



Short communication

De novo Absence Status Epilepticus in a pediatric cohort: Electroclinical pattern in a multicenter Italian patients cohortC. Pepi^{a,b,*}, E. Cesaroni^c, P. Striano^d, D. Maiorani^e, D. Pruna^f, S. Cossu^f, M. Di Capua^g, F. Vigeveno^a, N. Specchio^a, R. Cusmai^g^a Child Neurology Unit, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children's Hospital Research Institute, Rome, Italy^b Child Neurology and Psychiatry Unit, System Medicine Unit, Tor Vergata University, Rome, Italy^c Child Neuropsychiatric Unit, University of Ancona, Ancona, Italy^d Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, "G. Gaslini" Institute, University of Genoa, Genova, Italy^e Division of Pediatrics, Ospedale Belcolle, Viterbo, Rome, Italy^f Pediatric Neurology and Epileptology Unit, Brotzu Hospital Trust, Cagliari, Italy^g Unit of Neurophysiology, Department of Neurosciences, Bambino Gesù Children's Hospital Research Institute, Rome, Italy

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ABSTRACT

Purpose: Absence Status epilepticus (AS) is a form of Non Convulsive Status Epilepticus defined as a prolonged, generalized and non-convulsive seizure, with an altered content of consciousness. We aim to describe a group of healthy children, who presented recurrent and unprovoked *de novo* AS as the only manifestation of their epilepsy, with an excellent response to antiepileptic drugs.

Method: We retrospectively reviewed the electroclinical and genetic features of 13 pediatric patients, referring to our epilepsy centers from 2005 to 2019, on the following criteria: (1) regular psychomotor development, (2) one or more unprovoked AS as the only epileptic manifestation, (3) normal blood testing, (4) normal neuroimaging, (5) EEG recording, (6) available follow-up (1–14 years).

Results: Patients are 7 females and 6 males, aged 7–22, with a mean age at AS onset of 9.3 years. All of them started an antiepileptic therapy, with an excellent response to Valproic Acid (VPA) or Ethosuximide (ETS). 5 patients did not start the therapy immediately after the first AS and they presented recurrent AS (from 2 to 4 episodes). 10 of them performed aCGH, karyotype, NGS panel or Whole Exome Sequencing.

Conclusions: We suggest that *de novo* AS may be a well-defined age-related and self-limited epilepsy syndrome, with a good prognosis and excellent response to therapy, but it comes with a high risk of relapsing if not adequately treated with antiepileptic drugs.

1. Introduction

Absence status epilepticus (AS) is a form of Non Convulsive Status Epilepticus (NCSE) characterized by ongoing or intermittent epileptic activity with behavioral and cognitive changes that usually last for hours and even for days [1]. It is defined as a prolonged, generalized and non-convulsive seizure characterized by an altered content of consciousness [2], sometimes associated with other clinical manifestations such as language impairment (mutism, echolalia, reduced speech), automatisms or subtle perioral or limb myoclonia, extrapyramidal signs (catatonias), autonomic phenomena or psychiatric symptoms [3].

In 2015 [4], the International League Against Epilepsy (ILAE)

proposed a new clinical classification with diagnostic criteria for Convulsive Status Epilepticus (CSE) and Non Convulsive Status Epilepticus (NCSE), according to semiology, patient age, underlying causes and EEG correlations, in which AS is included as Generalized NCSE without coma.

For the diagnosis of Absence Status, 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.

Some authors speak about *typical* AS, occurring in the setting of Genetic Generalized Epilepsies (GGEs), and *atypical* AS, which has been reported in patients with developmental or epileptic encephalopathies,

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such as Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, Dravet syndrome, epilepsy with myoclonic absences, Angelman syndrome, Rett syndrome and ring chromosome 20 syndrome [5].

Absence status epilepticus can occur as a “Late-onset *de-novo* AS” [6], especially in the elderly who lack a history of epilepsy, typically triggered by drug use or therapy withdrawal (benzodiazepine withdrawal, psychotropic drugs, antidepressants, antibiotics, chemotherapy agents and even antiepileptic drugs).

