Original Article

Differential improvement of the sleep quality among patients with juvenile myoclonic epilepsy with valproic acid: A longitudinal sleep questionnaire-based study

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Abstract

Objectives: The aim of this study was to assess the effect of sodium valproic acid (SVA) on the sleep quality of patients with juvenile myoclonic epilepsy (JME). **Materials and Methods:** Standardized sleep questionnaires viz. Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were administered to 30 drug-naïve patients with JME (male:female (M:F) = 14:16; age: 21 ± 3.7 years) and the changes following SVA monotherapy was analyzed using *t*- and chi-squared tests. **Results:** The mean age at onset of seizures and diagnosis was 15.43 ± 3.8 and 21 ± 5.1, years respectively. All had myoclonic jerks with mean duration of 5.23 ± 2.7 years, aggravated by sleep deprivation (23, 76.7%) and sleep-wake transition (29, 96.7%). Twenty-seven (90%) had generalized tonic-clonic seizures (GTCS), majority (70%) on awakening from sleep. Seizures were controlled in 25 patients (83.33%) with SVA monotherapy. Abnormal ESS was noted in five (16.66%) drug naïve patients compared to six (20%) patients while on SVA ($P = 0.782$). Mean ESS remained unchanged before and after SVA therapy (6.27 ± 4.4 vs 6.97 ± 4.7, $P = 0.262$). On the other hand, only four (13.3%) patients had abnormal PSQI scores at follow-up after initiation of SVA, as compared to 14 (46.7%) subjects in the drug naïve state ($P = 0.037$). Further, we also found significant reduction in mean PSQI scores after initiating SVA monotherapy (6.7 ± 5.6 vs 2.7 ± 2.84, P £ 0.0001). **Conclusion:** This study showed that the mean PSQI as well as the number of patients with abnormal PSQI significantly reduced after initiating SVA therapy, suggesting a significant improvement in night-time sleep quality with SVA treatment. However, SVA therapy did not alter ESS.

Key Words

Juvenile myoclonic epilepsy, sleep, SVA

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Ann Indian Acad Neurol 2015;18:403-407

Introduction

Excessive daytime sleepiness (EDS) and daytime fatigue are common complaints of patients with epilepsy worldwide. This is independent of seizure control, type of antiepileptic drugs (AEDs) used, adherence to proper sleep hygiene, and underlying medical or psychiatric comorbidities. A reduced socio-occupational performance and quality of life is not uncommon in patients with epilepsy, which is often attributed to disturbed sleep, rather than to seizures themselves. It is also a common cause of noncompliance to AED therapy, which leads to poor seizure control. Altered sleep architecture in the form of frequent nocturnal awakenings, increased number of stage shifts, increase in stages N1 and N2, reduction in stages R and N3, increase in sleep latency, and rapid eye movement (REM) latency[1,2] are commonly observed in polysomnogram (PSG) done on patients with epilepsy. Studies have demonstrated a higher prevalence of EDS and poor quality of night time sleep in patients with juvenile myoclonic epilepsy (JME).[3]

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.165472

Most AEDs adversely affect sleep even at therapeutic doses. These effects are variable and often difficult to distinguish from the effects of seizures. One of the most widely used drugs in patients with JME is sodium valproic acid (SVA). SVA exerts its antiepileptic effect by inhibiting enzymes that degrade gamma-aminobutyric acid (GABA) namely,

GABA-T and succinic semialdehyde dehydrogenase, blocking voltage-gated sodium channels, and inhibiting low threshold calcium currents.[4,5] The available literature suggests a variable effect of SVA on sleep.[6,7] Longitudinal studies that have assessed the effect of SVA on sleep in patients with JME are lacking.

The aim of this study was to assess:
a. Sleep disturbances in drug naïve patients with JME using validated sleep questionnaires, and
b. Change in sleep profile after the introduction of SVA monotherapy

Materials and Methods

This longitudinal, prospective, hospital-based study was conducted at a tertiary care university teaching hospital in south India from March 2010 to February 2013.

