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Perspective

Subacute encephalopathy with seizures in alcoholics (SESA) syndrome: Relevant questions

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ABSTRACT

Objective: The aim of this article is to answer three relevant issues: i/What epileptic condition is referred to as subacute encephalopathy with seizures in alcoholics (SESA) syndrome; ii/ Why it can be important to distinguish SESA syndrome in clinical practice and iii/ What do we know about its pathophysiology.
Methods: We reviewed all cases published in the English language from the initial description of the syndrome to the present. All met the previously established criteria for SESA syndrome were included in our analysis.
Results: We found 34 patients diagnosed with SESA syndrome Fourteen (41.1%) out of 34 patients were over 60 years of age. In 12 (35.2 %), abstinence, and in 4 (11.7 %) excessive consumption of alcohol, were considered precipitating factors, respectively. Triggering causes were unknown in 18 cases (53.0 %). All cases (100 %) presented with altered mental status. Fourteen (41.1 %) subjects had a history of epileptic seizures in the context of alcohol withdrawal syndrome (AWS). Twenty (58.8 %) patients had focal motor seizures (FMSs), 24 (70.5 %) bilateral tonic-clonic seizures (BTCSs), and 15 (44.1 %) focal impaired awareness seizures (FIASs). In 8 (23.5 %), criteria for focal nonconvulsive status epilepticus (NCSE) were met. Twenty-eight (82.3 %) subjects had transient neurological deficits. In 29 (85.2 %) subjects, lateralized periodic discharges (LPDs) were observed on the EEG. Areas of signal hyperintensities and restricted diffusion in neuroimaging were mentioned in 22 subjects (64.7 %). Transfer to the intensive care unit was necessary in 8 (23.5 %) subjects. Thirteen (38.2 %) had recurrent episodes. Enduring brain damage was mentioned in 9 (26.4 %) cases. The most used anti-seizure medication (ASM) was levetiracetam, followed by phenytoin and lacosamide.
Conclusions: SESA syndrome represents a well-defined subtype of focal NCSE in patients with chronic alcoholism. Its prompt recognition can facilitate the initiation of early ASM therapy and help design appropriate video-EEG evaluation and a treatment strategy.

1. Introduction

Chronic alcoholism or alcohol use disorder (AUD) is a common cause of convulsive status epilepticus. However, the role of alcohol as a triggering factor for focal nonconvulsive status epilepticus (NCSE) is little known and frequently underestimated. Niedermeyer, Freund, and Krumholz in 1981 first observed the existence of prominent, albeit transient, electroencephalogram (EEG) abnormalities and neurological deficits in chronic alcoholics [1]. These authors realized that this entity was radically distinct from an EEG standpoint compared to the classical complications of chronic alcoholism such as Wernicke's encephalopathy, alcohol withdrawal syndrome (AWS) or delirium tremens and coined the term "*subacute encephalopathy with seizures in alcoholics*" (subsequently referred to by the acronym SESA).

The objective of this article is to answer three issues: i/What epileptic condition is referred to as SESA syndrome; ii/ Why it may be important to distinguish SESA syndrome in clinical practice and; iii/ What is known about its pathophysiology.

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2. What epileptic condition is referred to as SESA syndrome

To answer this question, we reviewed all cases published in the English language from the initial description of the syndrome to the present. A comprehensive systematic review of the available literature was conducted in PubMed, searching for case reports and case series on SESA syndrome. The following search terms were employed: [("Subacute encephalopathy with seizures in alcoholics")/OR (SESA syndrome)].

In addition, we included four own cases obtained from a retrospective analysis of prospectively collected consecutive patients between January 2019 and September 2023 in our department. All patients who met the previously established criteria for SESA syndrome were included in the study [Fig. 1] [2,3]. A detailed description of these four subjects may be found elsewhere [3].

We focused data collection on precipitating factors, types of seizures, presence of neurological deficits, EEG abnormalities, findings from cerebral magnetic resonance imaging (MRI), need for transfer to the Intensive Care Unit (ICU), anti-seizure medication (ASM), SESA recurrences, and prognosis.

