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Effect of sleep quality on memory, executive function, and language performance in patients with refractory focal epilepsy and controlled epilepsy versus healthy controls – A prospective study☆,☆☆,★,★★

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ABSTRACT

We aimed to evaluate the effect of sleep quality on memory, executive function, and language performance in patients with refractory focal epilepsy and controlled epilepsy and compare these with healthy individuals. We prospectively enrolled 37 adolescent and adult patients with refractory focal epilepsy (Group 1) and controlled epilepsy (Group 2) in each group. History pertaining to epilepsy and sleep were recorded, and all patients underwent overnight polysomnography. Language, memory, and executive function assessments were done using Western Aphasia Battery, Post Graduate Institute (PGI) memory scale, and battery of four executive function tests (Trail Making Test A & B, Digit symbol test, Stroop Task, and Verbal Fluency Test), respectively. Forty age- and sex-matched controls were also included in the study. Significant differences were noted in both objective and subjective sleep parameters among all the groups. On polysomnography, parameters like total sleep time, sleep efficiency, sleep latency, and rapid eye movement (REM) latency were found to be significantly worse in Group 1 as compared with Group 2. Cognitive and executive parameters were significantly impaired in Group 1. Shorter total sleep time, poorer sleep efficiency, and prolonged sleep latencies were observed to be associated with poor memory and executive function in patients with refractory epilepsy. Our study strongly suggests that sleep disturbances, mainly shorter total sleep time, poor sleep efficiency, and prolonged sleep latencies, are associated with impaired memory and executive function in patients with refractory focal epilepsy and to a lesser extent, among those with medically controlled epilepsy.

1. Introduction

Epilepsy and sleep disorders are both major health concerns across the globe. Sleep disturbance is common in people with epilepsy, and the nature of sleep disturbances in epilepsy is diverse [1]. Various studies have shown a high prevalence of sleep disturbances [obstructive sleep apnea syndrome (OSAS), excessive daytime sleepiness (EDS), hypersomnia, narcolepsy, periodic limb movement disorder (PLMD), and restless legs syndrome (RLS)] in patients with epilepsy compared with the general population [2–4]. In a previous publication, we have reported significant impairment of subjective and objective sleep parameters in both refractory as well as controlled epilepsy, former much more than latter [5,6].

Sleep disturbances have been shown to worsen epilepsy by increasing seizure frequency, sometimes resulting in intractable pharmacoresistant epilepsy and causing a vicious cycle between epileptic phenomena and sleep disturbances [7]. More importantly, sleep disruption could also

Abbreviations: AASM, American Academy of Sleep Medicine; AED, antiepileptic drug; AQ, aphasia quotient; AHI, apnea–hypopnea index; AI, arousal index; CQ, cortical quotient; DI, desaturation index; ESES, epilepsy with status epilepticus in sleep; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; IED, interictal epileptiform discharge; IQ, intelligence quotient; MISIC, Malin's Intelligence Scale for Indian Children; OSAS, obstructive sleep apnea syndrome; PLMD, periodic limb movement disorder; PLMI, periodic limb movement index; PSQI, Pittsburg Sleep Quality Index; PSG, polysomnography; REM, rapid eye movement; RLS, restless legs syndrome; SD, standard deviation; STN, subthalamic nucleus; TSS, total stage shift; TST, total sleep time; VAIS, Verbal Adult Intelligence Scale; VIQ, Verbal Intelligence Quotient; WASO, wake after sleep onset; WAB, Western Aphasia Battery; WED, Willis Ekbom disease.

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contribute to disturbances in cognition, behavior, or both. This effect on memory in persons with epilepsy has been addressed in some reports [4,8].

Cognitive decline in epilepsy has been studied extensively in last few decades but many questions still remain to be answered. There is a high prevalence of memory impairment, executive dysfunction, low verbal intelligence quotient (IQ), expressive and receptive grammar, and receptive vocabulary problems among persons with epilepsy [9–14]. In our previous study, we found highly prevalent memory disturbance and executive dysfunction irrespective of the anatomical location of the seizure focus; which may subtly point towards the role of other potential causative factors for the cognitive impairment in such patients [15].

Most existing literature on this relationship between sleep and cognition in the specific population of patients with epilepsy comes from the pediatric age group, especially from children with epilepsy with status epilepticus in sleep (ESES) [16–18].

There is paucity of literature exploring the role of different clinical as well as polysomnographic sleep parameters on different cognitive domains in patients with epilepsy, in a comprehensive manner.

We hypothesized that sleep disturbances would be observed more often in medically refractory focal epilepsy compared with controlled and that sleep quality is one of the contributing factors for poor cognitive performance among the patients with drug-resistant and controlled epilepsy. This study aimed at assessing the effect of sleep quality on the three major cognitive abilities (memory, executive function, and language) in refractory focal epilepsy and controlled epilepsy, in comparison with healthy individuals.

2. Methods

This prospective cohort study was carried out at the Department of Neurology, AIIMS, New Delhi during the study period between January 2013 and June 2014.

