Original article

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De novo absence status epilepticus in three paediatric patients: a new idiopathic epilepsy syndrome?

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ABSTRACT – *Aim*. Absence status epilepticus (ASE) is a prolonged generalized absence seizure that usually lasts for hours and can even last for days. The main symptom is the altered content of consciousness while the patient may be alert and partly responsive.
Methods. We describe the electroclinical features, treatment, and evolution of three paediatric patients with *de novo* ASE with an excellent response to valproic acid (VPA).
Results. Three paediatric patients presented with non-convulsive status epilepticus and an acute confusional state with impaired consciousness and EEG abnormalities compatible with typical ASE, associated with generalized spike-and-wave paroxysms at 2.5-4 Hz, as the first epileptic manifestation at eight, three, and nine years of age, respectively. No significant personal and/or family history was reported. None of the patients had absence seizures or any other type of seizure before the occurrence of the ASE. All of them responded well to VPA and had a benign disease course. Neuroradiological imaging was normal in all patients. These three cases presented with ASE as the first manifestation of their epilepsy; none of them had any other type of seizure before the event or during their follow-up, which was long-term in one. All patients had an excellent response to VPA.
Conclusion. Our three cases presented with generalized typical ASE as the first manifestation of their epilepsy. *De novo* ASE might be considered as a well-defined idiopathic epilepsy syndrome or a variant of an idiopathic generalized epilepsy syndrome, such as a particular type or variant of childhood absence epilepsy.

Key words: absence, benign, childhood, *de novo*, status epilepticus, confusional state, NCSE

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Absence status epilepticus (ASE) is a prolonged generalized absence seizure that usually lasts for hours and can even last for days. The main symptom is the altered content of consciousness while the patient may be alert and partly responsive (Shorvon and Walker, 2005). Most patients suffer from idiopathic genetic generalized epilepsy, such as juvenile absence epilepsy, eyelid myoclonia with absences, perioral myoclonia with absences, and idiopathic generalized epilepsy with phantom absences (Genton *et al*., 2008), however, ASE may also appear *de novo*. ASE may be preceded by other seizure types, such as absences, myoclonic jerks, and generalized tonic-clonic seizures, many years before (Panayiotopoulos, 2008; Koutroumanidis *et al*., 2008). Nevertheless, ASE can also be the initial clinical manifestation both in adults and children (Agathonikou *et al*., 1998; Grin and DiMario, 1998; Genton *et al*., 2008; Bilo *et al*., 2014; Adams *et al*., 2016; Paschen *et al*., 2016; Brigo *et al*., 2018).

ASE may be clinically variable and subtle and may go unrecognized, especially in children. Thus, recognition of this electroclinical pattern may be difficult and the electroencephalographic recording is crucial to diagnose ASE.

Here, we describe the electroclinical features, treatment, and evolution of three paediatric patients with *de novo* ASE with an excellent response to valproic acid (VPA).

Case reports

Patient 1

A healthy eight-year-old boy with no remarkable personal or family history was noted to be disoriented and confused while awake. He had become unable to perform self-care tasks, such as eating, grooming, dressing, bathing, and toileting. He was only able to talk with difficulty and follow simple commands. He had trouble recognizing his family. His father, a paediatric neurologist, quickly had an EEG recording performed which he sent to one of the authors of this study. The recording showed paroxysms of diffuse and asymmetric spikes and waves up to 2.5-3 Hz, compatible with ASE (*figure 1*). VPA at 40 mg/kg/day was introduced; the boy improved and one hour after treatment initiation, he appeared alert, coherent, and wanted to resume his normal daily activities. The control EEG three hours later was normal. The boy had no further episodes of ASE, typical absence, or any other type of seizure. VPA was discontinued at 10 years of age. The patient is currently 31 years old and living a normal life.

Patient 2

A three-year-old girl was referred to the Department of Neurology because of a 48-hour history of altered mental status associated with infrequent masticatory automatisms and changes in postural tone. Responsiveness was slow and the girl failed to follow instructions. When she spoke, her speech was incoherent and not comprehensible. Her medical history did not reveal any significant disease and her family history was negative for epilepsy. At the time of admission, an EEG was recorded showing continuous generalized 3-Hz spike-wave activity, consistent with ASE (*figure 2*). Intravenous lorazepam at 2 mg temporarily aborted the ASE. Subsequently, she was treated with levetiracetam at 20 mg/kg intravenously without improvement. When the metabolic laboratory results turned out to be normal, she was put on VPA at 20 mg/kg with immediate clinical and electrographic response. The neurological examination and brain MRI were normal. Cerebrospinal fluid (CSF) revealed no evidence of inflammation. Bacteriological and viral examination of the CSF was normal as well. Anti-NMDA antibodies were negative. The CSF/serum glucose ratio was normal. The interictal EEG showed normal background rhythm with occipital delta activity (OIRDA).

