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Typical absence status epilepticus in older people: syndromic delineation

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ABSTRACT

Objective. We describe the clinical, electroencephalographic and neuroimaging findings of older patients with typical absence status epilepticus (ASE).

Methods. This investigation was a retrospective analysis of prospectively collected consecutive patients between January 2011 and October 2021. All patients ≥60 years with impairment of awareness and continuous generalized, rhythmic, synchronous and symmetric epileptiform discharges and normal background on video-electroencephalogram (vEEG) were included.

Results. Six patients were identified with a diagnosis of typical ASE. The mean age was 67 years. Five could be classified as idiopathic generalized epilepsy (IGE) though two had been erroneously categorized as cryptogenic focal epilepsy (FE). In one, the episode of ASE was thought to represent the beginning of late-onset IGE (*de novo* late-onset typical ASE). In all cases, ASE was controlled within the first 24 hours.

Significance. Typical ASE is a rare cause of confusion in the elderly population requiring urgent vEEG evaluation. It most frequently represents reactivation of a previous IGE, although it can be the form of presentation in elderly people with epilepsy that begins in childhood or adolescence and that has not been diagnosed or treated. It may be rarely the debut of (de novo) late-onset IGE.

Key words: absence status epilepticus, typical absence status epilepticus, generalized non-convulsive status epilepticus, older people, elderly patients, electroencephalogram

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In the last 20 years, there has been a plethora of publications on non-convulsive status epilepticus (NCSE). These investigations have led to a syndromic description that facilitates diagnosis, early treatment, and characterizes the long-term prognosis and risk of recurrence [1]. Single case reports aside, little study has focused on typical absence status epilepticus (ASE) in the elderly, or later life [2, 3].

Our aim was to describe the clinical, electroencephalographic and neuroimaging findings of patients with typical ASE in older patients.

Methods

Data collection and patients

This investigation is a retrospective analysis of prospectively collected consecutive patients between January 2011 and October 2021. The Department of Clinical Neurophysiology at Marqués de Valdecilla University Hospital provides an adult neurophysiological service to 591,886 inhabitants in an urban and rural area of the region of Cantabria, located in the north of Spain. It is the only neurophysiology department

in the area, and we perform around 2,500 video-electroencephalograms (vEEGs) per year. All patients ≥60 years diagnosed with typical ASE were included in the study.

vEEGs were performed using 21 electrodes placed according to the international 10-20 system. Continuous vEEG was obtained for at least 30 minutes and included photic, sensory and verbal stimulation. All tracings were reviewed by a board-certified clinical neurophysiologist (JLF-T or PO). Interest was focused on accurately determining the level of consciousness and patient's mental status, and the response to the acute administration of intravenous benzodiazepines (IVBZPs) when used for diagnosis. The effect of IVBZPs was evaluated during the EEG recording for 5-10 minutes after administration. Not all patients were treated with acute IVBZPs for safety reasons.

All clinical data were gathered from chart review, EEG reports and protocols, discharge summaries, and resident sign-out notes. We collected baseline demographic data (age, gender) and past medical history, focusing our attention on causes precipitating the episode of ASE and to exclude alcohol abuse, psychotropic drug intake, treatment with chemotherapeutic drugs or severe concomitant disorders such as leukaemia, lymphoma, renal failure, cancer and infection [4].

All mentally normal patients with impairment of awareness or behaviour and a pattern of continuous or intermittent generalized, rhythmic, synchronous, symmetric paroxysmal activity of polyspike-and-wave complexes (PSWC) and/or spike-and-wave complexes (SWC), as well as normal background activity on the EEG, were included [5, 6]. We excluded patients with atypical ASE (occurring in the context of developmental or epileptic encephalopathies), situation-related ASE and subjects with antecedents of frontal epilepsy and who were critically ill.

Results

Six patients were identified with a diagnosis of typical ASE. Five had epilepsy. Three had a previous diagnosis of idiopathic generalized epilepsy (IGE). All demographic, clinical, EEG and neuroimaging features are summarized in *table 1*. There were three women (50%) and three men (50%). The mean age was 67 years (range: 60 to 77 years). In all cases, ASE was controlled within the first 24 hours. In one (Patient 2), the episode of ASE was believed to represent the debut of late-onset IGE epilepsy, and therefore classified as *de novo* late-onset typical ASE [7].

