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Subacute Encephalopathy With Seizures in Alcoholics Syndrome: A Subtype of Nonconvulsive Status Epilepticus

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Abstract

A recent assessment of the classification of nonconvulsive status epilepticus (NCSE) has incorporated the specific electroencephalographic (EEG) patterns on a syndromic basis. Such a clinical EEG syndromic approach may enable more accurate and expedited diagnosis of particular subtypes of NCSE so as to improve therapy. Herein, we review the characteristics of subacute encephalopathy with seizures in alcoholics syndrome, a subtype of focal NCSE occurring in chronic alcoholism with specific features, including encephalopathy, lateralized periodic discharges on the EEG, chronic microvascular ischemia on neuroimaging studies, and possible recurrence when chronic antiseizure treatment is stopped.

Keywords

SESA syndrome, Alcoholics, complex partial status epilepticus, nonconvulsive status epilepticus, lateralized periodic discharges

Introduction

Neurologists have long been aware of the diversity of neurological syndromes associated with alcoholism. Traditionally, alcohol withdrawal syndrome (AWS), delirium tremens, hepatic encephalopathy, alcoholic hallucinosis, and Wernicke encephalopathy or Korsakoff psychosis are the best known. Epileptic seizures are frequent clinical features that can occur in different settings. Optimization of treatment and accurate syndromic diagnosis and classification determine the ultimate prognosis.

Alcohol withdrawal syndrome is a well-known and common condition occurring after intentional or unintentional abrupt cessation of alcohol consumption.[1] This picture typically occurs within 24 to 48 hours of stopping alcohol, and signs and symptoms may include tremor, irritability, psychomotor agitation, disorientation, hallucinations, anxiety, and generalized tonic–clonic seizures (GTCSs).

An underrecognized clinical disorder of *subacute encephalopathy with seizures in alcoholics* (SESA) syndrome was first described in 1981.[2,3] The SESA syndrome appears as a distinct neurological disorder in which the encephalopathy occurs in the context of focal motor or GTCSs (but often not proximate to alcohol cessation) and includes specific focal electroencephalography (EEG) abnormalities. However, SESA syndrome also occurs in patients with a history of alcohol withdrawal seizures. Awareness of this entity, its clinical findings, and EEG characteristics is essential to making an appropriate diagnosis, which in turn leads to correct and prompt treatment.

Historical Overview of SESA Syndrome

An unusual picture of a subacute encephalopathy in chronic alcoholics characterized by confusion or lethargy, transient neurological deficits, and marked EEG abnormalities was initially characterized by Niedermeyer et al[2] and Freund and Niedermeyer.[3] The EEG findings included focal slowing, spiking, and lateralized periodic discharges (LPDs). Focal motor and GTCSs were common and convulsive status epilepticus was also reported. The patients did not fit criteria for other known neurologic complications in alcoholics, and the authors coined the term *SESA syndrome* to characterize this condition. Surprisingly, few cases of SESA syndrome have been reported in

the English literature since these early reports.[4-15] When initially described, the cause of delirium remained speculative and early authors assumed a vascular etiology.[2]

Twenty-five years later, Fernández-Torre et al[7,8] reported cases of SESA syndrome with complex partial status epilepticus (CPSE) that had arisen in temporal and extratemporal regions and that was associated with focal deficits and confusion. They suggested that the syndrome was more common than reported and that the existence of CPSE could readily explain the alteration in mental state. The encephalopathy may have led to underrecognition and possibly masking of an associated nonconvulsive ictal state. As a result, 2 additional cases were used to argue for a revision of the characteristics of SESA syndrome,[11] including supporting evidence from neuroimaging, thus updating EEG and clinical and prognostic syndromic characteristics. Most recently, the full spectrum of neuroimaging features has been described in detail by Drake-Pérez et al[13] expanding the diagnostic criteria for this epileptic entity. In addition, Kaplan et al[15] described a patient who had frontoparietal "ping-pong" nonconvulsive status epilepticus (NCSE) that responded to nonsedating antiseizure drugs (ASDs), while a second patient had focal frontocentral confusional NCSE that was more refractory to treatment.

