Epilepsy & Behavior 43 (2015) 143–148

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Impact of sleep duration on seizure frequency in adults with epilepsy: A sleep diary study ☆

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ARTICLE INFO

Article history:
Received 15 August 2014
Revised 8 December 2014
Accepted 9 December 2014
Available online 23 January 2015

Keywords:
Epilepsy
Sleep duration
Sleep deprivation
Sleep diary
Sleep disorders
Health-related quality of life
Stress
Seizure triggers

ABSTRACT

Background: Prolonged sleep deprivation activates epileptiform EEG abnormalities and seizures in people with epilepsy. Few studies have addressed the effect of chronic partial sleep deprivation on seizure occurrence in populations with epilepsy. We tested the primary hypothesis that partial sleep deprivation over 24- and 72-hour periods increases seizure occurrence in adults with epilepsy.
Methods: Forty-four subjects completed a series of self-reported instruments, as well as 1-month sleep and seizure diaries, to characterize their sleep and quality of life. Diaries were used to determine the relationship between seizure occurrence and total sleep time 24 and 72 h before seizure occurrence using random effects models and a logistic regression model fit by generalized estimating equations.
Results: A total of 237 seizures were recorded during 1295 diary days, representing 5.5 ± 7.0 (mean ± SD) seizures per month. Random effects models for 24- and 72-hour total sleep times showed no clinically or statistically significant differences in the total sleep time between preseizure periods and seizure-free periods. The average 24-hour total sleep time during preseizure 24-hour periods was 8 min shorter than that during seizure-free periods ($p = 0.51$). The average 72-hour total sleep time during preseizure periods was 20 min longer than that during seizure-free periods ($p = 0.86$). The presence of triggers was a significant predictor of seizure occurrence, with stress/anxiety noted most often as a trigger. Mean total sleep time was 9 h, and subjects took an average of 12 ± 10 naps per month, having a mean duration of 1.9 ± 1.2 h. Daytime sleepiness, fatigue, and insomnia symptoms were commonly reported.
Conclusions: Small degrees of sleep loss were not associated with seizure occurrence in our sample of adults with epilepsy. Our results also include valuable observations of the altered sleep times and frequent napping habits of adults with refractory epilepsy and the potential contribution of these habits to quality of life and seizure control.

1. Introduction

Sleep deprivation is an emerging public health crisis. Estimates from the National Sleep Foundation in 2009 indicated that adult Americans sleep for only 6.7 h on average on weeknights and 7.1 h on weekends, and 12% report sleeping less than 6 h on worknights [1,2]. Sleep deprivation is associated with a variety of health and social consequences including increased all-cause mortality, cardiovascular disease, diabetes mellitus, obesity, hypertension, and respiratory diseases [3].

Sleep deprivation for 24 h or longer can lead to seizures even in individuals without epilepsy [4–8]. Sleep deprivation of this magnitude is often referred to as total sleep deprivation (TSD). In contrast, the role of partial sleep deprivation (PSD) as a seizure activator remains unknown. While two diary-based studies support the activating effect of PSD on seizure occurrence [9,10] and a significant percentage of patients with epilepsy subjectively report this as a trigger [11,12], a video electroencephalographic-based study found no relationship between PSD and seizure occurrence in adults with epilepsy in an epilepsy monitoring unit setting [13].

We, therefore, tested the hypothesis that PSD over 24- and 72-hour periods provokes seizures in adults with epilepsy. Then, we tested the hypothesis that lower habitual sleep duration (HSD) is associated with

☆ This research was funded by the Epilepsy Foundation Health Sciences Student Fellowship (Grant number 211619), the Cleveland Clinic Lerner College of Medicine, and a Cleveland Clinic Neurological Institute Knowledge Program Pilot Project grant.
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http://dx.doi.org/10.1016/j.yebeh.2014.12.012
1525-5050/

reduced health-related quality of life (HrQOL). In addition, we analyzed sleep diary data in order to describe sleep–wake patterns in our sample.

2. Material and methods

The study was approved by the Cleveland Clinic Institutional Review Board. Subjects provided informed consent prior to completing any research procedures.

2.1. Sample inclusion and exclusion criteria

Adults with epilepsy and a baseline seizure frequency excluding auras of at least 2 seizures per year (to increase chances of having seizures during the study duration) and not exceeding 1 seizure per day (to limit seizure clustering that might complicate analysis) were invited to participate. Patients who were unable to provide informed consent and comply with study procedures and those with unquantifiable seizures, history of substance abuse, and nonepileptic events that could not be reliably differentiated from epileptic seizures were excluded.

2.2. Data collection

Data were collected from a review of the electronic medical record including demographics (age, gender, height, weight, and smoking status), epilepsy characteristics (epilepsy type, seizure types, and mean monthly seizure frequency over 6 months prior to enrollment), antiepileptic drugs (AEDs) and daily dosage, and use of sedative hypnotics and psychotropic medications. Benzodiazepines were classified as used daily or intermittently. Epilepsy type was classified as focal or generalized, and seizure types were classified as generalized (convulsive or nonconvulsive) or focal (with or without impairment of consciousness) excluding auras.