2.1. Summary of published cases in the English language

Nineteen articles were included in the review [1–19]. We have found 34 patients diagnosed with SESA syndrome to date including four of own cases. The main clinical features, EEG, and neuroimaging findings that constitute the syndrome can be found in Fig. 2. Fourteen (41.1%) out of 34 patients were elderly (age $\geq$ 60 years). In 12 (35.2%), abstinence, and in 4 (11.7%) excessive consumption of alcohol, were considered precipitating factors, respectively. However, triggering causes were unknown in 18 cases (53.0%). In addition, some patients reported cannabis or cocaine use. All cases (100%) presented an altered mental status including disorientation and poor attention, psychomotor agitation, confusion, lethargy, stupor, or coma. Fourteen (41.1%) subjects had a history of epileptic seizures in the context of AWS. Twenty (58.8%) patients had focal motor seizures (FMSs), 24 (70.5%) bilateral tonic-clonic seizures (BTCSs), and 15 (44.1%) focal impaired awareness seizures (FIASs). In 8 (23.5%), criteria for focal NCSE were met. Twenty-eight (82.3%) subjects had transient neurological deficits such as hemiparesis, hemianopsia, sensory or motor neglect, aphasia or speech disturbances and focal paresis. In 29 (85.2%) subjects, lateralized periodic discharges (LPDs) were observed on the EEG. Other EEG findings such as interhemispheric asymmetry, diffuse slowing, lateralized rhythmic delta activity (LRDA) or brief potentially ictal rhythmic discharges (BIRDs) were mentioned in 24 (70.5%). T2/fluid attenuated inversion recovery (FLAIR) signal hyperintensities and restricted diffusion on diffusion-weighted images (DWI) were mentioned in 22 subjects (64.7%). Transfer to the ICU was necessary in 8 (23.5%) subjects. The duration of hospital admission ranged from a few days to several weeks. Thirteen (38.2%) had recurrent SESA episodes. Enduring brain damage was mentioned in 9 (26.4%) cases. The most used ASM was levetiracetam, followed by phenytoin and lacosamide. Other ASM such as valproate, lamotrigine, brivaracetam and different benzodiazepines had also been used.

2.2. Electroencephalographic and neuroimaging observations

2.2.1. Focal nonconvulsive seizures and focal NCSE

Focal nonconvulsive seizures in SESA syndrome occur in a cyclic form recurring without complete clinical recovery between seizures. We noted recurrent focal seizures with impairment of consciousness with typical spatiotemporal evolution that fulfill the Salzburg Consensus Criteria for focal NCSE. Therefore, in cases of suspected SESA syndrome,

Diagnostic criteria for SESA syndrome
Adult patients with history of chronic alcoholism.
Antecedents of alcohol abstinence or acute intoxication. Some patients also reported cannabis or cocaine use.
Abnormally prolonged postictal confusion/stupor.
Transient focal neurologic deficits such as monoparesis, hemiparesis, neglect, hemianopsia, aphasia, speech disturbances, etc.
FMSs, focal to BTCSs and/or BTCSs
IIC patterns (LRDA, LPDs, LPDs +F, +R; BIRDs) on the EEG. Background slowing and interhemispheric asymmetry.
Recurrent FIASs compatible with the diagnosis of focal NCSE (cEEG or prolonged routine EEG is highly recommended).
T2/FLAIR signal hyperintensities; restricted diffusion on DWI; chronic multifocal vascular pathology and cerebral atrophy.
Good response to treatment with ASM.
Episodes of recurrence whether medication withdrawal and/or alcohol consumption.
Exclusion criterion: stroke(s) localized in the territory of large arteries.

