SHORT NOTE

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Stimulus-Induced, Sleep-Bound, Focal Seizures: A Case Report

Francesca Siclari, MD[1,3]; Lino Nobili, MD, PhD[6]; Giorgio Lo Russo, MD[6]; Alessio Moscato, Phy MSc[6]; Alfred Buck, MD[2]; Claudio L. Bassetti, MD[1,4]; Ramin Khatami, MD[1,5]

[1]Department of Neurology and [2]Nuclear medicine, University Hospital Zürich, Switzerland; [3]University Hospital Lausanne, Switzerland; [4]Neurocenter of Southern Switzerland, Lugano, Switzerland; [5]Barmelweid Sleep Clinic, Barmelweid, Switzerland; [6]Epilepsy Surgery Center, Niguarda Hospital Milan, Italy

Study Objectives: In nocturnal frontal lobe epilepsy (NFLE), seizures occur almost exclusively during NREM sleep. Why precisely these seizures are sleep-bound remains unknown. Studies of patients with nonlesional familial forms of NFLE have suggested the arousal system may play a major role in their pathogenesis. We report the case of a patient with pharmaco-resistant, probably cryptogenic form of non-familial NFLE and strictly sleep-bound seizures that could be elicited by alerting stimuli and were associated with ictal bilateral thalamic and right orbital-insular hyperperfusion on SPECT imaging.

Design: Case report.

Setting: University Hospital Zürich.

Patients or Participants: One patient with pharmaco-resistant epilepsy.

Conclusion: This case shows that the arousal system plays a fundamental role also in cryptogenic non-familial forms of NFLE.

Keywords: Nocturnal frontal lobe epilepsy, arousal, SPECT, PET

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INTRODUCTION

In nocturnal frontal lobe epilepsy (NFLE), seizures occur almost exclusively during NREM sleep. The precise reasons for this sleep-related occurrence remain enigmatic. Converging evidence at different levels supports the notion that the arousal system plays a major role in NFLE pathogenesis. Electrophysiological studies, for instance, demonstrated that seizures are often associated with electroencephalographic markers of arousal, such as typical and atypical K-complexes[1-3] and phase A of the cyclic alternating pattern.[4] Familial forms of NFLE with an autosomal dominant inheritance pattern (ADNFLE), have been shown to be caused by mutations in the arousal promoting cholinergic system.[5] In particular, a PET study performed in these patients documented a particular high density of acetylcholine receptors in the epithalamus (a structure that is functionally connected to the thalamus) when compared to control subjects, leading the authors to suspect the presence of upregulated mesopontine arousal pathways.[6] Finally, at a clinical level, alerting stimuli have been shown to trigger seizures in patients with ADNFLE.[1]

These studies were predominantly performed in patients with genetic (non-lesional) forms of NFLE. It is not known how other forms of sleep-bound epilepsy relate to the arousal system. We report the case of a patient with probably cryptogenic, strictly sleep-bound epilepsy, in whom seizures could be clinically elicited by alerting stimuli, and present electrophysiological and ictal SPECT findings.

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Address correspondence to: Dr. Ramin Khatami, Klinik Barmelweid, 5017 Barmelweid, Switzerland; Tel: 0041 62 857 22 20; Fax: 004162 857 22 25; E-mail: ramin.khatami@barmelweid.ch

CASE DESCRIPTION

A 24-year-old female patient underwent presurgical evaluation for pharmaco-resistant, exclusively sleep-bound seizures, which were first noted at the age of 7. Seizures were characterized by prominent oral automatisms with tongue protrusion and dystonic posturing of both arms with superimposed stereotypic movements. She was not responsive during seizures and had no recollection of the episodes, but was rapidly oriented once the motor manifestations had ceased. Family members had noted that seizures could be triggered by noise (such as the sound of an opening door or the squeaking of the mattress), but not by touching the patient. The patient denied experiencing exaggerated startle reactions during daytime. Seizures did not respond to levetiracetam, valproic acid, clobazam, and oxcarbazepine, and her current treatment (carbamazepine 1200 mg/d and pregabalin 225 mg/d) only alleviated seizure frequency to approximately 20 times per night. She had been born at term after an uneventful pregnancy and had reached normal age-specific developmental milestones. Her family history and personal medical history were otherwise unremarkable, particularly with regard to parasomnias (sleepwalking), head trauma, and central nervous system infections. Neurological examination was normal. Cerebral MRI did not show a clear-cut signal alteration.

