

Hemiconvulsion-hemiplegia-epilepsy syndrome. Magnetic resonance findings in a 3-year-old boy

Zespół padaczkowy z drgawkami połowicznymi i porażeniem połowicznym. Wyniki badania za pomocą rezonansu magnetycznego u trzyletniego chłopca

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Abstract

The term 'hemiconvulsion-hemiplegia-epilepsy syndrome' (HHE) was first used by Gastaut *et al.* to describe the sequential combination of unilateral or predominantly unilateral clonic seizures (hemiconvulsion), occurring during the first 2 years of life, immediately followed by an ipsilateral flaccid hemiplegia lasting 7 or more days. In the following phase partial epileptic seizures occur.

We report a case of HHE syndrome in a 3-year-old boy with partial seizures (hemiconvulsion lasting 15-30 minutes) followed by left hemiplegia and hyporeflexia. Magnetic resonance imaging showed diffuse and high signal hyperintensity of the whole right cerebral hemisphere. Diffusion-weighted images showed a reduction of the apparent diffusion coefficient in the subcortical region. Magnetic resonance arteriography showed a narrow flow signal in the distal territory of the right middle cerebral artery. The authors emphasize the importance of neuroradiological findings in early diagnosis and in the follow-up of HHE syndrome.

Key words: hemiconvulsion-hemiplegia, epilepsy, magnetic resonance imaging.

Streszczenie

Określenia „zespół padaczkowy z drgawkami połowicznymi i z porażeniem połowicznym” (*hemiconvulsion-hemiplegia epilepsy* – HHE) użyli po raz pierwszy Gastaut i wsp., aby opisać połączenie jednostronnych lub głównie jednostronnych drgawek klonicznych, pojawiających się w pierwszych dwóch latach życia, po których następuje tożstronne wiotkie porażenie połowiczne utrzymujące się przez co najmniej tydzień. Następnie występują napady padaczkowe częściowe.

W artykule przedstawiono przypadek zespołu HHE u trzyletniego chłopca z napadami częściowymi (drgawki połowiczne trwające 15–30 minut), po których nastąpiło lewostronne porażenie połowiczne z osłabionymi odruchami głębokimi. W badaniu za pomocą rezonansu magnetycznego uwidoczono rozlane zmiany hiperintensywne w całej prawej półkuli mózgu. W obrazowaniu dyfuzji stwierdzono zmniejszenie współczynnika dyfuzji w obszarach podkorowych. W arteriografii rezonansu magnetycznego uwidoczono wąski sygnał przepływu w dystalnych gałęziach prawej tętnicy środkowej mózgu. Autorzy podkreślają znaczenie wyników badań obrazowych układu nerwowego we wczesnym rozpoznaniu i obserwacji chorych na HHE.

Słowa kluczowe: drgawki połowiczne z porażeniem połowicznym, padaczka, obrazowanie za pomocą rezonansu magnetycznego.

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Introduction

Gastaut *et al.* [1] initially described hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome in 1957 as an epileptic disorder characterized by occurrence of prolonged clonic seizures with unilateral predominance, followed by ipsilateral hemiplegia. The motor deficit could be transitory, with a full recovery within 1 to 12 months, or permanent. The causes of HHE are still unknown. Many factors are probably involved, including primary viral infections, genetic causes of prolonged febrile seizures and systemic factors such as hypoxia, hypoglycaemia, arterial hypotension and hyperthermia.

The debate over whether HHE is a direct consequence of prolonged ictal activity or is caused by excitatory neurotransmitter toxicity is still open.

The incidence of this syndrome has declined considerably in the industrialized countries in the past years, as a result of the improved management of status epilepticus. Brain magnetic resonance imaging (MRI) shows abnormal cerebral hemi-hyperintensity and diffusion-weighted imaging (DWI) may show signal changes related to decreased water diffusion in the white matter of one hemisphere in the acute phase, followed by hemiatrophy in the late phase.