2.1. Study population

Consecutive patients with medically refractory focal epilepsy (Group 1) and medically controlled epilepsy (Group 2) who attended our Epilepsy Clinic were recruited. Patients included in Group 1 were those who failed with two adequately chosen and tried antiepileptic drugs (AEDs), with at least one seizure per month for at least 18 months, and no seizure-free periods longer than three months [19]. Those included in Group 2 were patients with focal epilepsy, who were seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever was longer, on their current AED regimen. Healthy controls (Group 3) were chosen from the relatives of patients, who were residing with the patients to ensure matched sleep environment between the groups. We excluded patients who did not give consent or those with diagnosed comorbidities like autism spectrum disorder, cerebral palsy, mental retardation, psychiatric disorders, or with coexisting medical illnesses like hypothyroidism, chronic respiratory diseases, or known primary sleep disorders like obstructive sleep apnea (OSA), or narcolepsy. Patients were recruited based on the 'purposeful sampling method' with 1:1:1 age and sex-matched controls depending on the availability of polysomnography (PSG) appointments for research purpose during the period of study. The study was approved by the Institutional Ethics Committee of AIIMS.

2.2. Epilepsy evaluation

Following an informed consent, a detailed history including age, sex, birth and developmental history, history of any antecedent events, age at epilepsy onset, duration of epilepsy, frequency and semiology of seizures, and drug (AEDs, others) history was taken through a prestructured questionnaire, by a senior neurology trainee, and confirmed by a qualified neurologist or senior neurologist with advanced training in epileptology and sleep medicine.

2.3. Clinical sleep evaluation

Sleep history was collected through another prestructured questionnaire to specifically question for features of sleep disordered breathing, RLS/Willis Ekbom disease (RLS/WED), PLMD, narcolepsy, insomnia, or circadian rhythm sleep disorders. Details about sleep habits were also asked for. The clinical sleep evaluation was carried out by the neurology trainee and confirmed by a senior sleep disorders fellow. Self-reported quality of sleep was assessed through a prestructured questionnaire, also used in our previous studies [5]. Epworth sleepiness scale (ESS) [20] and Pittsburg Sleep Quality Index (PSQI) [21] were scored, and all subjects were required to fill a 1-week sleep log immediately preceding the PSG study.

2.4. Polysomnography

An overnight PSG study was performed by trained sleep technologists, according to the latest American Academy of Sleep Medicine (AASM) (2012) guidelines [22], for all patients (Groups 1 & 2). The monitored parameters included the following: left and right Electrooculogram (EOG), extended electroencephalogram (EEG), mental and submental Electromyogram (EMG), left and right anterior tibialis EMG, single Electrocardiogram (ECG) waveform, snoring, continuous airflow via thermistor, nasal pressure transducer, chest and abdominal effort, oxygen saturation, and body position, which was also confirmed through video monitoring. Definitions of all PSG parameters, as well as specific diagnosis, e.g., OSA, PLMD, were based on (AASM) guidelines.

The sleep parameters assessed on PSG were the following: total sleep time (TST), sleep latency, rapid eye movement (REM) latency, sleep efficiency, awakenings (wake after sleep onset [WASO]), arousal index (AI), apnea–hypopnea index (AHI), periodic limb movement index (PLMI), and desaturation index (DI).

All PSG studies were manually scored firstly by sleep technologists and checked by senior fellow in sleep medicine. In case of any doubts, scoring and interpretation were checked and confirmed by senior neurologist with advanced training in sleep medicine.

2.5. Evaluation of cognitive functions

Verbal Intelligence Quotient (VIQ) was assessed for all patients. The main purpose for the assessment of VIQ was to screen out those with mental retardation, and hence, it was not used in further analysis of cognitive functions. Malin's Intelligence Scale for Indian Children (MISIC) was used to assess the VIQ in those below 16 years of age whereas Verbal Adult Intelligence Scale (VAIS) was used for those above 16 years of age [23,24]. Malin's Intelligence Scale for Indian Children is an Indian adaptation of Wechsler's Intelligence Scale for Children. It consists of 6 verbal and 5 performance subtests and yields a VIQ, Performance Intelligence Quotient, and Full Scale Intelligence Quotient. Only four subtests namely Information, Comprehension, Arithmetic, and Digit Span were used to calculate VIQ. Verbal Adult Intelligence Scale is a test of verbal intelligence developed in India. The items are translated and adapted from verbal subtests of Wechsler's Adult Intelligence Scale – Revised. There are four subtests namely Information, Comprehension, Arithmetic, and Digit Span. For both MISIC and VAIS, the raw scores from subtests are converted to test quotients using age appropriate norms, and then an average of test quotients is obtained to arrive at VIQ. Patients obtaining a VIQ < 70 were excluded from the study.