Subjects completed the following instruments during their visits to the Epilepsy Center at the time of enrollment through the Cleveland Clinic Neurological Institute's Knowledge Program (KP), a computer tablet system for providing data to clinicians from patient-reported outcomes obtained prior to clinic visits:

1. Quality of Life in Epilepsy-10 (QOLIE-10) [14]: a 10-item questionnaire assessing HrQOL in adults with epilepsy;
2. Liverpool Seizure Severity Scale (LSSS) [15]: a 16-item scale with 2 subscales for seizure control and ictal/postictal effects;
3. Generalized Anxiety Disorder-7 (GAD-7) [16]: a 7-item validated instrument used to screen for anxiety disorder and to evaluate treatment outcomes;
4. Patient Health Questionnaire-9 (PHQ-9) [17]: a 9-item validated instrument used to screen for depression and to evaluate treatment outcomes;
5. EuroQOL 5D [18]: a 5-item questionnaire covering self-mobility, self-care, usual activity, pain/discomfort and anxiety/depression, as well as a visual analog scale (VAS) indicating overall well-being.

In addition, subjects completed the following sleep assessments:

1. Epworth Sleepiness Scale [19]: an 8-item survey ascertaining one's propensity to doze in common situations, in which a score of 10 or higher is considered abnormal;
2. Fatigue Severity Scale [20]: a 9-item tool for assessing fatigue using a 7-point Likert scale, in which a score of 36 or greater suggests significant fatigue;
3. Insomnia Severity Index [21]: a self-reported measure to evaluate perceived sleep difficulties, in which a score of 8 or greater suggests insomnia;
4. Sleep Apnea Subset of the Sleep Disorders Questionnaire (SA SDQ) [22]: a sleep apnea instrument with epilepsy-specific cutoffs of 26 or higher for women and 29 or higher for men [23] assessing the likelihood of having obstructive sleep apnea (OSA) based on variables including snoring, age, body mass index (BMI), tobacco use, and hypertension history.

Subjects were provided with a 1-month sleep and seizure diary and instructed on its use. On each day of data collection, subjects recorded the following:

1. Bedtime, wake time, time spent napping, and wake time after sleep onset (any time spent awake between listed bedtime and wake time), rounded to the nearest 30 min;
2. Presence or absence of seizure triggers including missed doses of AEDs, menstruation [24], more-than-usual stress [11,25,26], and alcohol use [27];
3. Seizures coded by type based on classification at the time of enrollment.

Total sleep time for each 24-hour period (from midnight to midnight of the following day) was computed from the diary. Total sleep time incorporated both night sleep and time spent napping while excluding wake time after sleep onset. Habitual sleep duration was the average total sleep time across the period of recorded diary days. A variable called "sleep deprivation" representing daily sleep changes was calculated as the difference between habitual sleep time and total sleep time for each 24-hour period recorded.

The presence or absence of any seizure triggers was recorded as an indicator value. Ideally, each trigger type would have been included individually, but many were noted for only a very small number of nights, so it would not be appropriate to comment regarding how these individually affect sleep or the chances of having seizures. This more conservative approach only identifies whether each night had something unusual that could affect sleep patterns and seizure activity.

Twenty-four-hour diary days were categorized as follows: seizure periods (days in which seizures occurred), preseizure periods (24-hour periods preceding a seizure period), and seizure-free periods (periods not preceding seizures or having seizures, see Fig. 1). Seventy-two-hour periods were similarly defined. Isolated auras were excluded.

2.3. Statistical analysis

Descriptive statistics were calculated for variables including age; gender; BMI; smoking status; and epilepsy characteristics including seizure types, seizure frequency, number of AEDs and AED standardized (STD) dose, scores on self-reported instruments, and summaries of sleep diary variables. The STD dose variable represents the amount of AED taken daily using the defined daily dose (DDD), a measure based on the assumed average daily dose in its main indication for adults assigned by the World Health Organization. Drugs taken as needed for prolonged seizures or seizure clusters were excluded. The prescribed daily dose (PDD)/DDD ratio was calculated and summed over all drugs for each subject. Standardized AED values >1 indicate dose regimens higher than the average.

Random effects models were used to compare total sleep time for seizure-free periods to sleep time during the 24- and 72-hour preseizure periods while accounting for correlations due to repeated measurements. Separately, a logistic regression model fit by generalized estimating equations was used to determine if sleep deprivation for over 24 h was associated with increased odds of seizure occurrence while controlling for age, gender, AED STD dose, and seizure triggers. Additionally, for the sake of consistency with existing literature, this logistic regression was repeated, with sleep deprivation coded as either present (at least 30 min of sleep deprivation that day) or absent, instead of treating it as a continuous variable.

To confirm that sleep times in well-rested patients did not mask a seizure-promoting effect of sleep deprivation in those with lower