Case report

A 3-year-old boy was the third son of non-consanguineous parents. The family history was positive for neurological disorders: the father and the older brother had presented febrile and non-febrile seizures, respectively; the maternal grandfather was affected by Parkinson disease. The child was delivered at term with an unremarkable perinatal history. He had presented motor delay (ability to sit reached at 9 months, uncertain gait at 3 years) and speech retardation (he was able to say 2-3 words at 3 years).

At the age of 14 months, he had presented a first episode of seizures, characterized by prolonged generalized hypotonia and loss of consciousness. The total duration of the episode was around 30 minutes and improved without medications. At the first admission to our unit, routine serological laboratory examinations and cerebrospinal fluid (CSF) analysis were normal. Electroencephalography (EEG) showed asymmetric rhythm with slow and low amplitude electrical activity in the right hemisphere. After two weeks, seizures were controlled by valproic acid (20 mg/kg/day).

For more than one year, his general conditions were good and he did not present any seizure. At 2 years and

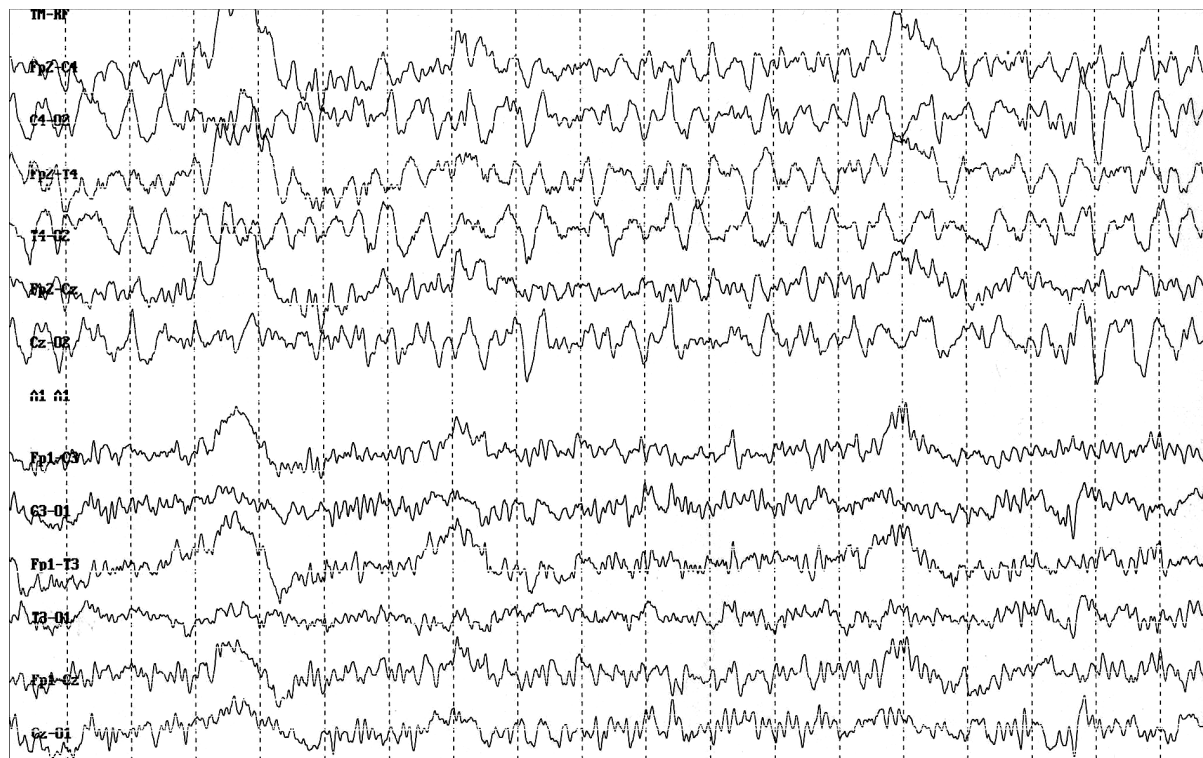


Fig. 1. Electroencephalography performed at the age of 14 months, showing asymmetric rhythm with slow and low amplitude electrical activity in the right hemisphere