Detailed assessment of memory and language was carried out by trained clinical psychologists using the PGI memory scale [25] and Western Aphasia Battery (WAB) [26], respectively. PGI memory scale is a test developed in India for the comprehensive assessment

of memory. It includes 10 subtests namely remote memory, recent memory, mental balance (working memory), attention and concentration, immediate recall, delayed recall, verbal retention for similar and dissimilar pairs, visual retention, and visual recognition. The last two subtests assess nonverbal memory whereas the rest subtests assess verbal memory. A total score is obtained by adding scores on all subtests (score range: 0—100). Western Aphasia Battery is a widely used instrument for the assessment of language functions. Hindi adaptation of WAB was used for the present study [27]. Western Aphasia Battery has four main subscales to assess spoken language namely spontaneous speech, comprehension, naming, and repetition. The raw scores on these four subscales are utilized to calculate aphasia quotient (AQ), a global index of spoken language functions [28]. In addition to these functions, WAB also has four other subscales which include reading subscale, writing subscale, apraxia subscale and construction, visuospatial and calculation subscale. A cortical quotient (CQ) can be computed on the basis of raw scores from all eight subscales. Executive function performance was assessed by using a battery of 4 tests including Stroop Task, Trail Making Test, Digit symbol test, and Verbal Fluency Test [29–31]. These tests were specifically chosen for the following reasons: Stroop test is a test of response inhibition, Trail B assesses mental flexibility and attentional switching, while Trail A is the test for visual scanning, impairment of which could affect the performance on Trail B test. Digit symbol test assesses the speed of processing. Based on our clinical experience, impairment in speed of processing can be the underlying source of various other cognitive impairments. The time taken for evaluating executive functions using these tests was just about 2–3 min. Hence, these were selected instead of the time consuming and cumbersome tests like Wisconsin card sorting test, Tower of London test, and Iowa Gambling Task. These tests had also been validated and found to be highly sensitive in our previous study evaluating cognitive disturbances in epilepsy [15]. The assessment was preferably conducted on the day following or preceding the PSG night, according to the convenience of individual patients.

2.6. Statistical analysis

The statistical analyses were carried out, using SPSS version 16.0, under the guidance and direct supervision of a senior Professor of Biostatistics. Central tendencies were represented using mean ± standard deviation (SD) or median (with range). The comparison between two groups for continuous variables was done by applying Student's *t*-test or Mann–Whitney test, as applicable. The qualitative data were compared by applying chi-square or Fisher's exact test. Analyses between three groups were done using one-way analysis of variance (ANOVA). Log transformation was also applied to variables with skewed distribution. A p-value less than 0.05 was considered significant. Pearson's correlation coefficient was used to test the correlation between cognitive parameters and sleep parameters among all patients with epilepsy. Pearson's correlation coefficient was considered significant at 0.01.

3. Results

3.1. Baseline characteristics

In this study, we recruited 74 consecutive patients from our epilepsy clinic, 37 each with medically refractory epilepsy (Group 1) and medically controlled epilepsy (Group 2). Forty age- and sex-matched controls were also recruited (Group 3).

During the evaluation for sleep disorders, we found very few patients to have coexistent sleep disorders (OSA in 1 patient each with drug refractory and medically controlled epilepsy, and RLS in two patients with refractory epilepsy). No other sleep disorders were noted in the both the groups.

A total of 100 patients of both drug refractory and medically controlled epilepsy were initially screened out, of which 15 were excluded because of coexistent medical disorders like hypothyroidism, associated psychiatric illness, and mental retardations. An additional 11 patients were similarly excluded for not completing the neuropsychological tests.

At baseline, all the groups had similar age and gender distribution (Table 1).

Table 1
Demographic details of patients with epilepsy and controls.

Variable	Refractory epilepsy (Group 1) N-37	Controlled epilepsy (Group 2) N-37	Healthy controls (Group 3) N-40	P value
Age (in years) (Mean, SD)	24.72 ± 9.71	24.02 ± 10.11	25.1 ± 9.9	0.89
Male:female	24:13	27:10	27:13	0.74
BMI (mean, SD)	21.83 ± 2.31	21.93 ± 2.28	22.6 ± 2.19	0.27
Educational status				
Primary education	6	4	1	
High school	15	11	12	***0.03***
Graduate	11	16	26	
Post graduate	5	6	1	
Verbal IQ (mean, SD)	84.86 ± 6.72	91.72 ± 6.18	102.22 ± 8.68	***0.000***

Abbreviations: SD – standard deviation, BMI – body mass index, verbal IQ – verbal intelligence quotient.
Bold-italic data is statistically significant at $p < 0.05$.

Table 2
Details of epilepsy parameters among patients with medically refractory versus controlled epilepsy.

