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Early-onset absence epilepsy at eight months of age

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ABSTRACT – Early-onset absence epilepsy refers to patients with absence seizures beginning before age four and comprises a heterogeneous group of epilepsies. Onset of absence seizures in the first year of life is very rare. We report a girl with intractable absence seizures with onset at age eight months. Her seizures were characterised by loss of responsiveness, with eyes drifting upwards and some myoclonic jerks of the upper and lower limbs. These symptoms were accompanied by bilaterally symmetric high-amplitude 2-2.5 Hz generalised spike-and-wave discharges on the electroencephalogram. Her seizures were refractory to conventional antiepileptic drugs; treatment with adrenocorticotropic hormone was transiently effective. Comprehensive metabolic screening, cytogenetic, and genetic analysis did not determine an underlying cause of her condition. Patients with intractable, very early-onset absence epilepsy with a myoclonic component have an unfavourable outcome and may be classified under a new epileptic syndrome, such as *"early infantile absence epilepsy"*.

Key words: early-onset, absence, early infancy, ACTH

Epileptic absences are the result of generalised non-convulsive seizures. Childhood absence epilepsy (CAE), a well-defined form of idiopathic generalised epilepsy, is characterised by typical absence seizures with onset usually between ages four and 10 years (Hirsch and Panayiotopoulos, 2005). Early-onset absence epilepsy generally refers to patients with absence seizures beginning before four years of age (Suls *et al*., 2009) and comprises a heterogeneous group of epilepsies with varied aetiology, clinical features, and outcome. Among the clinical features, onset in the first year of life is very rare. To date, only five patients have been described in two reports (Cavazzuti *et al*., 1989; Guerrini *et al*., 2002). Recently, glucose transporter type 1 (GLUT1) deficiency syndrome has been reported as one of the underlying causes of early-onset absence epilepsy (Suls *et al*., 2009), however,

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early-onset absences are still difficult to classify with regards to established syndromes.
To provide new data regarding the atypical clinical features and treatment of early-onset absence epilepsy, we report a patient with intractable absence seizures with an onset at age eight months.

Case report

A female patient was born at 39 weeks gestational age by spontaneous delivery. Pregnancy, labour, and neonatal period were uneventful. At birth, body weight was 2,990 g, body length was 47.3 cm, and head circumference was 33.0 cm. Her father suffered from Brugada syndrome and underwent implantation of a cardioverter defibrillator. Her early development was almost normal; her first smile was observed at two months of age, head control at three months, and she was able to roll over at six months. At the age of seven months, she began to have unconscious episodes with deviation of the eyes for one to two minutes. Her EEG was normal at seven months of age. At the age of eight months, she had multiple daily episodes of vacant staring and interruption of motor activity, each lasting a few seconds. She was considered to have partial seizures and was started on treatment with carbamazepine at eight months of age by the referring doctor, however, this was not effective. Soon after, carbamazepine was replaced by sodium valproate at nine months of age.

When she was referred to our hospital at age 10 months, seizures were not controlled despite an optimal dose of sodium valproate. Her weight was 7.5 kg (-1.1 SD), height was 71 cm (-0.1 SD) and head circumference was 46 cm (+1.1 SD). Neurological examination revealed slight hypotonia without muscle weakness. Her psychomotor development was delayed; she was able to roll over, but was unable to sit alone and crawl by herself.
Her seizures were marked by loss of responsiveness with eyes drifting upwards and some mild myoclonic movement of the upper and sometimes lower limbs. The seizures occurred 30-50 times per day, with duration varying between four and seven seconds.
At 10 months of age, her ictal EEG demonstrated high-amplitude 2-2.5 Hz generalised spike-and-wave complexes (*figure 1*). The onset and end of spike-and-wave discharge were abrupt. Interictal EEG also revealed infrequent bursts of generalised slow spike-and-wave discharges, particularly in sleep. The background rhythm was slow for her age, with a maximum posterior dominant rhythm of 3-4 Hz. Intermittent photic stimulation was not performed.
Her laboratory findings were normal, including CSF analysis, blood amino acid analysis, and urine organic acid analysis. Twelve-lead electrocardiograms (ECGs) and brain MRI were normal. Interictal single photon emission computed tomography showed slight hypoperfusion of the right basal ganglia compared to the opposite side. Results of peripheral blood lymphocyte standard chromosomal analysis and subtelomeric

