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How should we manage adult patients who present with an absence status? A study of case series

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Abstract

Background & Objective: Absence status epilepticus (ASE) is a generalized, prolonged absence seizure that can persist for hours or even days. In adults, it is often misdiagnosed or overlooked, frequently mistaken for focal impaired consciousness non-convulsive status epilepticus or, particularly in the elderly, for confusional episodes related to cerebrovascular disorders. In this study, we retrospectively analyzed adult patients with absence status, considering their clinical and electrophysiological characteristics, as well as their prognosis. *Methods:* We reviewed hospital records from 2002 to 2023 to analyze clinical symptoms, ictal and interictal electroencephalography (EEG) findings, blood test results, cranial imaging, and treatment approaches in adult patients with absence status at our clinic. *Results:* Five cases were identified as exhibiting ASE. The mean age at the first ASE episode was 48 years. The primary clinical symptom during ASE episodes was varying degrees of confusion. Ictal EEG findings were consistent with typical absence status. Three patients had a prior diagnosis of genetic generalized epilepsy before developing ASE, while two patients were diagnosed with ASE following recurrent ASE episodes. The main triggering factors included noncompliance with anti-seizure medications (ASMs), inappropriate ASMs, and lithium therapy. Valproate and levetiracetam were effective in terminating ASE episodes.
Conclusion: This study presents the clinical and electrophysiological findings of ASE in adults and evaluates prognosis with feasible treatment approaches.

Keywords: Confusional attack, absence status epilepticus in adulthood, ictal EEG, anti-seizure medications

INTRODUCTION

Absence status epilepticus (ASE) is a prolonged, generalized absence seizure that typically lasts for hours or even days, though it is formally defined as lasting more than 30 minutes. It is the most common form of nonconvulsive status epilepticus (NCSE), with reported prevalence rates ranging from 53% to 94% in various studies.[1-5] ASE can manifest in two ways: as a prolonged absence seizure or as recurrent absence seizures. In children, both prolonged and repeated absence seizures have been shown to develop into ASE. In contrast, in adults, ASE usually presents as a single prolonged absence seizure, often in individuals without a prior history of discrete absence seizures. Clinically, focal motor features—sometimes progressing to generalized convulsions—can occur in adults with ASE. However, these motor manifestations are not typically observed in children with ASE. The long-term prognosis also differs by age; while children do not necessarily experience poor seizure outcomes, adults with ASE tend to have a persistently unfavorable prognosis.[6]

In adults, ASE is frequently misdiagnosed or overlooked, often mistaken for focal impaired consciousness NCSE or, in elderly patients, for confusional episodes associated with cerebrovascular disorders. Ictal electroencephalography (EEG) is essential for accurate diagnosis, as it typically reveals continuous or repetitive generalized discharges of spikes, multiple spikes, and slow waves. Shorvon's classification of ASE includes four main subtypes.[7,8] Genetic Generalized Epilepsy (GGE)-Associated ASE: This subtype is linked to GGEs, with EEG discharges exceeding 2.5 Hz. Atypical ASE: Seen in epileptic encephalopathy, such as Lennox-Gastaut syndrome, this form is characterized by slower EEG discharges (<2.5 Hz). De novo late-onset ASE: This variant primarily results from anti-seizure medications (ASMs)

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withdrawal and develops in adults without a prior history of epilepsy. ASE associated with other epileptic syndromes: This includes cases related to progressive myoclonic epilepsies, electrical status epilepticus during slow sleep, Landau-Kleffner syndrome, metabolic or degenerative generalized epilepsies, and electrographic status epilepticus. The prognosis of ASE largely depends on its subtype and the underlying epileptic syndrome. In this study, we retrospectively analyzed adult patients with ASE, examining their clinical and electrophysiological characteristics while assessing their long-term outcomes.

METHODS

We retrospectively reviewed adult patients who presented with ASE at our clinic, analyzing hospital data from 2002 to 2023. ASE is characterized by cognitive and behavioral changes linked to clearly symmetrical and bilateral epileptic activity on EEG, which improved following the administration of ASMs. During ASE episodes, we evaluated blood biochemistry parameters and investigated whether patients had a history of intoxication or drug withdrawal. EEG recordings were performed using scalp electrodes placed according to the International 10-20 system, employing both bipolar and referential montages. Video-EEG was recorded during ASE episodes. Ictal video-EEG assessments focused on discharge morphology, continuity, regularity, frequency, associated clinical symptoms, and response to intravenous diazepam. ASE resolution was determined based on clinical symptom improvement, with EEG confirmation of seizure cessation. Interictal EEG recordings were analyzed for background activity, responses to hyperventilation, intermittent photic stimulation, and eye-opening/closure. Brain imaging was performed for all patients. Additionally, patients were classified according to the 2017 ILAE-recommended epileptic syndrome criteria.[9]