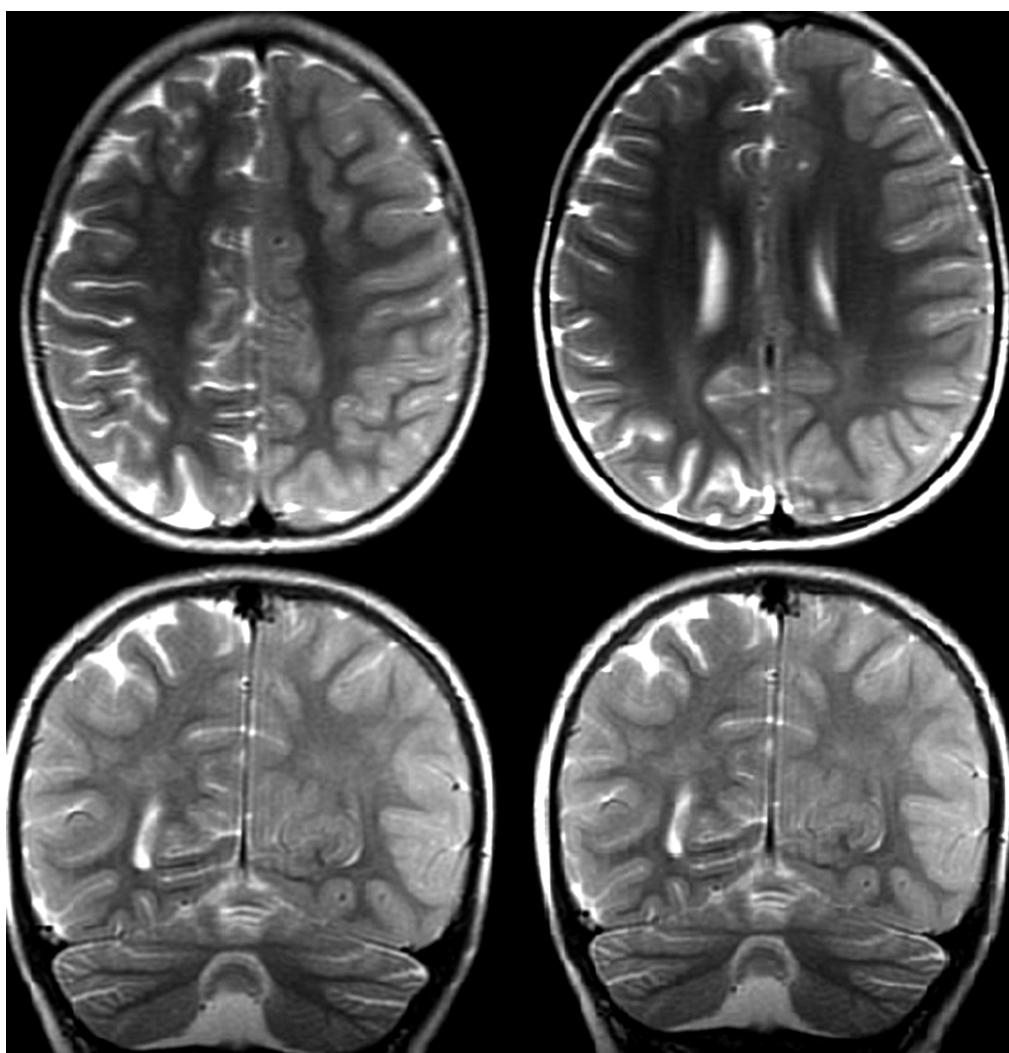


Fig. 2. Magnetic resonance imaging showing diffuse hyperintensity of the whole right cerebral hemisphere

8 months of age, the patient was again hospitalized for febrile seizures characterized by hypertonia in the right arm, fixed gaze and loss of consciousness for 20 minutes.

