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The temporal relation between seizure onset and arousal-awakening in temporal lobe seizures

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ABSTRACT

Purpose: Our main aim was to determine the time interval between the seizure onsets and arousal-awakening related to these seizures in patients with temporal lobe epilepsy (TLE) and to discuss the role of lateralization on arousal-awakening mechanisms.

Methods: Thirty-three TLE patients who underwent video-EEG monitoring with simultaneous polysomnography (PSG) and had recorded nocturnal seizures were retrospectively examined. These TLE patients had 64 seizures during sleep. The onsets of seizures and arousal-awakening related to these seizures were marked according to clinical and electrophysiological features. The time interval between the seizure onset and arousal-awakening related to the seizure was compared in patients with right- or left-sided temporal lobe seizures.

Results: In our TLE patients nocturnal seizures mostly followed arousal-awakening (64%). The time interval between the seizure onset and arousal-awakening related to the seizure was significantly shorter in patients with left-sided temporal lobe seizures ($p = 0.01$).

Conclusion: Video-EEG monitoring and PSG with scalp electrodes in our TLE patients showed that nocturnal seizures mostly followed arousal-awakening, and it was more pronounced in those with left-sided seizures. Arousal-awakening might be a signal for subsequent seizures in patients with TLE.

1. Introduction

The reciprocal relationship between epilepsy and sleep is complex. During sleep, epileptiform discharges are more common [1,2] and the occurrence of seizures during sleep depends on sleep stage [3]. Epilepsy also changes the organization and microstructure of sleep [4]. Since patients with epilepsy have seizures during sleep, this reciprocal interaction has led researchers to investigate the relationship between the pathologic processes underlying seizures and the physiological structures of sleep [5–9]. Arousal or awakening systems that separate sleep and wakefulness are characterized by excitability and increased electrical activity of sensory and motor systems. That effect facilitates the appearanceof epileptic seizures [10]. Furthermore, due to the violent behavioral components of seizures, arousal-awakening might be seen after seizure onset. Intracranial recordings also showed that arousal actually follows the onset of the seizure rather than preceding it [11]. However, in some patients with focal epilepsy associated with the temporal lobes, seizures were recorded after or during times of mini-arousals in a cycling alternating pattern (CAP) [12,13].

The cortical centers for arousal-awakening are not as clear as those in the brainstem [14,15] to indicate the effect of epileptic tissue localization in the cortex on awakening. There are a number of studies about the relationship between arousal-awakening and seizures [11,13,16–18]. In our previous study we observed that awakening was mostly seen after onset of seizures in patients with temporal lobe epilepsy (TLE) or frontal lobe epilepsy (FLE). Furthermore, in patients with FLE, the time interval between the seizure onset and awakening related to the seizure was shorter than in patients with TLE [18]. We thought that frontal onset ictal epileptic activity may reach the arousal centers (e.g., frontal cortical centers) in a shorter period than temporal onset epileptic activity.

In the present study our main aim was to determine the time between onset of seizures and arousal-awakening in a larger number of patients with TLE and to discuss the role of lateralization on arousal-awakening mechanisms.

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2. Methods

2.1. Patients

In our center we have a PSG recording device with video-EEG in one of two rooms and patients were randomly hospitalized in these rooms. For this study all reports were retrospectively examined and patients who underwent video-EEG monitoring and simultaneous PSG from 2010 to 2015 and were having temporal lobe seizures during sleep were included. We used these PSG recordings for our research related to "sleep and epilepsy patients" that was approved by the ethical committee of our university, and written informed consents were obtained from all subjects before recordings. We did not use their PSG findings during routine presurgical investigations.

Patients with bitemporal lobe epilepsy were excluded. There were 41 adults with unilateral TLE. Recordings of 8 patients were excluded from the study due to technical problems. The remaining 33 TLE patients had 64 nocturnal seizures during sleep.

The diagnosis of right or left TLE was discussed in a multidisciplinary case conference including neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. The clinical and electrographic features of seizures, magnetic resonance imaging (MRI) findings and positron emission tomography, and ictal or interictal single photon emission computerized tomography when available were evaluated. Patients' seizure types and epilepsy syndromes were determined according to the International League Against Epilepsy (ILAE) classifications [19].

