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Early-onset absence epilepsy aggravated by valproic acid: a video-EEG report

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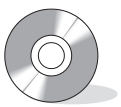
ABSTRACT – Early-onset absence epilepsy refers to patients with absence seizures beginning before age 4 and comprises a heterogeneous group of epilepsies. Onset of absence seizures in the first year of life is very rare. We report a boy with absence seizures with onset at age 11 months, whose seizures increased in frequency after the introduction of valproic acid (VPA) treatment and substantially improved upon cessation of treatment. The mechanism of seizure worsening did not involve VPA toxicity, encephalopathy, Glut-1 deficiency or overdosage, and the reason for absence seizure aggravation remained unclear. The patient showed complete control of absence seizures with levetiracetam treatment and the course was benign, both in terms of seizure control and neuropsychological aspects. The similar overall electroclinical picture and outcome between children with early-onset absences and those with CAE support the view that these conditions are a continuum within the wide spectrum of IGE. [*Published with video sequences*]

Key words: early-onset absence epilepsy, myoclonic epilepsy of infancy, seizure worsening, GLUT-1 deficiency

Seizure aggravation induced by AEDs is a rare phenomenon and occurs mostly in generalised epilepsies treated with drugs that are particularly efficacious against partial seizures. AEDs may aggravate the existing seizures or induce a new seizure type (Genton, 2000; Striano *et al*., 2008). Less commonly, in patients with idiopathic generalised epilepsies (IGEs), broad-spectrum AEDs, such as lamotrigine, levetiracetam (LEV), topiramate, zonisamide, and, rarely, valproic acid (VPA), can also exacerbate seizures (Striano and Belcastro, 2012). Exacerbation of seizures by VPA appears to be relatively rare and most events are considered to induce encephalopathy. VPA-induced seizure aggravation without encephalopathy has been reported only in a few patients with childhood absence epilepsy (CAE) (Lerman-Sagie *et al*., 2001) or juvenile absence epilepsy (JAE) (Buechler and Buchhalter, 2007).



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We report a boy with early-onset absence seizures associated with myoclonic seizures whose episodes increased in frequency after the introduction of VPA treatment and substantially improved upon cessation of treatment. We also review the electroclinical features of early-onset absence seizures and the role of *SLC2A1* screening in IGE featuring absence epilepsies starting in the first year of life.

Case report

A 36-month-old boy was born from non-consanguineous parents after a full-term pregnancy. His family history was remarkable for febrile seizures (FS) and autosomal dominant IGE, featuring absence seizures with variable age at onset. A simple FS was reported at the age of 6 months. The neonatal period and growth were normal until the age of 11 months, when the parents noted that the boy was experiencing stereotyped daily episodes of staring spells associated with brief and isolated jerks of the upper limbs. At that time, a video-EEG recording was obtained. During wakefulness, the interictal EEG recording was normal and intermittent photic stimulation (IPS) was unremarkable, while in a state of drowsiness, a discharge comprising a generalised 3-4-Hz spike-wave with interposed fast polyspikes was observed (*figure 1*). The ictal video-EEG recording showed a short absence seizure with brief upward rotation of the eyes and a mild clonic component of the upper limbs (*see video sequence*). EEG epileptiform discharges were not enhanced in slow sleep.

The patient was started with VPA treatment at a dosage of 20 mg/kg body weight (65.5 μg/mL) but brief absences seizure occurred two to three times, daily. For this reason, VPA dosage was increased to 30 mg/kg body weight. Of note, the parents observed a dramatic daily increase in the frequency of absence seizures. To exclude the possibility that VPA intoxication might have caused the increase in absence seizure frequency, serum levels were obtained, however, serum levels of VPA did not show any significant change (*i.e.* 85.5 μg/mL). Moreover, routine blood analyses and ammoniemia were normal. The video-EEG recording performed in a state of drowsiness showed an absence seizure with a mild clonic component of the upper limbs and brief upward rotation of the eyes. Moreover, during slow sleep, frequent generalised 3-4-Hz spike-and-wave complexes with interposed fast polyspikes were also observed (*figure 2*).

To exclude the possibility that VPA might have caused the increase in seizures, the drug was progressively discontinued over a few days and LEV, at 20 mg/kg body weight, was added. Notably, VPA withdrawal was associated with a sustained reduction of seizures. With LEV at 20 mg/kg body weight, he did not experience any seizures. *SLC2A1* gene testing was negative.