Clinical Features in SESA

Encephalopathy with lethargy, delirium, confusion, obtundation, agitation, inattention, and disorientation is frequent. In addition, transient episodes of hemiparesis, aphasia, neglect, hemianopsia, and cortical blindness have been described (Table 1). Focal motor and grand mal seizures were reported in the original description.[2,3] However, it was not until 2006 that Fernández-Torre and colleagues described the occurrence of complex partial seizures (CPSs) and episodes of CPSE.[7,8] Nonetheless, the original description in 1981 noted probable subclinical focal seizures in cases 1, 2, and 5. Recurrences occurred in 3 patients. Subsequently, recurrence has been corroborated by other authors.[7,10]

Electroencephalography Abnormalities in SESA

As pointed out by Niedermeyer et al,[2] EEG changes in chronic alcoholism are not particularly striking.[1,16] In contrast, in SESA syndrome, EEG abnormalities constitute one of the cornerstones of diagnosis. Focal slowing and spiking and LPDs over the temporal, central, frontal, parietal, and occipital regions were observed by Niedermeyer and associates. They proposed a diverse range of underlying pathogenic mechanisms in their patients, including vascular in 2 patients, traumatic in 1 patient, and "uncertain" in 4 patients.

Neuroimaging Findings in SESA

Recently, Drake-Pérez et al[13] reviewed the full spectrum of neuroimaging findings in 10 published cases of SESA. Initial magnetic resonance imaging (MRI) studies revealed cortical–subcortical areas of increased T_2/fluid-attenuated inversion recovery (FLAIR) signal and restricted diffusion in 6 patients. In 5 patients, the affected region included the temporal lobe. The areas of abnormal signal correlated with the origin of the LPDs on the EEG for all 6 cases. Hyperperfusion of the region was observed in 3 of the 6 patients (1 patient had increased distal flow on the magnetic resonance angiography [MRA], and the other 2 had a single-photon emission computed tomography [SPECT] revealing hyperperfusion). The other 3 patients did not have confirmatory SPECT or MRAs. Atrophy was present in 62.5% of the patients, with 2 patients showing a temporal predominance, while 3 had diffuse or unspecified atrophy. Chronic microvascular ischemic changes were described in half. Other isolated findings included hydrocephalus, Chiari I malformation, and choroid fissure cyst. Follow-up MRI in 50% of the patients showed resolution of the hyperintense lesions but revealed emerging focal atrophic changes in 75%. Residual T_2 hyperintensities were seen in the right temporal lobe and in the splenium of the corpus callosum in other cases.

Kim et al[14] reported a high signal intensity lesion in the right thalamus associated with focal NCSE in a patient with suspected SESA. In 2 new cases, T_2 FLAIR hyperintensities and diffusion restriction in the cingulate gyri, insula, and thalami and in the right thalamus and mesial temporal lobe, respectively, were observed.[15] To summarize, neuroimaging findings include transient cortical–subcortical T_2-hyperintense areas with restricted diffusion along with atrophy and chronic multifocal vascular lesions.

Recently, Fernández-Torre et al[16] have described both focal hyperperfusion (SPECT) and hypermetabolism (positron emission tomography [PET]), which were strongly suggestive of an epileptic event in the clinical context. The author concluded that cerebral SPECT and PET closely correlated with EEG can play an important role in the optimization of ASD therapy and diagnosis of SESA syndrome.

