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How do people with drug-resistant mesial temporal lobe epilepsy sleep? A clinical and video-EEG with EOG and submental EMG for sleep staging study

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ABSTRACT

This study aimed to assess subjective and objective sleep parameters in a homogeneous group of drug-resistant mesial temporal lobe epilepsy (MTLE)[1] patients through internationally validated clinical questionnaires, video-electroencephalographic (VEEG)[2] and polysomnographic (PSG)[3] studies. Fifty-six patients with definite diagnosis of MTLE who were candidates for epilepsy surgery underwent a detailed clinical history, the Pittsburgh Sleep Quality Index (PSQI),[4] Epworth Sleepiness Scale (ESS),[5] Stanford Sleepiness Scale (SSS),[6] neurological examination, 1.5 T brain magnetic resonance imaging, VEEG and PSG. Sixteen percent of patients reported significant daytime sleepiness as measured by ESS and 27% reported low levels of sleep quality as measured by PSQI. Patients with medically resistant epilepsy by MTLE showed increased wakefulness after sleep onset (WASO) with mean ± standard deviation of 17.4 ± 15.6, longer non-rapid eye movement (NREM)[7] 1 (7.5 ± 4.6%) and NREM3 sleep (26.6 ± 11.8%), abnormal rapid eye movement (REM)[8] latency in 30/56 patients, shorter REM sleep (16.7 ± 6.6%), and abnormal alpha delta patterns were observed in 41/56 patients. The analysis of interictal epileptic discharges (IEDs)[9] evidenced highest spiking rate during NREM3 sleep and higher concordance with imaging data when IEDs were recorded in sleep, mainly during REM sleep. We concluded that patients with MTLE showed disrupted sleep architecture that may result in daytime dysfunction and sleep complaints. Furthermore, NREM sleep activated focal IEDs and them - when recorded during sleep - had higher localizing value.

1. Introduction

There is a reciprocal interaction between sleep and epilepsy: while seizures tend to occur during sleep in some epileptic syndromes, epilepsy may disrupt the organization and microarchitecture of sleep [1]. Generalized seizures that occur during sleep may delay sleep onset, fragment sleep, increase non-rapid eye movement (NREM) 1 stage sleep, decrease the percentage of NREM2, NREM 3, rapid-eye movement (REM) and increase drowsiness on the day after seizures [2,3].

Patients living with epilepsy (PWE)[10] have a higher prevalence of sleep complaints and sleep disorders than healthy subjects [4]. Pizzatto et al. observed that PWE presented higher levels of daytime sleepiness measured by Epworth sleepiness scale (ESS) than healthy controls, and they demonstrated that factors responsible for disruption of sleep architecture may be beyond those found in the general population [5]. Polysomnographic (PSG) studies performed in patients with temporal lobe epilepsy (TLE)[11] showed that epilepsy itself disturbed sleep architecture, caused poorer sleep efficiency, a higher number of arousals and awakenings, longer NREM1 and NREM2, and shorter slow-wave-sleep (SWS)[12] [6]. In contrast, other authors reported increased SWS, shorter total sleep time and REM sleep [7]. Most of these studies recruited patients with diverse epileptic syndromes or included patients with

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[1] MTLE: mesial temporal lobe epilepsy;
[2] VEEG: video-electroencephalographic;
[3] PSG: polysomnographic;
[4] PSQI: Pittsburgh Sleep Quality Index;
[5] ESS: Epworth Sleepiness Scale;
[6] SSS: Stanford Sleepiness Scale;
[7] NREM: non-rapid eye movement;
[8] REM: rapid eye movement;
[9] IEDs: interictal epileptic discharges.
[10] PWE: Patients living with epilepsy;
[11] TLE: temporal lobe epilepsy;
[12] SWS: slow-wave-sleep;

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temporal lobe epilepsy by different etiologies altogether, which might have undermined their results.

