Original article

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Interictal epileptiform discharges and phasic phenomena of REM sleep

Petr Busek, Jitka Buskova, Sona Nevsimalova

Department of Neurology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic

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ABSTRACT – The objective of this study was to assess the effect of phasic rapid eye movement (REM) sleep events on interictal epileptiform discharges (IEDs). Twelve patients with focal epilepsy and IEDs during REM sleep were examined by video-EEG monitoring. The number of IEDs was calculated in different REM sleep episodes according to the rate of rapid eye movements. A negative correlation was identified between the occurrence of rapid eye movements and IEDs, indicating that the suppression of propagation of IEDs during REM sleep is enhanced by phasic REM sleep events, probably as a result of phasic activation of cholinergic neurons of the ponto-mesencephalic tegmentum. This study demonstrates that the degree of EEG desynchronization and IEDs is influenced by REM density.

Key words: epilepsy, interictal discharges, ponto-geniculo-occipital activity, REM sleep

Epileptic seizures and interictal epileptiform discharges (IEDs) are frequently enhanced by sleep. Predominantly focal seizures, with or without secondary generalisation, are reported to be activated by non-rapid eye movement (NREM) sleep synchronization phenomena (Shouse *et al.*, 1989, 2000), whereas seizures are considerably less frequent during REM sleep, despite some anecdotal reports of epileptiform discharges culminating in REM sleep (Genton *et al.*, 1992; Minecan *et al.*, 2002). REM sleep is characterized by activation of the cholinergic neurons of the ponto-mesencephalic tegmentum. Phasic disinhibition of cholinergic pedunculo-pontine and laterodorsal tegmental nuclei is responsible for ponto-geniculo-occipital (PGO) activity accompanied by rapid eye movements, muscle jerks, and phasic activation of dreams (Adrien, 2003). Since the antiepileptic properties of REM sleep are thought to be mediated by cholinergic mechanisms, the suppression of IEDs should be more pronounced during phasic disinhibition of cholinergic neurons. This study was undertaken to elucidate the influence of phasic events of REM sleep on IEDs.

Methods

Twelve patients with focal frontal, temporal or parietal lobe epilepsy (eight women and four men, aged 11-62 years; median 41 years) were studied retrospectively and included only subjects with IEDs in REM sleep. Their clinical characteristics are shown in *table 1*. All had undergone one to

Correspondence:
P. Busek, M.D., Ph.D.
Department of Neurology,
1st Faculty of Medicine and General University Hospital,
Charles University in Prague,
Katerinska 30, 120 00 Prague 2,
Czech Republic
<petrbusek@seznam.cz>

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Table 1. Clinical characteristics of the patients.

Subject	Diagnosis	Treatment
F, 11 years	Frontal lobe epilepsy, aetiology undetermined	Topiramate, carbamazepine
M, 55 years	Temporal lobe epilepsy, post-inflammatory gliotic changes in the right temporal lobe	Carbamazepine, levetiracetam, valproate – discontinued during video-EEG
F, 52 years	Temporal lobe epilepsy, mesiotemporal sclerosis	Carbamazepine, valproate – discontinued during video-EEG
M, 46 years	Temporal lobe epilepsy, mesiotemporal sclerosis	Phenytoin, levetiracetam – discontinued during video-EEG
M, 30 years	Temporal lobe epilepsy, mild dysplastic changes in the medial part of the left temporal lobe	No treatment
F, 24 years	Frontal lobe epilepsy, post-inflammatory aetiology	Carbamazepine, levetiracetam, pregabaline – discontinued during video-EEG
M, 62 years	Temporal lobe epilepsy, aetiology undetermined	Valproate – discontinued during video-EEG
F, 47 years	Frontal lobe epilepsy, aetiology undetermined	Carbamazepine, phenytoin – discontinued during video-EEG
F, 36 years	Parietal lobe epilepsy, gliotic changes in the right parietal lobe	Lamotrigine, topiramate – discontinued during video-EEG
F, 22 years	Parietal lobe epilepsy, juvenile glioma in the right parietal lobe	Valproate, lamotrigine – discontinued during video-EEG
F, 49 years	Parietal lobe epilepsy, aetiology undetermined	Carbamazepine
F, 20 years	Frontal lobe epilepsy, aetiology undetermined	Valproate – discontinued during video-EEG

F : female; M : male.

five-day video-EEG monitoring using the 10-20 international electrode system; the ocular movements were recorded with horizontal electrooculography (Brainlab, Rumst, Belgium). The principal reason for video-EEG monitoring was diagnostic.

