Epilepsy & Behavior 29 (2013) 63–66

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Excessive sleepiness and sleep patterns in patients with epilepsy: A case–control study

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ARTICLE INFO

Article history:
Received 24 April 2013
Revised 10 June 2013
Accepted 24 June 2013
Available online 10 August 2013

Keywords:
Epilepsy
Sleepiness
Sleep disorders

ABSTRACT

The aim of this study was to assess excessive daytime sleepiness (EDS), sleep quality, and sleep disorders in a cohort of patients with epilepsy in the city of Florianopolis in southern Brazil. One hundred and forty patients diagnosed with epilepsy were assessed by questionnaires that included demographic and clinical variables, the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), and the Fletcher & Luckett Adapted Questionnaire (FLAQ). These data were then compared to data from a control group ($n = 85$). Compared to controls, patients with epilepsy (PWE) had significantly higher scores on the ESS ($p = 0.003$), higher scores on the "daytime dysfunction" domain of the PSQI ($p = 0.002$), and more symptoms that suggested obstructive sleep apnea in the FLAQ ($p < 0.001$). By performing multiple linear regression models, we demonstrated that age, male gender, the presence of secondarily generalized seizures, and phenobarbital use were slightly to moderately correlated with PSQI ($r = 0.38$) and FLAQ ($r = 0.51$) but not with SSS scores. We concluded that PWE had more EDS, daytime dysfunction, and sleep disorders compared to a control group.

1. Introduction

The relationship between sleep and epilepsy has been recognized since antiquity, including observations that some patients only had seizures during sleep [1]. Currently, it is known that sleep can have a direct effect on interictal epileptic discharges (IED) and that sleep deprivation can precipitate seizures. Interictal epileptic discharges are more frequent during NREM sleep, possibly due to the neuronal synchronization that is typical of this sleep stage [2]. Furthermore, idiopathic generalized epilepsies primarily involve thalamocortical synchronization mechanisms that can resemble, in some aspects, those observed in NREM sleep [3,4].

Patients with epilepsy (PWE) often complain of excessive daytime sleepiness (EDS), which has a serious impact on their quality of life [5]. This symptom may be caused by the acute effect of seizures during sleep, the chronic effect of epilepsy on sleep architecture, the use of antiepileptic drugs (AEDs), or the coexistence of primary sleep disorders [6].

Moreover, the prevalence of sleep disorders is higher in PWE. In fact, obstructive sleep apnea (OSA) syndrome can affect many symptomatic aspects of PWE, such as seizure control, mood disorders, cognitive dysfunction, and quality of life [5,7,8].

Considering the frequent association between epilepsy and sleep disorders, the objectives of this study were to assess sleep quality and the symptoms of OSA in PWE and to evaluate their association with seizure frequency and AEDs. We also investigated the clinical, demographic, and pharmacological predictors for sleep quality and sleep disorder symptoms.

2. Methods

2.1. Patients

One hundred forty adult PWE (over 18 years old, both genders) were consecutively recruited between August 2009 and August 2011 from two institutions: the Epilepsy Center of Santa Catarina (CEPESC) at Governador Celso Ramos Hospital (HGCR) and the University Hospital of Federal University of Santa Catarina (HU-UFSC), Florianópolis City (southern Brazil). All patients had a definite diagnosis of epilepsy according to the criteria proposed by ILAE [9] based on clinical history, seizure semiology, electroencephalographic (EEG) data, and structural magnetic resonance imaging (MRI) findings. Exclusion criteria entailed the presence of illiteracy, psychiatric comorbidity, or a cognitive impairment that precluded the patient from completing the questionnaire. Psychiatric comorbidity was excluded after

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http://dx.doi.org/10.1016/j.yebeh.2013.06.029

a full evaluation done by a psychiatrist (RG) with experience in epilepsy using DSM-IV parameters, the Hospital Anxiety and Depression Scale (HADS), and the Inventory of Depression and Anxiety Symptoms (IDAS).

Participants completed a questionnaire that included demographic and clinical variables, the Pittsburgh Sleep Quality index (PSQI) questionnaire [10,11], the Epworth Sleepiness Scale (ESS) [12,13], the Stanford Sleepiness Scale (SSS) [14], and an adapted version of the Fletcher & Luckett Questionnaire (FLAQ) [15,16]. These data were then compared to a healthy control group (n = 85) from the general population who had no disease and who were matched for gender, age, weight, handedness, family income, and education. The scores were analyzed according to sex, age, AEDs in use, monthly complex partial and generalized seizure frequency, epilepsy duration, age at the onset of epilepsy (recurrent seizures), polytherapy, use of benzodiazepines, and the class of epilepsy syndrome.

The clinical and demographic data were evaluated from responses to a semistructured questionnaire that was answered by both patients and caregivers and by reviewing medical records collected under the supervision of a board-certified clinical electrophysiologist. The duration of epilepsy in years was defined as the interval between the patient's age at the onset of epilepsy and his/her age on the day of the interview. The seizure frequency was calculated by reviewing medical records and seizure calendars during the last 12 months. Patients were considered to be under monotherapy if they were using only one AED (carbamazepine — CBZ, phenobarbital — PB, sodium valproate — VPA, phenytoin — PHT, lamotrigine — LTG, oxcarbazepine — OCBZ, topiramate — TPM, levetiracetam — LEV or acetazolamide — AZM). Patients were considered to be under monotherapy plus benzodiazepines (BZDs) if they were using one AED and one BZD. Patients were considered to be under polytherapy if they were using two or more AEDs regardless of whether they were associated with BZDs. All BZDs were used in a chronic and continuous way as epilepsy adjuvant treatment. The BZDs used were clobazam and clonazepam.