In three patients (Patient 1, 4 and 6), ASE was considered as an aggravation or reactivation of persistent IGE (after 28, 52 and 50 years, respectively). Two patients (Patient 1 and 4) had recurrent episodes of ASE. Two patients (Patient 3 and 5) were erroneously categorized with cryptogenic focal epilepsy (FE). Patient 3 had epileptic seizures from the age of eight years with absence seizures on several vEEGs, and several episodes of NCSE. Patient 5 had a history of two generalized tonic-clonic seizures (GTCSs) at age 57 years in the context of acute renal failure and severe metabolic disorders. At both admissions, a vEEG was performed revealing generalized SWC at 3.0-5.0 Hz with frontal maximum or focal bifrontal SWC (*figure 1A*). In addition, the evolutive vEEGs after the episode of ASE showed brief paroxysms of PSWC supporting the diagnosis of IGE.

Patient 2 had no history of epilepsy and debuted with a GTCS and ASE. In addition, the ictal EEG showed well-formed generalized, symmetrical and synchronous polyspikes and PSWC at 1.5-2 Hz (*figure 1B*). One month later, GTCS recurred along with episodes of inattention. Antiseizure treatment was adjusted even though vEEGs failed to show epileptiform activity. She is now seizure-free on treatment with phenytoin (PHT).

Overall, ASE was controlled in two patients using a combination of valproate (VPA) and levetiracetam (LEV), in two patients with VPA, LEV and clonazepam (CLN), in one with VPA and CZP, and in one with PHT and CZP.

Discussion

All our patients had ASE in later life [8]. The special report of the ILAE Task Force on classification of status epilepticus provides examples of selected electroclinical syndromes according to age and proposes *de novo* or *relapsing* ASE of later life as an epileptic condition occurring in elderly patients (≥60 years). Although the qualifier "later life" is intuitive and descriptive, this terminology has been used in the past in different studies to include patients younger than 60 years of age [3, 9], making comparisons among different reports more challenging. Using the term "ASE of late onset or late-onset ASE" might avoid this confusion. In general, *de novo* ASE of late onset (dnASLO) is considered a situation-related type of generalized NCSE [1]. However, ASE that occurs for the first time in elderly people is not necessarily secondary to external provoking factors but may rarely be the (late) onset of IGE in the elderly (late-onset IGE; as in our Patient 2) [7, 10]. The EEG can help distinguish between the two groups. In our previous study of NCSE, all patients with typical ASE had generalized PSWC and SWC ranging from 2-6 Hz. By contrast, in the group of situation-related ASE, there was a predominance of sharp-slow wave complexes and biphasic sharp waves at 2-2.5 Hz [4]. Sometimes, differentiation between typical ASE in the elderly and dnASLO based on

▼ **Table 1.** All demographic, clinical, EEG and neuroimaging features of our patients.

Patient	Sex/ age	Medical history	Clinical presentation	History of epilepsy/type/ prior episodes of ASE	Precipitating factors	Ictal EEG	Neuroimaging
1	F/69	-	GTCS/ slow thinking/stupor	Yes/IGE/Yes	Unknown	**PS, PSWC 1.5-2.5 Hz	MR: small vessel ischaemia
2	F/68	Breast carcinoma	GTCS/confusion	No	Unknown	PSWC 1.5-2 Hz	MR: small vessel ischaemia; diffuse cortico-subcortical atrophy
3	M/ 77	Chronic bronchitis	Confusion/ GTCS	Yes/FE*/Yes	Unknown	SWC 2.5-3 Hz	CT: diffuse cortico-subcortical atrophy
4	F/66	Diabetes mellitus Dyslipidaemia	Slow thinking/ abnormal behaviour/GTCS	Yes/IGE/Yes	Sleep deprivation	PSWC/ SWC 3-4.5 Hz	MR: normal
5	M/ 64	Dilated cardiomyopathy Mild cognitive impairment	Slow thinking/ inattention/ disorientation	Yes/FE*/No	Unknown	PSWC/ SWC 3-5 Hz	CT normal; MR: normal
6	M/ 60	Diabetes mellitus Dyslipidaemia Parkinson Disease	Confusion/ psychomotor agitation	Yes/IGE/No	Influenza infection, fever	PSWC/ SWC 2-3 Hz	MR: small vessel ischaemia; diffuse cortico-subcortical atrophy

