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The role of sleep electroencephalography in patients with new onset epilepsy☆

Sakir Delil, Gulcin Benbir Senel *, Derya Yavuz Demiray, Naz Yeni

Istanbul University, Cerrahpasa Medical Faculty, Department of Neurology, Istanbul, Turkey

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ABSTRACT

Purpose: An increased propensity for seizures is associated with different stages of the sleep–wake cycle. In this study, we prospectively analyzed patients with new-onset epilepsy and investigated the clinical correlates of the yield obtained from sleep electroencephalography (EEG) recordings in patients with a normal wakefulness EEG.

Methods: All patients admitted to our epilepsy unit due to unprovoked epileptic seizures and not yet treated with antiepileptic drugs were recruited consecutively for the last three years. All had a routine EEG at wakefulness (WEEG), and those with no epileptiform activity had a video-EEG recording during sleep (SEEG).

Results: We investigated a total of 241 patients; 129 patients (53.5%) had both wakefulness and sleep EEG recordings. The patients with abnormal WEEG were older than those with normal WEEG ($p = 0.005$). Abnormal WEEG was detected in only 31.2% of patients with focal seizures, but in 77.3% of patients with generalized seizures ($p < 0.001$). WEEG was abnormal in 44.0% of patients with diurnal seizures, but in 27.5% of nocturnal seizures ($p = 0.007$). Abnormal WEEG was present in 75.5% of patients with a presumed genetic origin and in 59.3% of patients with structural etiology ($p < 0.001$). Sleep EEG detected an abnormality in 41.8% of patients with normal WEEG; of these, 82.8% were focal abnormalities. In contrast, the majority of abnormalities detected in WEEG were generalized (55.8%, $p < 0.001$).

Conclusion: Our results showed a greater likelihood of abnormal WEEG in older patients and in those with generalized epilepsy, diurnally precipitating seizures, and epilepsy of presumed genetic origin.

1. Introduction

Epileptiform abnormalities identified in the first routine interictal electroencephalography (EEG) were reported to vary between 20 and 50% in suspected epilepsy in both adults and children [1–6]. The diagnostic yield of routine EEG should therefore be increased by repetitive EEG recordings and additive use of activation methods. The chance of finding epileptiform activity was reported to increase up to approximately 80% with EEG recordings during sleep following sleep deprivation [6–8,34]. It is also well-known that some types of epilepsies, such as benign childhood epilepsy with centrotemporal spikes or West's syndrome, have a typical appearance during sleep [10]. However, the utility of sleep EEG in a patient with new-onset epilepsy and normal wakefulness EEG has not been determined.

An increased propensity for seizures occurs in different stages of the sleep–wake cycle [11]. Additionally, increased lateralizing and localizing values were reported for interictal epileptiform discharges occurring in NREM (non-rapid eye movement) sleep stages [7,9,12]. Precipitation of epileptic activities and seizures upon sleep and during sleep deprivation were reported in patients with confirmed epilepsy [13,14]. However, the utility of sleep EEG recordings in new-onset epilepsy with a normal EEG during wakefulness is unclear and should be proven by well-designed prospective studies. In this study, we prospectively analyzed patients with new-onset epilepsy and routine wakefulness and sleep EEG following sleep deprivation. We investigated the clinical correlates of the yield obtained from sleep EEG recordings in patients with normal wakefulness EEG.

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* Corresponding author at: Istanbul University, Cerrahpasa Faculty of Medicine, Department of Neurology, Sleep Disorders Unit, 34098 Istanbul, Turkey.
Tel.: +90 5332263797; fax: +90 2126329696.
E-mail address: drgulcinbenbir@yahoo.com (G.B. Senel).

