Clinical commentary

Epileptic Disord 2018; 20 (6): 557-61

Juvenile absence epilepsy relapsing as recurrent absence status, mimicking transient global amnesia, in an elderly patient

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Received April 19, 2018; Accepted October 04, 2018

ABSTRACT – We describe a 68-year-old woman who had typical absence seizures since 14 years of age. The absences were refractory to treatment and persisted into adulthood, with no seizure-free periods until seizure control at 59 years of age. After six years of being seizure-free, she presented with an episode characterized by mental confusion, abnormal behaviour, and amnesia, lasting for several hours. An EEG performed the day after, when the patient had already recovered, was unremarkable. The episode was interpreted as transient global amnesia. After two and three years, respectively, she presented with two analogous episodes lasting >24 hours. An EEG disclosed, on both occasions, subcontinuous generalized spike-and-wave discharges, consistent with absence status epilepticus (AS). The last episode occurred at 68 years of age and was successfully treated with intravenous lorazepam. After one month of follow-up, no further episodes occurred.
AS is common in juvenile absence epilepsy, however, our patient showed a rather atypical course, characterized by refractory and persistent absences during adolescence and adulthood, and a tendency for AS to recur with no more absences in later life. Despite the known epilepsy history, AS episodes were initially misdiagnosed. Moreover, EEG recording and subsequent treatment were not performed until the second day of status.

Key words: idiopathic generalized epilepsy, juvenile absence epilepsy, relapse, non-convulsive status epilepticus, absence status epilepticus, amnesia

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doi:10.1684/epd.2018.1016

Absence status epilepticus (AS) is classified as a generalized non-convulsive status epilepticus (NCSE) without coma. An absence seizure lasting more than 10-15 minutes is likely to be prolonged, leading to continuous seizure activity, and should therefore be treated (Trinka *et al*., 2015). AS is clinically characterized by prolonged confusional states of varying severity. Typical AS usually occurs in children and adolescents with genetic/idiopathic generalized epilepsies (IGEs) such as juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME), and is characterized by 2-4-Hz generalized spike or polyspike-and-slow wave (SW or PSW) discharges (Shorvon, 1995). Typical AS can also occur in middle-aged and elderly patients in whom seizures persist into adulthood, or may develop as a late-life complication of IGE, possibly after many years of seizure freedom (Berkovic *et al*., 1989; Tomson *et al*., 1992; Agathonikou *et al*., 1998; Bauer *et al*., 2007; Szucs *et al*., 2008; Fernández-Torre and Rebollo, 2009; Paschen *et al*., 2016). Lastly, AS can also be situation related and occur *de novo* in adults and elderly patients without a history of previous epileptic seizures. This form of AS can be precipitated by drugs, toxics, metabolic disturbances or electroconvulsive therapy (Fernández-Torre *et al*., 2015). Clinically, typical AS in adults may differ from that occurring in children with a less severe/incomplete loss of awareness. Also, focal motor manifestations of AS occur more commonly in adults than children and automatisms may be more complex in adult patients (Snead *et al*., 1997).

We present an atypical case of a patient with drug-resistant JAE who developed recurrent episodes of AS at a late age and discuss diagnostic challenges associated with this condition.

Case study

The patient was a 68-year-old woman with no family history of epilepsy, who developed typical absence seizures at 14 years of age. She also experienced two isolated generalized tonic-clonic seizures (GTCS), both during pregnancy. Absences persisted into adulthood with a frequency of two-three/month, despite antiepileptic therapy. The drugs she tried were ethosuximide, valproate (VPA) (stopped due to liver injury with concomitant HCV-related chronic hepatitis), and levetiracetam (stopped due to depression). At 59 years of age, the patient was started on lamotrigine (LTG) (200 mg/die), with seizure control.

At 65 years of age, she presented with a prolonged episode characterized by mental confusion, abnormal behaviour, and anterograde amnesia, lasting for a whole day. An EEG performed the following day, after clinical resolution of the episode, was unremarkable. Metabolic disturbances and acute ischaemic injury were ruled out by laboratory testing and CT of the brain. The latter showed only mild chronic microvascular ischaemic changes, already known from a previous MRI study. This episode was interpreted as transient global amnesia. A second event similar to the former occurred at 67 years of age and lasted for one and a half days. An EEG was performed at the end of the episode, when the patient's behaviour was almost unremarkable, and disclosed subcontinuous generalized SW discharges. The patient was not treated and fully recovered after sleeping for a couple of hours. The episode was diagnosed as AS, therefore LTG was uptitrated to 300 mg/die in order to prevent relapses. After one year, at age 68 years, the patient presented with a further episode characterized by the same clinical manifestations. The day after the onset, while the patient was still confused and behaved inappropriately, an EEG showed subcontinuous generalized SW discharges (*figure 1*). The patient was successfully treated with intravenous lorazepam at 2.5 mg. Given the recurrence of the episodes, LTG was further uptitrated to 400 mg. After one month of follow-up, the patient had not had any further episode. Possible factors that may trigger status epilepticus in the elderly, such as sleep deprivation, AED changes, poor compliance with AED therapy, recently introduced co-therapies or electrolyte imbalance, were excluded in all episodes. Interictal EEGs always showed normal background activity, abundant generalized SW discharges on different recordings, and no photosensitivity. The last typical absence seizure occurred at 59 years of age.