RESULTS

Five ASE cases were identified, with a mean onset age of 48 years. The predominant symptom was varying degrees of confusion, without concomitant motor signs such as perioral, eyelid, or generalized myoclonus. Three patients had a prior epilepsy diagnosis before ASE, while two were diagnosed afterwards. Table 1 presents the patients' demographic characteristics, previous seizure and ASE features, neurological examinations and imaging findings after ASE attacks. The primary triggering factors for ASE, ranked by frequency, were ASMs discontinuation, lithium therapy, and inappropriate antiepileptic treatment. Table 1 details these triggers case by case. Patient 5 had a prior epilepsy diagnosis but had been seizure-free and off ASMs before starting lithium therapy. Patient 2, diagnosed with bipolar disorder, experienced her first ASE episode during lithium treatment despite no prior epilepsy history. Initially, lithium was considered a potential cause, but after its cessation, she later developed another ASE episode due to ASMs discontinuation. Notably, lithium levels in both patients remained within the normal range. Additionally, Patient 1 had recurrent ASE episodes due to a misdiagnosis of focal epilepsy and treatment with carbamazepine.

Ictal EEG recordings revealed generalized multi-spike and slow-wave complexes in three patients (Patients 3, 4, and 5), spike and slow-wave complexes in one (Patient 2), and rhythmic sharp waves with occasional spike-and-wave complexes in another (Patient 1). Epileptiform discharges were continuous in four patients (Patients 2, 3, 4, and 5), whereas in Patient 1, they appeared as intermittent clusters with 1–2 second intervals (Figure 1). The spike-and-wave discharges ranged from 3 to 6 Hz and were unresponsive to sensory stimulation during EEG recording. For acute treatment, intravenous diazepam significantly improved clinical symptoms and EEG findings in three patients (Patients 1, 2, and 3) (Figure 2), while intravenous valproate or levetiracetam effectively terminated ASE in the remaining two (Patients 4 and 5). Interictal EEG, evaluated in four patients (Patients 2, 3, 4, and 5), showed normal background activity. Hyperventilation increased epileptiform activity in three patients (Patients 2, 3, and 4), whereas intermittent photic stimulation had no effect. Among the three patients diagnosed with epilepsy before ASE, two (Patients 1 and 4) had juvenile absence epilepsy (JAE), and one (Patient 5) had juvenile myoclonic epilepsy (JME). Patients 2 and 3 initially presented with ASE and later reported infrequent absence seizures in adolescence. Additionally, Patient 2 had a single generalized tonic-clonic seizure (GTCS) before the first ASE episode. Based on these findings, we classified their epilepsy as absence status epilepsy.

During clinical follow-up, all patients remained seizure-free with levetiracetam and/or valproate. Additionally, Patient 2 was prescribed lamotrigine, and Patient 5 received valproate, both benefiting from their mood-stabilizing properties,

Table 1: Clinical features and treatment of the cases

No. of case	1	2	3	4	5
Sex	M	F	F	F	F
Current age in yr	60	45	31	60	44
Epilepsy diagnosis before	yes	no	no	yes	yes
Age at first Seizure in yr	11	12	9	17	11
Other seizure types	GTCS	GTCS	None	GTCS	GTCS, mycl
Follow-up (years)	13	9	1	1	3
Neurological examination	N	N	N	N	N
Neuroimaging (CT/MRI)	N	N	N	N	N
Past medical disorder history	No	Bipolar disorder Hypothyroidism CAD	No	No	Bipolar
Age at first ASE	25	45	30	60	44
Number of ASE attacks	every 2 months	2	3	1	1
Duration of AS (min-max)	3 days	2 days	1 day	4 hours	3 hours
Precipitating factors of AS	inappropriate treatment	Li, drug discontinuation	drug discontinuation	drug discontinuation	Li
Treatment 1000mg/d	CBZ 800mg/d	Lev 1000mg/d	Lev 2000mg/d	Lev1000mg/d	Lev
	Changed to VPA 1gr/d	Lamotrigine 200mg/d		VPA 1gr/d	VPA 1gr/d
Outcome	Seizure free	Seizure free	Seizure free	Seizure free	Seizure free

No: number, M: male, F: female, GTCS: generalized tonic-clonic seizure, mycl: myoclonia, CAD: Coronary Artery Disease, AS: Absence Status, Li: Lithium, CBZ: Carbamazepine, VPA: Valproate

particularly useful for managing comorbid bipolar disorder. Table 1 details the treatment approaches for all patients.

