Clinical Neurophysiology 125 (2014) 2207–2211

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

A reduction of sleep spindles heralds seizures in focal epilepsy

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ARTICLE INFO

Article history:
Accepted 4 March 2014
Available online 12 March 2014

Keywords:
Sleep
Epilepsy
Epilepsy surgery
Sleep spindle
Seizure prediction

HIGHLIGHTS

- A strong relationship has been noted between sleep spindles and seizure occurrence in patients with temporal and extratemporal lobe epilepsy.
- The reduction of spindle density before secondarily generalized seizures was more pronounced in extratemporal lobe epilepsies than in temporal lobe ones.
- The occurrence of seizures and propensity of seizure generalisation in focal epilepsy is modulated by sleep spindles.

ABSTRACT

Objectives: Sleep has profound effects on epilepsy. It may alter the occurrence of interictal discharges (IEDs) and seizures. Vice versa, an active epilepsy changes sleep. Sleep spindles are typically associated with an increase of IEDs. We examined whether seizures change the number and power of spindles preceding nightly seizures.
Methods: We retrospectively examined the nightly EEG recordings of presurgical epilepsy patients from our EEG-video-monitoring unit. We evaluated the 200 s before the EEG seizure onset for spindle density (spindles per minute) and spindle power and compared that to the interictal baseline sleep.
Results: The spindle density and the spindle power decreased significantly before the first seizure. The reduction before secondarily generalized seizures (8.7 ± 2.5; $p = 0.001$) was more pronounced than before focal seizures (10.5 ± 2.5; $p = 0.003$) compared to baseline (12.2 ± 2.7). This finding was more pronounced in extratemporal lobe epilepsies than in temporal lobe epilepsies. The reduction of spindle power was also significant and was more pronounced in XTLE. These results were consistent for all other seizures during sleep, the mean spindle density decreased significantly in all focal (10.2 ± 1.9; $p = 0.001$) and generalized preictal period (8.8 ± 2.4; $p = 0.001$) compared to the mean interictal period (12.1 ± 2.1). These were also more significant in XTLE than TLE group.
Conclusions: Our data demonstrate that the occurrence of seizures and propensity of seizure generalisation in focal epilepsy is modulated by specific characteristics of light sleep such as sleep spindles.
Significance: This study supports the notion that changes in the epileptic network precede the seizure onset and have an influence on seizure generation and termination.

1. Introduction

Sleep and epilepsy have reciprocal influences on each other. NREM sleep promotes interictal epileptic activity (Sammaritano et al., 1991) and in some epilepsy syndromes, seizures occur in association with the sleep wake cycle (Herman et al., 2001). On the other hand, an active epilepsy will reduce the amount of deep sleep and patients have less refreshing sleep (Xu et al., 2006).

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http://dx.doi.org/10.1016/j.clinph.2014.03.001
1388-2457/

Sleep is not a uniform loss of consciousness, but it is rather a highly dynamic behavioral process, reflected by typical, systematic changes on EEG allowing to score different sleep stages. Sleep spindles are typical EEG sleep pattern, which are thought to reflect a higher level of EEG synchronization, resulting from an increased thalamocortical synchronicity (Steriade et al., 1993). A strong relationship has been noted between these EEG patterns and interictal epileptic activity, with an increase in IEDs during sleep spindles (Shouse, 1987). In contrast, the relationship between spindles and seizures is not well studied. Therefore, we investigated the relationship of spindles to nightly seizures in patients with focal epilepsies.

2. Methods

We retrospectively examined all EEG-video-monitoring records of our patients at the Faculty of Medicine, Hacettepe University from 1999 to 2012 who had been admitted for presurgical evaluation of refractory seizures. We identified 42 patients with secondarily generalized seizures during NREM sleep, with 22 of them also having focal seizures during sleep. Patients with intracranial electrodes were not included.

All patients had their antiepileptic drugs (AEDs) tapered during the monitoring session to facilitate the recording of seizures. For most patients, AEDs were decreased by almost one third at the time of admission, with subsequent further decreases as needed.

The patients were divided into two groups according to the localization of seizure onset: patients with temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (XTLE). The site of probable seizure onset was determined in an epilepsy case conference by using clinical and electrographic seizure characteristics, supplemented by interictal EEG, clinical history, and results of MRI, PET, and ictal and interictal SPECT, when available. Because most patients did not undergo intracranial EEG recording, these localizations are best estimates of the ictal onset zone.

Continuous video-EEG recordings were performed over 3–10 days with scalp electrodes which were placed according to the International 10–20 System with additional anterior temporal electrodes. Electrooculogram, electrocardiogram and submental electromyogram was included. Sleep stage was determined by the criteria described by Rechtschaffen and Kales (1968).