Sleep-related activation of interictal epileptiform discharges (IEDs) may be found and provide lateralizing information about the epileptogenic zone in patients with TLE [8]. It is believed that this activation may occur due to the synchronous synaptic effects related to NREM sleep [9,10] and may be influenced by factors such as: epileptic syndrome, vigilance state, age at epilepsy onset, duration of epilepsy, presence of secondarily generalized tonic-clonic seizures (GTCS),[13] presence of hippocampal sclerosis and timing of the last seizure [10]. Even though most studies demonstrated highest spike rates during SWS compared to other stages of sleep or wakefulness [9,10]; other ones observed maximal spiking during wakefulness, light NREM or REM. There is a significant interindividual variability regarding spiking rate which emphasizes the need for further studies [11].

In this article, we evaluated subjective and objective sleep parameters in a homogeneous group of patients with drug-resistant mesial temporal lobe epilepsy (MTLE) through video-electroencephalographic (VEEG) and PSG studies. We also investigated which clinical data may modulate the IEDs during the sleep-wake cycle and how this modulation could affect the IEDs.

2. Material and methods

2.1. Subjects

Fifty-six consecutive adult patients (over 18 years old) diagnosed with MTLE according to International League Against Epilepsy (ILAE)[14] [12–15] who were candidates for epilepsy surgery, underwent a comprehensive presurgical evaluation at the Epilepsy Center of Santa Catarina (CEPESC),[15] Governador Celso Ramos Hospital (HGCR),[16] Florianópolis, Brazil, between October 2009 and September 2013. It consisted of a detailed clinical history, neurological examination, 1.5 T brain magnetic resonance imaging (MRI),[17] neuropsychological, psychiatric and psychosocial assessments. Exclusion criteria were non-drug-resistant epilepsy, patients with known or suspected sleep disorders, and psychiatric comorbidities.

2.2. Clinical assessment

Subjects completed an extensive survey on the first day of hospitalization, in the afternoon before the PSG started, which included demographic and clinical variables, the Epworth Sleepiness Scale (ESS) [16], Pittsburgh Sleep Quality Index (PSQI) [17], and Stanford Sleepiness Scale (SSS) [18]. Exclusion criteria for completing these questionnaires were the presence of illiteracy or cognitive impairment that precluded the patient from completing them adequately. The ESS consists of 8 self-rated items, each scoring from 0 to 3 that measures an individual's habitual "likelihood of dozing or falling asleep" in common daily situations. The ESS score represents the sum of individual items and ranges from 0 to 24. Scores greater than ten are considered to indicate significant sleepiness. The Portuguese-language version of the ESS validated to be used in Brazil was useful to assess sleepiness in PWE [20]. The PSQI is a 19-item self-rated questionnaire to evaluate sleep quality over the previous month. The 19 questions are combined into seven clinically derived component scores (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep-inducing medication, and daytime dysfunction) that are each weighted equally and scored from 0 to 3. The 7 component scores are added to obtain a global score ranging from 0 to 21, with higher scores indicating worse sleep quality. A global score greater than five is defined as a low sleep quality. The Portuguese-language version of the PSQI validated to Brazil was used to assess sleep quality index [21]. The SSS quantifies subjective sleepiness levels at the time of evaluation. Participants selected one of 7 options to identify their current level of sleepiness. A score equal or greater than three is associated with a decline in performance that is related to sleepiness. Participants also answered ten questions with yes or no alternatives to assess the presence of other common sleep disorders such as insomnia, nonrestorative sleep, restless sleep, sleep talking, sleepwalking, bruxism, abnormal dreams and sleep paralysis.

All patients were receiving maintenance antiepileptic medication (AEM)[18] therapy and pharmacological assessment. To allow comparisons among diverse AEM regimen, either as monotherapy or in combination, a measure of equipotency must be determined. Therefore, all AEM daily doses were standardized as a ratio of prescribed daily dose (PDD)[19] to defined daily dose (DDD)[20] for each patient. While PDD is the prescribed dose for each subject in our population, the DDD is determined by the World Health Organization (WHO)[21] as the average maintenance dose per day for each AEM used for its main indication in adults by analysis of literature and drug registration data; for instance, carbamazepine's DDD is 1000 mg/day. The DDD does not necessarily reflect the PDD and differences between PDD and DDD may reflect the severity of the disease [23,24].