Participants

Patients above the age of 12 years were prospectively recruited from the neurology outpatient services if they fulfilled the criteria laid down by the ILAE Commission on Classification and Terminology (1989) for the diagnosis of JME.[8] Exclusion criteria included:
a. Use of AEDs prior to study entry,
b. Use of any other medications known to affect sleep at study-entry or during follow-up,
c. Noncompliance to SVA monotherapy after study entry,
d. Drug or substance abuse,
e. Abnormal brain imaging,
f. Primary sleep disorder, and
g. Coexisting medical, psychiatric, or surgical disorder known to affect sleep. A written informed consent was obtained from the study subjects and/or parents. The study was approved by the Institutional Ethics Committee.

Clinical evaluation

All patients underwent a structured evaluation, including a detailed clinical, family and treatment history, and a thorough neurological examination. All the patients underwent 16-channel digital electroencephalogram (EEG) recording (including a period of sleep record) using the international 10-20 system of electrode placement, brain imaging (magnetic resonance imaging (MRI)), and other investigations as indicated.

Sleep questionnaires administration

Validated sleep questionnaires namely Epworth Sleepiness Scale (ESS) to assess daytime somnolence[9] and Pittsburgh Sleep Quality Index (PSQI) to assess night-time sleep,[10] were administered to all subjects at the time of study entry. After establishing the diagnosis and initial evaluation with above sleep questionnaires, all patients were started on SVA at weight-adjusted doses.

Follow-up evaluation after initiation of SVA

All patients were followed-up for seizure control, drug compliance, and side effects with SVA. Serum SVA levels were not measured. During follow-up, all patients were reassessed using the ESS and PSQI after 6 months of SVA monotherapy. Nine patients were followed-up via telephonic interview, as they could not come for follow-up in person. Both ESS and PSQI have been previously administered for telephonic interviews.[11,12] An independent script was developed for telephone administration of these questionnaires describing the component items and response options in detail. Following this, each question of the questionnaires was read out to the patients over telephone in their preferred language. Patients were given adequate time to ponder and respond to each question, and if required, evaluation was completed in two sessions. They were also offered the choice of completing the questionnaire at their own convenient time, after noting down the questions over telephone. A gentle reminder to return the responses of the questionnaires was made via telephone in three patients and patients were thanked for their cooperation.

Data analysis

The data was incorporated into a predesigned pro forma and analyzed using Statistical Package for the Social Sciences (SPSS version 15). Chi-square test was employed to study qualitative parameters and independent t-test for quantitative parameters. Comparison between patients and controls, drug-naïve patients, and patients on SVA monotherapy, as well as patients with and without sleep disturbances was performed. Multivariate regression analysis was carried out to determine the effect of age of patient, duration of epilepsy, duration of SVA exposure, and dose of SVA on the change in ESS and PSQI scores at follow-up.

Results

Thirty-five drug naïve patients who fulfilled the inclusion criteria were initially recruited from the neurology outpatient services. Five patients were excluded from the study at follow-up because of lack of adequate compliance to therapy and/or inadequate seizure control that necessitated the introduction of additional AEDs.

Clinical profile

The mean age of patients with drug naïve JME (male:female (M:F) = 14:16) was 21 ± 3.7 (mean: 22; range: 18-35) years. The mean age at onset of seizures was 15.43 ± 3.8 years, while the mean age at diagnosis was 21.0 ± 5.1 years. Twenty (66.7%) patients had seizure onset during puberty. The first seizure type was generalized tonic-clonic seizures (GTCS) in 22 (73.3%) and myoclonus in eight (26.6%). The mean body mass index (BMI) at initial evaluation was 22.74 ± 5.51 kg/m^2; BMI > 25 was seen in five (16.6%).