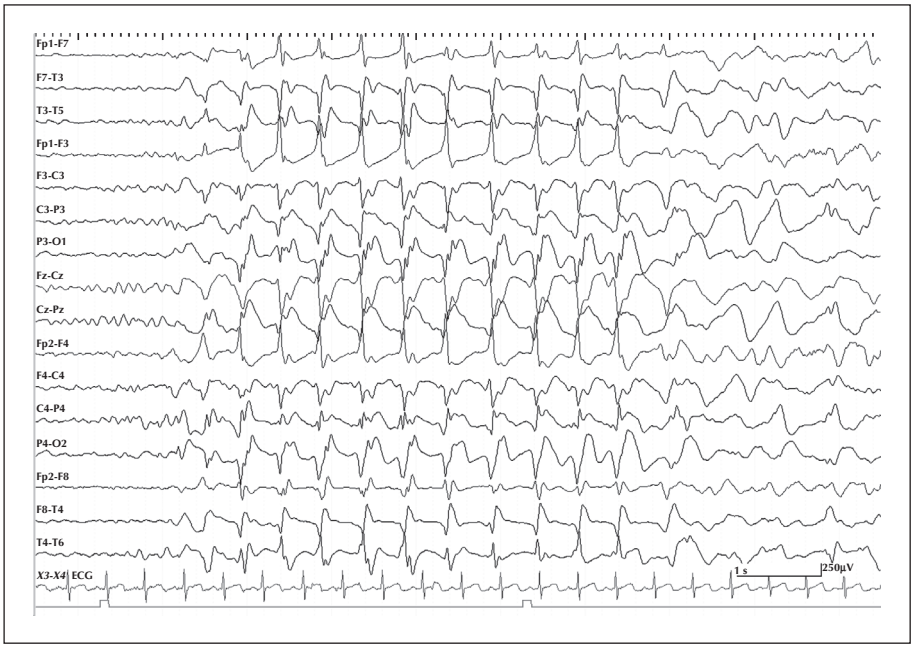

Figure 1. Ictal EEG at the age of 10 months showing a paroxysm of symmetric and synchronous generalised spike-and-wave discharges at 2 Hz, lasting 6 seconds.