2.3. MRI data

Neuroimaging studies included high-resolution MRI (1.5 T) with special protocols for epilepsy [25]. All patients had clear MRI findings consistent with hippocampal sclerosis (HS),[22] defined by the presence on visual inspection of atrophy, increased T2-weighted signal, decreased T1-weighted signal, and disrupted internal hippocampal structure [26–28]. Based on visual analysis of MRI, the neurologists classified HS as (a) unilateral, when HS was observed on one side; or (b) bilateral, when HS was observed on both sides.

2.4. Polysomnographic evaluation

Overnight (one night) PSG study was performed on the first night of hospital admission. In order to avoid the "first night effect" affecting PSG parameters we encouraged the patients to bring their personal belongings to make the laboratory environment as familiar as possible, all patients were admitted in the morning, started recordings at 7 AM and spent the entire daytime under monitorization and getting acquainted with the VEEG/sleep equipment before the overnight PSG study started. The video-polysomnography included extended 18-channel electroencephalogram (EEG)[23] montage based on the International 10–20 System (IS)[24] [29,30] and analyzed the following parameters: standard electrooculography (EOG),[25] chin electromyogram (EMG),[26] airflow (oronasal thermistor and nasal pressure), snoring, arterial oxygen saturation, body position and electrocardiogram (EKG)[27] [31,32].

Nurses instructed the patients to sleep at 10 PM and awakened them at 6 AM. All patients were recorded in a single room on a hospital ward, and all efforts were made to optimize sleeping conditions - during recordings, the doors of the room remained closed, the lights off and the patients undisturbed unless a seizure occurred. Following seizures, patients were encouraged to return to sleep.

[13] GTCS: generalized tonic-clonic seizures.
[14] ILAE: International League Against Epilepsy;
[15] CEPESC: Epilepsy Center of Santa Catarina;
[16] HGCR: Governador Celso Ramos Hospital;
[17] MRI: magnetic resonance imaging.
[18] AEM: antiepileptic medication.
[19] PDD: prescribed daily dose;
[20] DDD: defined daily dose;
[21] WHO: World Health Organization;
[22] HS: hippocampal sclerosis;
[23] EEG: electroencephalogram;
[24] IS: International 10–20 System;
[25] EOG: electrooculography;
[26] EMG: electromyogram
[27] EKG: electrocardiogram;

All PSG studies were scored in 30-second intervals, based on the American Academy of Sleep Medicine (AASM)[28] guidelines [33], by reformatting digital EEG to PSG channels and settings. The sleep parameters evaluated on PSG were: total sleep time (TST),[29] sleep latency, REM latency, sleep efficiency, percentage of time in each sleep stage, wake after sleep onset (WASO),[30] awakening, arousals, and arousal index (AI),[31] desaturation index (DI)[32] and electroencephalogram pattern. The scoring began at sleep onset (defined by three consecutive epochs of stage NREM1 or one epoch of stage NREM2 sleep) and continued until awakening in the morning by the staff. Sleep efficiency was calculated as Bazil et al.: percentage of time asleep from sleep onset until awakening [3]. The occurrence of sleep onset REM period (SOREMP),[33] REM abnormalities, and seizures during the night studies were also noted. To evaluate the sleep epochs that had epileptic electrical activity, we used the method proposed by Marzec et al. [34] in which epochs with seizure activity were unscored, and epochs after a seizure were scored when the waveforms were comparable to pre-ictal sleep stages. Seizure and postictal epochs were not included in TST.

We performed PSG on the first night of admission, however the patients were interviewed to estimate how many hours of sleep they had the night before and when was the last seizure occurred, therefore, to identify those who were sleep deprived or those who have had seizure in the day of PSG study, factors which could impact on sleep parameters.