At the last control, she had had no further ASE, typical absence, or any other type of seizure for two years. The girl is currently five years old and has a mild language disorder.

Patient 3

A nine-year-old boy presented at the Department of Neurology because of an episode of prolonged altered mental state. The parents had noted that the boy responded slowly and seemed mildly confused. His speech was not comprehensible and he failed to follow instructions. A similar episode had occurred two weeks earlier. That time, the boy recovered without intervention three hours later.

The video-EEG showed a continuous pattern of 3-4-Hz spike-and-slow-wave discharges, compatible with ASE (*figure 3*).

The boy's neurodevelopment was according to age. His medical history was unremarkable and his family history was negative for epilepsy. Neurological examination and brain MRI were normal.

The patient was treated with intravenous lorazepam three hours after symptom onset and recovered immediately. VPA at 300 mg, twice a day, was initiated for seizure prophylaxis.

Over the following 12 months, the patient did not have any further episodes of confusion or abnormal behaviour, and a control EEG showed a

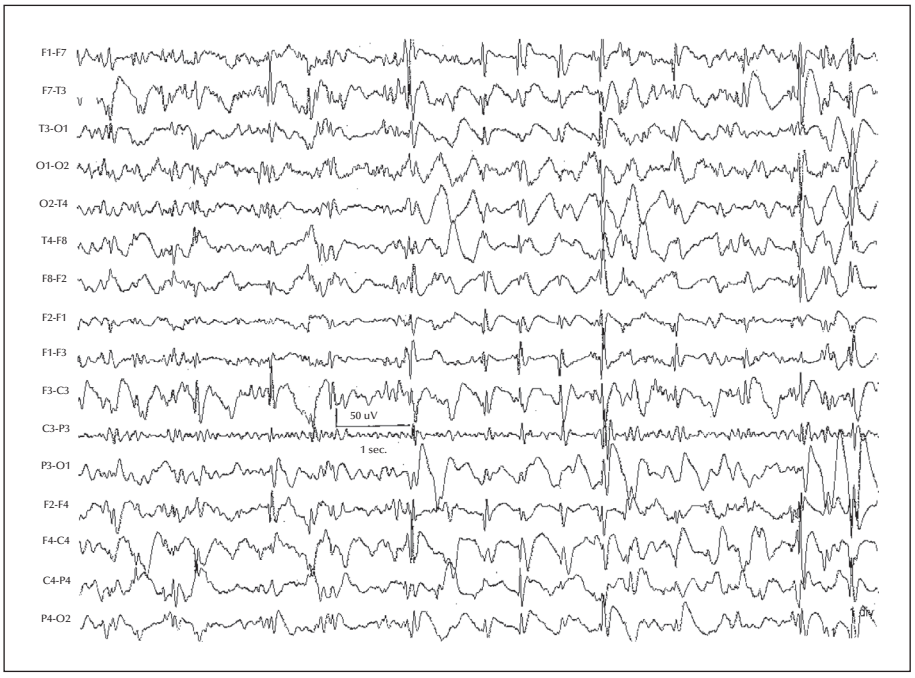

Figure 1. The ictal EEG during ASE shows diffuse, asymmetric and irregular spike-and-wave discharges at 3 Hz.

