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# Markedly disturbed sleep in medically refractory compared to controlled epilepsy – A clinical and polysomnography study

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ABSTRACT

*Purpose:* To evaluate sleep disturbances or sleep related events and their characteristics among patients with medically refractory epilepsy, compared to those with controlled epilepsy.
*Methods:* In a prospective case-controlled study, patients of medically refractory and controlled epilepsy were recruited and history pertaining to epilepsy and sleep related events and Epworth sleepiness scores were recorded and all patients underwent over night polysomnography.
*Results:* Among 40 patients, 20 with medically refractory (Group 1) and 20 with controlled epilepsy (Group 2) (median age 18, range 10–35 years), the self reported sleep parameters in Group 1 patients were found to be significantly different as compared to Group 2, in terms of the duration of night time sleep, day time sleep, day time nap frequency, total sleep hours per day, excessive daytime sleepiness (EDS)(45% vs. 15%) and average sleep hours over the week prior to polysomnography. On PSG, Group 1 patients showed significantly less total sleep time [340.4 min (147–673) vs. 450.3 min (330–570)] with delayed sleep latency and REM latency, poor sleep efficiency [80.45 (40.5–98.0) vs. 95.45 (88.4–99.7)] and frequent arousals and wake after sleep onset (WASO) compared to Group 2 patients. Four patients (20%) in Group 1 compared to none in Group 2 were found to have mild obstructive sleep apnea.
*Conclusions:* Our results indicate that medically refractory epilepsy patients believe that they spend more time sleeping, in contrast to the documented shorter sleep duration on polysomnography. This difference between perceived and actual sleep seems, by their data, to arise mainly from sleep fragmentation, disturbed architecture and the interesting finding of associated sleep apnea among the medically refractory epilepsy patients.


## 1. Introduction

Epilepsy and sleep disorders are both major health problems across the globe and simultaneous occurrence of sleep disorders and epilepsy is not uncommon.[1] Various studies have showed high prevalence of sleep disturbances [including obstructive sleep apnea syndrome (OSAS), excessive daytime sleepiness (EDS), hypersomnia, narcolepsy, periodic limb movement disorder (PLMD) and restless leg syndrome (RLS)] in epilepsy patients compared to general population, and sleep disturbance in patients with epilepsy is even independent of drug treatment and may be inherent to the disorder itself.[2–6] The etiology for sleep disturbances in epilepsy seems to be multi-factorial and includes abnormal architecture of sleep due to epilepsy, effects of antiepileptic drugs (AEDs), detrimental effects of seizures on sleep, in addition to insufficient sleep time, poor sleep hygiene and coexistence of primary sleep disorders or co-morbid illness.[7]

Considering these effects of seizures and epilepsy, as a disorder, in general, on sleep, it is possible that sleep related events are more prevalent in medically refractory epilepsy as compared to medically controlled epilepsy. Direct comparison of sleep related events among patients with medically refractory and controlled epilepsy is not reported in literature. We hypothesize that sleep related events and sleep disturbances would be observed more often in medically refractory epilepsy compared to controlled epilepsy. The aim of the study is to evaluate sleep disturbances or sleep related events and their characteristics in medically refractory epilepsy compared to controlled epilepsy.

## 2. Materials and methods

### 2.1. Subjects and controls

This is a prospective cohort study, conducted at the Department of Neurology, All India Institute of Medical Sciences (AIIMS), New

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Delhi, India. In this study, we recruited consecutive patients with medically refractory epilepsy (Group 1) and medically controlled epilepsy (Group 2) attending our Epilepsy Clinic. Patients included in Group 1 were those with seizures persisting at a frequency of >1 per month for at least 6 months prior to assessment, on optimum doses of >2 AEDs with good compliance; and those included in Group 2 had history of seizures controlled on one or two AEDs for the past 6 months. Exclusion criteria were co-morbid neurological illness which can affect sleep, like stroke, encephalitis/meningitis, metabolic encephalopathy and others; coexisting medical illnesses like hypothyroidism and chronic respiratory diseases or known primary sleep disorders like obstructive sleep apnea (OSA) or narcolepsy in absence of epilepsy disorder. This study was approved by the Institutional Ethics Committee of AIIMS.

### 2.2. Sample size and selection of controls

Since there is no single published study, which has compared clinical and polysomnographic parameters between medically refractory epilepsy and controlled epilepsy cohorts, we intended to recruit patients based on the 'purposeful sampling method' with 1:1 age and sex matched controls depending on the availability of polysomnography appointments for research purpose during the period of study.

