current knowledge, we suggest that genetic factors, progressive maturation of the corpus callosum or focal epileptogenic lesion may play a role in the HH/HHE syndrome pathogenesis. Data are needed to improve our understanding of this condition that is responsible of definitive motor impairment and refractory focal epilepsy. Prospective collaborative studies are needed.

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