Fig. 1. Diagnostic criteria for SESA syndrome (after Niedermeyer et al [1] and Fernández-Torre and Kaplan [2]). ASM: anti-seizure medication; BTCSs: bilateral tonic-clonic seizures; BIRDs: brief potentially ictal rhythmic discharges; cEEG: continuous electroencephalogram monitoring; EEG: electroencephalogram; DWI: diffusion-weighted images; FIASs: focal impaired awareness seizures; FMSs: focal motor seizures; IIC: ictal-interictal continuum; LPDs: lateralized periodic discharges; LPDs + F: lateralized periodic discharges plus superimposed fast activity; LPDs + R: lateralized periodic discharges plus superimposed rhythmic delta activity; LRDA: lateralized rhythmic delta activity; NCSE: nonconvulsive status epilepticus; SESA: subacute encephalopathy with seizures in alcoholics.

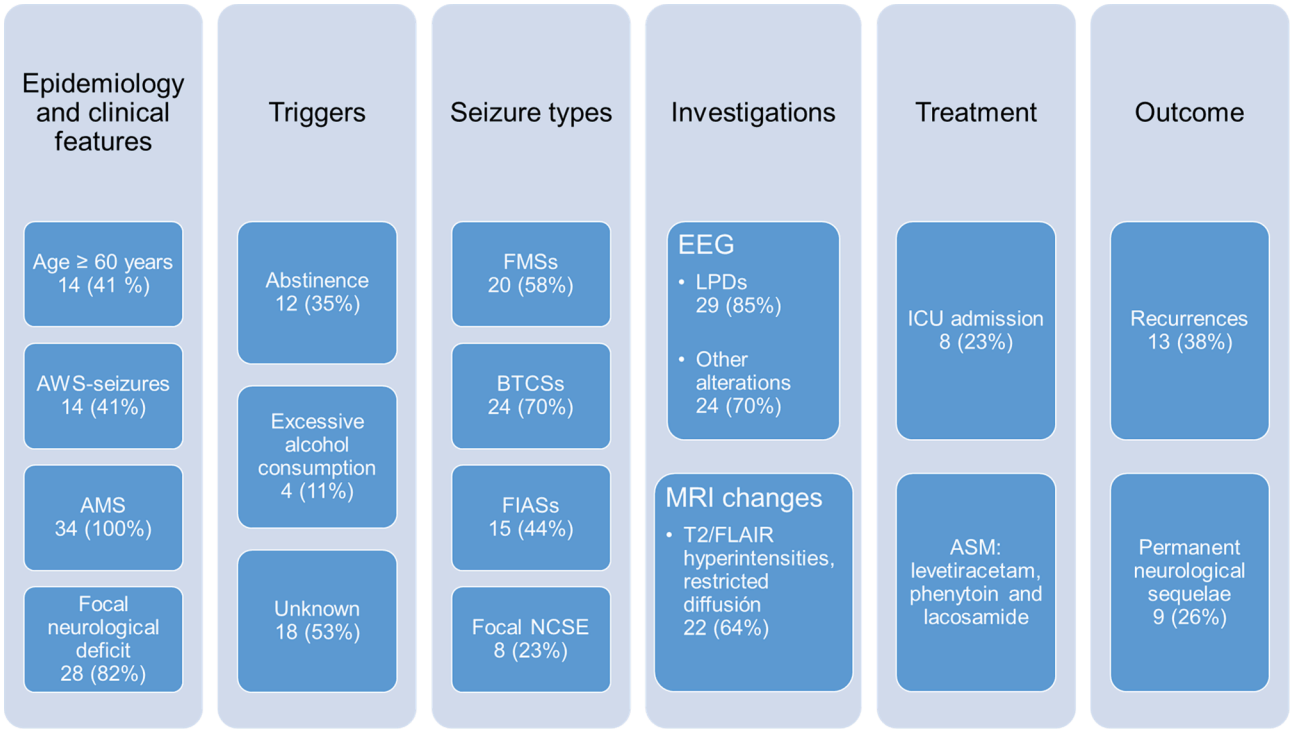

Fig. 2. Bar graph showing the main clinical, EEG and neuroimaging findings of the 34 patients described in the English literature with SESA syndrome. AMS: altered mental status; ASM: anti-seizure medication; AWS: alcohol withdrawal syndrome; BTCSs: bilateral tonic-clonic seizures; EEG: electroencephalogram; FIASs: focal impaired awareness seizures; FLAIR: fluid attenuated inversion recovery; FMSs: focal motor seizures; ICU: intensive care unit; LPDs: lateralized periodic discharges; NCSE: nonconvulsive status epilepticus; SESA: subacute encephalopathy with seizures in alcoholics.

a strategy to increase the likelihood of capturing recurrent focal non-convulsive seizures is to extend the recording time to 45 min or even 1 h if continuous video-EEG monitoring is not available. When available continuous video-EEG monitoring is highly recommended [2,3].