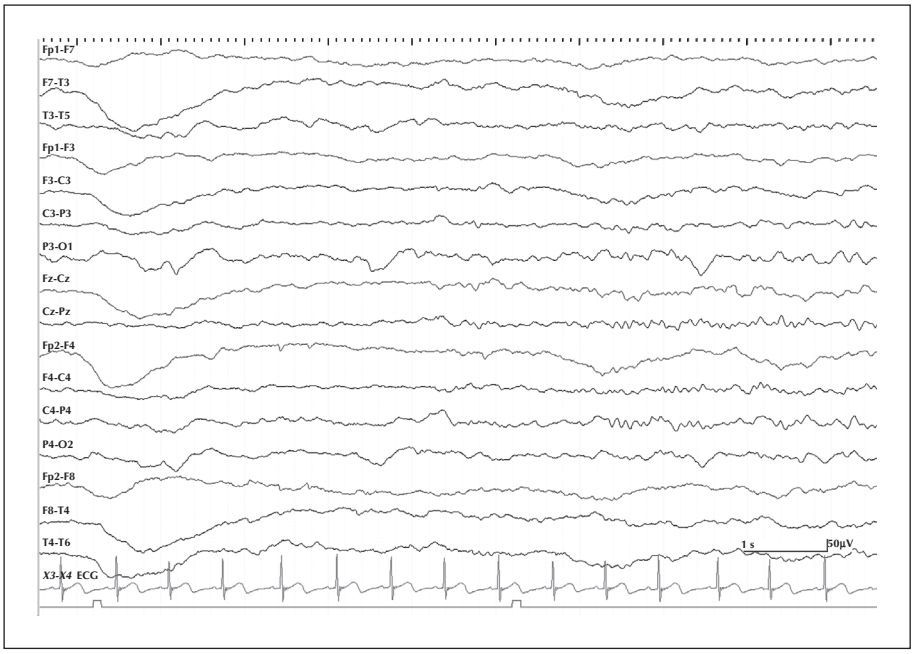

Figure 2. Interictal EEG during sleep at the age of 13 months after ACTH therapy. Epileptic discharges disappeared.

fluorescence *in situ* hybridization (FISH) analysis were normal. In addition, the patient underwent genetic testing for Angelman syndrome and GLUT1 deficiency, including FISH at D15S10 locus, the *SNURF-SNRPN* DNA methylation test, sequencing of *UBE3A*, and sequencing of *SLC2A1*, the gene encoding the GLUT1 glucose transporter. All genetic tests were normal.

The patient's absence seizures were refractory to conventional antiepileptic drugs such as sodium valproate, clonazepam, ethosuximide, zonisamide, and vitamin B6. Treatment with adrenocorticotropic hormone (ACTH) was started at 12 months of age, and successfully controlled her seizures with an improved EEG (*figure 2*). However, the seizures relapsed only one week after ACTH therapy was completed. Subsequently, treatment with lamotrigine and clobazam was started and the frequency of the seizures further decreased to only a few per day.

Despite the reduction of seizure frequency, her psychomotor development was delayed. She had become able to sit without support at age 13 months, but was unable to walk and spoke no meaningful words at age 24 months.

Discussion

The seizures in our patient were categorised as complex absence seizures with a mild myoclonic component based on the presence of rhythmic myoclonic movement of the upper and lower limbs during the seizure and ictal discharges of 2-2.5 Hz generalised spike-and-wave complexes on EEG. Her ictal EEG showed a discharge with regular rhythm, a constant spike-and-slow-wave pattern and abrupt onset and termination. Thus, based on clinical and EEG characteristics, our patient conformed to a diagnosis of absence epilepsy. Early onset of absences is not common. Chaix *et al*. (2003) stated that such patients represent ~1% of epilepsies with onset before age three. Above all, onset in the first year of life is very rare. Cavazzuti *et al*. (1989) first reported a case with typical absence seizures at age 6.5 months. In addition, Guerrini *et al*. (2002) described six children with a clinical syndrome associating early-onset absence epilepsy with paroxysmal dyskinesia. Four of the six children had their first episodes within the first year of life, giving a total of just five previous reported cases. The present case represents the sixth reported case of early-onset absence epilepsy with onset during the first year of life.

In a previous study regarding absence epilepsy with onset before age three, significant heterogeneity was reported (Chaix *et al*., 2003). In that study, some patients fulfilled the criteria for CAE or epilepsy with myoclonic absence (EMA), but such patients were only a minority among those with early-onset absences. EMA is characterised by rhythmic and bilateral myoclonic jerks of severe intensity with impairment of consciousness. The jerking of the arms is commonly accompanied by progressive elevations of the upper extremities. The EEG shows a rhythmic

spike-and-wave discharge at 3 Hz. Verrotti *et al*. (1999) described EMA with early onset at between six and 27.8 months. Our patient exhibited mild myoclonic movement of the upper and lower limbs, but tonic contraction was slight. Thus, our case was different from EMA. Lennox-Gastaut syndrome (LGS) can also present with atypical absence seizures during infancy. Our patient's condition was distinct from LGS, as demonstrated by the lack of tonic seizures and rapid rhythms on the EEG during sleep.