Eleven patients were treated with antiepileptics, which were discontinued during the monitoring of nine patients. The antiepileptics were not discontinued for the purpose of this study, but rather to either enhance the diagnostic value of video-EEG monitoring performed to localize the epileptogenic zone in patients with pharmacoresistant epilepsy or objectify the nature of the seizures for more precise diagnosis and further treatment.

REM sleep was divided into 10-second episodes classified according to the number of rapid eye movements in each:
– episodes with no rapid eye movement;
– episodes with one rapid eye movement;
– episodes with two rapid eye movements;
– episodes with three rapid eye movements;
– episodes with four rapid eye movements;
– episodes with five or more rapid eye movements.

The first rapid eye movement marked the onset of REM sleep lasting until the EEG changed or until the point when, during three consecutive 10 second-episodes, no rapid eye movement appeared in spite of unaltered EEG.

We used these modified criteria of REM sleep scoring because the chin EMG was not recorded. This modified definition probably resulted in a partial loss of analyzed REM sleep, thus, more importantly, eliminating the risk of including some parts of NREM sleep in the analysis. For each of the REM sleep episodes the number of IEDs was determined and the average frequency of IEDs in each episode was subsequently calculated. To reveal the correlation between the frequency of rapid eye movements and IEDs, the Pearson Correlation Coefficient and Linear Regression Model were used.

Results

In total, 67,060 seconds (18 hours and 37.7 minutes) of REM sleep were analyzed. On average, 52.69 ± 11.89% represented episodes with no rapid eye movements, 12.38 ± 2.49% episodes with one REM, 10.80 ± 2.07% episodes with two REMs, 7.06 ± 1.97% episodes with three REMs, 6.78 ± 3.35% episodes with four REMs, and 10.29 ± 5.96% episodes with five or more REMs. The average frequency of IEDs during REM sleep was 0.052 ± 0.094 IEDs per second. The average frequency of IEDs in each REM sleep category is presented in *table 2*.

To reduce the effect of considerable inter-individual variability, the absolute frequency of IEDs was transformed into a relative frequency by dividing the frequency of IEDs in each category of REM sleep episode by that of IEDs found in episodes with no rapid eye movement. A negative correlation was identified between the number of REMs and frequency of IEDs during REM sleep. This relationship was statistically significant ($r = -0.512$, $p < 0.01$) and is presented in *figure 1*.

Table 2. Average and relative frequencies of interictal epileptiform discharges in different REM sleep episodes.

Number of rapid eye movements in 10-second episodes	0	1	2	3	4	≥ 5
Frequency of IEDs ± SD (IEDs/second)	0.074 ± 0.118	0.062 ± 0.123	0.035 ± 0.066	0.033 ± 0.080	0.023 ± 0.056	0.021 ± 0.052
Relative frequency of IEDs ± SD	1	0.608 ± 0.406	0.416 ± 0.344	0.247 ± 0.225	0.179 ± 0.191	0.149 ± 0.167