At the last follow-up visit, LEV was definitively withdrawn and no seizures occurred. Moreover, the course was benign, both in terms of seizure control and neuropsychological aspects.

Discussion

Early-onset absence epilepsy (EOAE) includes a heterogeneous group of epilepsies with different electroclinical features and prognosis (Caraballo *et al*., 2011). Among patients with EOAE, those who meet Panayiotopoulos' criteria for typical absence epilepsy (Panayiotopoulos, 2008) have a prognosis comparable to that of CAE and it is not advisable to methodically screen these cases for *SLC2A1* gene mutations (Agostinelli *et al*., 2013). In our case, we screened *SLC2A1* mutations because of: i) the family history for IGE with dominant inheritance and absence epilepsy as the prominent feature (Striano *et al*., 2012); ii) the presence of short absence seizures with early onset and myoclonic seizures which have been associated with Glut-1 deficiency syndrome (Suls *et al*., 2009); and iii) the fact that VPA may interfere with brain glucose metabolism and, thus, exacerbate Glut-1 deficiency (Wong *et al*., 2005), leading to seizure aggravation.

Our patient showed an increase in absence seizure frequency with VPA medication, particularly at the dosage of 30 mg/kg body weight. Interestingly, VPA treatment has only been mentioned in association with absence seizure worsening in a few reports (Lerman-Sagie *et al*., 2001; Buechler and Buchhalter, 2007). In our patient, the mechanism of seizure worsening does not involve toxicity, encephalopathy, Glut-1 deficiency or overdosage, and the reason for absence seizure aggravation is unclear. The increase of the seizures may be due to a paradoxical mechanism (Thomas *et al*., 2006). However, to the best of our knowledge, this is the first report of absence seizure aggravation induced by VPA in a patient with EOAE.

The electroclinical features of our patient corresponded to myoclonic epilepsy of infancy (MEI). Although myoclonic seizures are rarely associated with other seizure types in such patients, except rare simple FS (Dravet and Bureau, 2005), absence seizures with early onset have been described in patients with electroclinical features of BMEI (Darra *et al*., 2006; Caraballo *et al*., 2011). Recently, Caraballo *et al*. described 18 patients with complex absence seizures associated with myoclonic seizures with good outcome. Interestingly, the authors found that the majority of children with absence seizures, that started in the first three years of life, had associated myoclonic seizures (Caraballo *et al*., 2011). Our patient falls into

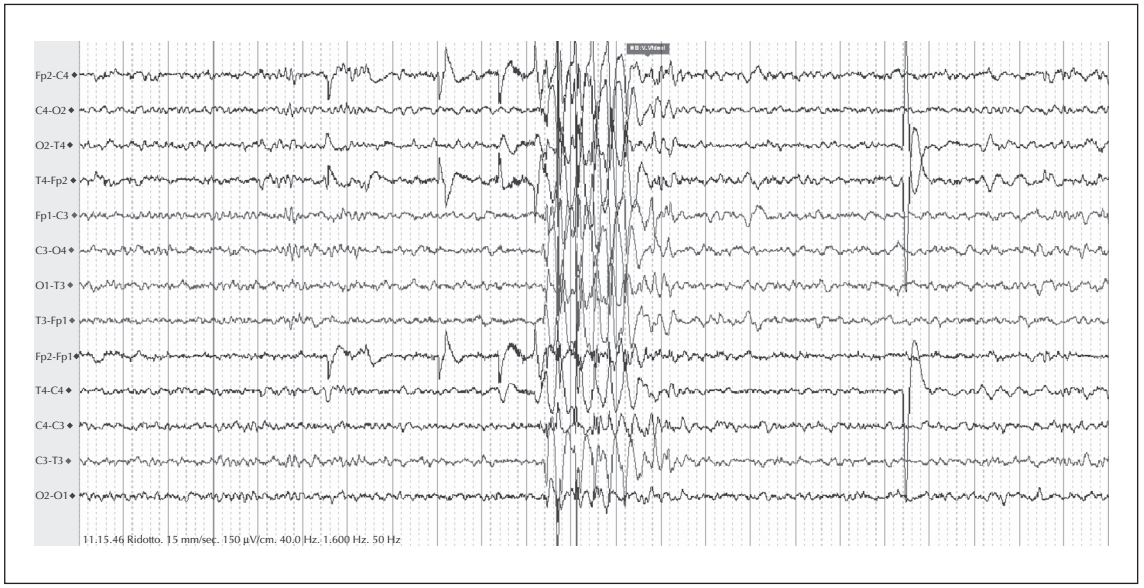

Figure 1. Generalised 3-4-Hz spike-waves with interposed fast polyspikes coincide with a short absence seizure with brief upward rotation of the eyes and a mild clonic component of the upper limbs.