2.5. VEEG evaluation

Patients underwent 2–6 days of continuous VEEG monitoring as recommended by the American Clinical Neurophysiology Society [35] on the next day following PSG study. EEG signals were obtained by using a digital VEEG system with 32-channel EEG recording; with the usual 10–20 IS full scalp electrodes array, along with electrodes placed according to 10–10 IS in the temporal lobes. Activation procedures, such as hyperventilation (HV)[34] and photic stimulation, were used to increase the diagnostic yield of the test.

2.6. Interpretation of neurophysiological data

The VEEG and PSG studies were analyzed during the patient's admission by two board-certified individuals (AVSL and LSC) and accepted only when there was an agreement between the two examiners; otherwise, a third examiner (KL) was included.

The visual determination of sleep IEDs and their localization was performed into 10-s epochs in PSG using bipolar, average and Pz referential montages after sleep staging had been completed. The criteria for IEDs were those described by Gloor [36]. The interictal EEG was reviewed for at least 1 hour in the wake state and each sleep stages, during PSG, the latter including both NREM and REM sleep. If any stage of sleep did not complete an hour, the entire duration of this sleep stage was analyzed.

2.6.1. Spike measures definitions

The following measures were calculated as described by Clemens et al. [10]:

2.6.1.1 Spiking rates: number of spikes in a stage/time spent in each stage.

2.6.1.2 Mean spiking rate: mean of spiking rates determined for all sleep stages and wakefulness.

2.6.1.3 Relative spike densities for each state: spiking rate in a state/mean spiking rate. This variable was introduced to investigate the distribution of spikes between different states, due to the significant differences in spiking rates among patients, even during the same vigilance states.

To evaluate the localizing value of IEDs, the interictal EEG localization for wakefulness and all sleep stages were compared with overall localization data on VEEG and MRI.

2.7. Statistical analysis and ethical aspects

Statistical analysis was performed using IBM® SPSS® software package for Mac, standard version 21.0. Descriptive analysis was made to characterize the sample. Quantitative variables were expressed as mean ± standard deviation (SD)[35] and qualitative variables were expressed as percentage values. The following standard statistical tests were used for in-group and between-group comparison purposes wherever appropriate: chi-square test, Fisher's exact test, Student's *t*-test and Pearson's correlation. A p-value < 0.05 was considered to be statistically significant.

This study was carried out by the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2014) and the Uniform Requirements for manuscripts submitted to Biomedical journals. The Ethics Committee for Human Research of the Federal University of Santa Catarina and Governardor Celso Ramos Hospital approved this study. All subjects signed an informed consent form and voluntarily agreed to participate in this study.

3. Results

3.1. Clinical and demographic data

A total of 56 patients, 28 (50%) male, with an age range of 18–56 years (mean 35.8 ± SD 9.8), 91.1% right-handed, mean education years of 8.3 ± 3.71, with definite diagnosis of MTLE (32 patients with left, 23 right and 1 bilateral HS) were recruited. The mean age at onset of epilepsy was 14.0 ± 9.2 years, and the mean duration of epilepsy was 21.6 ± 9.7 years, while the mean frequency of focal dyscognitive seizures of 11.9 ± 20.6 per month.

The percentage of patients in polytherapy was 85.7% (48/56), with PDD/DDD = 2.61 ± 1.10 (minimum-maximum = 0.86–5.40). Fifty-five percent (31/56) were taking benzodiazepines; 37.5% (21/56) were using Clobazam and 17.9% (10/56) Clonazepam. Most commonly used AEM were: Carbamazepine (37/56; mean serum level = 7.48 ± 2.55 mcg/ml), Phenobarbital (22/56; mean serum level = 18.17 ± 8.58 mcg/ml), Valproate (15/56; mean serum level = 59.63 ± 35.73 mcg/ml), Phenytoin (8/56; mean serum level = 15.66 ± 7.40 mcg/ml), Oxcarbazepine (6/56), Lamotrigine (5/56) and Topiramate (4/56).

3.2. Self-reported clinical sleep parameters

Thirty-eight patients (67.8%) completed the ESS, SSS, PSQI and FLAQ questionnaires and obtained mean overall scores ± standard deviation of 7.7 ± 4.5 (ESS), 1.5 ± 0.9 (SSS), and 5.3 ± 2.8 (PSQI). Nine (16.1%) patients had clinically significant excessive daytime sleepiness (EDS; ESS >10). Four patients (7.1%) had SSS ≥3, that is, considerable sleepiness at the time of evaluation. Fifteen (26.8%) had a global score of PSQI >5, defining low sleep quality over the previous month.