### 2.3. Characteristics of subjects and controls

Following an informed consent, a detailed history, including age, sex, age of onset, duration of epilepsy; frequency and semiology of seizures; and drugs (AEDs, others) history was taken through a pre-structured questionnaire. Sleep history was collected through another pre-structured questionnaire to specifically question for features of sleep disordered breathing, RLS, PLMD, narcolepsy, insomnia and circadian rhythm sleep disorders. Details about usual sleep habits were also asked for. Epworth sleepiness scale (ESS) was scored for all patients, and they were all required to fill a 1-week sleep log immediately preceding the polysomnography (PSG) study. The clinical examination of all patients was performed in detail.

### 2.4. Sleep study, sleep parameters, and polysomnographic diagnosis

PSG studies were performed with the simultaneous use of a pressure transducer and thermistor for nasal flow, piezoelectric chest and abdominal belts, and end-tidal $CO_2$ monitoring, as well as pulse oximetry, a snore microphone, two leg channels, a chin electromyogram, extended electroencephalogram montage, an electrocardiogram, and simultaneous video monitoring.[8] Definition of all PSG parameters as well as specific diagnosis *e.g.*, OSA, PMLD, was based on American Academy of Sleep Medicine (AASM) guidelines.[9]

### 2.5. Outcome measures

The following sleep parameters were assessed on PSG: total sleep time (TST), sleep latency, REM latency, sleep efficiency, awakening, arousals, arousal index (AI), apnea-hypopnea index (AHI), total periodic leg movements, periodic limb movement index (PLMI), and desaturation index (DI).

### 2.6. Statistical analysis

The statistical analysis was carried out by using SPSS version 15.0 and EpiInfo version 6.4. The data was represented as mean ± SD (standard deviation) as well as median (with range). The comparison between two groups for continuous variables, was done by applying Student's *t* test or Mann–Whitney test, wherever applicable. The qualitative data were compared by applying chi-square or Fisher's exact test. Log transformation was also applied to skewed variables. *p*-Value less than 0.05 was considered as significant.

## 3. Results

### 3.1. Baseline characteristics

In this study, we recruited consecutive 40 patients, 20 each of medically refractory epilepsy (Group 1) and medically controlled epilepsy (Group 2) attending our Epilepsy Clinic. At baseline, both the groups had similar clinical and demographic features (Table 1) in terms of age and gender. The age of onset of seizures, duration and frequency of seizures, and number and duration of AEDs were significantly higher in Group 1. The commonest seizure type was focal dyscognitive seizure with secondary generalization (70%) in Group 1, compared to simple focal motor seizures (45%) in Group 2. Apart from 2 patients in Group 1, none of the other patients in either group had seizures during the week prior to and on the night of the PSG recording. In Group 1, the number of patients taking clobazam and levetiractam was significantly higher than Group 2 with *p* value of 0.01. The frequency of abnormal imaging was significantly higher in Group 1, which mainly constituted mesial temporal sclerosis, and frontal or parietal cortical dysplasia, and peri-natal insult with peri-ventricular white matter hyper-intensity.

### 3.2. Clinical sleep parameters

On evaluation of the clinical aspect of sleep, we found that among patients in Group 1, the duration of night time sleep, day time sleep, day time nap frequency, total sleep hours per day, ESS scores and average sleep hours in last week before PSG were significantly higher as compared to Group 2 (Table 2). Although ESS scores were significantly higher in Group 1, the number of patients with ESS >10 (representing clinically significant EDS), was found to be similar in both the groups.

### 3.3. Polysomnographic parameters

An interesting PSG finding in this study is that the average of total sleep time is in fact shorter among patients in Group 1, in contrast to self-reported average sleep time per 24 h (Table 3). The sleep efficiency, arousals and AI were significantly more abnormal and there were significantly more frequent awakenings in this group of patients. Respiratory events were observed more frequently in Group 1, although not reaching statistical significance. Higher arousal indices in Group 1 were independent of seizure occurrences (not observed in any patient during PSG recording), and mostly spontaneous except in 2 patients with OSA, who had respiratory disturbance associated arousals. A significantly higher number of patients (4/20) in Group 1 were found to have an AHI >5, which denotes mild OSA; as compared to none in Group 2 ($p = 0.01$). Significantly more frequent desaturations were also observed in Group 1. Patients in Group 2 had significantly higher numbers of limb movements; however, PLMI was comparable in both the groups.