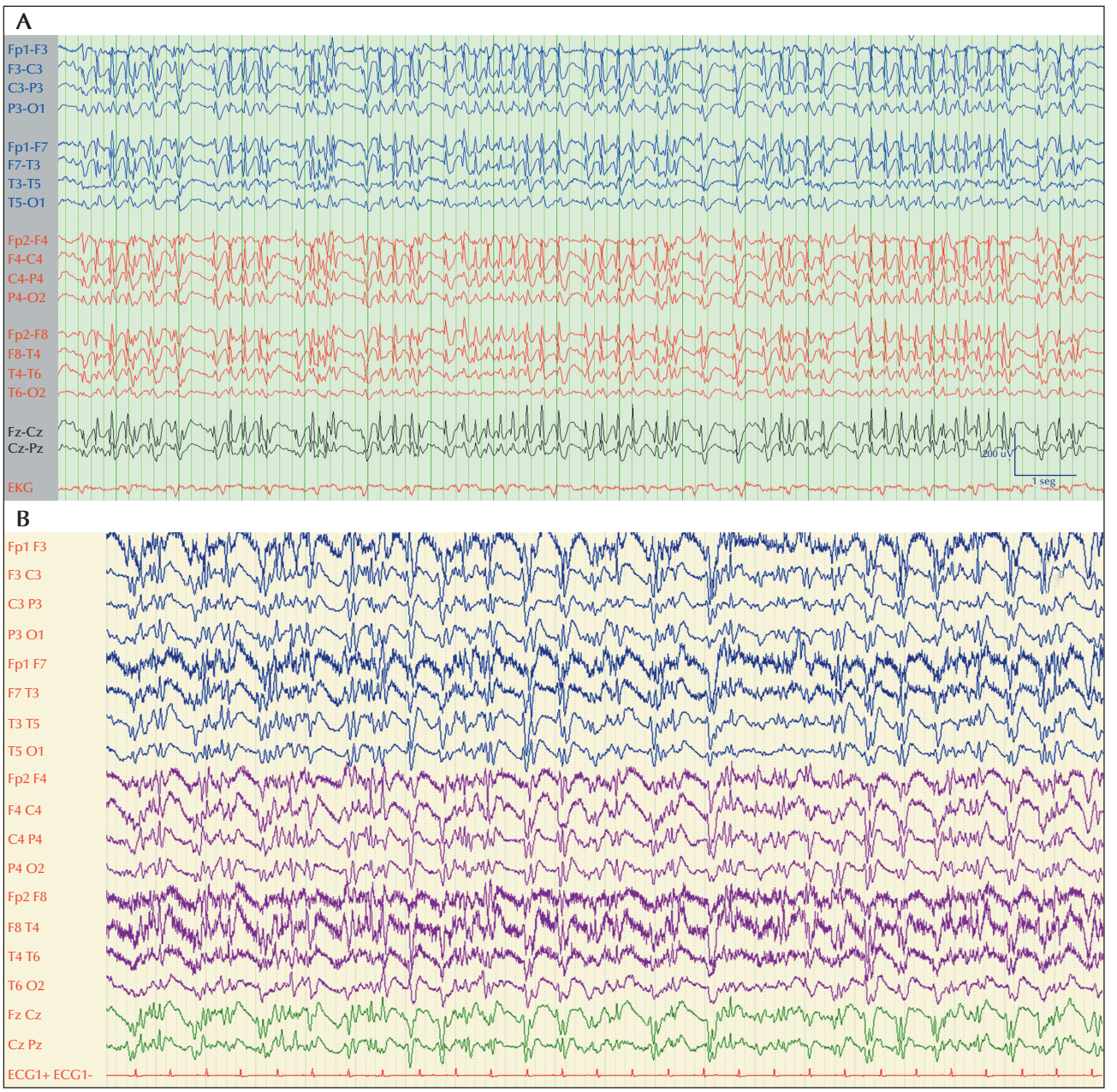
CT: brain computed tomography; FE*: patients with a history compatible with IGE misdiagnosed with cryptogenic focal epilepsy; GTCS: generalized tonic-clonic seizure; MR: brain magnetic resonance; PSWC: polyspike-and-wave complexes; SWC: spike-and-wave complexes; **poly-spikes and short bursts of slow PWSC.

morphology or frequency of the generalized spike-wave discharges on acute EEG is not straightforward. Avoiding dogma, the acute clinical context should be considered when looking for possible exogenous triggers (mainly psychotropic drug withdrawal or acute metabolic/toxic insults). Clinical and EEG follow-up after the resolution of the status epilepticus may (or may not) show interictal evidence of IGE [11]. ASE in the elderly falls into four categories:

- ASE during the course of a known pre-existing IGE. In such cases, typical ASE represents an aggravation or reactivation of the disease [12].
- ASE during the course of an undiagnosed benign IGE [2,13]. Although in these patients, there is no *a priori* diagnosis of IGE, a detailed clinical history and consecutive vEEGs can confirm the existence of benign forms of IGE complicated by an episode of typical ASE.
- ASE as the debut of a late-onset IGE in the elderly [7,10]. In these patients, the episode can be categorized as true *de novo* typical ASE of late onset (*de novo* late-onset typical ASE).
- dnASLO that represents a situation-related generalized NCSE. This is typically seen in non-epileptic adults or elderly subjects and precipitated by drugs, alcohol, metabolic disturbances or electroconvulsive therapy.