Discussion

We describe a patient affected by IGE with typical absence seizures that started in adolescence as the main seizure type (fulfilling the diagnostic criteria of JAE), presenting with recurrent episodes of AS at an older age. Patients with JAE tend to have seizures persisting into adulthood, which usually respond well to treatment. Indeed, approximately three in five patients with JAE achieve terminal seizure remission for five or more years, with a median age at last seizure of 44 years (Vorderwülbecke *et al*., 2017). In our patient, seizures were only partially controlled when she was middle-aged, with seizure control achieved at 59 years of age with LTG. After six years of being seizure-free, she presented with three episodes of long-lasting confusion and amnesia, which occurred over a three-year period. In all the episodes, the patient was assessed in an emergency room setting, without an available epileptologist and with a delay in EEG monitoring. In the latter two episodes, due to the prolonged duration of the status, an electrical correlate of generalized

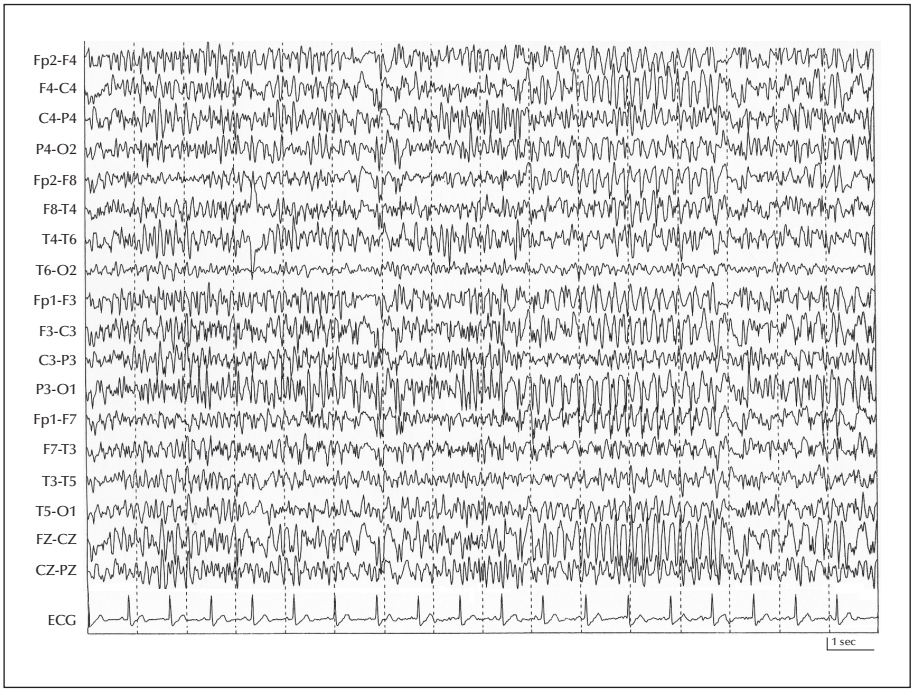

Figure 1. EEG recording during the third episode showed almost continuous generalized SW activity at about 4 Hz, prevalent over the fronto-central and, occasionally, over the left posterior leads. Sensitivity: 14.0 μV/mm.

subcontinuous SW discharges was documented, allowing the diagnosis of AS.

AS was initially misdiagnosed as transient global amnesia (TGA) because of the sudden onset of anterograde amnesia. Differential diagnosis should also include transient epileptic amnesia (TEA), a focal epilepsy syndrome with onset in middle-aged individuals in which amnestic attacks are the main ictal manifestations (Mosbah *et al*., 2014). To clinically identify these conditions, it is useful to remember that repetitive questioning is classically more associated with TGA and that amnestic seizures in TEA are often associated with symptoms related to temporal lobe epilepsy, such as *déjà vu*, automatisms, and epigastric and olfactory auras (Mosbah *et al*., 2014). AS, on the other hand, is typically associated with confusion and/or altered awareness, which are not present in typical episodes of TEA or TGA (Mosbah *et al*., 2014). A history of IGE, as well as seizure freedom for several years, should also suggest possible AS as late-life exacerbation of the underlying epilepsy. While clinical suspicion is the first step towards correct diagnosis, EEG remains a key tool to overcome diagnostic uncertainty based on generalized SW in AS, focal abnormalities predominant on temporal leads in TEA, and no epileptiform activity in TGA. EEG is also very useful to distinguish AS from focal NCSE, which may have the same clinical presentation.