Variable		Refractory epilepsy (Group 1) N-37 Mean ± SD	Controlled epilepsy (Group 2) N-37 Mean ± SD	P value
Age at onset of seizure (years)		12.52 ± 9.4	14.82 ± 9.75	0.18
Duration of epilepsy (in years)		12.62 ± 6.35	9.32 ± 7.38	***0.01***
Seizure frequency per month		28.26 ± 51.91	0.07 ± 0.02	***0.001***
Type of epilepsy, n (%)				
Temporal		19 (51.35%)	26 (70.27%)	0.09
Extratemporal		18 (48.65%)	11 (29.73%)	
Type of seizure, n (%)				
Focal motor seizure		8 (21.62%)	9 (24.3%)	0.86
Dyscognitive seizure		6 (16.21%)	10 (27.02%)	0.44
Dyscognitive seizure with generalization		13 (35.13%)	15 (43.24%)	0.68
Nocturnal seizure		7 (18.9%)	1 (2.7%)	0.05
Bilateral convulsive (generalized tonic–clonic) seizures		3 (8.1%)	2 (5.4%)	0.61
Timing of seizures, n (%)				
Day		9 (24.3%)	23 (62.1%)	***0.002***
Night		7 (18.9%)	1 (2.7%)	
Day and night		21 (56.75%)	13 (35.13%)	
AEDs				
No. of AEDS	Mean ± SD	2.62 ± 0.89	1.59 ± 0.55	***0.00***
	Median (range)	3 (1–4)	2 (1–4)	
Duration of AEDS (in years)	Mean ± SD	10.7 ± 5.65	8.94 ± 5.43	***0.00***
	Median (range)	11 (2–22)	5 (1–18.5)	
Type of AEDS, n (%)				
DPH		6 (16.21%)	6 (16.21%)	1.00
CBZ		17 (45.9%)	10 (27.02%)	0.09
OXC		15 (40.5%)	11 (29.72%)	0.33
PHB		4 (10.8%)	1 (2.7%)	0.36
VLP		7 (18.9%)	5 (13.51%)	0.52
LEV		13 (35.1%)	12 (32.43%)	0.81
LMT		3 (8%)	0 (0%)	0.24
CLB		24 (64.86%)	10 (27.02%)	***0.001***
ZNS		7 (18.9%)	1 (2.7%)	***0.05***
TPM		4 (10.8%)	0 (0%)	0.11
LCM		9 (24.32%)	2 (5.4%)	0.04
Imaging, n (%)				
Abnormal		35 (94.6%)	14 (46%) n-30	***0.01***

Abbreviations: SD – standard deviation; AEDs – antiepileptic drugs; DPH – diphenhydratoin; CBZ – carbamazepine; OXC – oxcarbazepine; PBT – phenobarbitone; VLP – sodium valproate; LEV – levetiracetam; LMT – lamotrigine; CLB – clobazam, ZNS – zonisamide; TPM – topiramate; LCM - lacosamide.
Bold-italic data is statistically significant at $p < 0.05$.

Table 3
Clinical sleep parameters in the groups with epilepsy and controls.

Variable Median, range	Refractory epilepsy (Group 1) N-37	Controlled epilepsy (Group 2) N-37	Healthy controls (Group 3) N-40	P value
Sleep duration in night (in hours)	8.5 (6–11)	7.5 (5–10)	7.5 (6.5–10)	***0.000***
Sleep duration in daytime (in hours)	1 (0–2)	0.75 (0–2)	0.12 (0–2)	***0.001***
Total sleep time per 24 h	9.5 (6.25–13)	8.25 (6–10.5)	7.62 (6.75–10)	***0.000***
Previous week avg. sleep time in hours	9.25 (6.5–12.25)	8.25 (6–10.5)	7.62 (7–10)	***0.000***
PSQI	4 (3–15)	3 (1–13)	3 (1–5)	***0.002***
ESS	7 (3–15)	7 (2–14)	4 (2–7)	***0.000***
ESS > 10, n (%)	12 (32.4%)	7 (18.9%)	0	***0.000***
Sleep quality score	3 (0–6)	2 (0–6)	1 (0–3)	***0.000***
Daytime nap, n (%)	32 (86.4%)	22 (59.4%)	10 (25%)	***0.000***
Complaint of EDS, n (%)	14 (37.85%)	5 (13.5%)	0	***0.000***
Complaint of nonrefreshing sleep, n (%)	17 (45.94%)	9 (24.32%)	1 (2.5%)	***0.000***
Frequent awakenings, n (%)	10 (27%)	6 (16.21%)	1 (2.5%)	***0.001***
Sleepiness temporally related with AED dose, n (%)	21 (56.75%)	5 (13.51%)	0	***0.000***

Abbreviations: PSQI – Pittsburgh sleep quality index; ESS – Epworth sleepiness score; EDS – excessive daytime sleepiness; AEDs – antiepileptic drugs.
Bold-italic data is statistically significant at $p < 0.05$.

3.2. Epilepsy parameters

The age at onset of seizures was significantly lower while duration and frequency of seizures and number and duration of AEDs were significantly higher in Group 1 (Table 2). Temporal lobe epilepsy constituted about 51% in Group 1 and about 70% in Group 2. Patients in Group 1 also had more nighttime seizures (19%) in comparison with Group 2 (2.7%). The commonest seizure type was focal dyscognitive seizures with/without generalization (35.1%) in Group 1 and (43.24%) in Group 2. Apart from 6 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, either carbamazepine (CBZ) (45.9%) or oxcarbazepine (OXC) (40.5%) was the preferred first line therapy, and clobazam (64.86%) was the preferred add-on therapy. In Group 2, levetiracetam (LEV) (32.43%) and OXC (29.72%) were the most commonly used AEDs. The frequency of abnormal imaging was significantly higher in Group 1, and mainly constituted mesial temporal sclerosis, frontal or parietal cortical dysplasia, and perinatal insult with predominantly parieto-occipital periventricular white matter T2 and fluid attenuated inversion recovery (FLAIR) hyperintensities.