All patients had myoclonic jerks; other seizure types included: GTCS (n = 27, 90%) and absence seizures (n = 1, 3.3%). The mean duration and frequency of myoclonus was 5.23 ± 2.7 years and 6.90 ± 2.53 jerks per day, respectively. Twenty-three (76.7%) patients reported worsening of myoclonus with sleep deprivation, while 29 (96.7%) patients reported myoclonic jerks on awakening. Worsening of myoclonic jerks with physical or mental stress was noted in five (16.7%) patients, and precipitation with photic stimulation in three (10%). Heralding myoclonic jerks

preceding GTCS was reported by six (22.2%) patients; whereas, GTCS on waking from sleep was seen in 21 (77.8%) patients. None had status epilepticus during the disease course. Three patients (10%) had febrile seizures in childhood. Family history of seizures was present in two (6.7%) patients. All patients had a normal birth and development history, along with normal general systemic and neurological examination. SVA was initiated in all patients as monotherapy. The demographic and clinical data of JME patients is summarized in Table 1.

Follow-up after initiation of SVA

Subjects were followed-up after a mean duration of 9.21 ± 2.08 months. The mean BMI at follow-up was 24.34 ± 6.12 kg/m^2; seven (23.33%) were overweight (BMI > 25 kg/m^2). The mean dose of SVA was 793.33 ± 244.9 mg/d. The daily dosage of SVA was: 1,000-1,500 mg in six; 800-999 mg in 14; 600-799 mg in seven, and 400-599 mg in three. Seizure control was achieved in 25/30 (83.3%) patients. The reported side effects after starting SVA in the order of frequency were weight gain — seven (23.3%), sedation — six (20%), alopecia — four (13.3%), menstrual abnormality — four (13.3%), tremors — two (6.7%), and gastric intolerance — one (3.3%). None of the patients reported skin hypersensitivity or hepatotoxicity during the period of follow-up.

EEG and MRI observations

MRI brain was normal in all patients. All patients underwent a routine scalp EEG recording at the time of first evaluation. The background was normal in all; the background consisted predominantly of low amplitude fast activity in four (13.3%). EEG abnormalities were observed in 27 patients (90%) and consisted of generalized spike and wave pattern in 15/27 (55.55%) patients, out of which six (40%) were precipitated by hyperventilation and photic stimulation. Polyspike-and-wave pattern was seen in 10 (37.03%); and generalized spikes or sharp waves in two (7.4%). At follow-up, only seven patients underwent a repeat EEG recording and abnormalities in the form of occasional generalized spike and wave discharges was seen in only one patient (14.3%).

Sleep questionnaire assessment

An abnormal ESS (≥11) was observed in five (16.66%) drug naïve patients, compared to six (20%) patients following the initiation of SVA monotherapy, and this was not statistically significant (P = 0.782). The mean ESS were also comparable before (6.27 ± 4.41) and after (6.97 ± 4.7) SVA monotherapy (P = 0.262). On the other hand, there was a statistically significant reduction in the number of patients with abnormal PSQI scores (^{3} 6) before and after SVA treatment (N = 14, 46.66%, vs N = 4, 13.33%; P = 0.037). The mean PSQI also significantly improved in patients after initiating SVA monotherapy (2.7 ± 2.8 vs 6.7 ± 5.6, $P \leq 0.0001$). The PSQI and ESS in patients with JME, before and after initiating SVA monotherapy is shown in Table 2.

Mean scores of ESS and PSQI in patients with good seizure control (n = 25) were compared with those with poor seizure control (n = 5). ESS (P = 0.32) and PSQI scores (P = 0.51) in both the subgroups were comparable.