MRIs were obtained using either 1.5 or 3.0 T scanners (Symphony and Allegra, respectively, Siemens, Erlangen, Germany). The MRI protocol included coronal 3D T1-weighted (W) gradient echo imaging (MPRAGE) obtained parallel to the brainstem, and fluid-attenuated inversion recovery (FLAIR) and T2-W turbo spin- echo and T1-W inversion recovery images obtained perpendicular to the hippocampi in addition to routine brain imaging.

Each patient was monitored for 3–10 days in a video-EEG monitoring unit using a 32-channel EEG system (Grass-Telefactor). There was no standard procedure for withdrawal of the antiepileptic drug during monitoring. Scalp electrodes were placed according to the International 10–20 system with additional anterior temporal electrodes (T1–T2). The other parameters recorded included electrooculogram (EOG), submental electromyogram and electrocardiogram (ECG), respiratory effort and airflow, oxyhemoglobin saturation, and anterior tibialis EMG. Digital EEG-PSG systems allow for monitoring of 32 inputs, to provide EEG coverage sufficient to define ictal patterns. The studies were manually scored for sleep stages in 30-s epochs with an expanded EEG montage by an experienced neurophysiologist. Sleep was scored according to the revised AASM criteria [20].

Seizures were defined by an EEG pattern that represents a clear change from background frequencies and evolves in frequency and amplitude [21]. The obvious ictal EEG onsets were marked in an expanded EEG montage according to the 10–20 system. Remontaging assists in distinguishing epileptic seizures from artifacts. Video recordings were also evaluated with simultaneous EEG recordings to define seizure semiology and arousal-awakening. The onset of semiology was noted on EEG. The first event related to a seizure, whether EEG or semiological changes, was regarded as seizure onset. Seizures with unclear ictal EEG onsets and ictal behavioral changes were not included. We scored arousal during sleep stages N1, N2, N3, or R if there is an abrupt shift of EEG frequency including alpha, theta and/or frequencies greater than 16 Hz that lasts at least 3 s [20]. Intrusion of sustained alpha activity over 50% of the epoch was defined as wakefulness-awakening [20,21]. In the video recordings any behavior unrelated to seizure semiology or sleep including eye opening was also noted. That onset of arousal-awakening was marked on EEG.

We also obtained other information including age, duration of epilepsy, seizure frequency, neuroimaging findings, and history of epilepsy surgery from the patients' medical records.

2.2. Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 21.0). The Shapiro–Wilk test, Mann–Whitney *U* test, Kruskal–Wallis test, and Pearson's chi-square test were used to determine potentially significant differences, and a p value less than 0.05 was considered significant. In multiple comparisons, Bonferroni correction was used.

3. Results

Overall, video-EEG recordings with PSG were performed in 41 TLE patients. Thirty- three of the 41 patients were included in the study. The ages of patients ranged between 15 and 64, and 14 (42%) of them were female. Fourteen of patients had right TLE, while the others had left TLE. Twenty-one patients had hippocampal sclerosis or atrophy, 7 of them had cortical dysplasia, 1 of them had a small cavernoma and the remaining 4 patients had temporal lobe atrophy on MRI. All patients had left hemisphere dominancy for speech that was shown by functional MR imaging or neuropsychiatric tests. The mean duration of epilepsy was 14.37 ± 12.84 years (Table 1).

All seizures were analyzed and the seizures with undetectable lateralization and/or localization were not included. All 33 patients had a total of 107 lateralized/localized temporal lobe seizures, of which 64 were nocturnal seizures (for each patient, range 1–6) occurring during sleep. These 64 seizures were analyzed in the 33 patients.

All seizures occurred during non-rapid eye movement sleep (NREM) and more often in NREM stage 2 (64%). There was no significant difference between right and left temporal lobe onsets for the sleep stages during which seizures occurred ($p > 0.05$) (Table 2).

In 41 seizures (64%) seizure onset followed arousal-awakening, while in the other 23 seizures the opposite occurred. In all patients according to the onset of arousal-awakening before or after seizures, the mean time interval between the seizure onset and arousal-awakening related to the seizure was 14.12 ± 8.38 s in right temporal lobe seizures and 8.77 ± 6.21 s in left temporal lobe seizures. The time interval between the seizure onset and arousal-awakening related to the seizure was significantly shorter in patients with left temporal lobe seizures ($p = 0.01$) (Fig. 1). In other words the time interval between the seizure onset and arousal-awakening related to the seizure was shorter than 10 s in 23 of left sided and 15 of right sided seizures ($p = 0.02$).