## 4. Discussion

In the present study we sought to characterize abnormalities in sleep architecture and quality, as well as distribution of primary sleep disorders, if any, in a cohort of patients with medically refractory vs. controlled epilepsy. Self reported total sleep time per 24 h was significantly longer in patients with refractory epilepsy,

**Table 1**
Demographic and clinical details of patients with epilepsy undergoing PSG evaluation.

| Variables | Intractable epilepsy group (Group 1) ($n=20$) | Controlled epilepsy group (Group 2) ($n=20$) | $p$-Value |
|---|---|---|---|
| Age (median) | 18 (10–35) | 18.5 (11–35) | 0.43 |
| Sex – male:female | 13:7 | 15:5 | 0.49 |
| Age of onset, duration and frequency of seizures (median and range) | | | |
| Age of onset of seizures (years) | 4.75 (0–32) | 15.0 (1–30) | 0.01 |
| Duration of Seizures (years) | 12.5 (0.1–34) | 3 (0.5–34) | 0.01 |
| Frequency (per month) | 52.5 (4–8500) | 0.75 (0.3–2) | 0.01 |
| Type of seizures (number and percentage) | | | |
| Simple focal motor | 0 (0%) | 9 (45%) | <0.01 |
| Focal dyscognitive | 6 (30%) | 1 (5%) | 0.09 |
| Focal dyscognitive with secondary generalization | 14 (70%) | 4 (20%) | 0.001 |
| Generalized | 0 (0%) | 6 (30%) | 0.02 |
| Time of seizures (number and percentage) | | | |
| Day | 8 (40%) | 8 (40%) | |
| Night | 0 (0%) | 2 (10%) | 0.34 |
| Day/night | 12 (60%) | 10 (50%) | |
| AEDs (number, percentage or median and range) | | | |
| Number of AEDs | 3 (2–6) | 1 (1–2) | 0.01 |
| Duration of AEDs (years) | 12 (0.1–33) | 2 (0.5–5) | 0.01 |
| Duration of last change of AEDs (years) | 0.4 (0–3.0) | 2. 0 (0.5–4) | 0.01 |
| DPH | 3 (15%) | 3 (15%) | 1.0 |
| VLP | 10 (50%) | 9 (45%) | 0.75 |
| CBZ | 6 (30%) | 4 (20%) | 0.46 |
| OxCBZ | 8 (42.2%) | 4 (20%) | 0.14 |
| PBT | 2 (10%) | 1 (5%) | 1.0 |
| LEV | 15 (75%) | 1 (5%) | 0.01 |
| LMT | 1 (5%) | 1 (5%) | 1.0 |
| CLB | 12 (60%) | 5 (25%) | 0.02 |
| ZNS | 3 (15%) | 0 (0%) | 0.23 |
| TPM | 3 (15.8%) | 0 (0%) | 0.11 |
| Imaging (number and percentage) | | | |
| Abnormal imaging | 20 (100%) | 8 (40%) | 0.01 |

Abbreviations: AEDs – antiepileptic drugs; DPH – diphenhydratoin; VLP – sodium valproate; CBZ – carbamazepine; OxCBZ – oxcarbamazepine; PBT – phenobarbitone; LEV – levetiracetam; LMT – lamotrigine; CLB – clobazam, ZNS – zonisamide; TPM – topiramate.

**Table 2**
Self reported clinical sleep parameters among the patients with epilepsy.

| Variables Percentage, median (range) | Intractable epilepsy group (Group 1) ($n=20$) | Controlled epilepsy group (Group 2) ($n=20$) | $p$-Value |
|---|---|---|---|
| Sleep duration in night | 9.0 (7.0–11.0) | 8.0 (6.0–10.0) | 0.01 |
| Sleep duration in daytime | 2.0 (0–5) | 0.0 (0–3) | 0.03 |
| Total sleep time per 24 h | 10.5 (8.0–15.0) | 9.0 (7.0–11.0) | 0.04 |
| Day time nap | 15 (75%) | 8 (40%) | 0.03 |
| EDS | 9 (45%) | 3 (15%) | 0.04 |
| ESS >10 | 6 (30%) | 2 (10%) | 0.24 |
| Previous week average sleep time (h) | 10.0 (8.0–13.0) | 8.75 (7.0–10.0) | <0.01 |

Abbreviations: EDS – excessive daytime sleepiness; ESS – Epworth sleepiness scale.

