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Original Article

Sleep disorders and circadian rhythm in epilepsy revisited: a prospective controlled study

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ABSTRACT

Objective: Sleep disturbance is reported to be frequent in epilepsy. The role of comorbidity, which is frequently accompanied by sleep disturbance, has not been investigated. The present study assessed sleep disorders and circadian rhythm in patients with epilepsy, in whom relevant comorbidity was carefully excluded.

Methods: Two hundred patients with epilepsy (100 generalized, 100 partial), without relevant psychiatric, neurological or internal comorbidity, were compared with 100 matched controls. The questionnaire contained specifically tailored questions to address the association between epilepsy and sleep disturbance, and validated questionnaires aimed at sleep quality, excessive daytime sleepiness (EDS), circadian rhythm, sleep disorders, and quality of life.

Results: Forty-one percent of the participants reported on the acute effects of present or past seizures on sleep-wake rhythm, whereas chronic effects were not evident. Participants and controls did not differ in the rates of chronic sleep disturbance, EDS, and presence of sleep disorders (all p-values non-significant or n.s.). Apart from earlier sleep times on workdays ($p = 0.001$) in those with epilepsy, circadian variables were similarly distributed. Epilepsy was well controlled, with 75.9% being seizure free for ≥1 year. Longer durations of epilepsy showed a negative correlation with sleep quality (rho = –0.256, $p < 0.001$). Participants with generalized and partial epilepsies did not differ in rates of sleep disturbance, EDS, sleep disorders, and variables of circadian rhythm (all p-values n.s.).

Conclusion: The present study demonstrated that chronic sleep disturbance is not increased in patients with well-controlled epilepsy without relevant comorbidity. This supports comorbidity and insufficient seizure control as major contributors of sleep disturbance in epilepsy.

1. Introduction

Sleep disturbance is a frequently reported complaint in patients with epilepsy [1]. To date, five controlled questionnaire studies with a main focus on sleep disorders, circadian rhythm, and excessive daytime sleepiness (EDS) comprising ≥100 participants with epilepsy have been published [2–6]. The largest of these studies contained data from a mailed questionnaire survey of 486 patients with partial epilepsies. This study demonstrated that the rate of sleep disturbance was twice as high as in the controls [4]. In addition, those with epilepsy and sleep disturbance had a worse quality of life than those without sleep disturbance [4]. A three-time increased rate of sleep disturbance was reported in a more heterogeneous sample of 100 patients with both partial and generalized epilepsies [5]. Concerning circadian rhythm, people with epilepsy have been shown to be more morning-oriented, with earlier mid-sleep, and have longer sleep duration on non-work days compared with a population-based control sample [6]. Two other studies have looked at possible factors related to subjective daytime sleepiness in epilepsy [2,3]. Both authors showed that symptoms suggestive of obstructive sleep apnea are independent predictors of subjective daytime sleepiness in epilepsy [2,3]. In addition, seizure frequency was found to be an epilepsy-intrinsic contributor to daytime sleepiness [3].

The influence of associated comorbidities on the presence of sleep disturbance or EDS has not been addressed in these studies [2–6]. Of note, mood or anxiety disorders are frequent in patients with epilepsy, and can affect up to 39% of subjects [7]. Mood and anxiety disorders, however, are often associated with increased rates of sleep disturbance [8,9]. It can therefore be speculated that it is not epilepsy itself, but its associated comorbidities, that contribute to the increased rate of sleep disturbance in epilepsy. In addition, none of the previous studies have been adequately powered to compare between patients with partial and generalized epilepsies [2,3,5,6].

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In this light, the present study aimed to investigate sleep disorders and circadian rhythm in both partial and generalized epilepsies compared with healthy controls, in an adequately powered sample size after exclusion of psychiatric, neurological or internal comorbidities. This question is of great relevance to understanding the role of epilepsy itself in chronic sleep disturbance in patients with epilepsy.

2. Design and methods

2.1. Study population

A total of 100 consecutive patients with idiopathic, generalized epilepsy, and 100 consecutive patients with partial epilepsy were recruited at the outpatient epilepsy clinic of Medical University of Innsbruck between November 2012 and November 2013. Inclusion criteria were: the presence of either unequivocal, generalized or partial epilepsy, based on clinico-electrographic characteristics as well as magnetic resonance imaging (MRI); being aged between 18 and 80 years at the time of investigation; and an onset of epilepsy prior to 60 years of age. Major exclusion criteria were: shiftwork; a Mini Mental State Examination score below 26 [10]; documented or suspected non-epileptic seizures; and psychiatric, neurological or relevant internal comorbidity. Psychiatric comorbidity was based on the patient's history, a score above 10 in the Hospital Anxiety and Depression Scale [11], information gathered from the treating physician, and a review of the electronic hospital management information system. Both groups of patients with epilepsy were compared with 100 gender- and age-matched (+/– 2.5 years) healthy controls. These controls were recruited from either non-related acquaintances of patients, or hospital staff and their acquaintances or family members. The exclusion criteria for the controls corresponded to those of the patients with epilepsy, except that central nervous system active medication was a further exclusion criterion for the healthy controls.