3.3. Polysomnographic parameters

The PSG parameters are described on Table 1 - 21 (37.5%) patients presented sleep efficiency lower than 85%, 18 (32.1%) patients had sleep latency higher than 30 min, 14 (25.0%) subjects presented REM

[28] AASM: American Academy of Sleep Medicine;
[29] TST: total sleep time;
[30] WASO: wake after sleep onset;
[31] AI: arousal index;
[32] DI: desaturation index;
[33] SOREMP: sleep onset REM period.
[34] HV: hyperventilation.
[35] SD: standard deviation.

latency <70 min [while 16 (28.6%) subjects >120 min], 49 (87.5%) presented WASO >5%, 35 (62.5%) individuals had percentage of NREM1 to total sleep time >5%, 18 (32.1%) individuals had percentage of NREM2 to total sleep time <45%, 35 (62.5%) patients had percentage of NREM3 to total sleep time >23%, 38 (67.9%) patients had percentage of REM to total sleep time <20%, and 13 (23.2%) subjects had arousal index (number/hour) >16. There was no statistical difference between PSQI ≤5 and PSQI >5 compared to polysomnographic parameters. Only two patients presented SOREMP, ten patients presented REM without atonia and alpha delta sleep pattern was observed in 41 patients.

Thirty-five (62.5%) patients did not have seizures at least 24 h before sleep onset and during the PSG recording (seizure free group). Ten (17.9%) patients had seizures on the day that PSG was performed (daytime seizures - seizure between 7 AM and 11 PM) and 4 (7.1%) had seizures during the recording (night seizures - after sleep onset). Their PSG and self-reported clinical sleep parameters are described in Table 2. Night seizures, but not daytime seizures, significantly reduced sleep efficiency. No statistically significant differences in total sleep time, percentage of wakefulness after sleep onset, percentage and REM latency, arousal index, desaturation index and nor self-reported clinical sleep parameters were observed between these three groups.

3.4. Role of sleep in the localizing value of interictal EEG and interictal epileptic discharge activation

IEDs were found in 53/56 patients (94.6%) during wakefulness, sleep or both: 34/53 (64.1%) showed IEDs exclusively during sleep, 4/53 (7.5%) patients showed IEDs only in wakefulness, and 15/53 (28.3%) had IEDs in both. Among the patients with IEDs during sleep, 37/49 (75.5%) had unilateral IEDs during NREM sleep. Nineteen (35.8%) patients showed IEDs during awake state, 12/19 (63.1%) with unilateral IEDs (Table 3).

Table 2
Sleep structure and self-reported clinical sleep parameters in patients following seizures.

Sleep parameters	No seizures[a] (N = 35)	Daytime sz[b] (N = 10)	Night sz[c] (N = 4)	p-Values[d]
Hours of sleep the night before PSG	6.0 ± 2.0	7.7 ± 2.0	5.3 ± 3.2	0.07
Total sleep time (hours)	6.7 ± 0.8	6.5 ± 1.0	5.8 ± 0.7	0.13
Sleep efficiency[e] (%)	86.5 ± 10.6	89.2 ± 6.9	73.9 ± 6.9	**0.03**
REM latency[f] (minutes)	112.1 ± 71.4	86.5 ± 38.8	107.7 ± 29.0	0.54
REM (%)	17.2 ± 6.9	15.8 ± 6.1	12.2 ± 2.4	0.45
WASO (%)	17.1 ± 17.4	12.7 ± 9.5	34.4 ± 13.6	0.07
Arousal index[g] (number/hour)	12.1 ± 7.8	9.8 ± 3.5	15.1 ± 1.3	0.40
Desaturation index[h] (number/hour)	1.3 ± 2.6	0.3 ± 0.3	0.8 ± 1.1	0.49
ESS	8.0 ± 3.9	7.4 ± 5.9	0.0 ± 0.0[i]	0.20
SSS	1.6 ± 1.0	1.0 ± 0.0	1.0 ± 0.0[i]	0.38
PSQI	5.3 ± 2.8	4.4 ± 2.3	9.0 ± 0.0[i]	0.36

ESS = Epworth Sleepiness Scale; NREM = non-rapid eye movement sleep; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement sleep; SSS = Stanford Sleepiness Scale; TST = total sleep time; WASO = wake after sleep onset.

