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Impact of sleep disorders on the risk of seizure recurrence in juvenile myoclonic epilepsy

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ABSTRACT

Objective: The aim of this study was to investigate the presence of sleep disturbances in patients with juvenile myoclonic epilepsy (JME) using sleep questionnaires. Further, we tried to evaluate whether alterations in sleep quality may influence the clinical expression of JME.
Methods: Sixty-two patients with JME treated with levetiracetam were included. Demographic and clinical variables were collected. Moreover, all patients submitted the Pittsburgh Sleep Quality index (PSQI) and the Epworth Sleepiness Scale (ESS) in order to respectively assess sleep quality during the last month and daytime sleepiness. All patients were followed up for a 6-month period and divided in two groups: seizure-free (Group 1) and seizure recurrence (Group 2). The PSQI and ESS scores were synthesized as binary variables $<5/\geq 5$ and $<10/\geq 10$, respectively. A comprehensive analysis was performed to evaluate the independent effect of the sleep quality and daytime sleepiness on the risk of having seizures during the follow-up.
Results: Both reduced sleep quality during the last month and daytime sleepiness were associated with an increased risk of suffering from seizures during the follow-up period. In fact, a PSQI score < 5 or an ESS score < 10 resulted significantly associated with the absence of seizure recurrence ($p < 0.004$ and $p < 0.001$, respectively). Increasing age had a significantly protective effect in the risk of seizure relapse.
Conclusions: Our findings show that reduced sleep quality and daytime sleepiness in patients with JME increase the risk of seizure occurrence in spite of an appropriate pharmacological treatment. This negative effect seems to be more relevant in younger patients. Sleep disorders and their specific correction should be taken into consideration for the management of patients with JME.

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1. Introduction

The interactions between sleep and epilepsy are complex and based on multiple and composite mechanisms [1]. An increased prevalence of sleep disturbances has been described in patients with epilepsy. In particular, they often complaint from unusual nocturnal events, excessive daytime sleepiness, or difficulties in initiating or maintaining sleep [2]. On the other hand, sleep disorders may impact the clinical expression of epilepsy, through an effect on both interictal and ictal discharges [3]. The relevant role of sleep in the clinical expression of epilepsy is also underlined by the use, for diagnostic purposes, of sleep deprivation as a trigger for the induction of electrical abnormalities, with or without clinical manifestations of epilepsy [4]. Treatment of epilepsy improves sleep architecture and quality, and a satisfactory management of sleep disorders has beneficial effects on seizure control [5,6].

The role of sleep as an influencing factor of the clinical expression is particularly evident in juvenile myoclonic epilepsy (JME), the most common and well-defined idiopathic generalized epilepsy (IGE) syndrome [7]. Seizures usually occur shortly after awakening, and they are often precipitated by sleep deprivation and sudden arousal. The other recognized precipitating factors, including emotional stress, alcohol and drug use, or light stimulation, exert their effects through a change in sleep architecture and wake–sleep profile [8].

Despite the relatively high prevalence of JME, the potential therapeutic implications, and the strong association with sleep, only few comprehensive studies have been performed in the attempt to characterize sleep quality in this form of IGE, but no information is available about the impact of sleep disturbances on seizure control [9–11].

In order to expand knowledge about the possible negative influence of sleep disturbances on the clinical expression of the disease, in this study we evaluated whether reduced sleep quality in the last month

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and increased diurnal somnolence were associated with an increased risk of seizure occurrence in patients with JME.

2. Subjects and methods

All patients consecutively observed from July 2012 to March 2014 at the outpatient service for Epilepsy of the Neurological Clinic, Marche Polytechnic University of Ancona, Italy with a diagnosis of JME, according to the ILAE criteria [12], who had a satisfactory control of the disease, defined as the lack or the presence of sporadic seizures (not more than two per year) while on a stable antiepileptic drug (AED) regimen from ≥12 months were considered. Only patients undergoing levetiracetam (LEV) monotherapy [13,14] were selected to minimize the potential confounding effects of the antiepileptic treatment on the sleep architecture [15,16].

Exclusion criteria were the presence of major psychiatric or other neurological diseases, ongoing treatments able to affect sleep architecture, and drug abuse and working activities inducing sleep deprivation. The assessment of inclusion/exclusion criteria was performed by two expert neurologists (LB, MS) through a careful and structured evaluation, including neurological examination and a detailed clinical, family, and treatment history.

In all included patients, besides demographic and clinical characteristics, the sleep quality in the last month with the Pittsburgh Sleep Quality Index (PSQI) [17] and a quantification of diurnal somnolence with the Epworth sleepiness scale (ESS) [18] were assessed. All patients were followed up for six months. Clinical conditions and adherence to prescribed therapy were assessed every month. Each patient had a seizure diary to fill in and to present at each visit. At the end of the follow-up, patients were divided in two groups: Group 1, seizure-free and Group 2, seizure recurrence.

The study was approved by the Ethics Committee of the Marche Polytechnic University. All participants gave their informed written consent according to the Declaration of Helsinki.