DISCUSSION

Our cases suggest that confusional attacks in adults may indicate ASE. In all cases, ASE onset occurred after the second decade of life. While ASE can occur at any age, it is rare before the age of 10.[10,11] Moreover, although typical absence seizures in GGE are more frequent and severe in childhood and adolescence, the reasons why ASE primarily manifests in adulthood remain unclear. Additionally, it is more prevalent in women[10], as observed in our cases.

Typical ASE appears to be associated with specific epilepsy syndromes, with prevalence rates ranging from 57.1% in perioral myoclonia with absences and 46.2% in 'phantom' absences with GTCSs to 20% in JAE and 6.7% in JME.[14] Recurrent ASE episodes may also occur in adults, primarily characterized by repeated, spontaneous, typical ASE attacks. Most affected patients exhibited rare GTCSs, generally associated with ASE, while a smaller subset had infrequent typical absence seizures. These patients displayed clinical and laboratory features of GGE but did not meet the criteria for any established GGE syndromes involving typical absences or GTCSs. Genton *et*

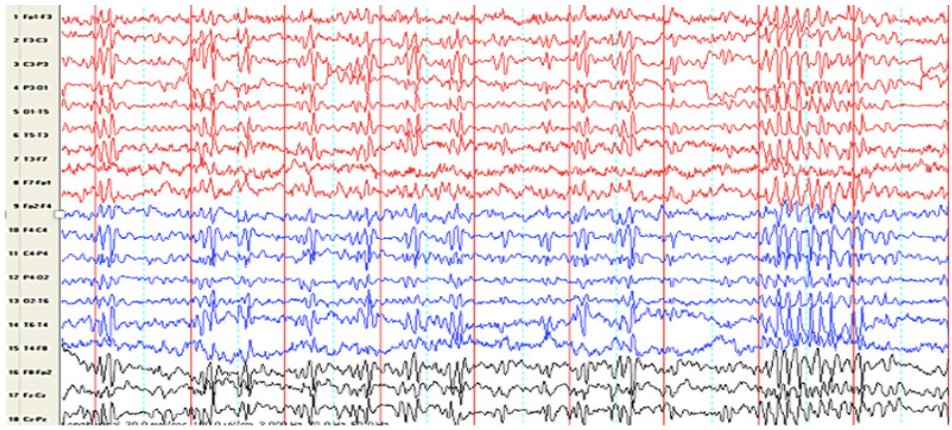

Figure 1. Ictal electroencephalographic findings in patient 1 during absence status attack.
Intermittent clusters of rhythmic sharp waves with intervals lasting 1-2 seconds (Longitudinal bipolar montage; high-cut filter, 35Hz; low-cut filter 1.6 Hz; sensitivity 100 uV/mm, 10 seconds/page)

al. proposed that this may represent a distinct and uncommon epilepsy form, termed 'absence status epilepsy'.[15] Although ASE is rare in JME and JAE, three of our cases were initially diagnosed with JAE or JME before developing typical ASE. In the remaining two patients, ASE was the primary presentation, yet they could not be classified under a specific epileptic syndrome. Based on Genton *et al*.'s classification, these cases were categorized as absence status epilepsy.

The diagnosis of ASE is confirmed by generalized spike-and-wave discharges on EEG that are either continuous or frequently recurrent.[10,16] These discharges are also unreactive to sensory stimulation, a hallmark of ictal discharges.[17,18] This distinction is particularly crucial in adult patients with encephalopathy, especially when EEG shows generalized periodic discharges. A key diagnostic criterion is stimulus-induced wakefulness with transient EEG improvement, confirming that the observed EEG activity is not ictal.[19] Moreover, patients with GGE taking inappropriate medications, such as carbamazepine or pregabalin, may exhibit bilateral bursts or continuous discharges of sharp and/or slow waves at 2–4 Hz on ictal EEG rather than the expected organized spike-and-wave complexes.[20] However, the ictal EEG in typical ASE does not distinguish between a preexisting GGE syndrome and a new-onset ASE episode.[21] Interictal EEG findings, particularly generalized spike-and-wave or polyspike-and-wave discharges at 2–4 Hz on a normal background, provide supportive evidence for GGE in ASE cases. Upon reviewing our cases, ictal EEG exhibited characteristic discharges in four patients. However, in Patient 1, ictal

