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Interrelationship of sleep and juvenile myoclonic epilepsy (JME): A sleep questionnaire-, EEG-, and polysomnography (PSG)-based prospective case–control study

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ABSTRACT

We studied the effects of 'epilepsy on sleep and its architecture' and 'sleep on the occurrence and distribution of interictal epileptiform discharges (ED)' using 'sleep questionnaires', 'EEG', and 'PSG' in patients with JME. Forty patients with JME [20 on valproate (Group I — 20.8 ± 4.0 years; M: F = 9:11) and 20 drug-naïve (Group II — 24.4 ± 6.7 years; M: F = 9:11)] and 20 controls (M: F = 9:11; age: 23.5 ± 4.7 years) underwent assessment with Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), overnight PSG, and scalp-EEG. Epileptiform discharges (EDs) were quantified in different sleep stages. The 'ED Index' was derived as number of EDs/min per stage. Statistical Package for the Social Sciences (SPSS) vs. 11 was used for statistical analysis. A 'p' <0.05 was considered as statistically significant. There was poor sleep quality in patients compared to controls ($p = 0.02$), while there was no significant difference in ESS scores between the groups. The PSG parameters were comparable in both groups. Routine EEG revealed EDs in 22/40 (Group I: 7 and Group II: 15) patients. Thirty-five patients had EDs in various sleep stages during PSG (Group I: 17 and Group II: 18): N1 — Group I: 9 and Group II: 14, N2 — Group I: 14 and Group II: 14, N3 — Group I: 14 and Group II: 10, and REM — Group I: 9 and Group II: 11. The ED Index was higher during N2/N3 in Group I and N1/REM in Group II. The epileptiform discharges were frequently associated with arousals in N1/REM and K-complexes in N2. There was no other significant difference between Groups I and II. In conclusion, there was poor sleep quality in patients with JME compared to controls, especially those on valproate who had altered sleep architecture. Epileptiform activity was observed more often in sleep than wakefulness. Sleep stages had variable effect on epileptiform discharges with light sleep having a facilitatory effect in the drug-naïve group and slow wave sleep having a facilitatory effect in the valproate group.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a common primary epilepsy syndrome characterized by adolescent-onset myoclonic jerks (MJ) with or without generalized tonic-clonic (GTCS) or absence seizures. Myoclonic jerks or GTCS classically occur on awakening and following a night of sleep deprivation, either partial or total. Routine electroencephalograph (EEG) shows generalized 4- to 6-Hz spike–polyspike–slow wave discharges. Seizures have specific precipitating factors such as physical and mental stress, photic stimulation, menstrual cycles, alcohol consumption, and very particularly, sleep deprivation [1]. Seizures in about 70–85% of the patients respond to valproate monotherapy [2].

Epilepsy has a complex relationship with sleep, the latter affecting the former and vice versa. Sleep has been known to play a protective role in JME [3], whereas certain seizure types are known to occur more commonly in sleep than the waking state [4,5]. In another study from the same center, patients with JME had significant sleep disturbances characterized by excessive daytime sleepiness and disturbed night sleep, despite adequate medications and good seizure control [6]. Although sleep has been known to have a protective effect in JME, interictal epileptiform discharges (ED) are known to occur in sleep [7–9]. What about the IEDs occurring during sleep in JME? Are they any different with AED therapy? In this study, we sought to understand this complex relationship using overnight polysomnography (PSG) studies in patients with JME on valproate monotherapy and others who were drug-naïve.

To do so, we studied the effects of 'epilepsy on sleep and its architecture' and 'sleep on the occurrence and distribution of interictal epileptiform discharges (ED) across various stages of sleep' and compared between drug-naïve patients with JME, JME on valproic acid (VPA) monotherapy, and healthy volunteers using structured sleep questionnaires, EEG, and overnight PSG studies.

2. Patients and methods

Forty patients with JME (M: F = 18:22, age at evaluation: 22.6 ± 5.7 years) meeting the ILAE diagnostic criteria [10,11] and 20 age- and gender-matched controls (M: F = 9:11; age: 23.5 ± 4.7 years) were

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recruited from Aug 2010 to July 2011 for the study from the out-patient neurological services of a university teaching hospital and major referral center for neuro-psychiatric illness in south India. The sleep studies were carried out in the sleep laboratory, Department of Neurology at our center. Ethical approval from the institutional ethics committee and written informed consent from all the subjects were obtained.

Patients with co-morbid illness (medical or psychiatric) or on medication affecting sleep (other than VPA) were excluded from the study to minimize the effect of confounding factors. Twenty age- and gender-matched healthy controls were also recruited for the study (Male: Female = 9:11; age: 23.5 ± 4.7 years) who were friends of the patients and hospital medical personnel on routine day duties. They were not related to any of the patients and did not have a family history of epilepsy. Forty patients with JME could be subdivided into two groups of twenty patients each: (a) Group I — on valproate monotherapy (age: 20.8 ± 4.0 years; Male: Female = 9:11) and (b) Group II — drug-naïve (age: 24.4 ± 6.7 years; Male: Female = 9:11). Patients in Group II were either never on VPA or who had stopped VPA or other AEDs on their own for more than 4 weeks prior to evaluation. Drug-naïve patients were evaluated on the same day of recruitment into the study including PSG on the same night, and the appropriate AED was initiated the very next day. Patients also could be divided into two subgroups: Gr A (n = 18): controlled seizures (those on valproate — 18/20) and Gr B (n = 22): had seizures during initial evaluation (Day 1), i.e., drug-naïve — 20 plus 2/20 of the valproate group.