Some genetic syndromes and metabolic diseases are known to cause absence seizures during early infancy. In Angelman syndrome, the onset of epilepsy occurs in infancy or early childhood for most patients and atypical absence seizures are one of the main ictal phenomena. Recently, GLUT1 deficiency was reported as one underlying cause of early-onset absence epilepsy (Suls *et al*., 2009). In our patient, the CSF/plasma glucose ratio was normal and the results of cytogenetic and molecular tests excluded these two disorders.

It has been reported that some patients with generalised epilepsy with febrile seizures plus (GEFS+), associated with mutations in *SCN1B* and *GABRG2*, develop early-onset absence epilepsy (Audenaert *et al*., 2003; Marini *et al*., 2003). However, early-onset absence epilepsy is now considered to be uncommon in the GEFS+ spectrum. Although our patient was not tested for gene mutation associated with febrile seizures, it is unlikely that our patient's condition was associated with mutations of these genes, given the developmental delays and lack of febrile seizure.

Synchronous spike-and-wave discharges before one year of age are scarcely observed. As West syndrome in the first year evolves into LGS with more synchronous spike-and-wave discharges, the association between cerebral maturation and synchronisation of the spike-and-wave discharges seems to be crucial. To generate synchronous spike-and-wave discharges of typical absence seizures, a thalamocortical oscillatory system which includes neocortical neurons, the thalamic relay neurons, and neurons of the nucleus reticularis thalami seems to play a major role (Arzimanoglou *et al*., 2004). In contrast, in a rat model of atypical absence seizures, ictal discharges generalise well beyond the thalamus and cortex, extending to include hippocampal circuitry (Cortez *et al*., 2001). Although it is not known exactly why synchronous spike-and-wave discharges occur at such an early age, as in our patient, it is assumed that some specific genetic factors may affect the role of cerebral maturation and the stability of neurotransmitters in the immature brain by involving the cortex and/or the deep structures.

ACTH therapy was used to treat our patient's absence seizures. It is generally accepted that ACTH is useful for the treatment of West syndrome. ACTH has also been reported to be effective in patients with intractable generalised seizures other than spasms, particularly in patients with atypical absence seizures compared to those with other generalised seizures such as brief tonic, atonic and myoclonic seizures (Okumura *et al*., 2006). In our patient, it is notable that ACTH therapy at one year was transiently effective without adverse events; absence seizures ceased and the EEG improved. Her seizures recurred after completing ACTH therapy, but were partially controlled with subsequent antiepileptic treatment. These results suggest that ACTH therapy may lessen epileptic activity underlying absence seizures.

In one reported case of a 6.5-month-old patient (Cavazzuti *et al*., 1989), absence seizures were easily controlled by administering nitrazepam. However, resistance to multiple drugs was observed in five other patients with early-onset absence seizures and paroxysmal dyskinesia (Guerrini *et al*., 2002). Covanis (1998) reported 19 cases with typical absence seizures at less than three years of age. Among these patients, relapses after antiepileptic drug withdrawal were common in the myoclonic group (70%), compared to the non-myoclonic group (20%), even after a long duration of successful therapy of 4.3 ± 0.8 and 6.6 ± 3 years, respectively. Patients with intractable very early-onset absence epilepsy with myoclonic component or dyskinesia have a more unfavourable outcome than those with classic CAE (Covanis, 1998; Chaix *et al*., 2003). Early-onset absence epilepsy does not represent a homogeneous group, but rather an association of variable conditions related to aetiology, EEG pattern, and evolution. Among these, some patients with a myoclonic component, including the present case, might form a homogenous subgroup of intractable epilepsy and may be classified under a new epileptic syndrome such as *"early infantile absence epilepsy"*. To establish a new category of early-onset absence epilepsy, identification and characterisation of more patients will be necessary. □

Disclosure.

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None of the authors has any conflict of interest to disclose.

Legend for video sequence

This video shows an absence seizure with mild rhythmic myoclonic movement of the upper and lower limbs at 11 months old.

Key words for video research on www.epilepticdisorders.com
Etiology: unknown
Phenomenology: myoclonic seizure, absence seizure
Localization:—
Syndrome: idiopathic generalized not specified

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