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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