[a] No seizures meaning no seizures for at least 24 h before sleep onset and during the recording.

[b] Daytime seizure was defined as a seizure between 7 AM and 10 PM on the day the recording started.

[c] Night seizure was defined as a seizure during the recording (after sleep onset).

[d] All numbers were represented by mean ± standard deviation. The "p" levels of significance were determined by ANOVA, and a "p" value < 0.05 was considered to be statistically significant which is indicated in bold type.

[e] Sleep efficiency was calculated as percentage of time asleep from sleep onset until awakening.

[f] REM latency was calculated as sleep onset until first REM period.

[g] Total number of awakenings and arousals or micro-awakenings/hour of total sleep time.

[h] Desaturation number/hour of total sleep time.

[i] Only one out of four subject having seizure during PSG answered to the self-reported clinical sleep parameters questionnaires.

Table 1
Polysomnographic parameters observed in patients according to Pittsburgh Sleep Quality Index global scores.

Sleep staging	Normal range (NR)[a]	N subjects within NR[a]	Total[b]	PSQI ≤5[b]	PSQI >5[b]	p-Values[b]
Age			35.8 ± 9.8	37.1 ± 10.4	38.8 ± 8.3	0.92
Hours of sleep the night before PSG			6.2 ± 2.1	6.4 ± 1.3	4.9 ± 1.9	**0.008**
Total sleep time (hours)			6.5 ± 0.9	6.9 ± 0.8	6.3 ± 1.0	0.06
Sleep efficiency[c] (%)	>85%	35/56	86.1 ± 9.8	87.7 ± 11.4	85.9 ± 9.5	0.60
Sleep latency (NREM1, minutes)	<30 min	38/56	28.1 ± 25.3	29.7 ± 28.1	25.6 ± 23.2	0.64
NREM 2 latency[d] (minutes)			6.3 ± 8.6	5.5 ± 4.2	5.6 ± 11.9	0.99
NREM 3 latency[d] (minutes)			32.5 ± 22.6	30.4 ± 19.2	30.1 ± 20.9	0.97
REM latency[d] (minutes)	70–120 min	26/56	104.1 ± 60.2	111.6 ± 69.8	95.1 ± 56.0	0.45
WASO (%)	<5%	7/56	17.4 ± 15.6	15.7 ± 19.5	17.8 ± 14.3	0.72
NREM 1 (minutes)			28.7 ± 15.9	26.6 ± 12.2	25.7 ± 20.9	0.86
NREM 1[e] (%)	2–5%	19/56	7.5 ± 4.6	6.5 ± 3.6	7.0 ± 5.8	0.74
NREM 2 (minutes)			193.4 ± 48.1	202.8 ± 53.6	180.9 ± 52.2	0.22
NREM 2[e] (%)	45–55%	23/56	49.0 ± 10.6	48.6 ± 11.9	47.7 ± 11.4	0.82
NREM 3 (minutes)			106.1 ± 50.3	113.1 ± 57.8	109.9 ± 48.2	0.86
NREM 3[e] (%)	13–23%	15/56	26.6 ± 11.8	26.8 ± 13.4	29.0 ± 12.2	0.62
REM (minutes)			66.6 ± 31.0	74.4 ± 37.4	62.8 ± 28.6	0.31
REM[e] (%)	20–25%	10/56	16.7 ± 6.6	17.9 ± 8.0	16.1 ± 5.6	0.46
Number of awakenings in TST (mean)			18.2 ± 9.6	17.3 ± 9.6	15.8 ± 10.8	0.64
Number of micro-awakenings in TST (mean)			54.4 ± 33.7	58.3 ± 33.4	36.3 ± 21.2	**0.03**
Arousal index[f] (number/hour)	<16	43/56	11.5 ± 6.6	11.9 ± 6.7	8.5 ± 5.2	0.10
Desaturation index[g] (number/hour)			1.1 ± 2.4	1.4 ± 2.6	0.8 ± 1.9	0.45
Alpha delta pattern (number of patients/total)			41/56	18/23	12/15	0.89