Ethical committee approval was obtained at Medical University of Innsbruck. All patients granted written informed consent according to the Declaration of Helsinki.

2.2. Applied questionnaire

All study participants underwent a comprehensive structured sleep questionnaire, which consisted of a face-to-face semi-structured interview (Part 1) and self-administered validated scales (Part 2). The scales were distributed to all participants after giving them a short explanation on how to fill in the scales. Ambiguous answers were discussed. The completed questionnaires were re-checked for consistency or missing values. Demographic and clinical information were gathered from the participants' file notes.

The questionnaire consisted of questions specifically tailored to address the association between epilepsy and sleep disorders and sleep hygiene, as well as validated scales aimed at sleep quality (Pittsburgh sleep quality index) [12], EDS (Epworth sleepiness scale) [13], suspected sleep-related breathing disorders (Berlin questionnaire) [14], circadian rhythm (Munich chronotype questionnaire) [15], movement disorders during sleep, parasomnias and isolated findings (Munich parasomnia scale [16], Innsbruck REM sleep behavior disorder or RBD inventory [17], and quality of life or QOLIE-31 [18,19].

2.2.1. Pittsburgh sleep quality index

The Pittsburgh sleep quality index is composed of seven subscores aimed at subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of hypnotics, and daytime sleepiness. The maximum total score is 21 points. A score of 10 points and higher is indicative for the presence of chronic sleep disturbance [12].

2.2.2. Epworth sleepiness scale

The Epworth sleepiness scale assesses daytime sleepiness in eight different everyday-life situations. Each situation has to be rated from 0 to 4; the maximum score is 24. A cut-off of 10 and higher is accepted to indicate EDS [13].

2.2.3. Berlin questionnaire

This questionnaire screens for obstructive sleep apnea syndrome. It comprises three categories (Category 1 consists of five questions assessing snoring; Category 2 consists of four questions assessing EDS; Category 3 consists of one question asking for arterial hypertension). The Berlin questionnaire is rated to be positive when two of the three symptom categories are answered positively [14].

2.2.4. Munich chronotype questionnaire

This is a chronotype questionnaire that separately assesses sleep–wake pattern on working days and non-working days [15]. Reported outcome variables are the time of midsleep (midtime between sleep onset and sleep end), social jetlag (difference between the time of midsleep on workdays and the time of midsleep on non-working days), and accumulated sleep deprivation (difference between the average sleep duration and the sleep duration on work days, taking into account the number of work days/week).

2.2.5. Munich parasomnia scale

The Munich parasomnia scale is a self-rating instrument with 21 items assessing the lifetime prevalence and current frequency of parasomnias and nocturnal behaviors in adults. For the individual items, the sensitivity is equal to or greater than 90% for all but two of the 21 items, and specificity is above 80% for all items and above 90% for 19 of the 21 items [16].

2.2.6. Innsbruck REM sleep behavior disorder inventory

The Innsbruck RBD inventory is a five-item screening questionnaire for RBD. A cut-off of 0.25 is shown to be suggestive for potential RBD [17].

2.2.7. QOLIE-31

The QOLIE-31 is a 31-item quality of life questionnaire comprising seven subscales covering general and epilepsy-specific domains. Its subscales are grouped into two factors: emotional/psychological effects and medical/social effects. The present study calculated the total score as well as all seven subscores. The maximum total score is 100. A higher total score is associated with a better quality of life [18,19].

2.3. Sample size estimation and statistical analysis

The sample size was estimated with 100 subjects per group, based on the assumption of a significance level of 0.05, a power of 0.95, and a reported three-times increased frequency of sleep disturbance in patients with epilepsy compared with controls [5]. Normality distribution was assessed with the Kolmogorov–Smirnov Test. In case of normal distribution, means +\– standard deviations were given; in case of abnormal distribution, medians and ranges were given. Group comparisons were performed with independent *t*-tests in case of normal distribution, or the Mann–Whitney *U*-test or Kruskal–Wallis test in case of abnormal distribution. Categorical variables were compared with the Chi-squared test (Pearson test or two-sided Fisher's exact test, as applicable). Bonferroni correction was applied in order to correct for multiple comparisons, and the level of significance was set accordingly. Further, to account for the intake of antiepileptic medication, binary logistic analysis was performed; sex, age, and intake of antiepileptic medication were entered as covariates. To