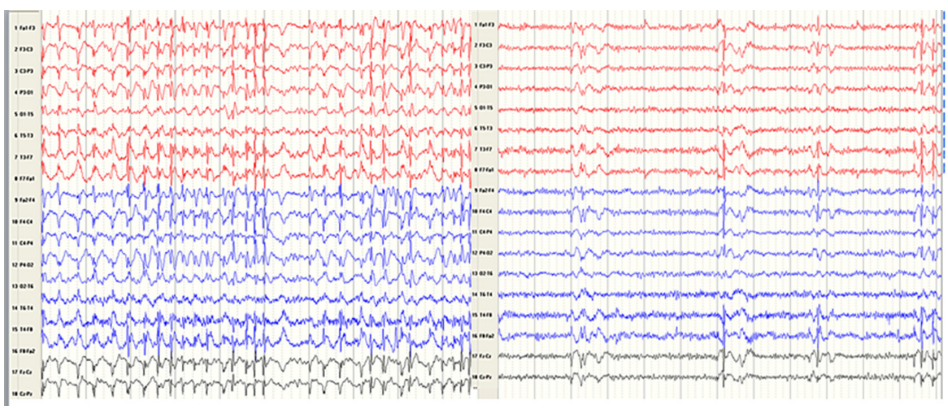

Figure 2A. Ictal electroencephalography of patient 2 during absence status, generalized, 3-3.5 Hz, spike, and wave complexes.
2B. Administering diazepam intravenously reduced these discharges seen on the electroencephalogram (Longitudinal bipolar montage; high-cut filter, 35Hz; low-cut filter 1.6 Hz; sensitivity 100 uV/mm, 10 seconds/page)

discharges predominantly consisted of repetitive sharp wave bursts. This patient had previously been treated with carbamazepine before the ASE episode, leading us to a hypothesis that this ictal pattern may have been drug-related. Interictal EEG findings were consistent with GGE in all cases. Notably, in two cases classified as absence status epilepticus, generalized discharges were predominantly observed during hyperventilation.

Sleep deprivation, withdrawal or non-compliance with ASMs, febrile illness, surgery, and menstruation have all been identified as precipitating factors for ASE, similar to other seizure types associated with GGE.[22,23] In our cases, non-compliance with ASMs was the most common ASE trigger. Case studies and anecdotal evidence have reported various seizure types—including GTCS, myoclonic seizures, and NCSE—in patients receiving lithium therapy.[25,27] Notably, epileptic seizures may occur not only due to lithium toxicity but also within its therapeutic range.[28] Furthermore, absence seizures have been reported with lithium use, particularly in combination with fluoxetine[29], a side effect observed in two of our cases. Additionally, absence seizures may resemble focal seizures with impaired awareness if seizure semiology is unclear. In such cases, sodium channel antagonists, including carbamazepine, may be considered for treatment. However, these drugs are unsuitable for GGE and may contribute to recurrent ASE episodes.[24] In one of our cases, recurrent ASE attacks were attributed to inappropriate antiepileptic treatment.

ASE does not necessitate the same level of intensive therapeutic intervention as convulsive status epilepticus.[30] Krumholz's findings suggest that typical ASE does not have severe consequences and may be classified as an "inhibitory" seizure.[31] However, in our cases, we administered intravenous levetiracetam and valproate to terminate ASE episodes as quickly as possible. Both treatments were effective for both acute and chronic management. In the literature, intravenous benzodiazepines and valproate are reported as first-line treatments for ASE, while levetiracetam has also been shown to be effective. Altenmüller *et al*. described a case of ASE successfully terminated with intravenous levetiracetam treatment.[32] Additionally, in chronic treatment, Verotti *et al*. suggested that monotherapy with levetiracetam could be an effective and well-tolerated option for patients with childhood absence epilepsy and juvenile absence epilepsy.[33-35] Levetiracetam is a particularly favorable option for women, especially those of reproductive age. Ethosuximide is also an effective agent for absence seizures; however, due to its teratogenic effects, we did not use it for chronic treatment in our female patients of childbearing age. Moreover, ethosuximide is only effective for absence seizures, whereas our patients also experienced other seizure types commonly observed in GGE. Therefore, for chronic treatment, we selected levetiracetam and valproate.

In summary, ASE should be considered in the differential diagnosis of adults presenting with confusional attacks, most commonly in individuals with GGE, particularly due to non-compliance with ASMs. Moreover, ASE triggered by novel medications such as lithium may reveal underlying epileptogenicity, potentially serving as its first clinical manifestation. Ictal EEG plays a crucial role in diagnosing and classifying the specific type of ASE, while interictal EEG can provide valuable insights into the underlying cause of an ASE episode. Levetiracetam is an effective treatment for ASE and represents a viable option, particularly for women of reproductive age.

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