2.2.2. T2/FLAIR signal hyperintensities with restricted diffusion, chronic microvascular ischemic lesions, and brain atrophy

T2/FLAIR signal hyperintensities and restricted diffusion are frequently seen in these patients. Arterial spin-labelling flow maps showed increased perfusion in the localization of LPDs in some subjects [3]. Moreover, cerebral single photon emission computed tomography (SPECT) and ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) closely correlated with the EEG and can play an important role in proving that the electroencephalographic patterns lie on the ictal-interictal continuum (IIC) [15]. Of note, strokes are not seen in the territories of large arteries, a likely relevant feature to include as an exclusion criterion to rule out post-stroke epilepsy [3].

3. Why it can be important to distinguish SESA syndrome in clinical practice

The identification and diagnosis of the different clinical disorders in which NCSE plays a pivotal role require a comprehensive approach. Therefore, approaching and categorizing NCSE within the context of specific syndromes with their respective clinical features and subtypes can be relevant to facilitate recognition and diagnosis of SESA [20]. Thus, for example, it is well known the existence of different subtypes of absence status epilepticus in the elderly whose recognition make easy diagnosis and treatment [21]. In SESA syndrome, a high degree of suspicion is warranted, and its early recognition can facilitate the initiation of prompt ASM therapy and help design an appropriate video-EEG evaluation and neuroimaging approach.

4. What do we know about its pathophysiology

The continued abuse of alcohol likely leads to a maladaptive homeostatic plasticity phenomenon with a down-regulation of post-synaptic γ-aminobutyric acid type A ($GABA_A$) and an up-regulation of N-methyl-d-aspartate (NMDA) receptors [22]. These homeostatic changes maintain the activity of brain circuits involved at baseline. Additionally, in these individuals, chronic multifocal vascular pathology is invariably present [12]. Therefore, we hypothesize that those patients who develop SESA syndrome frequently have pre-existing cerebrovascular lesions which, under circumstances such as alcohol withdrawal, metabolic disturbances, toxins, or a combination of these become highly epileptogenic, favored by an underlying maladaptive homeostatic plasticity, globally responsible for the occurrence of IIC patterns and recurrent focal nonconvulsive seizures [Fig. 3]. In addition, other contributing factors such as sleep deprivation, cocaine and cannabis abuse can be also seen.

5. Limitations, concerns, and strengths

There are limitations, concerns and strengths related to the definition of SESA syndrome [Fig. 4]. Although Fernández-Torre and Kaplan [2] proposed diagnostic criteria in 2014, these have not been validated or agreed upon by a committee of experts. In fact, as we mentioned previously, the absence of cerebral infarcts affecting large vessel territories should be considered an exclusion criterion to exclude patients with post-stroke epilepsy [3].

Further, the existence of focal NCSE has been demonstrated in only a small group of patients. Possibly, due to the recurrent nature of focal nonconvulsive seizures, focal NCSE has been underdiagnosed in the past. We believe that continuous video-EEG monitoring in SESA can further delineate EEG findings and support clinical manifestations, detect focal NCSE and help optimize ASM therapy.