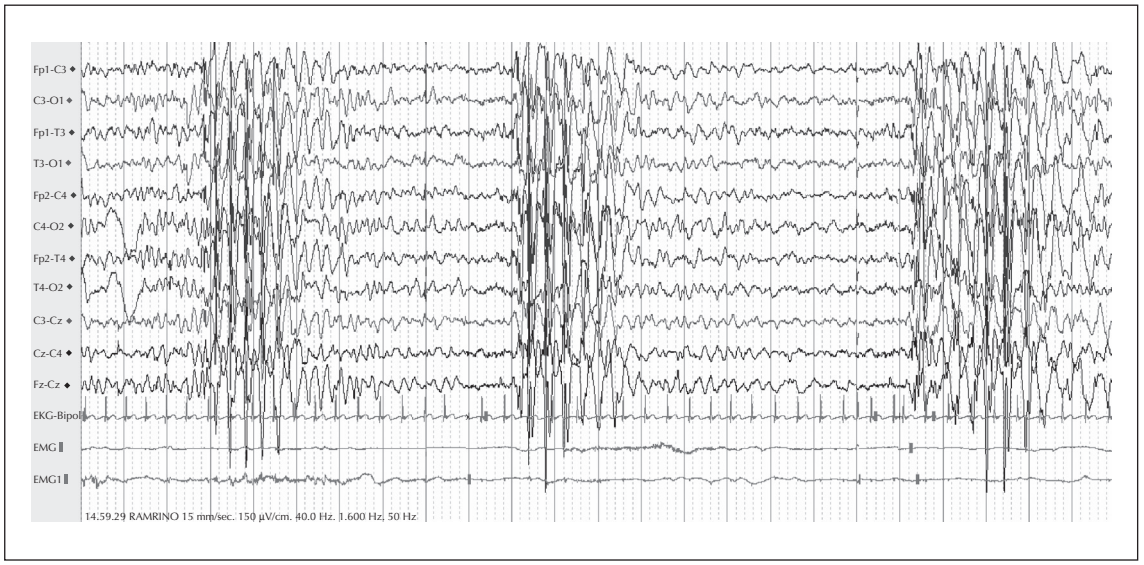

Figure 2. During slow sleep, with VPA treatment, the boy shows frequent generalised 3-4-Hz spike-and-wave complexes with interposed fast polyspikes.

this group of EOAE. Since the 1960s (Doose *et al*., 1965) and in the following years, several authors reported an epileptic condition characterised by absences with onset in early childhood and, in some reports, onset of absences which occurred at a few months of age (Aicardi, 1995; Suls *et al*., 2009; Caraballo *et al*., 2011; Agostinelli *et al*., 2013). Before the age of 3, absence seizures may differ from those of CAE; they may occur with a lower frequency and irregular 3-4-Hz spike-and-wave complexes may be present during the ictal EEG (Panayiotopoulos, 2005). Of note, typical absences starting in early childhood may be the first manifestations of various IGE syndromes (Doose, 1994). Interestingly, our patient demonstrated complete control of absence seizures as well as myoclonic seizures with LEV treatment, moreover, epilepsy remission was similar to that reported for patients with CAE.

We consider that absence seizures may start in the first years of life, as the main type of seizure, in well-defined epileptic syndromes, such as MEI, as shown in the video-EEG recording. The strong similarities regarding the overall electroclinical picture and outcome

between children with early-onset absences and those with CAE support the view that these conditions are a continuum within the wide spectrum of IGE (Mangano *et al*., 2011). □

Disclosures.
The authors do not have any conflict of interest to disclose and did not receive any fund for this study.

Legends for video sequences

The ictal video-EEG recording shows generalised 3-4-Hz spike-waves that coincide with a short absence seizure with brief upward rotation of the eyes and a mild clonic component of the upper limbs.

Key words for video research on www.epilepticdisorders.com

Syndrome: childhood absence epilepsy (CAE)
Etiology: AED aggravation
Phenomenology: absence (dialeptic) seizure
Localization: not applicable

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