In the first part of the study, when patients had one and more than one secondarily generalized seizure during sleep, only the first seizure (42 patients) was investigated to exclude the effect of seizures on sleep. In this group if patients had additional focal seizures to secondarily generalized seizures during sleep, their first focal seizure (22 of 42 patients) was also investigated. First seizures during sleep of all patients occurred in the third night or later time of EEG-video-monitoring, except two of them. These two patients had their first seizures in the first night sleep of monitoring. But their last seizures before monitoring were 4–7 days prior, and they did not occur during sleep. So these previous seizures should not affect the sleep. For each subject, the 200 s just before the ictal EEG onset were analyzed for spindle density and spindle power (Fig. 1A). If there was an awakening or an arousal period shortly before the seizure onset, these periods were not included in analyzing the spindle density. Most of the patients had seizures at the beginning of the Non-REM 2 sleep, so we could not select longer time period for analysis. This selected time period is referred to as the "preseizure period". Sleep spindles were scored according to the published criteria as sleep EEG spindles with a frequency between 11 and 16 Hz and a duration >0.5 s (Iber et al., 2007). For baseline comparison, EEG samples of equal duration containing spindles were selected from nights without any seizure and are referred to as the "interictal period" (Fig. 1B). The AED doses had to be the same as in the seizure nights to include those recordings. The spindle density was measured as number of spindles per 60 s. Additionally 200 s of EEG recordings with normal background activity during restful waking of each patient was evaluated to give a baseline for power calculations.

In the second part, to check the consistency within a given patient we also investigated all seizures, when patients had more than one focal or secondarily generalized seizure during sleep. Also for each patient, 4–5 interictal EEG periods containing spindles were selected from nights without any seizure, to compare the baseline-interictal period. The mean of these 4–5 interictal periods are referred to as the "average interictal period".

The spectral power of the spindle band was calculated for nine channels (F3, F4, Fz, C3, C4, Cz, P3, P4 and Pz) after adjusting for the spectral power of the non-spindle baseline. These channels were selected, because two types of spindles are reported topographically, frontal and centro-parietal spindles (Werth et al., 1997).

The spectral analysis was performed on segmented, non-overlapping 2 s EEG samples and artifact rejection was performed automatically on the basis of thresholding. Each single sweep was Hamming-windowed to control for spectral leakage (Gerloff et al., 1998). The power spectra in the range of 11–16 Hz were calculated for each epoch with a minimum of 20 epochs and averaged over the frequency bins. The state dependent power was calculated as the percentage change in the power between the two conditions as follows (Gerloff et al., 1998):

$$\mathrm{SDpower}_{\mathrm{interictal,rest}} = 100 * \left(\mathrm{SDpower}_{\mathrm{interictal}} - \mathrm{SDpower}_{\mathrm{rest}}\right) / \mathrm{SDpower}_{\mathrm{rest}} \quad (1)$$

$$\mathrm{SDpower}_{\mathrm{preseizure,rest}} = 100 * \left(\mathrm{SDpower}_{\mathrm{preseizure}} - \mathrm{SDpower}_{\mathrm{rest}}\right) / \mathrm{SDpower}_{\mathrm{rest}} \quad (2)$$

$$\mathrm{SDpower}_{\mathrm{preseizure,interictal}} = 100 * \left(\mathrm{SDpower}_{\mathrm{preseizure}} - \mathrm{SDpower}_{\mathrm{interictal}}\right) / \mathrm{SDpower}_{\mathrm{interictal}} \quad (3)$$

In order to account for the variance of spectral power estimates a logarithmic transformation was used (Halliday et al., 1995):

$$\log_{10}(\mathrm{SDpower}_{\mathrm{interictal,rest}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{interictal}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{rest}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{rest}}) \quad (4)$$

$$\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure,rest}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{rest}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{rest}}) \quad (5)$$

$$\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure,interictal}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{interictal}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{interictal}}) \quad (6)$$

3. Data analysis

Statistical analysis was performed using the SPSS 16.0 (SPSS Inc., Chicago, USA). A *t*-test for independent samples was used for continuous variables. Group results for TLE and XTLE were compared with the Mann–Whitney-*U*-test. The differences in mean of the spindle density and power of spindle waves between interictal and preseizure periods were analyzed with the Wilcoxon Ranking Scale test. Statistical significance was assumed at a *p*-value of less than 0.05, multiple testing was accounted for by a Bonferroni–Holm review but no result had to be rejected.