NREM = non-rapid eye movement sleep; PSQI = Pittsburgh sleep quality index; REM = rapid eye movement sleep; TST = total sleep time; WASO = wake after sleep onset.

[a] Reference values according to Rechtschaffen & Kales [55].

[b] All numbers were represented by mean ± standard deviation, except for "alpha delta pattern". The "p" levels of significance were determined by Student's *t*-test, except for "alpha delta pattern" (Pearson's Chi-square), a "p" value < 0.05 was considered to be statistically significant which is indicated in bold type.

[c] Sleep efficiency was calculated as percentage of time asleep from sleep onset until awakening.

[d] NREM 1, 2, 3 and REM latency were calculated as sleep onset until first NREM 1, 2, 3 and REM periods, respectively.

[e] Percentage of NREM 1, 2, 3 and REM to total sleep time.

[f] Total number of awakenings and arousals or micro-awakenings/hour of total sleep time.

[g] Desaturation number/hour of total sleep time.

Those patients who had IEDs during sleep, 34/49 (69.4%) had IEDs lateralized to the side of the lesion seen on imaging, and those who had IEDs in wakefulness, 11/19 (57.9%) patients showed IEDs concordant with the side of the lesion on MRI. From those patients who had bilateral IEDs during NREM sleep, 5/12 (41.6%) had unilateral IEDs during REM, which were concordant with MRI side in 4/5 (80%) patients (Table 4).

Forty-two (85.7%) patients exhibited maximal spiking rates during NREM sleep. Of these, 27 (64.3%) had maximal spiking rates during NREM3, 11 (26.2%) during NREM2, and 4 (9.5%) during NREM1. Eleven (20.7%) patients had distinctly different distribution of IEDs: 9 (16.9%) patients had maximal spiking rates in wakefulness, and 2 (3.7%) during REM sleep.

3.5. Correlation data

Table 5 summarizes spike measures correlation data with the variables epilepsy duration, age at epilepsy onset, focal dyscognitive seizure frequency, and PDD/DDD ratio.

None of the spike measures showed any significant correlation with epilepsy duration in years.

There were significant correlations when comparing age at epilepsy onset and spiking rate in NREM1, REM and mean spiking rates in all sleep stages. Seizure frequency had statistically significant correlation with NREM1 spiking rates. Also, relative spiking density in NREM 2 and NREM3 stages showed statistically significant correlation with PDD/DDD.

Additionally, since benzodiazepines and phenobarbital are AEMs known to affect sleep, subjects taking and not taking them were compared regarding all PSG parameters and self-reported clinical questionnaire scores with no statistically significant differences between groups. Concerning Carbamazepine, the most commonly used AEM by our patients, there was a tendency towards a significant association between the use of Carbamazepine and NREM 3 (%) sleep higher than 25% [$\chi^2(1) = 3.2, p = 0.07$].

4. Discussion

Patients with medically resistant TLE-HS epilepsy presented sleep fragmentation, prolonged WASO, increased duration of NREM1 and NREM3 sleep, abnormal REM latency, reduced REM sleep and higher rates of alpha-delta patterns. Previous studies have also demonstrated similar disturbance of sleep architecture [1,6,7]. However, only one study reported an increase of NREM3 sleep [7]. The use of AEMs may explain these findings; most patients were taking Carbamazepine, an AEM that may cause increased duration of NREM3 sleep [37]. Additionally, decreased REM sleep among PWE may occur due to the AEMs (Carbamazepine, Phenobarbital) as well as the occurrence of diurnal and nocturnal seizures [3]. The increased alpha-delta sleep pattern was not reported previously in patients with TLE. This abnormal EEG pattern was first described among psychiatric patients and later it was linked to painful syndromes such as rheumatoid arthritis and fibromyalgia [38], excessive daytime sleepiness, nonrestorative sleep and light sleep sensation [39]. In fact, our patients showed higher sleepiness index and poor sleep quality that might be associated with this EEG pattern.