An overnight video-polysomnography documented 31 seizures during NREM 2 and 3, lasting 50-60 sec each. They started with tonic posturing of both arms (elbow flexion and wrist extension), occurring first and more prominently on the left side, and sustained tongue protrusion, and progressed to superimposed slow, stereotypic circular movements of the hands and rhythmic flexion and extension of the head and trunk. At the end of some seizures, the patient repeatedly touched her nose with her right hand.

Electroencephalographically, most seizures started with either a single K-complex or serial K-complexes (Figure 1) that

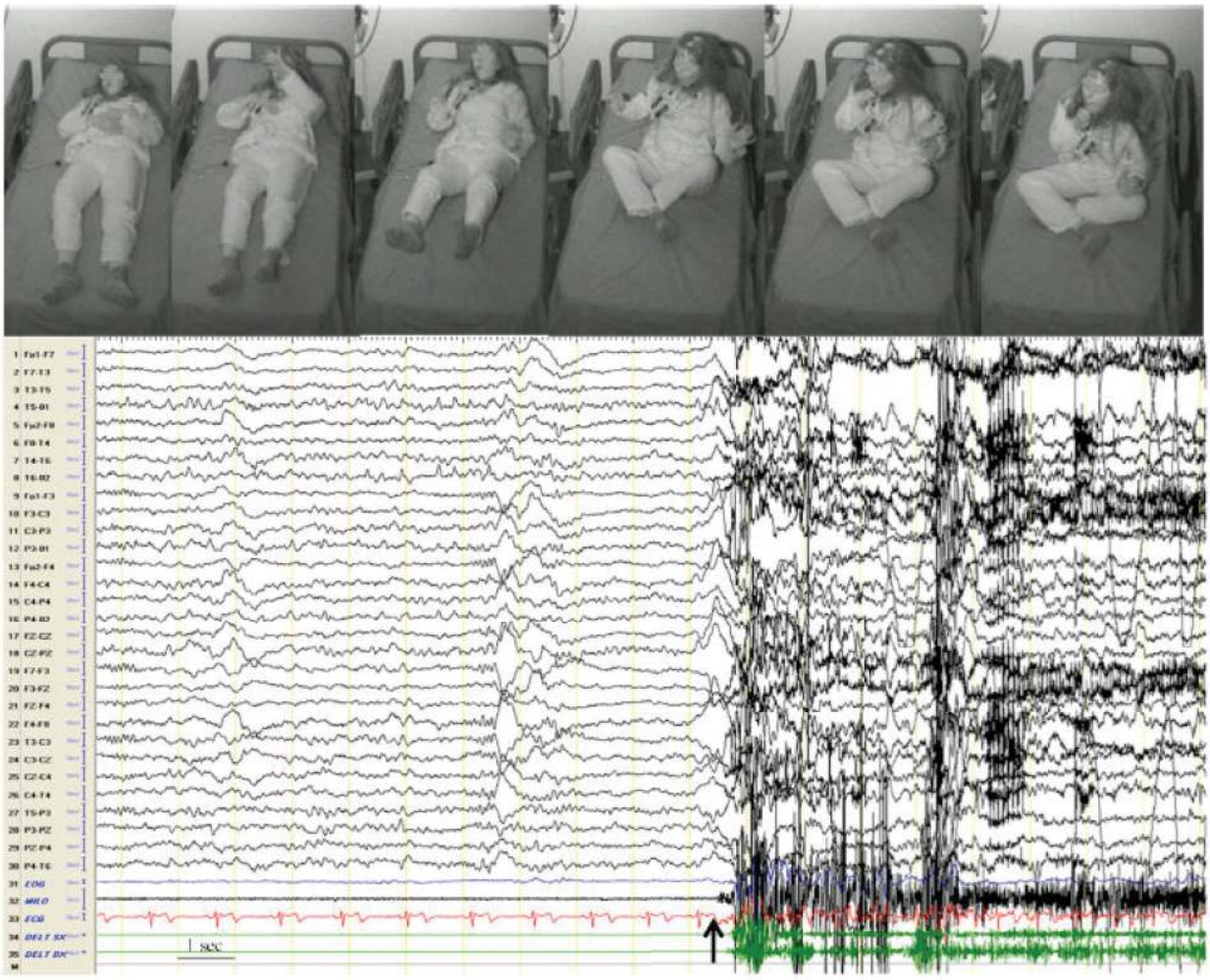

Figure 1—Video EEG recording of a stimulus-induced seizure. Noise (indicated by the black arrow on the bottom of the EEG) induced a seizure beginning with dystonic posturing of the left hand (second image from the left, corresponding to the first muscle artifact on deltoid and chin [MILO] EMG), followed by mouth dystonia with tongue protrusion. Scalp EEG shows a "spiky K-complex" at the beginning of the seizure.

sometimes had a "spiky" configuration and were followed by generalized alpha activity that evolved into bilateral rhythmic delta activity with a fronto-central maximum.

Seizures could consistently be triggered by loud hand clapping carried out by the examiner during NREM sleep. A seizure was considered stimulus-induced when clinical and electroencephalographic seizure correlates followed the acoustic stimulus within milliseconds. Seizures that occurred spontaneously, in the absence of acoustic stimulation, had identical clinical and electroencephalographic features as stimulus-induced seizures. Subclinical EEG discharges were not observed. The same acoustic stimulus during REM sleep did not induce seizures.