Although the difference was not statistically significant, patients with secondarily generalized seizures had a shorter time

Table 1
Demographic features of 33 TLE patients having nocturnal seizures during monitoring of long-term video EEG and polysomnography.

Age (mean ± SD)	31.24 ± 10.89
Sex (F/M)	14/19
Duration of epilepsy (year ± SD)	14.37 ± 12.84
Right temporal lobe epilepsy (n)	14
Left temporal lobe epilepsy (n)	19
Number of total seizures	107
Daytime seizures	43
Right-sided seizures during sleep	33
Left-sided seizures during sleep	31

Table 2
Features of 64 nocturnal seizures in 33 patients during monitoring of long- term video EEG and polysomnography.

	Right-sided seizures	Left-sided seizures	*p*
Number of seizures during sleep/total seizures (%)	33/51 (65%)	31/56 (55%)	0.43
Sleep stages of seizure occurrence (*n*)			
N1	8	12	0.15
N2	23	18	
N3	2	1	
REM	0	0	
Propagation of seizures to the other side (yes/no, *n*)	25/8	15/16	0.04
First event: arousal-awakening/seizure onset (*n*)	23/10	18/13	0.44
The time interval between the seizure onset and arousal-awakening related to the seizure (mean ± SD)	14.12 ± 8.38	8.77 ± 6.21	0.01
<10 s between arousal-awakening and seizure onset (%)	15 (45%)	23 (74%)	0.02

interval between the seizure onset and arousal-awakening related to the seizure ($p = 0.13$). The presence of propagation of seizures on EEG to the contralateral hemisphere was also investigated. While 37% ($n = 24$) of seizures were localized, 63% ($n = 40$) propagated to the other hemisphere. The median the time interval between the seizure onset and arousal-awakening related to the seizure was shorter in left-sided seizures (9 s) than in right-sided ones (16 s) with propagation to the other side ($p = 0.09$) (Table 2).

Nine of the 33 (27%) patients underwent temporal lobectomy during the study period. Pathologically 6 (63%) of them had hippocampal sclerosis and 3 (37%) of them had focal cortical dysplasia. Despite the limited number of patients with pathological findings, the time interval between the seizure onset and arousal-awakening related to the seizure was shorter in patients with FCD (8.32 ± 4.11 s) rather than with HS (13 ± 6.38 s) ($p = 0.36$).

4. Discussion

Epilepsy modifies sleep, causing greater sleep fragmentation and higher percentages of wakefulness and light sleep with a decrease in deep NREM and rapid eye movement (REM) sleep. In most cases the immediate effect of a seizure corresponds to an awakening or upward shift towards a more superficial sleep stage. Video EEG- PSG monitoring with scalp electrodes in our TLE patients showed that nocturnal seizures mostly followed arousal-awakening (64%). It is important to underline that the scalp EEG could not detect a subtle increase in interictal/ictal activity that led to arousal or awakening preceding the clinical onset of the seizures. To support that, some studies have suggested that

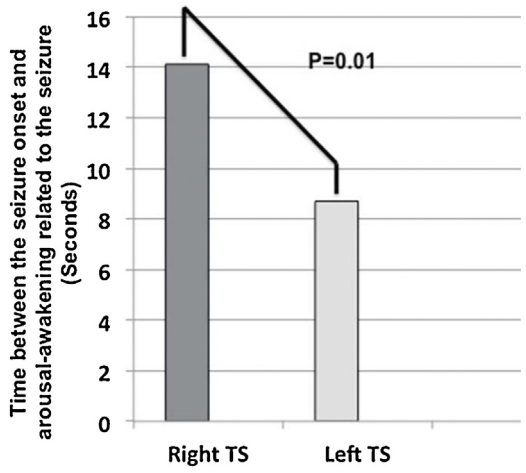

Fig. 1. The time interval between the seizure onset and arousal-awakening related to the seizure in the left-sided temporal lobe seizures was shorter than that in the right-sided ones ($p = 0.01$).