3.3. Clinical sleep parameters

On evaluation of the clinical (self-reported) sleep parameters, patients in Group 1 had significantly higher average duration of nighttime sleep, daytime sleep, daytime nap frequency, total sleep hours per day, PSQI scores, and average sleep hours in the last week before PSG as compared with Group 2 and Group 3 (Table 3). Pittsburg Sleep Quality Index scores and number of patients with ESS scores > 10 (representing clinically significant EDS) were significantly higher in Group 1. Self-reported sleep quality score and other sleep related parameters like number of daytime naps, complaint of excessive daytime somnolence, nonrefreshing sleep, frequent nighttime awakenings, and sleepiness with AEDs were also significantly higher in Group 1.

3.4. Polysomnographic parameters

On evaluation of polysomnographic parameters, the TST was significantly shorter and sleep efficiency significantly poorer in Group 1. Sleep latency and REM latency were significantly higher in Group 1 (Table 4). Arousal index, WASOs, AHI were more in Group 1, however, these did not reach statistical significance. Higher AIs in Group 1 were independent of seizure occurrences. The number of patients with abnormal AHI > 5 was similar in both the groups. Significantly more frequent desaturations were observed in Group 1. Percentage of REM sleep was less in Group 1, although it did not reach statistical significance. Nine patients in Group 1 and four patients in Group 2 had no REM sleep ($P = 0.01$). No seizures were recorded during the polysomnographic assessment of patients from either group.

3.5. Memory, language, and executive function and their correlation with various epilepsy parameters

Patients in Group 1 had dysfunction in all tested domains (memory, language, executive dysfunction), and the abnormalities in this group were significantly more profound in comparison with other groups (Table 5).

Table 4
Details of overnight polysomnographic parameters among patients with medically refractory versus controlled epilepsy.

Variable Mean ± SD Median, range	Refractory epilepsy (Group 1) N-37	Controlled epilepsy (Group 2) N-35	P value
Total sleep time (in min)	371.97 ± 94.22 395 (165–540)	426.48 ± 82.48 447 (104–530)	***0.01***
Sleep latency (in min)	19.79 ± 25.95 9.3 (1.1–143)	9.69 ± 8.75 6.3 (0–31.5)	***0.03***
REM latency (in min)	230.51 ± 92.3 (N = 28) 229 (74–432)	176.97 ± 93.27 (N = 31) 144 (63–438)	***0.03***
No REM, n (%)	9 (24.32%)	4 (11.42%)	***0.01***
Sleep efficiency (%)	76.25 ± 17.12 84.3 (33.8–98.0)	90.29 ± 9.66 91.7 (45.5–99.6)	***0.00***
N1%	22.91 ± 16.51 19 (0–62)	20.05 ± 14.94 17 (0–61)	0.44
N2%	52.86 ± 16.59 54 (14–86)	56.11 ± 15.25 54 (34–86)	0.39
N3%	14.37 ± 15.11 12 (0–552)	13.94 ± 12.34 11 (0–37)	0.89
REM %	8.37 ± 7.7 7 (0–27)	11.31 ± 8.09 11 (0–29)	0.11
Total stage shift	75.02 ± 48.14 64 (14–284)	77.28 ± 38.74 68 (9–189)	0.82
Stage shift per hour of sleep	12.69 ± 8.08 11 (2–43)	11.15 ± 5.92 9 (1–30)	0.36
Arousal index	13.26 ± 9.87 10.1 (2.9–45.6)	11.30 ± 6.19 8.6 (4.7–27.7)	0.32
WASO	18.21 ± 12.88 15 (2–61)	18.11 ± 10.75 16 (1–39)	0.97
WASO percentage	5.3 ± 4.31 4.17 (0.5–19.8)	4.25 ± 2.55 3.57 (0.2–10.4)	0.21
AHI	3.65 ± 6.46 1.16 (0–35.47)	2.62 ± 3.88 1.09 (0–16.49)	0.41
AHI > 5	7 (18.9%)	6 (17.1%)	0.54
Desaturation index	0.3 (0–9.5)	0.1 (0–6.4)	0.34

Abbreviations: SD – standard deviation; REM – rapid eye movement; WASO – wake after sleep onset; AHI – apnoea–hypopnea index.
Bold-italic data is statistically significant at $p < 0.05$.

Table 5
Observations on memory, language, and executive function testing on patients with medically refractory versus controlled epilepsy versus healthy controls.