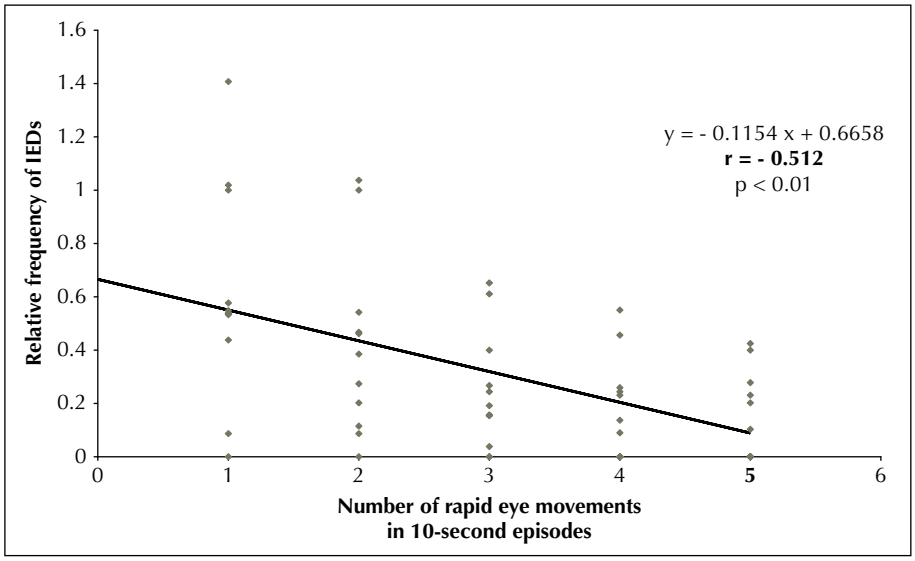

Figure 1. Negative correlation between IED frequency and number of rapid eye movements.

A 10 second-episode of REM sleep with one rapid eye movement and one IED (A) and another one with more than five REMs and no IED (B) is presented in *figure 2*.

Discussion

The seizures which most frequently appear during sleep are frontal lobe seizures, 61% of which occur during sleep. In contrast to the high rate of frontal lobe seizures during sleep, temporal, occipital, and parietal lobe seizures occur predominantly during wakefulness. Temporal lobe seizures appear only during sleep at a rate of 10.9% (Crespel *et al.*, 1998; Herman *et al.*, 2001). A more detailed analysis of the sleep-related seizures revealed that 95% were bound to NREM sleep, 61% of which to NREM stage 2, 20% to NREM stage 1, and 14% to NREM stages 3 and 4 (Minecan *et al.*, 2002).

The epileptiform discharges are facilitated by phasic activity during NREM sleep; sleep spindles and K-complexes. This finding reflects the synchronizing effect of the thalamocortical reverberation circuitry (Blumenfeld, 2005; Steriade, 2001). The fact that these phasic events are more pronounced over the frontocentral cortex could help explain the finding that frontal lobe seizures are more frequent during sleep in contrast to those originating from the temporal, parietal, and occipital lobes (Crespel *et al.*, 1998).

The suppression of IEDs during REM sleep is the result of limited propagation rather than reduced genesis in an epileptic focus. This fact explains the observation that patients, in whom we found IEDs during REM sleep, have focal epileptic syndromes and not generalised epilepsy. The suppressed propagation of IEDs during REM sleep limits their occurrence in scalp EEG, because IEDs can only be detected when approximately 6 cm^2 of the cortex is affected. The limited propagation of epileptic activity is also responsible for the considerably decreased probability of epileptic seizures during REM sleep. The reduced propagation of IEDs during REM sleep results from inhibition of the thalamocortical synchronizing mechanisms. The desynchronizing effect on the neuronal discharge pattern is mediated mainly by cholinergic nuclei of the ponto-mesencephalic tegmentum which