Distinguishing Between SESA and AWS

The question has been raised whether SESA is a distinct pathological condition or simply whether it represents the spectrum of CPSs, CPSE, and generalized seizures in the context of AWS or in acute intoxication in chronic alcoholic patients. However, there are significant differences between these entities, including the type of seizures, neurological symptoms, EEG abnormalities, neuroimaging features, and clinical evolution (Table 2). Thus, GTCSs, isolated or recurrent, are the most frequent type seen in AWS.[17,18] In these cases, the diagnostic value of the EEG is limited and, generally, epileptiform activity is absent.[19] Conversely, in SESA syndrome, although GTCSs or secondarily GTCSs are frequent, focal motor seizures occur in up to 40% of the cases. Moreover, frank epileptiform abnormalities on EEG constitute one of the major diagnostic criteria. Of note, when a patient has recurrence, clinical presentation, EEG, and evolution are frequently stereotyped.

Timing of the EEG is important. In some cases,[7,8,11] recurrent CPSs were recorded during the first hours or days of

Table 1. Summary of the Clinical, EEG, and Neuroimaging Features of All Published Patients With SESA Syndrome in the English Literature.

Author, Year	Number of Patients/ Age/Sex	Precipitating Factor	Seizure Type	Neurological Deficit	EEG Findings	Neuroimaging	ICU Stay	AEDs
Niedermeyer et al, 1981	7/41-61 (25)[a]/ 4M, 3F	Alcohol withdrawal independent	SPMS, GTCS	Lethargy, hemiparesis, hemianopsia	Focal slowing, LPDs	Diffuse cortical atrophy, low density areas	No	PRM, PHT
Otto and Kozian, 2001	1/66/M	Acute alcoholic intoxication	GTCS	Wernicke aphasia	L fronto-centro-temporal LPDs	Cerebral atrophy; subcortical/ periventricular hyperintensities	No	DZP, CLB
Rothmeier et al, 2001	1/60/M	Alcohol abstinence, hyponatremia	GTCS	Confusion, L homonymous hemianopsia, Wernicke aphasia	R parietooccipital LPDs	Disseminated foci of gliosis, white matter occipital lesions; enhanced signals bilaterally in the occipital white matter	No	CBZ, PHT, DZP
Mani et al, 2003	1/55/M	Acute alcoholic intoxication	SPMS, SGTCS	Confusion, inattention, R hemiparesis	L parietooccipital LPDs	Cerebral atrophy	No	CBZ
Fernández-Torre et al, 2006[b]	1/65/M	Alcohol withdrawal, hyponatremia, hypokalemia	GTCS, CPS, focal NCSE	Confusion, L upper limb paresis	R temporal LPDs	Cerebral atrophy, R temporal hyperintense lesions, R hemisphere hyperperfusion (SPECT)	No	PHT, CZP
Fernández-Torre et al, 2007	1/55/M	Alcohol withdrawal	SPM, SGTC, focal NCSE	Confusion, disorientation, R hemiparesis	L frontal and parasagittal LPDs, recurrent L frontal Szs	L frontal and insular hyperintense lesions; L frontal and right cerebellum hyperperfusion (SPECT)	No	PHT, VPA
Bugnicourt et al, 2008	1/63/M	Unknown	CPS,[c] focal NCSE	Confusion, disorientation, L hemiparesis, L hemianopsia	R hemisphere LPDs	R occipital stroke, R hemisphere transient cortical hyperintensities	No	VPA
LaRoche and Shivdat-Nanhoe, 2011	1/61/F	Unknown	SPMS, CPS, focal NCSE	Confusion, R hemiparesis	L hemisphere LPDs, L temporal and parietal Szs	Cortical gray matter frontal, parietal and temporal hyperintensities	Yes (cEEG)	LZP, fPHT, VPA, LCM
Choi et al, 2014[d] (patient 2)	1/54/F	Unknown	Secondarily GTCS	Drowsy, transcortical sensory aphasia, R hemiparesis	L parietooccipital LPDs + L frontotemporal rhythmic δ activities	L medial temporal, parietal and occipital T_2/ FLAIR/DWI/ADC hyperintensities; L middle cerebral artery hyperperfusion	No	LEV
Fernández-Torre and Kaplan, 2014	1/55/M	Alcohol withdrawal	GTCS, CPS, SPMS, focal NCSE	Stupor, L hemiparesis	R temporo-occipital LPDs	Cerebral atrophy; periventricular hypodensities	Yes	PHT, LEV
Fernández-Torre and Kaplan, 2014	1/58/M	Alcohol withdrawal	SPMS	Confusion, agitation, L hemiparesis	R temporal LPDs	Cerebral atrophy; R temporo-occipital and L parietal ischemic lesions	Yes	PHT, LEV, PPF
Kim et al, 2016	1/52/M	Alcohol withdrawal	GTCS, focal NCSE	Agitation, confusion, speech disturbances	R frontotemporal Szs, R frontotemporal LPDs	High signal intensity lesion in the R thalamus	No	CBZ
Drake-Pérez et al, 2016	1/69/M	Unknown	Secondarily GTCSs	Somnolence, L hemiparesis	R temporal LPDs	Atrophy (L medial temporal lobe), chronic white matter changes; R hippocampus enlarged, T_2 hyperintensity with restricted diffusion in R insula, parietal and cingulated cortex, and posteromedial thalamus	No	LEV