Diverse pharmacological agents, such as psychotropic medications, antidepressants, antiepileptic drugs, antibiotics and antineoplastic agents, have been reported as frequent causes [1]. dnASLO is not considered to be a seizure symptom of an epilepsy syndrome or type [11].

The term "*de novo*" used in patients in whom ASE is the debut of a late-onset IGE in the elderly may not be universally accepted. Some authors use the term only in



■ **Figure 1.** (A) EEG of Patient 5 showing the presence of continuous generalized synchronous and symmetrical SWC at 4.0-5.0 Hz, in keeping with the diagnosis of typical ASE. Low filter: 0.53 Hz; high filter: 70 Hz; notch filter: 50 Hz; vertical bar: 100 µV; distance between solid vertical lines: 1 second (speed: 30 mm/second). (B) EEG of Patient 2. This 68-year-old woman had no history of epilepsy. Note the presence of continuous, well-formed, polyspikes and slow PSWC. Low filter: 0.53 Hz; high filter: 70 Hz; notch filter: 50 Hz; vertical bar: 100 µV; distance between solid vertical lines: 1 second (speed: 15 mm/second).

situation-related NCSE. However, when epilepsy starts in old age with an episode of typical ASE (Case 2 of this series and cases from references [7] and [10]), the epilepsy is "new" and hence "*de novo*". Typical ASE occurs in mentally and neurologically normal patients with IGE or genetic generalized epilepsies. Therefore, adding "typical" would suggest that the patient has an IGE (unlike patients with dnASLO). The terminology "idiopathic late-onset ASE" has been used by others [10].

It is unclear whether Patient 2 has a typical ASE as first manifestation of late-onset IGE, or a post-convulsive generalized NCSE. However, generalized tonic-clonic seizures recurred after hospital discharge, and the patient also had episodes of inattention. In addition, the ictal EEG showed well-formed generalized symmetrical and synchronous PSWC (*figure 1B*). Classically, Bauer *et al*. reported post-convulsive ASE in patients with primary generalized epilepsy [14]. Fagan and Lee reported eight subjects with generalized NCSE and vEEGs with various patterns of ictal changes, including irregular SWC and high-amplitude generalized rhythmic sharp-slow-wave complexes [15]. One of their patients had a history of absence seizures. Of note, *de novo* typical ASE has been recently described as the first manifestation of epilepsy in children [16, 17].

In this study, three of the six patients had a previous diagnosis of IGE and two of cryptogenic FE. Furthermore, three of these five subjects had a history of recurrent episodes of ASE, an important factor when making diagnostic and therapeutic decisions. Narrow-spectrum antiseizure drugs (such as carbamazepine or PHT), may be ineffective or even worsen seizures [7, 18]. ASE with focal features (frontal NCSE), as described by Niedermeyer *et al*., could be excluded in our series [19]. Indeed, none of our patients had a previous history in keeping with a frontal epilepsy, and vEEGs recorded during status epilepticus always disclosed continuous or almost continuous generalized symmetric epileptic activity.

Serial EEGs and clinical data over time help confirm the effect of antiseizure drugs and detect generalized paroxysms of PSWC or SWD that support the diagnosis of an underlying IGE.

Older age may represent a period of vulnerability in certain patients with IGE, hitherto well controlled for years without anti-seizure treatment, but at risk of reactivation of seizures and ASE. This may be due to a variety of factors, including chronic ischaemia, white matter disease, cerebral atrophy, metabolic derangements, hormonal changes and polypharmacy. Four of our six patients had small vessel brain disease and/or cortical-subcortical atrophy based on neuroimaging studies. In our previous study of NCSE, three of 14 subjects with ASE were older and one had white matter lesions on brain MRI [4]. Some suggest that the increase in cerebrovascular lesion burden can alter the thalamocortical balance of cortical excitability [7], and hence a detailed metabolic and neuroimaging evaluation is recommended.

There are several limitations to this study, including the small sample size and retrospective nature, creating a probable selection bias. Moreover, there was a risk of under-reporting mild symptoms, and detailed genetic studies were absent.

To summarize, typical ASE is a rare cause of confusion among older population that requires urgent EEG evaluation. It is often due to reactivation of a previous IGE, although it can be the form of presentation in elderly people with epilepsy that begins in childhood or adolescence and that has not been diagnosed or treated. It may be rarely the debut (*de novo)* of a late-onset IGE syndrome. ■

Disclosures.
None of the authors have any conflicts of interest to disclose.

Ethical position statement.
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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TEST YOURSELF

(1) What type of epilepsy or epileptic syndrome do patients with *de novo* ASE of late onset have?

(2) Which classic antiepileptic drugs can precipitate episodes of ASE in patients with IGE.

(3) How would you assess the therapeutic effects of anti-seizure drugs and confirm the diagnosis of an IGE?

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