Moreover it has been described in association with sepsis, metabolic or electrolyte disturbance, cancer or dementia.

In children AS has been frequently associated with GGEs, such as Juvenile Absence Epilepsy (JAE), in which AS can occur in patients with poor adherence to antiepileptic drugs, as well as in other syndromes not yet recognized by the ILAE, such as GGE with phantom absences [7]. This latter condition creates serious difficulties in clinical differential diagnosis, especially in pediatric patients. In fact it is hard to assess whether these children had previous brief and subtle absence episodes, like “phantom absences”, which are, by definition, so mild that they are inconspicuous to the patient and imperceptible to the observer. Moreover, in “idiopathic generalized epilepsy with phantom absences” it has also been described [12] the occurrence of typical AS and generalized tonic-clonic seizures, which are common clinical manifestations but starting in adulthood, so they are not helpful in differentiating our pediatric patients with recurrent AS from children with phantom absences.

There are few reports about *de novo* AS in children who did not present previous epileptic seizures [8,9].

Recently Caraballo et al. [10] described three pediatric patients with *de novo* AS and good response to Valproic Acid.

In this multicenter study, we report a group of healthy pediatric patients who presented recurrent and unprovoked AS as the only manifestation of their epilepsy. None of them had any other type of seizure before the event or during their follow-up. All patients had an excellent response to Valproic Acid (VPA) or Ethosuximide (ETS).

2. Methods

We retrospectively reviewed the electroclinical and genetic features of 13 pediatric patients, which are summarized in Table 1, referring to three Italian pediatric epilepsy centers from 2005 to 2019, on the following criteria: (1) regular psychomotor development, without any neuropsychiatric comorbidity (2) one or more unprovoked episodes of typical AS as the only epileptic manifestation, (3) normal chemical and metabolic blood testing, (4) normal neuroimaging, (5) ictal or interictal EEG recording, showing continuous generalized spike-wave (SW) or polyspike-wave (PSW) activity at 2–4 Hz, (6) available electroclinical follow-up (from 1 to 14 years). They are 7 females and 6 males, aged from 7–22, with a mean age of 9,3 years (7–16 years) at onset of AS. 10 of them performed aCGH, karyotype, NGS panel or Whole Exome Sequencing.

3. Results and discussion

In our group of patients, we have found out that the clinical presentation of AS was the same for every patient, who experienced a sudden confusional state, characterized by reduction of responsiveness with intermittent loss of contact, slowing of speech and action, sometimes decontextualized answers, verbal and motor persistence. The duration of the AS ranges from 30 minutes to 15 days (patient n. 3), with a mean duration of 3 hours.

10 patients (77%) received a therapy with Benzodiazepine during the acute state (Midazolam in 7 cases, Diazepam in 2, Lorazepam in 1), with a complete resolution of the clinical and electrical state within 10 minutes, so that all children rapidly return to a normal state of consciousness and behaviour. We collected ictal EEG recordings during AS in 8 cases, showing typical AS electrical features (Fig. 1–2); we carried

Table 1
This table summarizes the electroclinical and pharmacologic features of our patients.