Technecium-99m was injected intravenously 4 sec after the onset of a typical seizure that occurred spontaneously during sleep stage N3 and lasted 50 sec. A brain scan was performed the next morning. Ictal images were compared to an interictal SPECT obtained after tracer injection during the same sleep stage on a subsequent night. Ictal SPECT documented increased bilateral thalamic (more evident in the right side) and right orbital- insular hyperperfusion (Figure 2). Interictal F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) was also performed, and showed right orbital hypometabolism (Figure 3).

DISCUSSION

The patient presented in the current case report had strictly sleep-bound, focal epilepsy with seizures that occurred spontaneously and in response to arousing stimuli, in association with increased ictal bilateral thalamic and right orbital-insular hyperperfusion documented by SPECT imaging.

Although the fact that seizures could be elicited by acoustic stimuli suggests startle epilepsy, other typical features of this entity, such as perinatal brain injuries, neurological impairment, and occurrence of seizures during daytime when exposed to a typical stimulus were not present. Rather, the sleep-related nature of seizures originating in the right orbito-opercular-insular region (as determined by SPECT imaging) confirmed NFLE in this patient.

Several features indicate that seizures were linked to an arousal reaction. Firstly, most spontaneous and all stimulus-induced seizures started with one or more K-complexes, which are known electroencephalographic markers of arousal.

Secondly, seizures could be elicited by alerting stimuli, in particular by sound. Alerting stimuli might be an underreport-