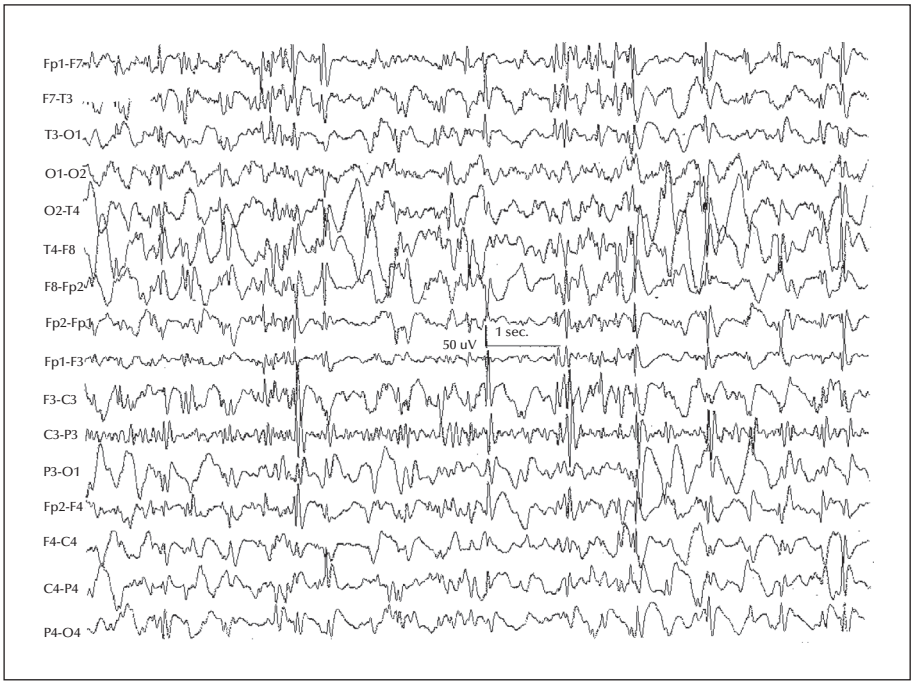

Figure 2. The ictal EEG recording shows diffuse spike-and-polyspike-and-wave paroxysms at 2.5-3 Hz, associated with ASE.

normal background without evidence of epileptiform activity. Currently, the boy continues on VPA without any further ASE, typical absence, or any other type of seizure, or adverse effects to the medication.

Discussion

In this study, we present three paediatric patients with non-convulsive status epilepticus (NCSE) with an acute confusional state with impairment of consciousness

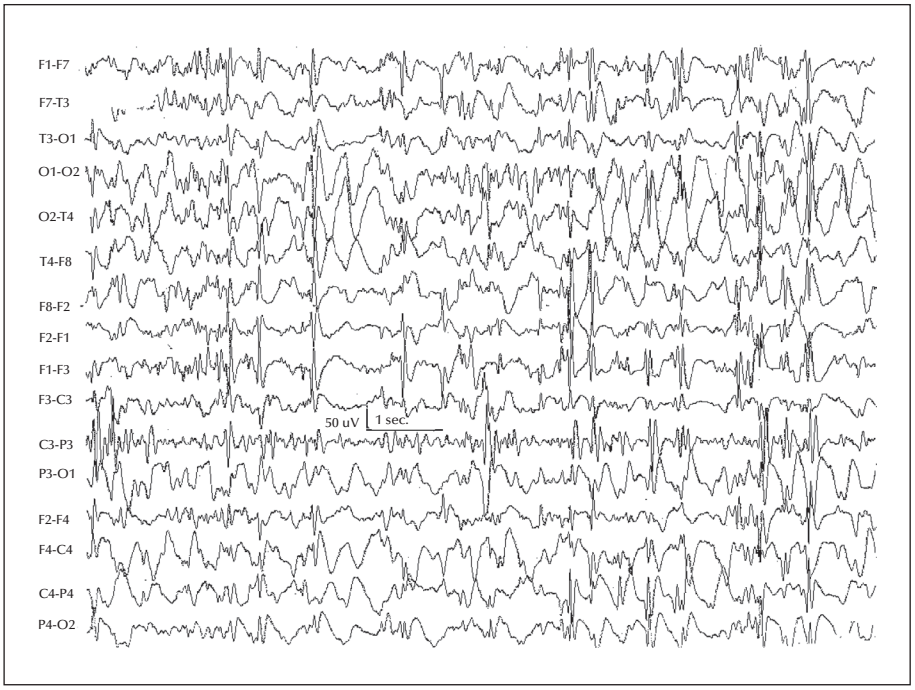

Figure 3. The ictal EEG recording shows asymmetric generalized spike-and-polyspike-and-wave discharges at 3 Hz, associated with a state of confusion.

and EEG abnormalities compatible with typical ASE, associated with generalized spike-and-wave paroxysms at 2.5-4 Hz as the first and only manifestation of epilepsy. NCSE is a term used for a range of conditions in which electrographic seizure activity is prolonged and results in non-convulsive symptoms. Nevertheless, convulsive elements, mainly myoclonic jerks, are common in generalized NCSE, as in eyelid ASE. For management purposes, it is important to differentiate between focal non-convulsive and generalized non-convulsive status epilepticus. Unified EEG terminology and criteria for NCSE have been proposed (Beniczky *et al*., 2013) and its various subtypes, including ASE, have been systematically classified (Sutter and Kaplan, 2013).