(continued)

Table 1. (continued)

Author, Year	Number of Patients/ Age/Sex	Precipitating Factor	Seizure Type	Neurological Deficit	EEG Findings	Neuroimaging	ICU Stay	AEDs
Kaplan et al, 2018	1/50/M	Unknown	SPMS, focal NCSE	Stupor, confusion	Ping-pong L and R frontoparietal Szs; R frontoparietal EDs, R LPDs	T_2 FLAIR hyperintensities and diffusion restriction in the cingulate gyri, insula, and thalami	Yes	LEV
Kaplan et al, 2018	1/54/M	Unknown	Secondarily GTCS, focal NCSE	Disorientation, L hemiparesis	R centrotemporal EDs; R centrotemporal Szs	Diffusion restriction in the R thalamic and mesial temporal lobe	No	LEV, fPHT, PHT, LCM
Fernández-Torre et al, 2018	1/66/F	Poor compliance of ASD therapy	SPMS, secondarily GTCS, convulsive SE	Disorientation, speech disturbances	L temporo-parieto-occipital LPDs	Increased T_2/FLAIR signal and restricted diffusion over the left parietooccipital region; moderate diffuse cerebral atrophy; hyperperfusion (SPECT) and hypermetabolism (PET)	No	LEV, LCM

Abbreviations: AEDs, antiepileptic drugs; ASD, antiseizure drug; CBZ, carbamazepine; cEEG, continuous electroencephalography; CLB, clobazam; CPS, complex partial seizure; CZP, clonazepam; F, female; FLAIR, fluid-attenuated inversion recovery; fPHT, fosphenytoin; GTCS, generalized tonic–clonic seizure; ICU, intensive care unit; L, left; LCM, lacosamide; LEV, levetiracetam, LZP, lorazepam; LPDs, lateralized periodic discharges; M, male; NCSE, nonconvulsive status epilepticus; OXC, oxcarbazepine; PET, positron emission tomography; PHT, phenytoin; PPF, propofol; PRM, primidone; R, right; SE, status epilepticus; SGTCS, secondarily generalized tonic–clonic seizure; SPECT: single-photon emission computed tomography; SPMS: simple partial motor seizures; Szs, seizures; VPA, valproate.

[a]One patient was a 25-year-old.

[b]First paper demonstrating the existence of complex partial seizures in SESA syndrome.

[c]Presumably complex partial seizures.

[d]Patient 1 of Choi et al's paper was not included because the patient had an abdominal aura and right hippocampal sclerosis suggesting a diagnosis of temporal lobe epilepsy.