2.1. Statistical analysis

Binary variables were coded as percentages. Continuous variables were tested for normality with Kolmogorov–Smirnov test, then we synthesized continuous variables with a normal distribution with mean (±SD), while we used interquartile range (IQR) to describe continuous variables with nonnormal distribution.

Age and years elapsed since the diagnosis of JME was collected as continuous variables. PSQI and ESS scores were collected as categorical variables and then recoded as binary variables adopting the cut-off values of ≥5 and ≥10, respectively. Sex and the presence of recurrent seizures were collected as binary variables. Basal seizure annual frequency, LEV daily doses and duration of treatment were synthesized and treated as continuous variables.

We compared binary and categorical variables with chi-squared test and continuous variables with *t*-test for independent variables.

A binary logistic regression analysis was conducted to predict the probability of absence of seizures, considering the PSQI binary variable as the main predictor, and age, years elapsed since the diagnosis, sex, LEV daily dose, LEV treatment duration, and basal seizure annual frequency as covariates. A test of the full model against a constant-only model was statistically significant, indicating that the predictors as a set, reliably distinguished between patients who had seizure recurrences from patients who did not have recurrences ($\chi^2 = 14{,}831$, $p < 0.05$, $df = 7$).

A second binary logistic regression analysis was conducted to predict the probability of absence of seizures, considering the ESS binary variable as the main predictor, and age, years elapsed since the diagnosis, sex, LEV daily dose, LEV treatment duration and basal seizure annual frequency as covariates. A test of the full model against a constant-only model was statistically significant, indicating that the predictors as a set reliably distinguished between patients who had seizure recurrences from patients who did not have recurrences ($\chi^2 = 20{,}897$, $p < 0.005$, $df = 7$).

Statistical analysis was conducted with SPSS 13.0 for Windows systems; forest plots were generated with MedCalc 12.5.0 for Windows systems.

3. Results

Of the 70 screened patients, three were excluded for concomitant use of drugs interfering with sleep profile and five for concomitant psychiatric diseases. Baseline characteristics of patients (whole population and divided in two groups according to the evolution of seizures' control: Group 1, seizure-free and Group 2, seizure recurrence) are synthesized in Table 1. Group 1 and 2 patients did not significantly differ regarding sex distribution, age, duration of disease, seizure frequency in the 12-month period preceding the study, duration and daily dose of LEV treatment.

When comparing Group 1 and Group 2 patients, a PSQI score < 5 or a ESS score < 10 resulted significantly associated with the absence of seizure recurrence, as shown Table 1.

The first binary logistic regression model had an overall prediction success of 87.1%. The Wald criterion demonstrated that only PSQI ($p = 0.036$) and age ($p = 0.044$) made a significant contribution to prediction in this model. Patients with PSQI score < 5 had a significantly higher probability of being free from seizures during the follow-up period than patients with PSQI score ≥ 5 (OR: 5.708; 95%CI: 1.118-29.136; $p = 0.036$), independently from years elapsed since seizures' onset, sex, LEV daily dose and duration of treatment, and basal seizure annual frequency (Fig. 1, Table 2).

The second binary logistic regression model had an overall prediction success of 90.3%. The Wald criterion demonstrated that only ESS ($p = 0.008$) and age ($p = 0.027$) made a significant contribution to

Table 1
Baseline characteristics of patients with juvenile myoclonic epilepsy (JME), whole population and divided in two groups according to the clinical evolution: Group 1, seizure-free and Group 2, seizure recurrence. Significant differences are marked.

Variable	Overall (n = 62)	Group 1 (n = 52)	Group 2 (n = 10)	p
Age [years] (mean, ±SD)	23.2 (±2.48)	23.4 (±2.52)	22.2 (±2.09)	0.148
Male sex (n, %)	26 (41.9%)	23 (44.2%)	3 (30.0%)	0.499
Years from JME onset [years] (mean, ±SD)	6.95 (±1.81)	6.92 (±1.87)	7.10 (±1.59)	0.231
Seizure frequency [attacks/year] (median, mean, IQR)	0 (0.58; 1)	0 (0.57; 1)	0.5 (0.60; 1)	0.925
LEV daily dose [mg/day] (mean, ±SD)	1786.29 (±355.9)	1783.65 (±357.1)	1800.0 (±368.9)	0.896
Years of LEV treatment [years] (mean, ±SD)	4.97 (±1.64)	4.92 (±1.64)	5.20 (±1.68)	0.629
PSQI score (mean, ±SD)	3.73 (±2.14)	3.37 (±1.92)	5.60 (±2.32)	**0.002**
PSQI score < 5 (n, %)	44 (71.0%)	41 (93.2%)	3 (6.8%)	**0.004**
ESS score (mean, ± SD)	5.27 (±3.37)	4.40 (±2.62)	9.80 (±3.29)	**0.001**
ESS score < 10 (n, %)	55 (88.7%)	50 (90.9%)	5 (9.1%)	**0.001**
Seizure recurrence (n, %)	10 (16.1%)	–	10 (100%)	–

Abbreviations: LEV, levetiracetam; PSQI, Pittsburgh Sleep Quality index; ESS, Epworth Sleepiness Scale.

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