Variable Median, range	Refractory epilepsy (Group 1) N-37	Controlled epilepsy (Group 2) N-37	Healthy controls (Group 3) N-40	P value
PGI memory scale	77 (17–89)	84 (34–92)	88 (75–96)	***0.000***
Western Aphasia Battery				
Spontaneous speech	18 (8–20)	20 (13–20)	20 (19–20)	***0.000***
Comprehension	184 (42–200)	192 (130–200)	195 (180–200)	***0.000***
Repetition	90 (22–100)	96 (70–100)	98 (90–100)	***0.000***
Naming	90 (37–98)	95 (68–100)	96 (90–99)	***0.000***
Aphasia quotient	90.6 (34.6–99.6)	97.6 (69.8–99.4)	98.6 (92.8–99.4)	***0.000***
Cortical quotient	91.4 (27.9–99.0)	97.3 (63.5–99.6)	98.8 (91.5–99.6)	***0.000***
Executive function				
Trail A (seconds)	32.5 (15–95) (N-32)	20 (15–90) (N-36)	20 (15–45)	***0.005***
Trail B (seconds)	131.5 (65–225) (N-28)	105 (60–205) (N-35)	95 (65–105)	***0.000***
Stroop test word	88 (56–110) (N-30)	92 (73–110) (N-35)	95.5 (80–110)	***0.000***
Stroop test Color	70.5 (31–97) (N-30)	74 (62–88) (N-35)	78 (62–90)	***0.002***
Stroop test Color word	39.5 (23–48) (N-30)	43 (32–50) (N-35)	44 (39–49)	***0.000***
Digit symbol test	37.5 (17–46) (N-32)	41 (29–46) (N-36)	44.5 (34–51)	***0.050***
Verbal Fluency Test	22 (8–28) (N-34)	27 (13–34)	30 (25–37)	***0.000***

Bold-italic data is statistically significant at $p < 0.05$.

3.6. Correlation of sleep quality with cognitive function among patients with epilepsy

A direct positive correlation was observed between polysomnographically recorded TST with total memory scores ($r = 0.634$; $P = 0.000$) and digit symbol ($r = 0.368$; $P = 0.002$), while a negative correlation was noted with Trail A ($r = -0.578$; $P = 0.000$) and Trail B ($r = -0.494$; $P = 0.000$) (Table 6). Similarly, sleep efficiency had a positive correlation with total memory scores ($r = 0.817$; $P = 0.000$) and digit symbol ($r = 0.513$; $P = 0.000$) while a negative correlation with Trail A ($r = -0.723$; $P = 0.000$) and Trail B ($r = -0.394$; $P = 0.001$). Sleep latency had a significant negative correlation with the memory performance ($r = -0.374$; $P = 0.001$) and Stroop test ($r = -0.393$; $P = 0.001$). These correlations were noted in both refractory epilepsy and medically controlled epilepsy. However, no correlation was noted between REM latency, AHI, TSS, WASO, and percentage of different sleep stages with the memory performance and executive function. No correlation was noted among the polysomnographically recorded sleep parameters and language parameters. Although not statistically significant, a negative correlation was found between both **self-reported** total time spent in sleep during the night, during the day, and over 24 h duration, with **memory performance**.

The frequency of interictal epileptiform discharges (IEDs) was highest in the N2 and N3 stages of sleep in both groups with epilepsy, with a significant difference in the number of IEDs and IED index (number of IEDs/h) during the N2 stage of sleep between the two groups (Tables 7 and 8). There was a significant positive correlation between the IED index and AI ($r = 0.372$; $P = 0.001$).

4. Discussion

In the present study, we sought to evaluate the effect of abnormalities in sleep architecture and quality on cognitive function, in a cohort of patients with medically refractory versus controlled epilepsy, in comparison with healthy controls. The main observations made were of significantly longer self-reported TST, with significantly shorter actual TST, prolonged sleep latency, and poorer sleep efficiency in patients with refractory focal epilepsy in comparison with controlled epilepsy and healthy controls. Our main observation is that higher polysomnographic TST and sleep efficiency has a positive correlation with memory and executive function performance. In a systematic review, [32] concluded that sleep deprivation and/or sleep disruption not only affects the neuronal mechanisms, important for the memory and learning process, but also influences the seizure and EEG discharges [26].

4.1. Sleep parameters among patients with epilepsy

Similar to the observations of this study, several studies have reported decrease in TST, sleep efficiency, longer sleep latency, percentage of N3 and REM, high AI, and WASO in patients with drug-refractory epilepsy [33–35]. Sudbrack-Oliveira et al., in a recent systematic review, analyzed 5 studies comprising 108 patients and 73 healthy controls and found a significant difference in WASO time among patients with refractory temporal lobe epilepsy and refractory frontal lobe epilepsy and healthy controls. The included studies also showed decreased TST and reduced N1, N2, REM sleep in patients with refractory epilepsy, although this was not found statistically significant [36]. We have previously reported decreased TST, sleep efficiency, prolonged latency, and

Table 6
Correlation of cognitive parameters with polysomnographic parameters.

	Total memory scores	Trail A	Trail B	Digit symbol	Stroop Color word	Total sleep time	Sleep efficiency	Sleep latency	REM latency
Total memory scores	1								
Trail A	−0.801**	1							
Trail B	−0.531**	0.549**	1						
Digit symbol	0.529**	−0.565**	−0.429**	1					
Stroop Color word	0.645**	−0.485**	−0.512**	0.502**	1				
Total sleep time	0.634**	−0.578**	−0.494**	0.368**	0.198	1			
Sleep efficiency	0.817**	−0.723**	−0.394**	0.513**	0.318**	0.781**	1		
Sleep latency	−0.374**	0.098	0.086	−0.079	−0.393**	−0.105	−0.253*	1	
REM latency	−0.118	0.000	−0.014	−0.238	−0.143	0.017	−0.181	−0.088	1

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 7
Interictal epileptiform discharges (IEDs) in different stages of sleep.