Table 2. Differentiating AWS From SESA Syndrome.[a]

	Alcohol Withdrawal Seizures	SESA Syndrome
Seizure type	Generalized tonic–clonic seizures	Partial focal motor, complex partial and generalized tonic–clonic seizures
Timing	Within 48-72 hours of alcohol cessation	Up to several days after alcohol cessation, not related to cessation or even associated with acute intoxication
Neurological examination	No focal deficits	Hemiparesis, aphasia, neglect, hemianopsia, cortical blindness
EEG	Normal or diffuse slowing	Focal slowing, LPDs, focal seizures
MRI	No acute abnormalities $\pm$ chronic vascular lesions	Transient cortical–subcortical T_2-hyperintense areas with and restricted diffusion observed in a patient with atrophy and chronic multifocal vascular lesions.
SPECT	-	Focal hyperperfusion
PET	-	Focal hypermetabolism
Chronic AED treatment	No	Yes. Frequent recurrences if antiepileptic treatment is stopped

Abbreviations: AED, antiepileptic drug; EEG, electroencephalography; LPDs, lateralized periodic discharges; MRI, magnetic resonance imaging; PET, positron emission tomography; SESA, subacute encephalopathy with seizures in alcoholics; SPECT, single-photon emission computed tomography.
[a]Modified from LaRoche and Shivdat-Nanhoe.[10]

symptom onset. Often, in the subsequent hours after GTCSs in alcoholic patients, a delirium is attributed to a postictal state or withdrawal syndrome. Underlying conditions along the ictal–interictal continuum, ranging from LPDs, to focal CPSE, should be considered. Both LPDs and NCSE in other settings have long been recognized as being associated with impaired cognition, focal neurologic signs, and a decreased level of consciousness, but the diagnosis of these conditions is subject to EEG sampling error, and routine 20-minute recordings might not capture them. Generally, LPDs disappear during focal CPSs and reappear after seizure resolution during which time the patient may remain confused. This dynamic represents an excellent example of the hypothesis of Pohlmann-Eden et al,[20] in which LPDs form part of a continuum between ictal and interictal states. Continuous EEG appears ideal for revealing this pathophysiological electroclinical evolution. A meticulous clinical evaluation and a high level of suspicion during the first 24 to 48 hours after admission are then essential for an expedited diagnosis and optimal management.

Patients who develop SESA syndrome frequently have preexisting cerebral lesions which, in the setting of alcohol withdrawal, acute intoxication, metabolic disturbances, or a combination, produce LPDs and recurrent focal seizures. While focal motor and GCTCs are the cause of the hospital admission, CPSs and CPSE remain underdiagnosed and hence undertreated.

Treatment and Response to ASDs in SESA

Patients with SESA syndrome respond well to ASDs. In some cases, confusion is prolonged and requires intensive care unit (ICU) management.[10,11,15] Several ASDs have been used, including phenytoin, valproate, benzodiazepines, and, more recently, levetiracetam and lacosamide. There are no studies that indicate which agent is most effective. Despite a good prognosis, SESA syndrome may warrant chronic treatment with ASDs and cessation of alcohol use to prevent recurrence.

Establishing a diagnosis of SESA syndrome contributes to the treatment and management. First, because we are defining what will probably be the patient's natural history and clinical course. Second, because diagnosis points to specific ancillary tests (eg, clinical EEG [cEEG] monitoring, MRI, SPECT, PET) that will help define the pathophysiology (ictal–interictal) and which will help optimize ASD therapy. Third, because knowing that recurrences are frequent may help convince the patient of the need for strict compliance and alcohol cessation.

Conclusions

Subacute encephalopathy with seizures in alcoholics (SESA) syndrome should now include the spectrum of conditions that lie along an ictal–interictal continuum and that may require cEEG monitoring and ICU management. The syndrome encompasses focal NCSE in alcoholic individuals who manifest transient neurologic deficits, interictal LPDs on the EEG, and transient cortical–subcortical T_2-hyperintense areas with restricted diffusion and multifocal chronic cerebrovascular abnormalities. Chronic treatment with ASDs is necessary as recurrence is common.

Declaration of Conflicting Interests

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