increased epileptiform activity and especially increased seizure activity during sleep may be related to arousals and sudden increases in excitability during sleep [13,22]. This could be due to either the localized increase in cortical excitability or the extrinsic excitation provided by glutamatergic and cholinergic projections associated with arousal-awakening. However, in other studies, it seems that seizure onset may actually precede arousal-awakening [11,18]. Malow et al. showed that 60 temporal lobe onset seizures preceded clinical arousals from sleep and only 7 seizures followed arousals [11] with a limitation of invasive procedures for coverage. However, EEG changes related to awakening can be missed by intracranial electrodes on a limited brain area. Similarly, we had also reported that awakening followed seizures in a group of patients including FLE in addition to TLE [18]. However, the degree and nature of the interaction between sleep and seizure could vary with the localization of focus.

The role of thalamocortical networks in arousal-awakening is known [23–28]. The perioral region of the somatosensory cortex in the frontal area is involved in this thalamocortical network [29–31]. The thalamocortical and corticothalamic projections mediate a complex pattern of reciprocal interactions between the thalamus and the cortex that is involved in the regulation of sleep and arousal. Accordingly, attempts were also made to explain the complex interaction between arousals and seizure onset by these networks. Arousal-related sleep transients activate the neural networks involved in frontal lobe seizures [32,33]. Recently, arousal from sleep has been found to precede frontal lobe seizures, again suggesting that arousal is the primary event [34]. Accordingly, localization of epileptic seizures (e.g., frontal onsets) can be important in terms of timing of arousal-awakening.

In studies to date, while examining the effect of sleep on epilepsy, in particular it has been investigated whether the effect of sleep on epilepsy is preventing, facilitating, or precipitating and whether this effect is connected with localization of epileptic seizures or the type of epileptic syndrome [4]. Although the relationship between localization and sleep/wakefulness has been investigated [11,18,21,32–34], to the best of our knowledge the relationship between arousal -awakening and lateralization has never been studied before. But there is a brief report including five patients having an arousal from sleep as the only manifestation of some epileptic seizures and four of these patients had left temporal lobe epilepsy [35]. Similar to that, our second interesting finding was the shortness of the time interval between the seizure onset and arousal- awakening related to the seizure in the left-sided temporal lobe seizures ($p = 0.01$). In most temporal lobe seizures starting from the left side, the duration between arousal-awakening and seizure was less than 10 s ($p = 0.02$). The lateralization of onset of seizures was important in terms of leading to rapid arousal-awakening, because the arousal-awakening time before the right-sided seizures was longer than that before the left-sided seizures, either with or without propagation

to the left. Furthermore, all these left sides were dominant hemispheres.

Connectivity within the frontoparietal regions and their thalamic connections appear to play a key role in the maintenance of consciousness similar to awakening. Gotman et al. found that deactivations were symmetrical in the anterior frontal and parietal regions but asymmetrical in temporal lobes, more pronounced on the left side in patients with generalized spike wave bursts [36]. Frontoparietal deactivation has also been recorded in temporal lobe seizures with loss of consciousness [37], which is more commonly associated with left hemisphere seizures [38]. We speculated that activation of the left temporal lobe during the seizures in left TLE decreased the deactivation of the left temporal lobe and also decreased the time interval between arousal-awakening and seizure onset.

A limitation of our study was that we had no invasive EEG recordings. There was only one patient with intracranial electrodes besides previous scalp EEG recordings, but she had no nocturnal seizures during invasive EEG recordings. Intracranial EEG recordings with simultaneous scalp EEG can be more informative in future studies.

Finally, all these efforts can be valuable in understanding arousal-awakening mechanisms more clearly. Furthermore, for seizures occurring after arousal-awakening, alternative therapeutic management like sleep regulation and neurostimulation may be considered.

5. Conclusion

Video EEG-PSG monitoring with scalp electrodes in our TLE patients showed that nocturnal seizures mostly followed arousal-awakening, and it was more pronounced in left- sided seizures. Arousal-awakening might be a signal for subsequent seizures in patients with TLE. Our findings can be useful in future studies investigating arousal-awakening mechanisms and seizure prediction/prevention.

Conflict of interest statement

All authors have read and approved the manuscript and take full responsibility for its content. The authors have no conflicts of interest in regard to this research or its funding. None of the authors has any conflict of interest to disclose.

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