Patient No. (sex)	Age at last FU (ys)	Follow up (ys)	Age at AS (ys)	Family History	Previous seizures	EEG	AS	Imaging	Comorbidity	Genetic Exam	Acute AED	Chronic AED
1 (F)	8	1	7	cousin with epilepsy	1 FS	Ictal AS	3 AS	CT, MRI	no	karyotype aCGH	MDZ 3 mg IV	LEV > VPA
2 (F)	9	2	7		no	Ictal AS	1 AS	CT, MRI	no	karyotype aCGH	DZP 10 mg ER	VPA (withdrawn)
3 (M)	16	7	9	aunt with epilepsy	no	Ictal AS	4 AS	CT	no	karyotype aCGH	MDZ 3 mg IV	VPA (withdrawn)
4 (M)	15	4	11		no		2 AS	MRI	no	NGS	MDZ 2 mg IV	VPA (withdrawn)
5 (F)	9	2	9		no	Ictal AS	1 AS	CT	no	karyotype aCGH	MDZ 10 mg buccal	ETS
6 (F)	9	2	9		no	Ictal AS	1 AS	CT	no	WHE	MDZ 2 mg IV	ETS
7 (M)	13	4	9	grandfather and cousin with epilepsy	no		1 AS	CT, MRI	no	karyotype aCGH	MDZ 2 mg IV	VPA (withdrawn)
8 (F)	11	1	11	aunt with epilepsy and ID	no		1 AS	CT, MRI	no	NGS	MDZ 2 mg IV	ETS
9 (M)	21	13	8		1 FS	Ictal AS	1 AS	MRI	no	WHE	MDZ 2 mg IV	VPA (withdrawn)
10 (M)	14	5	9	cousin with FS	no		3 AS	no	no			VPA
11 (F)	22	14	9	cousin with FS	no	Ictal AS	1 AS	no	no		LZP 4 mg IV	VPA (withdrawn)
12 (F)	22	7	16	no	no	Ictal AS	2 AS	MRI	hyperandrogenism	karyotype aCGH	DZP 10 mg ER	LEV > VPA
13 (M)	16	7	9	no	no		1 AS	MRI	no			VPA

FS: Febrile Seizure; AS: Absence Status; WHE: Whole Exome Sequencing; MDZ: Midazolam; DZP: Diazepam; LZP: Lorazepam; IV: intravenous; ER: endorectal.

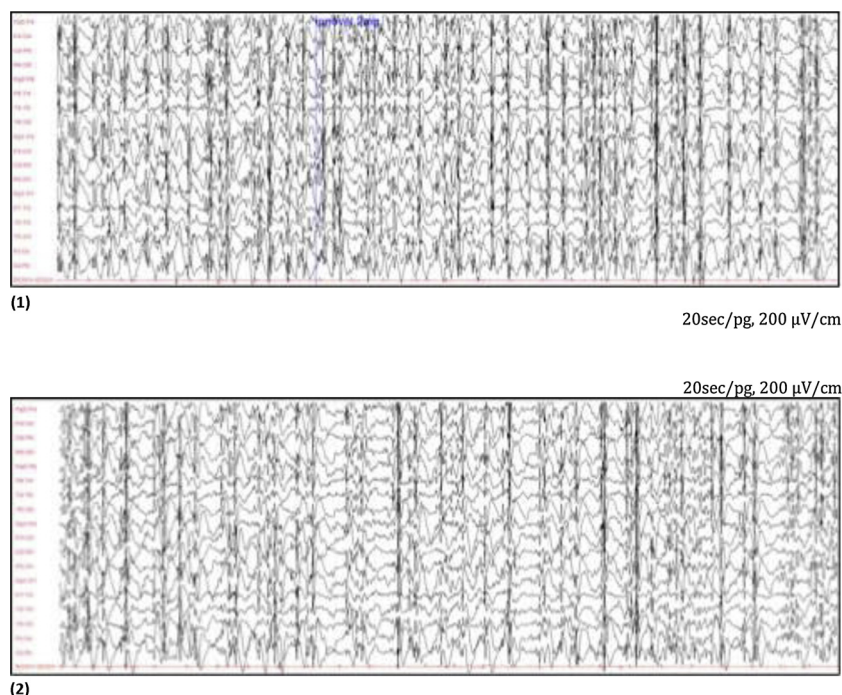


Fig. 1–2. Ictal EEG recording of AS: Continuous or almost continuous generalized spike-wave activity at 2–4 Hz, occasionally interrupted by short periods of normal background activity, during which patients remained confused.

on EEG-recordings for 3 hours after the resolution of the state. After the acute state, all patients underwent prolonged EEG recordings in the following days during hospitalization in order to rule out the presence of interictal abnormalities or typical absence seizures and none of them showed any interictal or ictal discharges.

3.1. Follow up

We evaluated a mean electroclinical follow-up time of 5 years (from 1 to 14 years).