Considering SESA syndrome as a subtype of focal NCSE offers

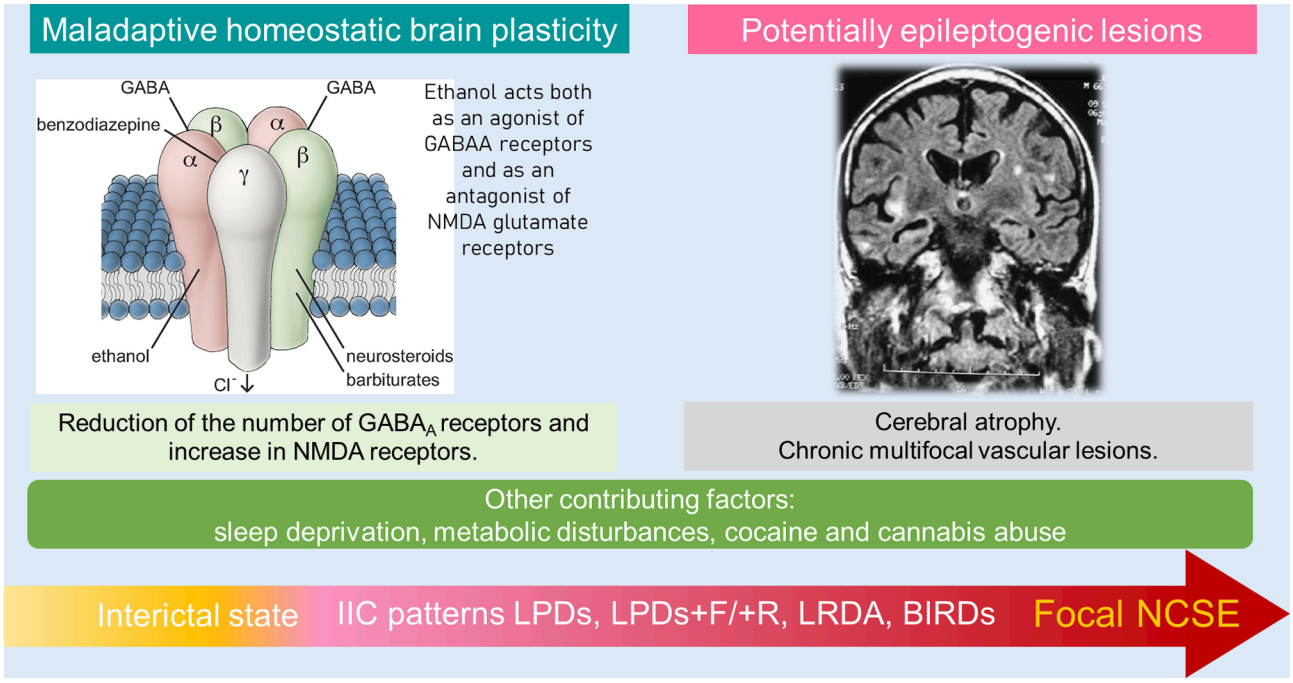

Fig. 3. Proposed pathophysiology in SESA syndrome. BIRDs: brief potentially ictal rhythmic discharges; GABA$_A$: γ-aminobutyric acid type A; IIC: ictal-interictal continuum; LPDs: lateralized periodic discharges; LPDs + F: lateralized periodic discharges plus superimposed fast activity; LPDs + R: lateralized periodic discharges plus superimposed rhythmic delta activity; LRDA: lateralized rhythmic delta activity; NCSE: nonconvulsive status epilepticus; NMDA: N-methyl-d-aspartate.