**Table 3**
Polysomnographic parameters observed in patients with epilepsy.

| Variables [% or median (range)] | Intractable epilepsy group (Group 1) ($n=20$) | Controlled epilepsy group (Group 2) ($n=20$) | $p$-Value |
|---|---|---|---|
| Sleep related events | | | |
| Total sleep time (min) | 340.4 (147–673) | 450.3 (330–570) | 0.01 |
| Sleep latency (min) | 14 (4.0–112.5) | 6 (1.0–55.3) | 0.01 |
| REM latency (min) | 126 (31–368) | 114 (60–360) | 0.14 |
| Sleep efficiency (%) | 80.5 (40.5–98.0) | 95. 5 (88.4–99.7) | 0.01 |
| WASO (%) | 19.5 (1–56) | 4.0 (1–14) | 0.01 |
| Arousals | 53.5 (0–167) | 37 (11–108) | 0.05 |
| Arousal index | 10.0 (0–31.4) | 5.2 (0–15.8) | 0.01 |
| AHI | 1.22 (0–11.93) | 0.88 (0–2.36) | 0.10 |
| AHI ≥ 5 (number, %) | 4 (20%) | 0 (0) | 0.01 |
| DI | 0.7 (0–7.6) | 0.25 (0–2.0) | 0.05 |
| LMs | 2.0 (0–13) | 6.0 (0–23) | 0.04 |
| PMLI | 0.3 (0–2.4) | 0.8 (0–2.8) | 0.12 |

Abbreviations: WASO – wakefulness after sleep onset; AHI – apnea hypopnea index; DI – desaturation index; LMs – limb movements; PLMI – periodic limb movement index.

while the same on PSG was significantly shorter. The architecture of sleep was markedly disturbed, the efficiency of sleep was poorer, and there were more frequent arousals and awakenings among the patients with medically refractory epilepsy. The prevalence of mild OSA was significantly higher in the medically refractory epilepsy group.

Published literature on detailed comparison of patients with refractory epilepsy and those controlled on AEDs, is sparse. Kaleyias et al.[10] in 2008, in 40 pediatric age group patients, reported that intractable epilepsy patients have longer sleep latency [43.5 (17–86.5) vs. 19.5 (11–71)], poor sleep efficiency [74 (70–82) vs. 83 (74–92)] along with higher arousal index [35 (22–40) vs. 20 (13–23)] as compared to medically controlled epilepsy. Our findings regarding total sleep time, sleep efficiency, REM latency, AHI, DI and AI are similar to those in the quoted study. The only major difference observed by us is the much shorter sleep latencies among our patients in both groups, while the inter-group differences noted were similar.

The interesting finding in our study was that significantly less number of Group 1 patients had LMs as compared to Group 2 patients. This finding is unlikely to be clinically significant as the index in both groups is quite low. The difference could, however, be attributed to AEDs, specifically carbamazepine and valproic acid, which might decrease PLMs.[11]

OSA was more frequently observed in Group 1 compared to Group 2 (20% vs. none) (mean (range) AHI 1.22 (0–11.9)/h in Group 1 vs. 0.88 (0–2.36)/h in Group 2), in our study. This finding of increased sleep apnea in the refractory group is confirmatory to previous work. In a study by Malow et al., the prevalence of OSA was 30% in intractable epilepsy group and 10% of unselected adult epilepsy group.[3] The reason for low prevalence in our study may be the younger age group of our subjects. However, more reasons need to be explored in future.

Our study demonstrates that medical refractoriness in patients with epilepsy has a deleterious effect on sleep quality in general. Although, this specific aspect of epilepsy and sleep relationship has not been discussed except in the study by Kaleyias et al.,[10] sleep disturbances may have a major impact on quality of life in patients with refractory epilepsy. Hence, treatment strategies specifically targeting refractory patients, e.g. epilepsy surgery, ketogenic diet, or vagal nerve stimulation may bear the potential to improve sleep quality and contribute to overall improvement in quality of life.

Interestingly, we did not record any seizures during any of the PSG recordings or a day before PSG, even in patients with high frequency seizures. However, this is a valuable coincidence, since, non-occurrence of seizures in both groups rules out the possibility of disturbed sleep being attributed to clinical phenomena disrupting sleep on the night of the PSG recording. One of the limitations of this study was that electroencephalogram (EEG) recorded was not a full 16 channel EEG; hence, commenting on epileptic phenomena on EEG also might be difficult.

Other limitations of our study include the relatively small sample size and the large number of variables studied. More studies focusing on individual clinical and polysomnographic aspects of sleep among larger number of patients in specific subsets of medically refractory epilepsy patients are needed to be conducted, in future, to see if these results can be generalized to all patients with medically refractory epilepsy.

Another limitation in our cohort is that, patients in Group 1 were taking statistically significantly more number of AEDs (especially, levetiracetam and clobazam) for longer duration. However, levetiracetam does not have major effects on sleep structure,[12] while clobazam is expected to reduce sleep stages 3, 4 and REM and to improve sleep consolidation,[13] which was not documented in our study.

## 5. Conclusion

Our results indicate that medically refractory epilepsy patients believe they spend more time in sleeping, in contrast to documented lesser sleep duration on PSG. This difference between perceived and actual sleep seems, by their data, to arise mainly from sleep fragmentation, disturbed architecture and interesting finding of associated sleep apnea in medically refractory epilepsy patients.

## Disclosures

None of the authors has any conflict of interest to disclose.

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