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Sleep disturbances in juvenile myoclonic epilepsy: A sleep questionnaire-based study

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ABSTRACT

Sleep and epilepsy share a complex pathophysiological association. Juvenile myoclonic epilepsy (JME) is a common sleep-sensitive epilepsy in which the effect of seizures could have therapeutic implications in terms of sleep disturbances and seizure control. This study aimed to analyze the effect of epilepsy on sleep in patients with JME. Fifty patients on valproic acid (VPA) monotherapy, and age- and gender-matched controls were recruited into this prospective, hospital-based, case-control study after informed consent and screening for inclusion criteria. They underwent a detailed clinical assessment, electroencephalogram (EEG) and neuroimaging, and were administered validated sleep questionnaires, which included the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and NIMHANS Sleep Disorders Questionnaire. The patient and control groups had identical numbers of males and females (M: F = 22: 28), without any significant difference in the age and body mass index (BMI). The clinical profile of JME was similar to published literature while the prevalence of EEG abnormalities was less compared to similar studies. The mean ESS and PSQI scores and the number of subjects with abnormal scores on one or both questionnaires were significantly more in patients. Patients had a higher prevalence of sleep disturbances, insomnia and excessive daytime somnolence. No significant seizure- or treatment-related factors influencing sleep could be identified. This study, the first of its kind, revealed that patients with JME have significant sleep disturbances characterized by excessive daytime sleepiness and disturbed night sleep, despite adequate medications and good seizure control. The role of VPA in the genesis of these symptoms needs clarification.

1. Introduction

Sleep disorders are described in patients with epilepsy, and can contribute to the intractability of temporal lobe epilepsy [1]. Sleep and epilepsy share a complex and intriguing pathophysiological relationship, but much of the research has focused on the effect of sleep on epilepsy with less emphasis on the complex effects of epilepsy on sleep. Most sleep disturbances in epilepsy patients are often hastily and erroneously attributed to drug effects and only few studies have sought to analyze the effect of the seizure phenomenon on the genesis of these symptoms [1].

Juvenile myoclonic epilepsy (JME) is the most common and well defined idiopathic generalized epilepsy (IGE) syndrome [2,3], having been recognized in 1985 [4]. The disorder may be inherited, and sex distribution is equal. Myoclonic jerks starting at puberty, multiple seizure types including generalized tonic–clonic seizures (GTCS) and infrequently absences, occurring shortly after awakening and often precipitated by sleep deprivation are the defining features [5]. Myoclonic jerks are bilateral, single or repetitive, arrhythmic, predominantly in the arms, and unassociated with disturbance in consciousness. Despite the wide prevalence of JME, potential therapeutic implications and its strong association with sleep, comprehensive studies of sleep in JME are scarce [6–9].

We studied the prevalence and spectrum of sleep disturbances in patients with JME using sleep questionnaires and compared various parameters in patients with JME with and without sleep disturbances.

2. Materials and methods

This prospective, cross-sectional, hospital-based, case-control study was conducted at a tertiary neurology center in South India from 1st August 2009 to 31st January 2011. The study was approved by the Institute Ethical Committee. Fifty patients with JME attending the neurological services and fulfilling the inclusion criteria were recruited. Fifty age- and gender-matched healthy controls consisting of friends/unrelated volunteers (n = 38) of the patients from similar educational and socioeconomic status and medical personnel (doctors = 7; medical technologists = 5) of the hospital on routine

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day duties were also recruited. Controls were not related to patients and did not have family history of epilepsy.

Diagnosis of JME was based on the ILAE criteria for JME [10,11]. Patients were ≥12 years old and on valproic acid (VPA) as the sole antiepileptic drug (AED). Serum VPA levels were not carried out. Patients with illnesses or medications known to affect sleep, other than VPA, and those with substance abuse of any degree were excluded. Imaging of brain was normal in all. Informed written consent was obtained from the study subjects. All patients underwent a structured evaluation, including a detailed clinical, family and treatment history, neurological examination, 16-channel digital electroencephalogram (EEG) using the international 10–20 system of electrode placement, neuroimaging (computerized tomography or magnetic resonance imaging), and other investigations when indicated. Validated sleep questionnaires, the Epworth Sleepiness Scale (ESS) to assess daytime somnolence 12] and the Pittsburgh Sleep Quality Index (PSQI) to assess nighttime sleep [13], were administered to all the study subjects. A 'NIMHANS comprehensive sleep disorders questionnaire' was designed at our center (NIMHANS) to document sleep-related symptoms [14]. Initially, a pilot study was undertaken with 50 individuals to assess the feasibility/applicability of the questionnaire and also estimated problems in response. Based on the assumption of 10% prevalence of sleep disorders in the general population, with 20% relative error and accommodating for non-response, the minimum numbers to be interviewed was 1035. A total of 1150 healthy persons (15–55 years) who accompanied the patients to the outpatient department of neurology were interviewed by random selection after obtaining their informed consent. The exclusion criteria included: hospital staff member and those reporting existing medical or surgical condition [14].

