Official Journal of the European Paediatric Neurology Society

Case study

Hemiconvulsion–Hemiplegia–Epilepsy syndrome associated with inflammatory-degenerative hystopathological findings in child with congenital adrenal hyperplasia

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ARTICLE INFO

Article history:
Received 25 July 2013
Received in revised form
16 October 2013
Accepted 1 November 2013

Keywords:
Hemiconvulsion–Hemiplegia
–Epilepsy
Congenital adrenal hyperplasia
Inflammation

ABSTRACT

Hemiconvulsion–Hemiplegia (HH) syndrome represents an uncommon consequence of prolonged unilateral clonic or hemiconvulsive status epilepticus in childhood, usually occurring during a febrile illness, followed by ipsilateral hemiplegia. The subsequent appearance of focal seizures configures the so called Hemiconvulsion–Hemiplegia–Epilepsy (HHE) syndrome. The pathogenesis of HH/HHE syndrome is still unclear. We describe the case of a 4 year-old girl with congenital adrenal hyperplasia (CAH) whom developed HH/HHE syndrome with drug resistant seizures at the age of 21 months and underwent left cerebral hemispherotomy at the age of 3 years and 6 months. Histopathological findings showed the presence of an underlying inflammatory-degenerative process. Disregulation of the inflammatory cascade has been proposed as one of the possible pathogenetic mechanisms underlying HH/HHE syndrome. To our knowledge however, this is the first report of an association with a histologically documented inflammatory process. The clinical and histopathological findings of our reported case lend support to the possible role of inflammation in the pathogenesis of HH/HHE syndrome.

1. Introduction

Hemiconvulsion–Hemiplegia (HH) syndrome, represents an uncommon consequence of prolonged unilateral clonic or hemiconvulsive status epilepticus in childhood, usually occurring during a febrile illness, followed by ipsilateral hemiplegia. In the acute phase, seizures are characterized by long-lasting hemiclonic seizures with variable topography, inconsistent impairment of consciousness, onset variability and presence of autonomic symptoms, associated with

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1090-3798/$ – see front matter
http://dx.doi.org/10.1016/j.ejpn.2013.11.001

controlateral rhythmical slow waves at the EEG, sometimes also present, with inferior amplitude, on the ipsilateral hemisphere.[1] A stable hemispheric global atrophy follows the acute phase, while focal seizures appear after a period which may be as brief as one month but can last several years depending on the reporting author,[1] configuring the so called Hemiconvulsion–Hemiplegia–Epilepsy (HHE) syndrome. This phase is mainly characterized by complex partial seizures originating from the temporal lobe, sometimes accompanied by focal motor seizures and/or generalized seizures. The pathogenesis of HH/HHE syndrome is still a matter of debate. So far, the proposed pathogenetic models pointed towards neuronal injury induced by excitotoxicity and/or venous thrombosis,[1] however in many patients no cause is obvious and reports on histopathological findings are scarce.[2] Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease characterized by impairment of cortisol biosynthesis. The association between CAH and HH/HHE syndrome has been previously reported and a possible link with inflammatory mechanisms has been proposed, however no histopathological evidence supporting such hypothesis was so far available. We describe the clinical characteristics and histopathological findings of a 4 year old girl with CAH whom developed HH/HHE syndrome.

2. Case report

2.1. *History of CAH*

N.D. is a 4 year old Caucasian girl with no family history of epilepsy or febrile convulsions. She was born at term. Pregnancy was complicated by threat of miscarriage during the 7th gestational month. At birth, evidence of a hypertrophic clitoris prompted an endocrinological evaluation. Ultrasonography showed hypertrophic surrenal glands. Diagnosis of CAH was made at day 10 and replacement therapy with glucocorticoids was initiated. Corrective surgery of clitoris was performed at age 9 months. Psychomotor development was normal.