AS was the only seizure type our patient experienced in the last three years of life, and she did not experience any typical absences during this period. JAE is the IGE most associated with AS, with a rate of occurrence as high as 20% (Agathonikou *et al*., 1998). While AS can also be recurrent in IGE, it usually does not represent the main seizure type and does not typically manifest in late life (Tomson *et al*., 1992; Agathonikou *et al*., 1998). The only exception is absence status epilepsy, a distinct IGE syndrome characterized by AS as the main seizure type with onset in adolescence or adulthood (Genton *et al*., 2008). A few cases of AS as a late-life complication of IGE have in fact been reported in some detail (Bauer *et al*., 2007; Szucs *et al*., 2008; Fernández-Torre and Rebollo, 2009; Paschen *et al*., 2016). Their characteristics are summarized in *table 1*. Many patients experienced a long seizure-free period before presenting with AS in late life, often at >30-40 years (Bauer *et al*., 2007; Paschen *et al*., 2016). Conversely, our patient did not have seizure-free periods until 59 years of age, just six years before AS onset. Once AS is recognized, the episodes are usually well controlled by antiepileptic therapy. In this regard, VPA seems to be the most effective drug (Berkovic *et al*., 1989; Bauer *et al*., 2007; Genton *et al*., 2008, Paschen *et al*., 2016). However, in our patient, it did not provide full control of the absences and can no longer be used due to liver toxicity. This could possibly explain the AS recurrence.

In conclusion, we describe a JAE patient with an atypical course characterized by refractory and persistent absence seizures from adolescence into adulthood,

Table 1. Cases of idiopathic generalized epilepsies with late-onset absence status

Reference	Patient* (gender)	Epilepsy history	IGE syndrome	AS, age at diagnosis (recurrency)	Treatment (control of AS)
Bauer *et al*., 2007	1 (F)	Asz during childhood, a few GTCS afterwards	CAE	60 (recurrent)	VPA (yes)
	2 (F)	Asz during childhood, some GTCS and possible AS at 55y	CAE	64 (recurrent)	VPA (yes)
	3 (F)	Asz during "young age", possible AS from 55y	CAE§	64 (recurrent)	VPA (yes)
	4 (F)	Asz during childhood, two GTCS in late life and probably AS from ~50y	CAE	78 (recurrent)	VPA (yes)
Szucs *et al*., 2008	1 (F)	Asz and GTCS with onset in childhood persisting into adulthood	JAE§	56 (single)	LTG (yes)
	2 (F)	GTCS and possibly AS from 45y	AS§	55 (possibly recurrent)	VPA (yes)
	3 (F)	GTCS from 15y†	IGE§	63 (single)	VPA (yes)
Fernández-Torre *et al*., 2009	1 (F)	GTCS during childhood	EGTCSA	68 (single)	VPA (yes)
Paschen *et al*., 2016	1 (M)	GTCS in adolescence until 22y	EGTCSA	62 (single)	VPA (yes)

AS: absence status; AS: absence status epilepsy; Asz: absence seizure; CAE: childhood absence epilepsy; EGTCSA: epilepsy with generalized tonic-clonic seizures alone; GTCS: generalized tonic-clonic seizure; IGE: idiopathic generalized epilepsy; JAE: juvenile absence epilepsy; LTG: lamotrigine; VPA: valproate; y: years.
*"1" if only one patient is described in the report.
†The authors state that the patient was treated for probable JAE, manifesting as frequent GTCS, which the authors considered to be probable episodes of AS, without offering any explanation.
§available data were not sufficient to make a syndromic diagnosis with any certainty.

who in late life showed recurrent AS, initially misdiagnosed as transient global amnesia, and no further absences. □

Acknowledgements and disclosures.
We thank Cecilia Baroncini for editing the English text.
Drs Muccioli, Licchetta, and Stipa report no disclosures. Prof. Tinuper received fees from Eisai, UCB, and LivaNova for consulting activity. Dr Bisulli received fees from Eisai for consulting activities and speaking engagements.

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TEST YOURSELF

(1) In which of the following syndromes does absence status epilepticus most frequently occur?
A. Childhood absence epilepsy
B. Juvenile absence epilepsy
C. Juvenile myoclonic epilepsy
D. Epilepsy with generalized tonic-clonic seizures alone

(2) Which antiepileptic drug is the most effective to prevent recurrence of absence status epilepticus, according to available reports?
A. Valproate
B. Carbamazepine
C. Levetiracetam
D. Phenytoin

(3) Which of the following is key to diagnose absence status epilepticus?
A. Laboratory testing
B. Clinical examination
C. EEG
D. Brain MRI

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".