Statistical analysis employed SPSS version 16 and involved comparison of various parameters between the 2 study groups. Chi square test was employed to study qualitative parameters and independent *t* test for quantitative parameters. Apart from the comparison between the patient and the control group, patients with and without sleep disturbances were compared.

3. Results

3.1. Clinical profile

The mean age of patients (M: F = 22:28) was 23.4 ± 7.2 years and that of controls was 22.9 ± 6.9 years (M: F = 22:28). The mean body mass index (BMI) was 22.8 ± 1.86 in patients and 22.7 ± 1.56 in controls. There was no significant difference in age and BMI in the patient and control group. Majority (86%) of the patients were less than 30 years of age; 44% were aged between 12 and 20 years while 42% were in their 3rd decade of life. The mean age of onset of seizures was 15.8 ± 3.6 years for males and 17.1 ± 3.8 years for females and duration of illness was 88 ± 26 months for males and 61.51 ± 23.7 months for females.

All patients had myoclonic jerks, three of them not developing any other seizure types. The mean age of onset of myoclonus was 15.82 ± 3.9 years for males and 17.14 ± 6.1 years for females. The classic attribute of the myoclonus was its propensity to aggravate with sleep deprivation and its appearance on awakening from sleep as seen in 47 (94%) and 46 (92%) patients respectively. In 14 patients (28%), myoclonus preceded onset of other seizure types. Except for three patients, the rest had GTCS and in 36 (72%) patients it was the first seizure type observed. The mean age of onset was 17.8 ± 5.1 years for males and 16.6 ± 7.1 years for females. In 32 (64%) patients, GTCS were preceded by a single or a series of myoclonic jerks. Majority (64%) had seizures on waking from sleep; in 36 (72%) patients there was history of sleep deprivation preceding the attacks. In 32 (64%) patients, seizures also occurred regardless of any sleep factors. Three patients had status epilepticus at some time during their disease course and four (8%) had absence seizures. Eight patients (16%) had history of febrile seizures in childhood.

A BMI >25 was noted in five patients and two controls. The mean duration of VPA treatment was 52.5 ± 56.2 months and the mean dose was 768 ± 209.5 mg/d. The average dose of VPA used by the patients was as follows: 1500 mg/d = 3; 800–1000 mg/d = 21; 600 mg/d = 23, and 400 mg/d = 3. Seizure control was achieved in 41 (82%) patients. Family history of seizures was noted in 18 (36%) patients, 11 of them being siblings. However, none of the affected family members was available for confirmation of seizure type.

3.2. EEG observations

EEG was normal in 30 (60%) patients. Background activity was normal in all and the predominant background activity was alpha with seven (14%) patients showing low amplitude fast activity as the dominant pattern. The EEG abnormalities observed in 20 patients (40%) consisted of generalized spike/polyspike-and-wave pattern in 12 (60%) patients, generalized spikes or sharp waves in four (20%) and focal epileptiform discharges in five (25%).

3.3. Sleep questionnaire assessment

An abnormal Epworth Sleepiness Scale (ESS score ≥11) was seen in 17 (34%) patients and an abnormal Pittsburgh Sleep Quality Index (PSQI score ≥6) in 24 (48%) patients, being highly significant ($p<0.001$) when compared to controls (Table 1). The mean ESS and PSQI scores were significantly high in patients ($p<0.001$). Patients with JME had a higher prevalence of sleep disturbances on interview, including excessive daytime somnolence (EDS) and insomnia, which was highly significant compared to the control group (Table 2). Patients also had a higher prevalence of family history of EDS with a trend towards significance. Obstructive sleep apnea (OSA) was noted in one patient. Most of the parasomnias were in the form of nightmares and talking in sleep.

All the seizure and treatment parameters were similar in the two gender groups. The only significant difference was the higher prevalence of EEG abnormalities observed in female patients. The mean daily VPA dose was higher in males ($p = 0.058$). Male patients were older, with an earlier age of onset, longer duration of the illness and longer period of VPA therapy. The mean ESS and PSQI scores were similar in the two gender groups, without any significant difference in the prevalence of sleep-related symptoms.

3.4. Comparison based on sleep questionnaire scores

None of the demographic, sleep- or seizure-related factors showed statistically significant difference in patients with abnormal scores on the sleep questionnaires compared to those with normal scores (Table 3). More patients with abnormal ESS score (i.e. ≥11) had a lower mean dose of VPA (≤600 mg/day). Eight patients had abnormal scores on both ESS and PSQI, but the numbers were few, therefore

Table 1
Comparison of PSQI and ESS in patients vs. controls.

Parameter	JME, n = 50	Controls, n = 50	P value	95% CI[a]
ESS score ≥ 11	17 (34%)	2 (4%)	<0.001[b]	–
ESS mean (SD)	8.89 (±4.44)	4.36 (±2.61)	<0.001[c]	3.05 to 5.94
PSQI ≥ 6	24 (48%)	4 (8%)	<0.001[b]	–
PSQI mean (SD)	5.16 (±2.98)	2.74 (±1.65)	<0.001[c]	1.62 to 3.21

ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index.
[a] Confidence Interval.
[b] Chi square test.
[c] Independent *T* test.