2.2. *Acute phase and onset of HHE*

Seizure onset was triggered by a febrile episode associated with diarrhea and vomit, at 21 months, and was characterized by right-sided hemiclonic status epilepticus (SE) followed by transitory homolateral hemiplegia. Electroencephalogram (EEG) showed asymmetrical background activity with left-sided depression and sharp waves over the frontal electrodes. The SE lasted several hours and was treated with midazolam, phenobarbital and phenytoin. During the acute phase, brain magnetic resonance with spectroscopy showed cytotoxic edema of the left hemisphere and a peak in lactate levels. Screening for Rotavirus infection was positive in blood and serum, but not in cerebral spinal fluid (CSF). CSF screening (physical–chemical analysis, viral DNA for HSV1, HSV2, HHV6, HHV8, VZV, CMV, EBV, viral RNA for enterovirus) was negative. She was discharged after 5 days of prolonged fever with phenobarbital and phenitoine oral therapy. At discharge, she showed right-sided hemiplegia which progressively evolved towards a stable hemiparesis. After two months the child developed drug-resistant right-sided hemiclonic seizures. Different combinations of antiepileptic drugs (phenitoine and phenobarbital, valproic acid and phenobarbital, valproic acid and levetiracetam, valproic acid and ethosuximide) proved ineffective. EEG at this time showed persisting left-sided depressed background activity associated with multifocal epileptiform anomalies over the left central–parietal area with controlateral diffusion. A two month seizure free period was later obtained with a 3 day cycle of glucocorticoids. After such period seizures reappeared. They were characterized by clusters of atonic seizures, multiple daily episodes of right upper limb myoclonias or sleep related right-sided tonic seizures. Clobazam was added to valproic acid and ethosuximide, but was ineffective. Serial magnetic resonance scans showed stable atrophy of the left hemisphere (Fig. 1).

2.3. *Presurgical evaluation and follow-up after surgery*

N.D. first came to our attention at age 3. Video-EEG monitoring showed asymmetrical background activity, characterized by normal organization of the right hemisphere and by slow theta–delta rhythms of lower voltage over the left hemisphere. Interictal activity during wake was characterized by asynchronous and arrhythmic medium-voltage spikes over the left hemisphere, which sometimes gave way to brief trains of slow spike-wave complexes at 1 Hz. During sleep, frequent brief trains of polyspike-wave complexes were recorded over the left parietal–temporal area (Fig. 1). Ictal EEG showed brief rhythmic sequences of medium voltage spikes at 8 Hz over the left central–parietal–temporal area lasting 4–8 s, clinically correlated with right facial and upper limb hypertonus. Neuropsychological testing revealed mild cognitive delay. The child underwent left cerebral hemispherotomy at the age of 3 years and 6 months. Bioptic material was obtained from a left frontal corticectomy. To date, after a 6 month follow-up period, the child is seizure free and undergoing neurorehabilitation. Antiepileptic drug treatment is being gradually withdrawn.

2.4. *Histopathology*

The surgical specimen consisted of a frontal lobe sample of $3.5 \times 2.5 \times 1.5$ cm in dimension. The arachnoid membrane was thickened and the parenchyma was edematous. Microscopic evaluation showed a dense inflammatory lymphomonocytic infiltrate of the arachnoid and of the subarachnoidal space with several clusters of perivascular monocytes (anti-CD68 10×) (Fig. 1). The cortical tissue was characterized by preservation of the laminar structure, mild increase in glial cells and focal satellitosis. Scattered neurons showed cytoplasmic shrinkage, dismorphism and pyknosis. The cortical-white matter junction was sharp. The white matter presented inflammatory and degenerative features (EE 10× e EE 20×) (Fig. 1) characterized by presence of diffuse foamy macrophages, microglial activation, spongiosis and moderate lymphoid infiltration, with perivascular distribution (CD4 20×) (Fig. 1). Immunophenotyping showed a mixed population composed of macrophages (50%), T-lymphocytes (30%, with mild