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2. Method

In this prospective study, all patients admitted to our epilepsy unit for the last three years due to unprovoked epileptic seizures who were not yet treated with antiepileptic drugs were recruited consecutively. Any number of seizures prior to study enrollment were allowed, and the duration of recurrent seizures was not restricted to a time period. The only strict inclusion criterion was that the patient should have never been treated with an antiepileptic drug. Detailed past medical histories were obtained from all patients, and neurological examinations were performed. Seizure types were noted and classified as focal or generalized epilepsy and syndromic definitions were based on the recommendations by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) in 2010 [15]. Seizure timing was noted as diurnal if they occurred only during wakefulness, nocturnal if they occurred only during sleep, and mixed if they occurred during both sleep and wakefulness. The number of seizures occurred before the entry to our study was noted, with "more than ten" seizures coded in the case of myoclonic jerks or absence seizures. If any patient experienced both myoclonic and absence seizures with bilateral convulsive seizures, the number of convulsive seizures were taken into account. All patients were imaged by cranial magnetic resonance imaging (MRI, 1.5 T).

The duration between the last (or the only) seizure and wake and sleep EEG recordings was more than 24 h and less than one month. All patients had a routine international 10–20 electrode montage system EEG including bipolar montages with longitudinal and transverse chains with a 20-channel Nihon Kohden EEG device (18 channels of EEG, one channel of electrocardiography and one channel of superficial electromyography of left masseter muscle). Digital recording parameters, including sensitivity, filter setting (notch filter) and the time base, were in accordance with the international guidelines [16]. The paper speed was set to 30 mm/s. Routine wakefulness EEG included hyperventilation for 3 min, with recording continued for at least 2 min after cessation [17]. Photic stimulation was performed via a lamp at a distance of 30 cm with trains of photo flashes with a duration of 10 s for each frequency at 10 s intervals. For each 10 s segment, eyes were opened and closed for 5 s each. The trains were performed at frequencies of 1, 2, 4, 6, 8, 10, 12, 13, 14, 15, 16, 17, 18, 20, 25, 30, 50 and 60 Hz. At least 30 min of artifact-free signals were recorded.

The routine EEG recordings were independently reviewed by the senior author (N.Y.) who was blinded to clinical and neuroimaging findings. No further testing was performed if routine EEG revealed epileptiform activities. Epileptiform activities included spike, sharp, spike and wave, sharp and wave, and diffuse/asymmetric diffuse spike and wave, sharp and wave, multiple spike/sharp wave discharges [18]. Changes in background activity were noted but did not exclude proceeding with sleep EEG studies. In the absence of epileptiform activities in normal routine EEG, each patient had a video-EEG recording during sleep following sleep deprivation (defined as half of usual total sleep time). The sleep EEG recordings were taken during the daytime, and patients were left to sleep for 3 h. A total sleep time duration of at least 15 min and a depth of at least NREM sleep stage 2 were required for inclusion. The presence of REM sleep was not a prerequisite for inclusion. Patients were allowed to sleep normally; in the event of a failure to fall asleep, no pharmacological agent was allowed. Sleep EEG recordings were evaluated by the same neurologist (N.Y.), who was also blind to the clinical and neuroimaging findings.

Statistical analysis was performed using SPSS software (version 15.0 for Windows; Chicago, IL). The variables are expressed as the mean ± standard deviation or as percentages. The relationship between nominal parameters was analyzed using the chi-square test; potential correlations between non-parametric and parametric demographic and EEG parameters were analyzed using the Mann Whitney *U* and Pearson correlation tests. Statistical significance was set at a p value of ≤ 0.05.

The study was approved by the ethics committee, and informed consent was obtained from every patient or their proxies. The study was sponsored by Istanbul University (UDP-42750).

3. Results

A total of 241 patients were evaluated; 77 patients (31.9%) had abnormal routine EEGs revealing epileptiform activity. A total of 12 patients (4.9%) with normal wakefulness EEG declined to participate in the study. Another 23 patients (9.5%) were excluded due to insufficient sleep during daytime sleep-EEG recordings. The remaining 129 patients (53.5%) completed both wakefulness and sleep EEG recordings. The mean patient age was 28.5 ± 17.2 years (ranging between 11 and 79 years), and the majority of participants were male (55.1%).