At 3 years and 8 months of age the patient presented an episode of loss of contact, fixed gaze and generalized hypotonia; also on this occasion, the crisis occurred during a febrile illness. At admission, his general conditions were poor and he presented sensory obtundation. At the neurological examination, asymmetry of the muscular tone with hypotonia and hypoesthesia on the left side was observed. Blood tests and CSF analysis were negative for infectious or inflammatory disease. EEG showed asymmetric activity with monotonous, slow rhythm and electrical activity of low amplitude in the right hemisphere (Fig. 1). Brain computed tomography was normal, but brain MRI showed diffuse hyperintensity of the whole

right cerebral hemisphere (Fig. 2). At the same time, other examinations were performed: a DWI examination showed that the subcortical U-fibers were predominantly involved with reduction of the apparent diffusion coefficient (ADC), while magnetic resonance arteriography (MRA) showed a narrow flow signal in the distal territory of the right middle cerebral artery (Fig. 3).

Intravenous antibiotic, antiviral and corticosteroid therapy was instituted. After two weeks, hypotonia and hypoesthesia improved. The patient was discharged with oral valproic acid therapy at the dosage of 25 mg/kg/day, and physiotherapy was recommended.

In the last two years, he has been regularly followed in our unit, and just after 6 months a recovery of the muscular tone has been observed, but he is still affected by mild hemiplegia. He did not present any seizure

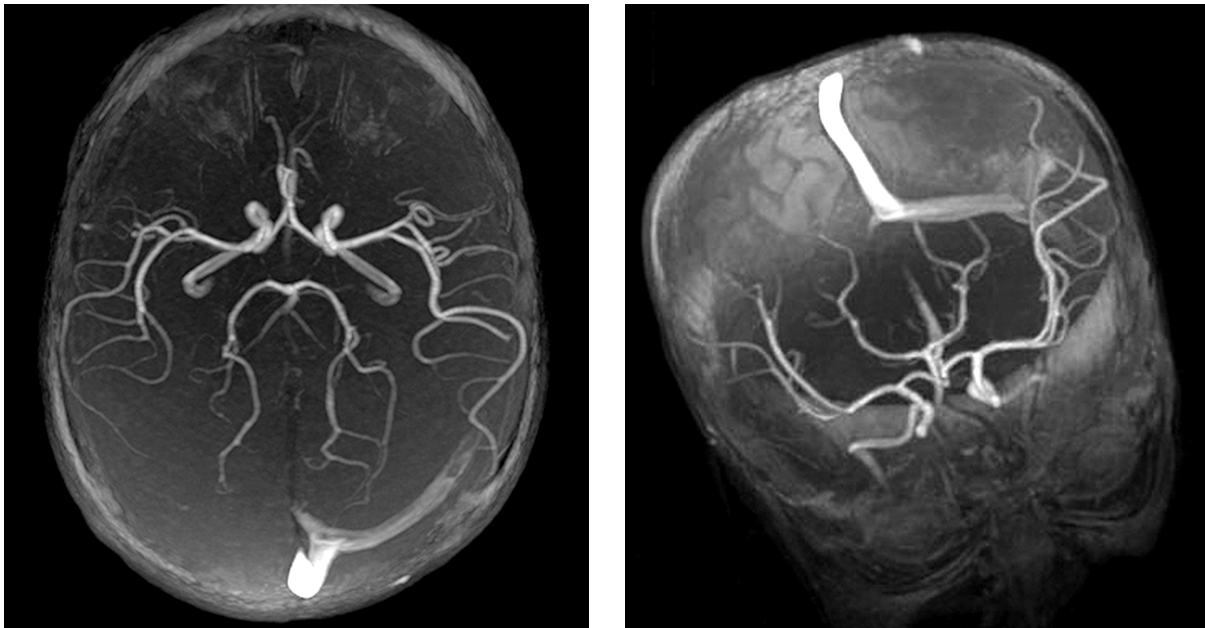


Fig. 3. Magnetic resonance angiography showing a narrow flow signal in the distal territory of the right middle cerebral artery

in the last years, but was affected by febrile episodes three times. EEG performed one year after the last seizure still showed an asymmetric rhythm with slow electrical activity in the right hemisphere. He presents mental retardation and I.Q., measured at the age of 6 years by the Wechsler Intelligence Scale for Children, fourth edition, was 72.