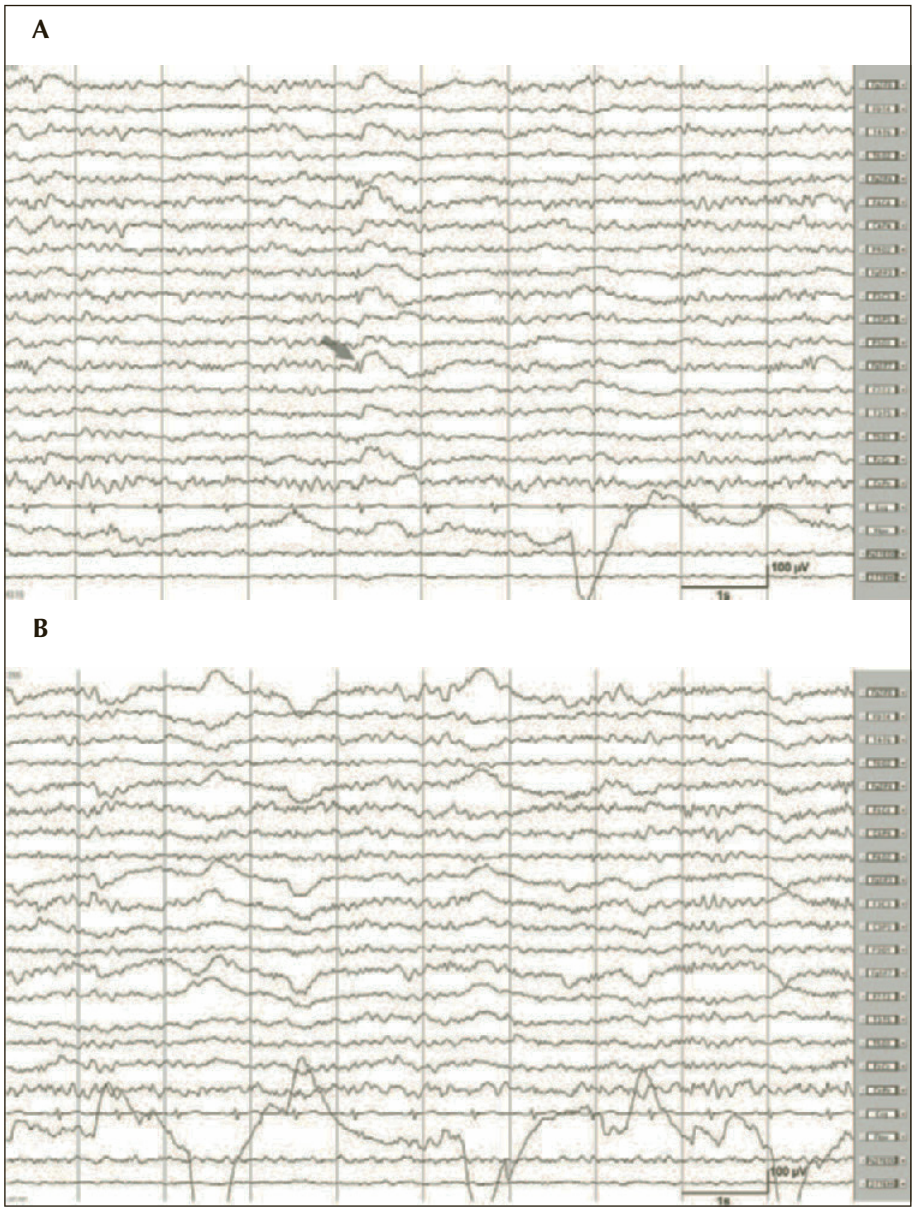

Figure 2. A) A 10-second episode of REM sleep with one rapid eye movement and one IED; the arrow points to an IED.
B) An episode with more than five rapid eye movements with no IED. Longitudinal montage, horizontal electrooculography is the third deviation from the bottom. The calibration for the EEG leads and electrooculography is the same.

are activated during REM sleep. Cholinergic and noradrenergic agonists desynchronize EEG and reduce IED propagation. In contrast, cholinergic and noradrenergic antagonists exert a synchronizing influence on EEG and have a pro-convulsive effect (Liljenström and Hasselmo, 1995; Shouse *et al.*, 1989).

Our study demonstrates that the desynchronizing effect seems to be accentuated during phasic REM sleep events or PGO activity probably as a consequence of a further cholinergic activity increase caused by phasic disinhibition of cholinergic neurons of the ponto-mesencephalic tegmentum. Thus, REM density may affect the occurrence of IEDs. To the best of our knowledge, this influence of phasic REM sleep events on IEDs has not been previously reported.

In a study by Sammaritano *et al.* (1991) a lower rate of IEDs during REM sleep was reported. The higher rate of IEDs in our study results from the method of enrolment since the principal aim of our study was not to assess a general IED rate in epileptic patients' REM sleep, but to compare the rate of IEDs between different parts of REM sleep; only subjects with a sufficiently high IED rate

during REM sleep were included. Most patients in our study were treated with antiepileptic drugs, nonetheless, the treatment was mostly discontinued during video-EEG monitoring. According to some studies, IEDs in focal epilepsy are, as a rule, barely influenced by antiepileptic treatment (Schmidt, 1982). Moreover, since antiepileptics influence all parts of REM sleep in the same way, the results observed in our study are unlikely to have been influenced by antiepileptic medication.
Modified criteria for REM sleep scoring were used because chin EMG tone was not recorded; this deviation is usually not part of standard video-EEG monitoring. The modification was tailored in such a manner as to reduce the possible risk of including other sleep stages. Moreover, the fact that only relative values from the REM episodes were statistically analyzed should have further eliminated the risk of distortion owing to incorrect scoring of some episodes without REMs □

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Disclosure.
None of the authors has any conflict of interest to disclose.

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