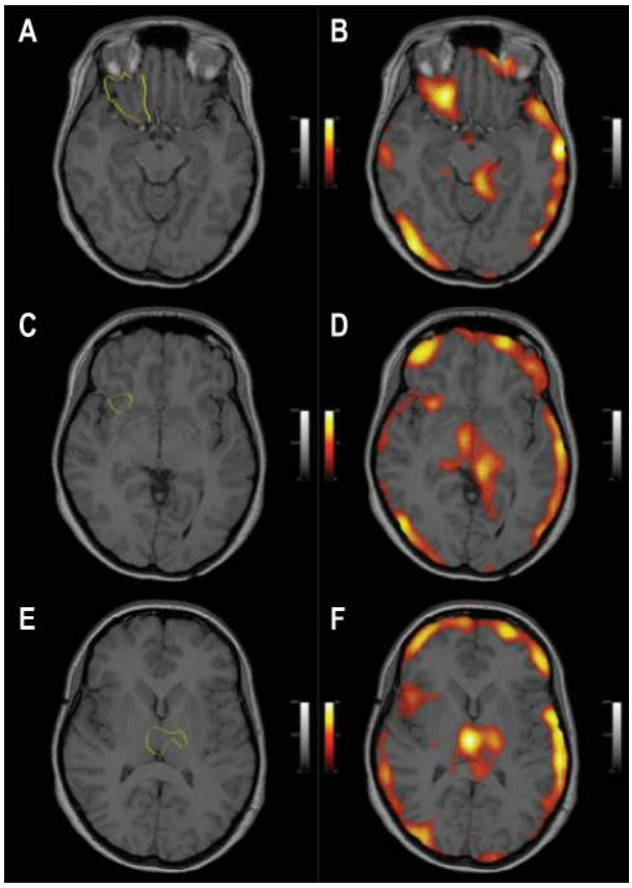

Figure 2—SPECT subtraction results superimposed on a high resolution MR image, showing increased ictal SPECT activation in the right orbital area **(A, B)**, right anterior insula **(C, D)**, and bilateral thalamus (although more evident in the right side), and again anterior insula **(E, F)**. All activations shown were obtained subtracting ictal SPECT signal from interictal SPECT, and then thresholding the obtained images at 25%.[12] Registration between SPECT and MR images was performed with a mutual information algorithm.[13]

ed, but relevant triggering factor of "spontaneous" sleep-related seizures, because patients generally sleep in a quiet environment with little exposure to arousing stimuli, and because the beginning of a seizure is rarely observed by bed partners who are most often asleep themselves.

Thirdly, the ictal bilateral thalamic hyperperfusion seen in our patient confirms a key role of the thalamus in the physiopathology of stimulus-induced seizures. Several observations suggest that thalamic hyperperfusion and stimulus-induced sleep-bound seizures are functionally related and not merely coincidental. At a genetic level it is well known that familial forms of NFLE presenting with strictly sleep bound seizures are mainly caused by mutations of nicotinergic acetylcholine receptors (nAchR), although mutations in the corticotropic releasing hormone gene have been shown in some families.[7] Acetylcholine is one of the most important transmitters of the ascending arousal system to promote arousal and wakefulness. At a clinical level, stimulus-induced epileptic activity on EEG recordings in a state of reduced vigilance has been described in comatose or critically ill patients, as an entity named "stimulus induced rhythmic, periodic or ictal discharges" (SIRPIDs).[8] In-

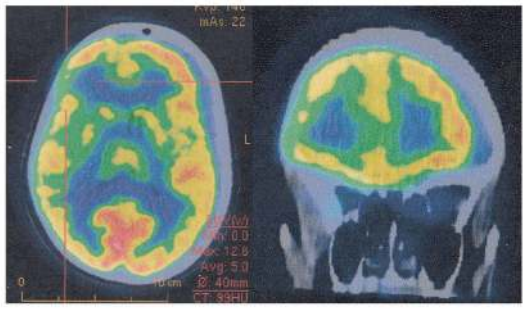

Figure 3—Interictal FDG-PET results superimposed on computed tomography (CT) scan, showing an area of reduced metabolism in the right orbital region.

terestingly, in a series of nine patients with clinically overt focal SIRPIDs, three patients showed bilateral thalamic abnormalities on MRI, one had an upper brainstem lesion, and five had prerolandic abnormalities.[9] The authors of that study postulated that these abnormalities in the arousal system may provoke seizures because of cortical hyperexcitability in response to activation of the arousal circuitry. Finally, a PET study in ADNFLE found an increased expression of nicotinic AchR in the epithalamus.[6] In fact, the mediodorsal thalamic nucleus acts as a relay station for the ascending cholinergic activating projections to the prefrontal cortex. The authors hypothesized the existence of hyperfunctioning mesopontine pathways that chronically overactivate the mediodorsal thalamic nucleus and transform sleep spindle oscillations into pathological thalamocortical oscillations. These oscillations would trigger seizures in the regions of maximal projection of the mediodorsal thalamic nucleus (that is, the orbital and dorsolateral prefrontal cortex).

In summary, seizures in the patient presented here were linked to activation of the arousal system (suggested by the stimulus-associated nature of seizures and bilateral thalamic hyperperfusion) and showed a *focal* epileptic origin, as documented by a right orbital-insular hyperperfusion and interictal hypoperfusion in the same region. We hypothesize that in case of an arousal (spontaneous or stimulus-induced), the epileptogenic region would facilitate transformation of normal thalamocortical oscillations into pathological oscillations, giving rise to focal seizures. The mechanisms mentioned above are in keeping with studies showing that seizures can emerge from cortical slow oscillations during sleep.[10] They would also explain why seizures could only be elicited in NREM sleep but not during REM sleep. In fact, thalamo-cortical interactions are highly synchronized during NREM sleep, while the thalamocortical network is maximally deactivated during REM sleep.[11]

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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