Table 1: Demographic and clinical data of JME patients

Parameters		Patients (n = 30) (%)
Age (in years; mean±SD)		21±3.7
Gender		14:16
Family h/o seizures		2 (6.66)
Age of onset		15.43±3.8
Age of diagnosis (in years)		21±5.1
Delay in diagnosis (in years)		5.56±5.8
Myoclonus 30 (100%)		
First seizure type observed (%)		8 (26.66)
Mean duration (in years)		5.23±2.7
Onset at puberty (%)		20 (66.7)
Frequency (jerks per day)		6.9±2.5
Preceded onset of other seizures		8 (26.66)
Aggravated by sleep deprivation		23 (76.7)
Sleep-wake transition (awakening)		29 (96.7)
Physical or mental stress		5 (16.7)
Photic stimulation		3 (10)
GTCS 27 (90%)		
First seizure type observed (%) (n = 27)		22 (73.3)
Preceded by myoclonic jerks (n = 27)		6 (22.22)
Aggravated by sleep deprivation (n = 27)		13 (48.14)
Sleep-wake transition (awakening) (n = 27)		21 (77.77)
Absence seizures		1 (3.3)
Febrile seizures		3 (10)
Mean dose of SVA (mg/d)		793.33±244.9
Compliance to SVA		30 (100)
Seizure control of GTCS (n = 27)		25 (92.6)
Seizure control of myoclonus (n = 30)		25 (83.33)
Side effects to SVA		
Weight gain		7 (23.3)
Sedation		6 (20)
Alopecia		4 (13.3)
Menstrual abnormality		4 (13.3)
Tremors		2 (6.7)
Gastric intolerance		1 (3.3)
Parameters	Drug naive patients (n = 30)	9.21±2.08 months after starting SVA (n = 30)
BMI (mean ± SD)	22.74±5.51	24.34±6.12
BMI >25	5 (16.66%)	7 (23.33%)
EEG: Epileptiform discharges present	27 (90%)	1/27 (3.7%)

SVA = Sodium valproic acid, GTCS = Generalized tonic-clonic seizures, BMI = Body mass index, SD = Standard deviation, EEG = Electroencephalogram, h/o = History of, JME = Juvenile myoclonic epilepsy

Multivariate regression analysis revealed that the change in ESS and PSQI scores was not affected by age of patient (P = 0.945 and 0.685, respectively), duration of epilepsy (P = 0.303 and 0.806, respectively), duration of SVA exposure (P = 0.892 and 0.634, respectively), or dose of SVA (P = 0.976 and 0.745, respectively).

Table 2: Comparison of PSQI and ESS scores in drug naïve JME patients and 6 months after starting sodium valproate

Parameter	Drug naïve (*n* = 30) (%)	9.21 ± 2.08 months after starting SVA (*n* = 30) (%)	*P*-value (95% CI)
ESS score ≥11	5 (16.66)	6 (20)	0.782
ESS (mean±SD)	6.27±4.41	6.97±4.7	0.262
PSQI ≥6 (%)	14 (46.66)	4 (13.33)	0.037
PSQI (mean±SD)	6.7±5.6	2.7±2.84	<0.0001

ESS = Epworth sleepiness scale, PSQI = Pittsburgh sleep quality index, JME = Juvenile myoclonic epilepsy, CI = Confidence interval

Discussion

Several epilepsy syndromes have been linked to sleep disturbances. JME is one such syndrome with onset in late childhood and early adolescence. Although this syndrome has a characteristic clinical presentation of generalized seizures with myoclonic jerks and/or absence seizures, the diagnosis is often delayed or missed due to various reasons including lack of familiarity in physicians, as well as, inability to elicit a history of myoclonic jerks in this patient group. The patients included in this cohort were phenotypically consistent with the published literature. Later age at onset was due to the fact that we included only patients above the age of 12 years. A later age at onset was also noted by Kleveland and Engelsen (1998)[13] and Bonakis and Koutroumanidis (2009).[15] All patients had myoclonic jerks and 90% had GTCS, which were prominent in sleep-wake transition period and aggravated by sleep deprivation. The reason for low prevalence of absence seizures remains to be ascertained. But, similar low prevalence have been reported previously (Krishnan *et al*., 2012).[3] All patients in this cohort received SVA monotherapy, and majority of the treated patients showed good drug compliance and seizure control. The most commonly experienced side effect was weight gain (23.3%) which was supported by an objective increase in mean BMI from 22.74 ± 5.51 kg/m^2 before starting SVA, to 24.34 ± 6.12 kg/m^2, at follow-up after initiating SVA. This was followed by sedation (20%), which corresponds with the percentage of abnormal ESS scores before (16.66%) and after (20%) starting SVA therapy.