All patients and controls underwent a structured evaluation, including a detailed clinical, family, and treatment history, neurological examination, 16-channel electroencephalogram (EEG), and other investigations when indicated. Imaging of the brain was normal in all patients and controls. They were administered validated sleep questionnaires such as the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). Following this evaluation, overnight PSG was recorded for only one night. During the PSG study, precautions were taken to keep the patient comfortable as per their routine as far as possible.

All subjects underwent PSG conducted at the sleep laboratory in the Department of Neurology according to the American Association of Sleep Medicine (AASM) 2007 guidelines. Valproic acid was continued unaltered during the study in Group I, but non-essential drugs (if any) were discontinued. The PSG recording was carried out using an eight-channel EEG, electrocardiograph, chin electromyography (EMG), right anterior tibialis EMG, electro-oculogram, nasal thermistor, snore monitor, chest and abdominal movements, pulse rate, and oximetry. Routine scalp-EEG was carried out before the overnight PSG using standard procedures. It was recorded on 16-channel "Galileo NT (EBN)" machine, employing the international 10-20 system of electrode placement using standard parameters and procedures, e.g., High Filter — 70 Hz; Low Filter — 0.1 Hz; Recording time: 30 min; Sensitivity: 7 uV/mm; Sweep speed: 10 s/page; and Sampling rate: 256 Hz. The paroxysmal abnormalities in the form of spike–polyspike and waves were noted during the awake segment of the routine EEG. The EEG and PSG records were reported according to the AASM 2007 guidelines [12] by 2 investigators (CTR, SS), and in case of disagreement, the conclusions were sorted out by discussion.

The epileptiform discharges (EDs), namely spike/polyspike–slow wave complexes and occasionally spikes, were identified and quantified throughout each PSG. The number of each ED event and duration was noted across all stages of sleep. The EDI (Epileptiform Discharge Index) per stage of sleep was calculated using the number of EDs in each sleep stage (in min) and ED rate by total EDs in min/sleep stage in min × 100 (modified from [13]). The presence of arousal in various stages of sleep and its relation with EDs and K-complexes were noted.

2.1. Statistics

Statistical Package for the Social Sciences (SPSS) (version 11) software was used to carry out the statistical analysis. Student's *t* test or modified *t* test was used to compare means of two groups. Analysis of variance was used for comparing means of three groups. Fisher's Exact Probability test was used to compare the counts (frequencies).

Table 1
Phenotypic features of 40 patients with juvenile myoclonic epilepsy (JME) and 20 healthy controls.

Parameters	Gr I (n = 20) [on VPA]	Gr II (n = 20) [drug-naïve]	Controls (n = 20)	p
Mean age (years)	20.8 ± 4.0	24.4 ± 6.7	23.5 ± 4.7	NS
M:F	9:11	9:11	9:11	1.0
MJs	20	20	–	1.0
GTCS	18	20	–	0.5
Absence	1	1	–	1.0
> 1 MJs/day	15	9	–	0.1
>1 GTCS/year	10	7	–	0.5
VPA dose (mg)	795 ± 196	–	–	–
Abnormal routine EEG	7	15	–	**0.02**
Abnormal EEG–PSG	17	18	–	1.0
ESS	6.9 ± 3.6	5.1 ± 3.6	4.6 ± 2.4	0.09
PSQI	4.3 ± 2.3	6.1 ± 4.9	2.8 ± 1.7	0.06
ESS ≥ 10	5	2	0	0.4
PSQI ≥ 5	9	10	3	0.9

GTCS: generalized tonic-clonic seizures; MJs: myoclonic jerks; PSG: polysomnograph. ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; VPA: sodium valproate.

3. Results

3.1. Phenotypic features

Forty patients with JME aged between 15 and 45 years (Male: Female = 18:22, age at evaluation: 22.6 ± 5.7 years) were studied. The mean body mass index (BMI) in both the subgroups and controls were Group I — 20.9 ± 2.7, Group II — 24.1 ± 6.6, and controls — 21.6 ± 2.8 (p = 0.068). The mean duration of seizures (in years) in Group I was 7.7 ± 4.9 and Group II — 7.5 ± 5.8. All the patients in Group I (age — 20.8 ± 4.0 years; Male: Female = 9:11) and Group II (age — 24.4 ± 6.7 years; Male: Female = 9:11) had myoclonic jerks (MJs — 100%). Along with MJs, eighteen (90%) patients in Group I and all twenty patients in Group II (100%) had GTCS, and only one (5%) patient in each group had absence seizures. Seizures were controlled in 18/20 patients in Group I with VPA. There was no GTCS at least for a week in either of the groups prior to the evaluation. Imaging was normal in all the 40 patients and 20 controls. (Table 1).

3.2. EEG observations

Routine 16-channel awake EEG revealed normal background in all the patients. The epileptiform discharges (EDs) were noted during the awake part of the routine EEG with significant abnormalities

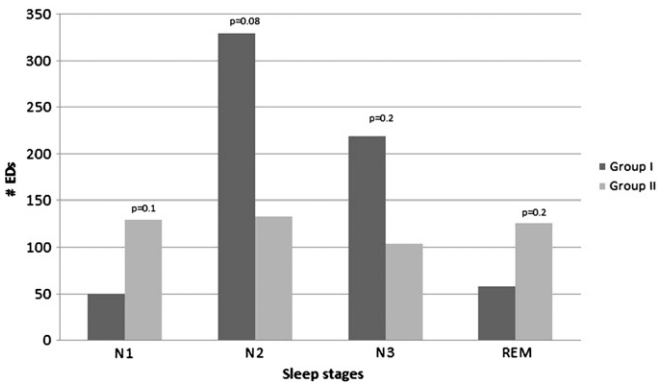

Fig. 1. Distribution of epileptiform discharges (EDs) in sleep stages in patients on VPA (Group I) vs. those who were drug-naïve (Group II).