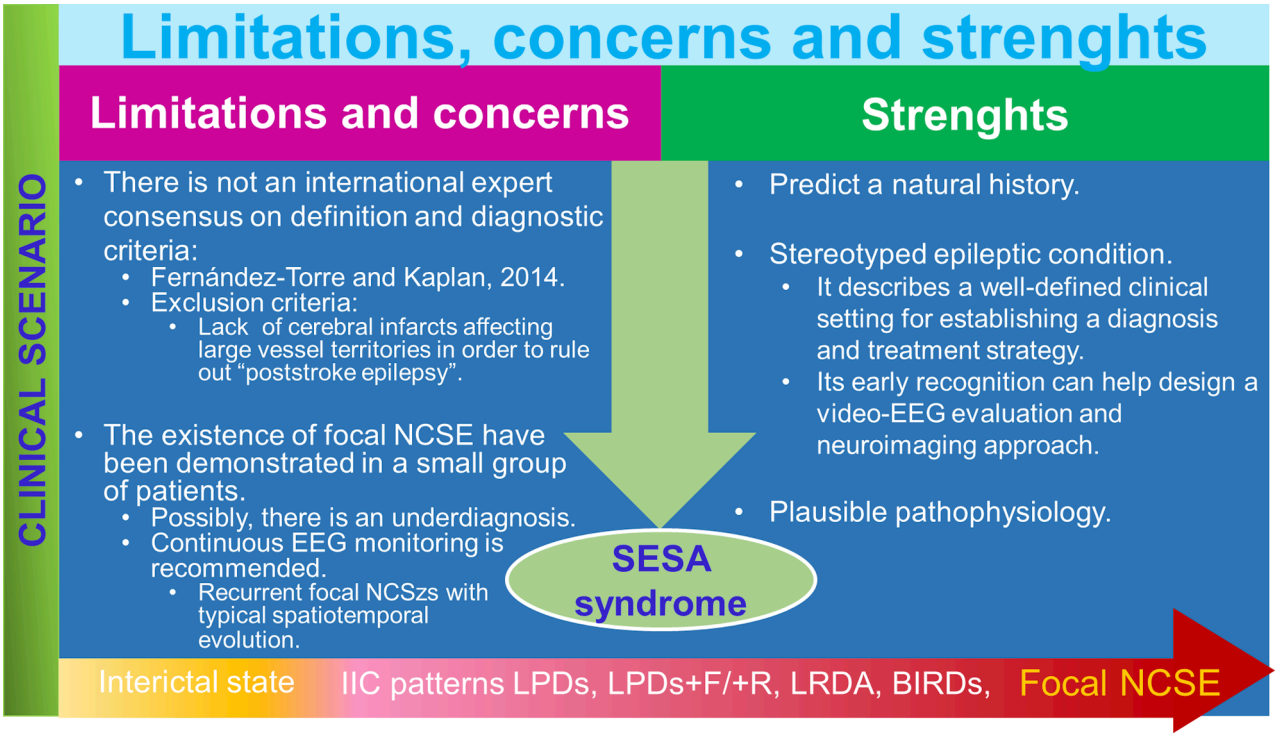

Fig. 4. Limitations, concerns and strengths of SESA syndrome definition. BIRDs: brief potentially ictal rhythmic discharges; IIC: ictal-interictal continuum; NCSzs: nonconvulsive seizures; NCSE: nonconvulsive status epilepticus; LPDs: lateralized periodic discharges; LPDs + F: lateralized periodic discharges plus superimposed fast activity: LPDs + R: lateralized periodic discharges plus superimposed rhythmic delta activity; LRDA: lateralized rhythmic delta activity.

advantages. It foretells the likelihood of recurrent stereotyped SESA episodes, generally with good seizure control but with frequent recurrences in patients who discontinue ASM and continue with heavy alcohol consumption. Additionally, its early recognition or high clinical suspicion can help design an appropriate video-EEG evaluation approach and neuroimaging protocol.

6. Conclusions

SESA syndrome represents a subtype of focal NCSE with stereotyped

clinical onset and evolution and presumed prognosis. Thus, the existence of recurrent focal nonconvulsive seizures and a dynamic clinic/EEG state along the IIC are main causes of misidentifying this entity. Maladaptive homeostatic plasticity due to alcohol abuse in a brain with chronic microvascular ischemic lesions may be a relevant pathophysiological mechanism in this epileptic condition.

Author contribution

JLF-T conceived and designed the study, acquired data, analyzed EEG recordings and videos, made the figures and wrote the manuscript. PWK critically revised the manuscript. MAH-H conceived and designed the study, acquired data, and critically revised the manuscript. All authors edited and approved the final version of the manuscript.

CRediT authorship contribution statement

José L. Fernández-Torre: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Peter W. Kaplan:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis. **Miguel A. Hernández-Hernández:** Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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