All our patients started an antiepileptic therapy: 8/13 with Valproic Acid (VPA), 2/13 with Levetiracetam (LEV), withdrawn because of psychomotor agitation and irritability and replaced with VPA, 3/13 with Ethosuximide (ETS).

6 patients (50%) withdrew therapy, after a mean treatment period of about 3,7 years.

In 8 patients of our population antiepileptic therapy was started immediately after the first AS, while the other 5 (patients n. 1, 3, 4, 10, 12) presented recurrent AS (from 2 to 4 episodes), with the same clinical features, before starting a therapy, because of a misdiagnosis of their epileptic condition.

However, after starting the therapy, no patients but two (patients n. 1 and 12) have presented another AS. These two children's relapsing AS occurred both during a pharmacological modification: in one case, the patient was performing a therapeutic shift from LEV to VPA because of behavioral aggravation and, in the other case, the patient voluntarily discontinued VPA.

During follow-up, every patients performed periodic clinical and EEG controls, with standard 20 minutes video-EEG recordings every 3–4 months, always showing a lack of epileptiform abnormalities, except for patients n. 1 and 12.

In these two patients, we were able to record, in the months following their relapsing AS, some paroxysmal and isolated generalized spike-wave complexes during hyperventilation, lasting 1–2 seconds. We tried to test these children during the epileptiform discharges and they apparently did not present a loss of contact. It has to be considered the limit of the very brief duration of spike-wave discharges. These

epileptiform abnormalities gradually disappeared after the reintroduction of antiepileptic drugs (within 1–2 months).

3.2. Genetic results

As concerns the genetic exam, karyotype and array-CGH were performed in 5 patients, NGS panel for epileptic encephalopathies, including 50 genes, in 2, and Whole Exome Sequencing is ongoing in 3 patients. Until now all the genetic exams resulted negative.

In scientific literature, there are many genes that are found out to be associated with Status Epilepticus [11], mainly associated with focal cortical dysplasia, inborn errors of metabolism, mitochondrial disease, or epileptic encephalopathy and childhood syndromes. By now there is none identified as 'pure status epilepticus genes'.

4. Conclusions

We describe here a group of patients, from different Italian neurology units, in whom the only seizure type is unprovoked *de novo* AS without any triggering factor.

Evidences suggest that family history is positive for epilepsy in a considerable rate of patients (54%).

The clinical features of these epileptic manifestations are quite stereotyped:

- 1 presentation in late childhood without any other epileptic events preceding this abrupt onset;
- 2 typical unprovoked events of sudden impairment of consciousness, lasting several hours, that could recur in absence of an early pharmacological treatment. The prognosis is favorable on adequate therapy.

Genton et al. [7] proposed that this condition, characterized by recurrent unprovoked AS in absence of other seizure types or any triggering factor in healthy patients, could be named "Absence Status Epilepsy".

In conclusion, we assume that *de novo* AS as the only epileptic

manifestation in healthy children may be considered a rare self-limited and age-related “idiopathic” epilepsy syndrome with a good prognosis, excellent response to therapy and resolution within the pubertal development. However it comes with a high risk of relapsing if not adequately treated with antiepileptic drugs.

Although our study has the limit of a small clinical sample, we hope that clinicians might pay more attention to this specific and often misdiagnosed clinical presentation, so that an earlier adequate treatment could be started. It is not always so easy, indeed, distinguishing AS from other chameleons [13], such as other disorders of consciousness (unresponsive states, coma), disturbances of speech (aphasia, echolalia, stuttering), psychiatric/behavioural conditions (psychosis, mood disturbance), cognitive dysfunction (amnesia, confusion, confabulation) and movement disorders (catatonia, gaze deviation, motor automatisms/dyskinesias).

Thus it is mandatory, according to our opinion, to perform a video-EEG recording during the acute state, especially when clinicians recognize a hyper-acute behavioural and cognitive modification in healthy children.

Therefore, considering our follow-up time (14 years in one case), we assumed that it is important to start the antiepileptic therapy as soon as you can, once you have recognize the absence status, knowing that an early discontinuation of drugs could lead to a clinical relapse.

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Declaration of Competing Interest

None.

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