Patients with JME present with seizures which are precipitated by sleep deprivation, and they predominantly occur on awakening from sleep. There is also an increase in the number of epileptiform discharges during drowsiness and light sleep. This increase in nocturnal epileptiform activity may be responsible for a variety of sleep disturbances seen in these patients. A previous study showed that patients with JME have a significantly higher prevalence of EDS and also poor quality of night time sleep.[3] Another study looking at the microarchitecture of sleep in JME patients found that EDs are facilitated by increased vigilance (A phase). But they may also enhance cyclical alternating pattern (CAP) by generating A phases, while those that occur at the "B to A" transition are interpreted as successfully breaking through the state of reduced arousal (phase B) because of increased epileptic pressure. This promotes sleep instability and further fosters epileptic activity, and resultant seizures.[15]

The present study showed that in patients with JME, mean ESS score (P = 0.262) and the proportion of patients with abnormal ESS score (P = 0.782) did not differ before (16.66%) and after (20%) the initiation of SVA monotherapy. In contrast, there was a significant improvement in mean PSQI after initiating SVA monotherapy, compared to the drug naïve state (P < 0.0001). The number of patients with an abnormal PSQI also significantly declined with SVA monotherapy (P = 0.037). Further, the above findings were not affected by seizure control in treated patients. This suggests that patients with JME show significant improvement in their night time sleep quality after the initiation of SVA which may not be completely attributed to seizure control. Reduction in sleep latency, reduction in the number of night time arousals and awakenings, and/or an improvement in sleep continuity and duration consequent to seizure control, may contribute to a better sleep profile noted with SVA monotherapy. Excessive daytime somnolence remained unchanged before and after therapy, probably due to the inherent sedating effect of SVA.

SVA is the most widely used drug in treating JME and available literature suggests that it does not significantly alter sleep architecture.[6,7,16] A study of 46 children with epilepsy using the "Sleep Habits Survey questionnaire" showed that there was no significant difference in bed and wake time, duration of sleep, time to fall asleep, and daytime sleepiness measures before and after the termination of SVA therapy.[17] On the contrary, other studies have reported that SVA causes definite sleep disturbances. A study on adult patients with localization-related epilepsy on SVA monotherapy reported some sleep disruption in the form of significant increase in stage 1 (SVA: 16.8 ± 9.8% vs control: 7.7 ± 4.8%; P = 0.007).[18] Another large study of 152 patients with epilepsy found that there were higher numbers of subjects on AED polytherapy among the poor sleepers (PSQI < 5) compared to noninsomniacs (P = 0.03 and 0.04, respectively); poorer sleep quality and higher degree of insomnia was associated with higher number of AEDs.[19] Other studies have also pointed out the influence of SVA on disrupting sleep architecture.[20,21]

Sleep-related side-effects of AEDs may hamper the quality of sleep in patients with JME, hence contributing to poor drug compliance. AED withdrawal invariably results in seizure recurrence, and a long-term AED therapy is considered mandatory. An AED that effectively controls seizures and causes minimal sleep disturbance is the need of the hour. Systematically designed follow-up studies of sleep disturbances caused by SVA in JME are lacking. Several factors contribute to the pathophysiology of disturbed sleep in patients with JME, and the present study attempted to look at the change in sleep quality of JME patients, before and after the initiation of SVA monotherapy.

This is probably the first study of its kind to prospectively assess the effect of SVA on sleep in patients with JME using validated sleep questionnaires. Further studies using a larger sample size, along with polysomnographic assessment in JME patients before and after treatment may better define the effects of SVA on sleep.

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How to cite this article: Nayak C, Sinha S, Ramachandraiah CT, Nagappa M, Thennarasu K, Taly AB, *et al*. Differential improvement of the sleep quality among patients with juvenile myoclonic epilepsy with valproic acid: A longitudinal sleep questionnaire-based study. Ann Indian Acad Neurol 2015;18:403-7.

Received: 16-03-15, **Revised:** 12-04-15, **Accepted:** 12-04-15

Source of Support: Nil, **Conflicts of Interest:** None declared.