Mean ± SD Median (range)	Refractory epilepsy N = 33	Controlled epilepsy N = 31	P value
IED W	1.18 ± 4.88 0 (0–28)	0.06 ± 0.35 0 (0–2)	***0.029***
IED N1	7.33 ± 20.9 4 (0–122)	1.1 ± 1.55 0 (0–6)	0.103
IED N2	27 ± 32.42 21 (0–165)	12.1 ± 16.36 6 (0–60)	***0.025***
IED N3	7.97 ± 19.14 3 (0–110)	2.61 ± 4.74 0 (0–21)	0.135
IED index N1 (/hour)	23.28 ± 76.49 2.12 (0–370.82)	1.13 ± 2.59 0 (0–13.42)	0.112
IED index N2 (/hour)	10.51 ± 14.84 6.52 (0–74.69)	3.82 ± 1.80 0 (0–27.5)	***0.024***
IED index N3 (/hour)	12.49 ± 19.9 0 (0–73.14)	3.91 ± 6.67 0 (0–23.67)	0.055

Abbreviations: SD – standard deviation; IED – interictal epileptiform discharges.

more arousals in patients with medically refractory epilepsy [5]. Animal studies have suggested that REM sleep is governed by the interaction of REM promoting and REM-inhibiting nuclei in pontomesencephalic tegmentum [37]. The pedunculopontine nucleus is proposed to be REM promoting. Recently, Xu AJ et al. proposed that interaction between projections from subthalamic nucleus (STN) and cholinergic projections from pedunculopontine tegmental nucleus may serve a major role in the control of REM sleep in refractory epilepsy [38]. Bazil et al. reported that seizures occurring on the previous day of PSG study had a significant reduction in the duration of REM sleep [39]. In our study, 10 patients in the group with refractory focal epilepsy and 3 patients in the group with controlled epilepsy had seizure within 7 days prior to PSG study. We propose that factors like occurrence of seizure, altered sleep architecture, involvement of specific regulatory centers of sleep–wake cycle, effect of AEDs on sleep architecture, and psychosocial factors might have affected the prolonged REM latency and shortened REM duration in drug refractory focal epilepsy.

4.2. Cognitive performance of patients with epilepsy

Several studies have demonstrated impairment of cognitive parameters and executive dysfunction in patients with epilepsy. Campiglia M et al. reported a global executive function impairment in a group of 56 pediatric patients with epilepsy irrespective of the type of epilepsy. Younger age of epilepsy onset was correlated with more executive abnormalities whereas number of AEDs correlated with impairment of working memory [40]. Lopes et al. reported that children with frontal lobe epilepsy showed significant deficits in verbal and visual memory. In addition, type of epilepsy, earlier age at epilepsy onset, and longer duration of active epilepsy were associated with memory problems [41]. Cognitive impairment involving executive function, language, and memory is very common in medically refractory epilepsy with executive dysfunction being the most prevalent impairment [15].

Bartha-Doering L et al. [42], in a systematic review, reported a pronounced heterogeneity of language abilities in patients with epilepsy, varying from intact language profiles to impairment in several language functions. In our study, we found significantly poorer language performance among patients with refractory epilepsy compared with those with controlled epilepsy and healthy controls.

4.3. The relationship between sleep and cognition among patients with epilepsy

We observed a significant correlation between disturbances in specific cognitive domains of memory, executive function, and language parameters with poor sleep quality among patients with epilepsy. Lambiase MJ et al., in 2014 [43], assessed sleep efficiency with actigraphy and executive function by Digit symbol test and Trail B test in 121 older women, and reported lower sleep efficiency was associated with poorer performance on executive function testing. Their findings are similar to those in the present study. Our study population, however, was unique, and our findings are more objective and extremely important for clinical applicability.

There is now a large body of literature supporting the hypothesis that sleep, mainly REM sleep, plays a major role in memory consolidation. The most prominent theory regarding the mechanism is that recently acquired representations are preferentially reactivated during sleep. In the context of declarative memories, this involves reactivations of memories in the mesial temporal lobes, during slow wave sleep [44] which strengthen and stabilize memories [45], making them more resistant to interference and more likely to be retained [46,47]. A recent study by van Schalkwijk et al. reported that REM latency had a significant negative correlation with overnight retention of autobiographical events. There was a significant positive correlation between slow wave sleep and word listing learning [48]. We also found a negative correlation between REM latency and cognitive domains but it did not reach statistical significance. However, we did not find any direct correlation between slow wave sleep and cognitive domains.

In our study, we found that impairment of both self-reported and polysomnographic sleep parameters was associated with low memory scores. Payne et al. [49] in 2012, in 207 healthy students, assessed the impact of sleep, wake, and time-of-day influences on the processing of declarative information with strong semantic links (semantically related word pairs) and information requiring the formation of novel associations (unrelated word pairs). They found that sleep is most beneficial to memory 24 h later if it occurs shortly after learning, and sleep stabilizes declarative memories [49].

4.4. The relationship between IEDs and cognition

We found the frequency of interictal spikes to be more in the N2 stage followed by N3 stage of sleep. The IEDs were significantly higher in the group with refractory epilepsy. A statistically, significant negative correlation was observed with digit symbol and N2 spike frequency.