The analysis of correlates in patients with normal versus abnormal routine EEG at wakefulness (WEEG) is shown in Table 1. We observed a small but significant difference between the mean age of the two groups; patients with abnormal WEEG were older than those with normal WEEG ($p = 0.005$). Gender did not differ between these two groups. Among seizure types classified as focal or generalized, abnormal WEEG was detected in only 31.2% of patients with focal seizures, but in 77.3% of patients with generalizedseizures ($p < 0.001$). The subtypes of focal seizures were not significantly different (Table 1). The majority of focal seizures were of temporal origin (34.6%), followed by frontal (26.6%), fronto-temporal (12.0%), parietal (9.4%), occipital (8.0%), temporo-parietal (5.4%), fronto-parietal (2.6%) and temporo-occipital (1.4%) origin. WEEG was abnormal in 44.0% of patients with diurnal seizures; an abnormal WEEG was detected in 27.5% of nocturnal and 18.2% of mixed (diurnal and nocturnal) seizures ($p = 0.007$). An etiological approach revealed that 75.5% of patients with a presumed genetic epilepsy origin had an abnormal WEEG, while 59.3% of patients with structural etiology and 77.0% of patients with unknown origin had an abnormal WEEG ($p < 0.001$). The number of seizures occurring prior to study enrollment was similar for patients with normal and abnormal WEEG. In the presence of an abnormal neuroimaging, the majority of patients (56.8%) had abnormal WEEG ($p < 0.001$). The most common

Table 1
Patient demographics on the basis of routine EEG findings at wakefulness.

Variables	Normal ($n = 164$)	Abnormal ($n = 77$)	p Value
Age (years)	29.1 ± 15.5	33.2 ± 22.2	**0.005**
Male gender	56.2%	53.3%	0.296
Seizure types			
Focal	68.8%	31.2%	**<0.001**
Generalized	22.7%	77.3%	
Focal seizure types			
Focal	27.3%	72.7%	0.195
Dyscognitive	68.5%	31.5%	
Focal evolving bilateral convulsions	66.7%	33.3%	
Timing of seizures			
Diurnal	56.0%	44.0%	**0.007**
Nocturnal	72.5%	27.5%	
Mixed	81.8%	18.2%	
Etiology			
Presumed genetic	24.5%	75.5%	
Structural	59.3%	40.7%	**<0.001**
Unknown	77.0%	23.0%	
Number of seizures	3.1 ± 3.5	2.9 ± 3.4	0.596
Abnormal MRI	43.2%	56.8%	**<0.001**

Table 2
Patient demographics on the basis of sleep EEG findings.

Variables	Normal (n = 164)	Abnormal (n = 77)	p Value
Age (years)	27.5 ± 13.9	25.7 ± 11.7	0.027
Male gender	59.7%	55.6%	0.392
Seizure types			
Focal	56.3%	43.7%	0.164
Generalized	33.3%	66.7%	
Focal seizure types			
Focal	100.0%	0	0.953
Dyscognitive	44.4%	55.6%	
Focal evolving bilateral convulsions	54.5%	45.5%	
Timing of seizures			
Diurnal	59.1%	40.9%	0.270
Nocturnal	56.8%	43.2%	
Mixed	25.0%	75.0%	
Etiology			
Presumed genetic	41.7%	58.3%	
Structural	58.1%	41.9%	0.534
Unknown	57.6%	42.4%	
Number of seizures	2.9 ± 3.7	3.3 ± 2.9	0.009
Abnormal MRI	34.8%	26.5%	0.228

cranial MRI abnormality was vascular lesions (ischemic or hemorrhagic, 31.1%), followed by mass-occupying lesions (27.8%), cortical dysplasia (18.0%), and others (including trauma, mesial temporal sclerosis, abscess formation, and demyelinating lesions).

A total of 129 patients had both WEEG and sleep EEG (SEEG). These patients had a mean age of 27.3 ± 13.8 years (ranging between 11 and 79 years); the majority (57.9%) were males. The mean sleep duration was 41.8 ± 26.8 min (ranging between 15 and 240 min); 61.2% of patients had sleep stages NREM 1 and 2, and 38.8% of patients had sleep stages NREM 1, 2, and 3. Of the 129 patients with SEEG, 54 patients (41.8%) had epileptiform activities. Sleep duration (p = 0.285) and the presence of superficial (NREM 1, 2) or deep (NREM 3) sleep (p = 0.612) were not related to the detection of epileptiform activities. The comparison of patients with normal versus abnormal SEEG is given in Table 2. Patients with abnormal SEEG were younger than those with normal SEEG (p = 0.027). Sex did not differ between the groups. Among all of the other variables, only the number of seizures occurring prior to study enrollment significantly differed between the groups and was higher in patients with abnormal SEEG (p = 0.009, Table 2). The analysis of abnormal EEG during sleep showed 82.8% focal abnormalities and 17.2% generalized epileptiform activity. In contrast, the majority of abnormalities detected in wakefulness EEG were generalized epileptiform activity (55.8%, $p < 0.001$).