Epilepsy syndromes were categorized as the following: 1) focal symptomatic etiology, when presented with focal seizures and a compatible MRI; 2) focal with unknown etiology and normal MRI; 3) focal with unknown etiology without MRI; and 4) idiopathic generalized epilepsy.

2.2. Sleep evaluation

The ESS is the most commonly used instrument to evaluate daytime sleepiness in PWE; it consists of 8 self-rated items, each scored from 0 to 3, that measure a subject's habitual "likelihood of dozing or falling asleep" in common daily situations. No specific time frame is specified. The ESS score represents the sum of individual items and ranges from 0 to 24. Scores that are greater than ten are considered to indicate significant sleepiness [12]. The Portuguese-language version of the ESS validated for Brazil was used to assess sleepiness in PWE [13]. The PSQI is a 19-item self-rated questionnaire for evaluating one's sleep quality over the previous month. The 19 questions are combined into 7 clinically derived component scores (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep-inducing medication, and daytime dysfunction) that are each weighted equally and scored from 0 to 3. The 7 component scores are added to obtain a global score ranging from 0 to 21, with higher scores indicating worse sleep quality. A global score greater than 5 is defined as a low quality of sleep [10]. The Portuguese-language version of the PSQI validated for Brazil was used to assess sleep quality index [11]. The SSS quantifies subjective sleepiness levels at the time of evaluation. Participants selected one of 7 options to identify their current level of sleepiness. A score greater than or equal to 3 is associated with a decline in performance that is related to sleepiness [14]. The FLAQ was adapted from the questionnaire developed by Fletcher and Luckett to assess the improvement of symptoms after treatment for OSA by continuous positive airway pressure (CPAP) [15,16], and it consists of 28 questions that grade the level of OSA symptomatology in various areas concerning daytime and nocturnal function. Each patient rated himself/herself with a score ranging from 0 (no symptoms) to 3 (maximal symptoms) on each of the 28 questions. The highest score (the sum of responses to all 28 questions) was divided by 28 to determine how each patient rated the level of their symptoms. Scores greater than 1 could indicate the presence of significant OSA symptoms [15]. Participants also answered ten questions with yes or no alternatives to assess the presence of other common sleep disorders such as insomnia, nonrestorative sleep, restless sleep, sleep talking, sleepwalking, bruxism, abnormal dreams, and sleep paralysis.

2.3. Statistical analysis

Statistical analysis was performed using SPSS for Windows, standard version 17.0 (SPSS Inc.). Univariate analysis was performed to evaluate the association between the scores of ESS, SSS, PSQI, FLAQ (dependent variables), and clinical/demographic variables (independent variables). Significance was determined by the following tests: chi-square or Fisher's exact tests for categorical variables, Student's *t*-test or ANOVA for continuous variables with normal distribution, Mann–Whitney or Kruskal–Wallis for continuous variables that have nonnormal distribution, and Pearson's or Spearman's correlation for continuous variables. Clinical/demographic variables that had an association with the dependent variables for a "p" level of significance less than 0.20 in the univariate analysis were included in a multiple linear regression. In this analysis, categorical variables were included in the model and classified as 0 or 1 (for dichotomous categories). The B coefficient, R coefficient, and adjusted R square of the final models that better explained the overall scales' scores were determined, and a "p" level lower than 0.05 was considered to be significant. Variables with clinical plausibility that had an association with a "p" level of significance lower than 0.10 were maintained in the final model to minimize the possibility of type II errors.

This study was approved by the Ethics Committee for Human Research of the Federal University of Santa Catarina (Protocol No. 515) and Governador Celso Ramos Hospital (Protocol 20012/0007). All subjects signed an informed consent form and voluntarily agreed to participate in this study.

3. Results

No statistical differences ($p \geq 0.23$) were found between the 140 PWE and the 85 controls according to gender, age, weight, handedness, family income, and education level (Table 1).

Of the PWE, 71 (50.3%) were men, with an average age of 36 (±12.3) years, a mean disease duration of 21.6 (±12.5) years, and age at epilepsy onset of 14.4 (±11.6) years. The majority of the patients were categorized as having symptomatic focal epilepsy

Table 1
Demographic features of patients and controls.

	Patients (n = 140)	Controls (n = 85)	"p" level[a]
Age, years, mean (SD)	36.0 (12.3)	36.4 (11.6)	0.83
Sex			
Male (%)	71 (51)	41 (48)	
Female (%)	69 (49)	44 (52)	0.41
Weight, pounds, mean (SD)	154 (33.2)	149.4 (23.5)	0.28
Handedness			
Right-handed (%)	129 (92)	79 (93)	
Other (%)	11 (8)	6 (7)	0.88
Education level, years, mean (SD)	7.2 (3.8)	7.8 (2.9)	0.23
Monthly family income, U.S. dollars, mean (SD)	621 (460)	678 (345)	0.33

[a] The "p" levels of significance were determined by Student's *t*-test or chi-square test.