Table 8
Correlation of cognitive parameters with interictal epileptiform discharge index (IED index) in various sleep stages.

	Total PGI score	Trail A	Trail B	Digit symbol	Stroop Color word	IED index N1	IED index N2	IED index N3
Total PGI score	1							
Trail A	−0.801**	1						
Trail B	−0.531**	0.549**	1					
Digit symbol	0.529**	−0.565**	−0.429**	1				
Stroop Color word	0.645**	−0.485**	−0.512**	0.502**	1			
IED index N1	−0.229	0.119	0.117	−0.249	0.024	1		
IED index N2	−0.358**	0.257*	0.129	−0.324*	−0.108	0.723**	1	
IED index N3	0.192	0.125	0.245	−0.273	−0.070	0.542**	0.520**	1

Abbreviations: IED index – interictal epileptiform discharges index.
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Other cognitive parameters also showed a negative correlation but did not reach statistical significance. Studies in benign rolandic epilepsy have demonstrated an inverse relation between sleep activated IEDs and cognitive scores [50,51]. Our study demonstrates that drug refractoriness in patients with epilepsy has a deleterious effect on sleep quality and sleep disturbances can have a major impact on the subsequent impairment of memory and executive function. We did not record any seizures during any of the PSG recordings or a day before PSG which ruled out the possibility of disturbed sleep being attributed to clinical phenomena disrupting sleep on the night of the PSG recording.

4.5. Effect of AEDs on cognition and sleep in patients with epilepsy

Antiepileptic drugs have a significant effect on almost all aspects of cognition and are now being considered as one of the major causes of drug intolerance in patients on long-term therapy. Impaired attention [52], verbal fluency, language, and reaction times are reported to be altered with CBZ [53]. Similarly, valproic acid [54,55] and phenytoin [56] may cause significant inattention and psychomotor retardation. The former, in addition, causes hyperammonemia which can cause profound mental slowing in some cases [57]. Levetiracetam is widely known to have widespread effects on neuropsychological functions and behavioral and emotional well-being [58,59]. Topiramate has been associated with impaired concentration [60], cognitive slowing [61–63], poor verbal fluency [63,64], and short-term memory loss [63,65]. Interestingly, clobazam has scanty evidence of causing similar issues. A study on effects of clobazam in children showed almost 72% improvement in cognition, especially in attention and alertness [66]. A subsequent study showed no deterioration of cognitive or behavioral effects in children with newly diagnosed epilepsy [67]. A recent study by Vega et al. also shows improved verbal IQ in patients with continuous spike–wave in sleep, receiving clobazam [68].

It is important to note that the total number and doses of antiepileptics administered and treatment duration have a significant influence on the cognition in patients with epilepsy. In our study, the most commonly used AEDs were CBZ (46%), OXC (40%), LEV (35%), and clobazam (65%). The effects of AEDs on cognition might have been one of the confounding factors in our study.

Our study had few limitations, one of which is that we could not perform PSG studies for healthy controls and sleep parameters in these patients were only self-reported. Secondly, the AED number was statistically different in the two groups with epilepsy included (especially clobazam). Effects of AEDs on sleep architecture are variable. Carbamazepine has been reported to decrease Sleep Latency (SL), increase Sleep Efficiency (SE), and increase in N3 [69]. Similarly, LEV has been found to increase TST, SE, and reduce REM in healthy individuals [70]. Clobazam may have an effect on the slow wave and REM sleep percentages and on sleep consolidation [71]. Animal studies have revealed that OXC increased TST, slow wave, and REM sleep [72]. Hence, the effects of AEDs on the sleep architectures might have been an inevitable confounding factor in our patients.

Another constraint faced by us was regarding the assessment of Stroop and Digit symbol tests. It is known that patients with epilepsy can have significantly slow processing speed. Hence, a constant time factor was introduced for these time consuming tests. For performing the Stroop test, each of the conditions (word reading, color naming, and color word interference), the response time was 45 s. The total number of responses was recorded, and the final score for each was calculated by subtracting the number of errors from the total number of responses. Similar method was followed for the Digit symbol test, keeping a time constant of 90 s. Not detailing the number of errors in the Trail Making Tests remains a methodological limitation. Emotional and behavioral symptoms at the time of assessment can have significant impact on the performance on cognitive tests. However, the clinical evaluation of epilepsy and sleep, neuropsychological assessment, and PSG required the patients to commit a huge amount of time for participating in the study, therefore, the evaluation of behavioral problems and mood could not be included in our study. Finally, we analyzed a large number of variables; however, considering the comprehensive nature and novel objective of this study, these inclusions were warranted. In future, more studies focusing on individual clinical and polysomnographic aspects of sleep among larger number of patients in specific subsets of patients with medically refractory epilepsy would have greater power to establish these intricate associations.

5. Conclusion

This study strongly suggests that sleep disturbances, mainly shorter TST, poor sleep efficiency, and prolonged sleep latencies, are associated with impaired memory and executive function in patients with refractory focal epilepsy and to a lesser extent, among those with medically controlled epilepsy. It further reiterates previous observations about sleep quality and architecture and cognitive function being poorer in refractory versus controlled epilepsy.

Disclosure

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

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