4. Discussion

Our results show a significantly greater likelihood of abnormal WEEG (demonstrating epileptiform activity) in older patients and in those with generalized epilepsy, diurnally precipitating seizures, and epilepsy of presumed genetic origin. The presence of a neuroimaging abnormality was also associated with higher ratios of abnormal WEEGs. Sleep EEG detected an abnormality in 41.8% of patients with normal WEEG in our study. The likelihood of abnormal SEEG was significantly correlated with a younger age. Although not significant, patients with focal and nocturnal (or nocturnal and diurnal) seizures, and those with structural or of unknown etiology, had higher ratios of abnormal SEEG. Neither sleep duration nor sleep stage was correlated with detection of epileptiform activities.

In 1947, in a study of 500 patients, Gibbs and Gibbs [33] observed that 36% of patients had interictal epileptiform discharges during awakening and 82% did so during sleep. Gloor et al. [19] observed that 57% patients had more interictal epileptiform discharges during sleep in a study of 300 patients. In a recent study by Angus-Leppan [20], epileptic activity was reported in about half of the sleep records; this was significantly greater than during photic stimulation or hyperventilation. All patients with epileptic activity during activation, but not during the resting EEG, showed epileptic activity during sleep. Sleep deprivation is an important epileptic trigger that increases interictal epileptiform activity, especially in the transition from wakefulness to light sleep by enhancing cortical excitability [21]. Sleep deprivation reportedly detects epileptiform abnormalities in 35% of patients with normal EEG, especially in primary generalized epilepsy, independent of the sleep effect [22,23]. There is some evidence of individual circadian effects of the discharges independent of the sleep/wake distribution reported Pavlova et al. [35]; however, further studies in larger groups and comparisons between different types of epilepsies are needed to better understand the circadian rhythm effects. Most sleep studies in epileptic patients have concentrated on the lateralization and localization of sleep EEG compared with routine EEG performed at wakefulness. Ictal EEG during sleep was demonstrated to be four times more localizing than ictal EEG at wakefulness [24]. Sleep seizures were more frequently reported in frontal lobe epilepsy [25,26], while seizures of temporal lobe epilepsy were more frequent in wakefulness [27]. Very recently, in concordance with our results, Singh et al. [26] showed that focal interictal epileptiform discharges were significantly more common in sleep than in waking, compared with generalized discharges.

The mechanism of the increased epileptiform abnormalities in sleep-EEG following sleep deprivation is unclear. One explanation may be the increased variability in cortical excitability during sleep [28], which may originate from an altered functional network organization following sleep deprivation [29]. A mechanism, such as increased synchronization during sleep and after sleep deprivation, may also be a reflection of increased cortical excitability [30,31]. The facilitating influences of spindle activity or delta synchronization may also activate interictal epileptiform discharges during the NREM sleep stages [32]. In general, the evaluation of the complex relationship between epilepsy and sleep represents an important area for further research.

One limitation of this study is that not all of the patients had both wake and sleep EEGs. This design could provide additional data to determine if both wake and sleep EEG or only sleep EEG is sufficient by identifying patients with abnormal wake EEG but normal sleep EEG. The duration between the last (or the only) seizure and wake and sleep EEG recordings were greater than 24 h and less than one month. Nevertheless, postictal focal slowing may have suppressed interictal epileptiform discharges and spikes on the WEEG. Finally, our study was not representative of all age groups; the youngest patient studied was 11 years of age. Thus, many patients with idiopathic (genetic) epilepsy were excluded.

5. Conclusion

Here, we aimed to identify clinical (and/or neuroradiological) markers that correlated well with the results of wake and/or sleep EEG recordings. Our results are promising in the context that clinical markers may guide physicians to predict which patient will better benefit from wake or sleep EEG recordings.

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None.

Conflict of interest statement

None.

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