Discussion

Hemiconvulsion-hemiplegia-epilepsy syndrome can be considered as one of the cerebral hemispheric pathologies characterized by holohemispheric involvement. Acute infantile hemiplegia, Dyke-Davidoff-Masson syndrome and Rasmussen syndrome are included in this group. Rarer conditions associated with cerebral hemiatrophy are progressive facial hemiatrophy (Parry-Romberg syndrome), hemiplegic migraine, unihemispheric cerebral vasculitis and hemiatrophy with multiple developmental venous anomalies [2].

Hemiconvulsion-hemiplegia-epilepsy syndrome is the consequence of prolonged status epilepticus, which was first recognized by Gastaut in 1957 [1]. It is characterized by clonic epileptic seizures of long duration, which affect one side of the body during a febrile illness. The crises usually originate in the contralateral hemisphere [3] and are usually clonic, as seen in our patient, and often prolonged in the form of status epilepticus that

may persist for several hours [4]. Subsequently, a transient or permanent hemiplegia of various severity occurs. In a group of 73 patients reported by Aicardi *et al.* [5], the crises lasted more than 24 hours in 31 cases and more than six hours in 20 patients.

Two varieties of this syndrome have been recognized. Type I, symptomatic, frequently follows febrile seizure after acute cerebral disorders such as meningitis, encephalitis, subdural hematoma and vascular lesions [6]. Type II is an idiopathic status epilepticus with subsequent temporal lobe epilepsy [7].

This syndrome has a peak of incidence during the first 2 years of life, with 60-85% of cases occurring between 5 months and 2 years of age. Only a few cases have been reported after 4 years of age [8,9].

The etiopathogenesis of HHE syndrome has been widely discussed, but nowadays it still needs to be fully explained [10,11]. Involvement of a primary viral infection, including human herpes virus 7, Varicella-zoster and parvovirus B19, was reported [12-14]. In particular, Kawada *et al.* [12] suggested that human herpes virus 7 infections could determine the cerebrovascular disorder that causes HHE syndrome. Yamazaki and colleagues reported on a 5-year-old Japanese girl with HHE syndrome occurring after a parvovirus B19 infection. This girl manifested S218L mutation in the CACNA1A locus associated with familial hemiplegic migraine [14]. Other diseases associated with HHE syndrome are: L-2-hydroxyglutaric aciduria, inherited

protein S deficiency, factor V Leiden deficiency, contralateral focal cortical dysplasia, and elevated CSF levels of interleukin 6 [15,16]. These data cannot explain why lesions occur unilaterally. At least, according to other authors, lesions of HHE syndrome may also represent a direct consequence of prolonged, unilateral febrile seizures: this prolonged ictal activity could cause excessive neuronal excitation via *N*-methyl-*D*-aspartic acid (NMDA) glutamate receptors, resulting in increased levels of intracellular calcium causing cytotoxic edema and eventual necrosis and apoptosis [10,17,18].

The pathophysiology of HHE syndrome remains unclear. In 1960 Gastaut and colleagues suspected that inflammatory and vascular mechanisms or a pre-existing cerebral lesion (such as neuronal migration disorders and gliotic lesions) could modify the cortical excitability of the rolandic area and lead to HHE syndrome [19].

Risk factors for the development of HHE syndrome include young age at presentation of seizures (less than 4 years) and prolonged febrile status epilepticus. Hypoxia and excitotoxicity have been suggested to explain the seizure-associated damage. However, genetic vulnerability is likely to play a role in the pathophysiology of HHE syndrome because many children with prolonged focal seizures do not develop this pathology [15]. For this reason, a possible cause or trigger event should be investigated in children with HHE syndrome. Analysis of the CSF is indicated in all children presenting with HHE syndrome to exclude central nervous system infections [15].