Typical absence seizures (TAS) have a sudden onset and termination, lasting for seconds. For the diagnosis of TAS, two components are required: the clinical manifestation of transient impairment of consciousness and the appearance of generalized >2.5-Hz spike- or polyspike-slow-wave discharges on the EEG (Panayiotopoulos, 2008).

The absences are frequent, occurring tens or hundreds of times per day, varying in duration from 4 to 30 seconds. Clinically, the most important feature of the absences is severe impairment of consciousness with unresponsiveness and interruption of the ongoing voluntary activity, which is restored immediately after the ictus finishes. Automatisms occur in two thirds of seizures, but are stereotyped. Absences are almost always triggered by hyperventilation (Caraballo and Dalla Bernardina, 2013). Cases of early-onset TAS have been previously published (Caraballo *et al*., 2011; Giordano *et al*., 2013).

De novo ASE has been reported more often in adult patients than in children (Agathonikou *et al*., 1998; Grin and DiMario, 1998; Genton *et al*., 2008; Bilo *et al*., 2014; Fisher *et al*., 2014; Adams *et al*., 2016; Paschen *et al*., 2016; Brigo *et al*., 2018). As to paediatric patients, our three patients and the only two children previously published in the literature (Grin and DiMario, 1998; Adams *et al*., 2016) had *de novo* ASE without experiencing absence seizures before the episode or during their follow-up, except for one (Grin and DiMario, 1998) who presented a typical absence event after the ASE. Thus, this group of paediatric patients present a well-defined electroclinical pattern characterized by ASE as the first and only manifestation of epilepsy.

ASE is often misdiagnosed as a focal status epilepticus, confusional non-epileptic condition, or epileptic prodrome. ASE may also occur due to the selection of an inappropriate antiepileptic drug, such as tiagabine, carbamazepine, oxcarbazepine, gabapentin, pregabalin, or vigabatrine. ASE is probably the most common type of status epilepticus among the idiopathic generalized epilepsies (Hessen *et al*., 2006). A typical ASE may begin at any time but rarely before 10 years of age (Agathonikou *et al*., 1998). ASE as a form of initial presentation of childhood

absence epilepsy (CAE) is extremely rare. Idiopathic generalized epilepsy with phantom absences was first reported in a child by Panayiotopoulos (2001). Koutroumanidis and Panayiotopoulos (2008) reported 15 patients with phantom absences of whom 53% presented with absence status during the course of their epilepsy.

Recognition of *de novo* ASE may be difficult, particularly when there has been no previous manifestation of seizures. Early awareness of this condition in children with impaired consciousness is fundamental to consider in the differential diagnosis of, for example, infection, intoxication, trauma, and psychiatric disorders. A few paediatric patients, similar to ours presented here, have been published. A child with ASE causing a prolonged acute confusional state has been described (Grin and DiMario, 1998). More recently, Adams *et al*. reported an eight-year-old boy who experienced two episodes of prolonged altered mental status, subsequently determined to be ASE with IGE and phantom absences, not CAE.

ASE has been described in elderly patients with a history of IGE in adolescence who had been seizure-free for decades (Iyer and Nisha, 2014; Paschen *et al*., 2016). Brigo *et al*. (2018) reported late-onset *de novo* ASE occurring at the age of 64 years, with clinical and EEG features suggestive of late-onset IGE. *De novo* ASE and ASE occurring in patients with IGE may be difficult to recognize, since elderly subjects may often overlook a previous history of epilepsy (Bilo *et al*., 2014).

Our three cases presented with generalized typical ASE as the first and only manifestation of their epilepsy. None of them had any other type of seizure before the event or during their follow-up. The follow-up was very long term in the first patient, two years in the second, and only 12 months in the third. As follow-up was not sufficiently long in this last patient, close monitoring, including video-EEG studies, to capture any further seizures over a prolonged period of time will be necessary. All patients responded very well to VPA.

De novo ASE as a single manifestation may be a well-defined idiopathic epilepsy syndrome or a variant of an IGE syndrome, such as a particular type or variant of CAE. □

Disclosures.

None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Can absence status epilepticus be the first and only epileptic manifestation in paediatric patients?

(2) Is absence status epilepticus refractory to antiepileptic drugs?

(3) Could absence status epilepticus be considered an idiopathic epilepsy syndrome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".