Electroencephalography discharge associated with the primary hemiconvulsion is characterized by asymmetric high-voltage, rhythmic (2-3 Hz) slow waves, which may be unilateral but usually involve both hemispheres. The amplitude is higher in the hemisphere contralateral to the side affected by seizures. Onset of the ictal discharge is generally recorded in the central-posterior part of the hemisphere and the diffusion is rapid. Occasionally, especially at the end of seizures, spikes and slow waves may alternate like in a true spike-wave complex. Polygraphic recordings do not demonstrate any consistent relationship between muscle jerks and EEG discharge. The postictal pattern is characterized by a brief extinction of all rhythms, followed by delta slowing, with higher amplitude in the hemisphere ictally engaged, alternating with short periods of suppressed activity.

Immediately after the HHE episode, computed tomography may show swelling and edema of the hemi-

sphere involved while in the chronic phase neuroradiological studies have revealed cerebral hemiatrophy on computed tomography and MRI scans in all patients [15].

Neuroradiological studies in HHE patients have shown a sequential relation between early repetitive seizures, brain edema and cortical-subcortical atrophy [17]. Toldo *et al.* [11] demonstrated that seven days after the hemiconvulsion, abnormal images on MRI, T2-weighted sequences and DWI are limited to the white matter of one hemisphere and, one month later, severe gliosis and unilateral brain atrophy are already evident. DWI is more sensitive than conventional MRI in the early stages of this syndrome because it shows signal changes related to decreased water diffusion when conventional T1- and T2-weighted images cannot reveal any abnormalities. In our patient, DWI was very useful in detecting brain lesions even before the cerebral hemiatrophy became apparent. DWI may be useful to underline the presence of organic lesions in children with repeated seizures and it may also contribute to treatment decisions, to show therapeutic effects and to formulate prognostic hypotheses. In our case, the subcortical U-fibers were involved in DWI, showing a reduction of the ADC. MRA showed paucity of distal vessels in the right middle cerebral artery due to a hypothetical thrombotic event causing ischaemia.

The prognosis of HHE syndrome is variable and related to the side of the involvement. HHE syndrome affecting the left cerebral hemisphere can result in diffuse neuropsychological dysfunctions with a broad range of impairments, not limited to the affected cerebral hemisphere. The motor deficit has variable course, ranging from complete resolution to definitive hemiplegia. The evolution of epilepsy in HHE syndrome is favorable, the crises disappearing in adolescence. Many patients develop temporal lobe epilepsy or multifocal epilepsy [20]. Selected cases may require surgery. Callosotomy is preferable to hemispherectomy, but can lead to significant language impairment [3]. Long-term cognitive outcome has been poorly studied. Mirsattari *et al.* [21] demonstrated that right hemispheric or bilateral involvement is associated with atypical evolution consisting in language impairment and poor cognitive outcome as evidenced by intelligence and memory test scores. Furthermore, mental retardation has been reported to be a common feature in patients who have been affected by HHE [4,5], but it has been demonstrated that outcome can vary depending on which hemisphere is affected and mental retardation is not universal [18,21].

In the future, as reported by Tenney and Schapiro, it would be advisable to invest in research aimed at preventing cytotoxic damage acutely with the use of NMDA antagonists or aggressive, early treatment of cerebral edema [18].

In conclusion, HHE syndrome represents a diagnostic challenge for the pediatrician because, at the present time, specific serologic markers or characteristic radiological findings are not available. We underline the importance of neuroimaging techniques (especially MRI, DWI and MRA) for an early diagnosis of HHE. In particular, T2-weighted and DWI anomalies appear to correlate with parenchymal damage caused by prolonged ictal activity.

Disclosure

Authors report no conflict of interest.

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