Table 3
Interictal epileptic discharges distribution during sleep and awake state.

	Number (%)
Patients that showed IEDs in wakefulness, sleep or both	53/56 (94.6%)
Sleep	
No IEDs in sleep	7/56 (12.5%)
Total of patients that showed IEDs in sleep	49/56 (87.5%)
Unilateral IEDs	37/49 (75.5%)
Right temporal lobe	18/49 (36.7%)
Left temporal lobe	19/49 (38.7%)
Bilateral IEDs	12/49 (24.4%)
Wakefulness	
No IEDs in wakefulness	37/56 (66.1%)
Total of patients that showed IEDs in wake	19/56 (33.9%)
Unilateral IEDs	12/19 (63.1%)
Right temporal lobe	5/19 (26.3%)
Left temporal lobe	5/19 (26.3%)
Bilateral IED	6/19 (31.5%)

IED = interictal epileptic discharges.

Drowsiness is a frequent complaint of PWE [40]. Clinical evaluation of PWE observed that the prevalence of EDS is approximately 10–32% [41–43]. We evaluated EDS by using the ESS, and this symptom was present in 16% of patients. Our patients obtained an overall mean score on ESS ± SD of 7.7 ± 4.5 while Brazilian healthy population scored 5.2 ± 3.0 in the validation study for the use of ESS in Brazil [20].

>25% of our patients evidenced poor sleep quality as measured by PSQI, with the overall mean score on PSQI ± SD of 5.3 ± 2.8, while Brazilian healthy population has a mean score of 2.5 ± 2.0 [21]. Although we did not find statistically significant differences in PSG parameters between good and poor sleepers (PSQI ≤5; PSQI >5), when we evaluated total sleep time, we observed a trend towards lower sleep duration among patients with poor sleep quality ($p = 0.06$). Ramachandraiah et al. found no differences in PSG parameters when comparing patients with juvenile myoclonic epilepsy and controls, despite PWE presented poorer sleep quality measured by PSQI [45]. These negative findings indicate that there are other factors (as sleep instability, psychological and environmental) beyond the conventional sleep parameters that can influence subjective sleep complaints. Furthermore, reduction in the seizure and IEDs frequency after successful surgery for drug-resistant TLE-HS has a positive impact on sleep quality even without significant improvement in PSG sleep parameters when comparing pre and post-operative periods [7,46].

We observed highest spiking rate during NREM3 and spiking frequency could be graded in the following order: NREM3 > NREM2 > NREM1 > Wakefulness > REM. These findings agree with previous studies which demonstrated that NREM3 is a well known IEDs activator [9,10] while REM reduced the IEDs [8]. This activating role of NREM sleep can be explained by the increased neuronal synchronization within thalamocortical projecting neurons, leading to neurochemical and neurophysiologic processes that initiate and maintain NREM sleep [8,9]. These synchronous synaptic effects could augment the magnitude and propagation of post-synaptic responses, including epileptic discharges. In contrast, REM sleep promotes asynchronous cellular discharge patterns. These different synaptic signals associated with asynchronous discharge patterns seem less likely to augment the magnitude or propagation of EEG discharges [47]. We found a small patient group with maximal spiking rates during wake state and REM sleep. This finding has also been previously reported [10]. Nevertheless, the small number of patients in these groups in our and earlier studies did not allow any conclusive remarks. Therefore, the underlying mechanisms of spiking behavior and the clinical importance of them remain unknown.

Our data demonstrated that focal IEDs during the sleep state, mainly in REM sleep, had higher concordance with imaging data than in wakefulness state, showing the lateralizing value of IEDs recorded during sleep. Previous studies performed in TLE had also similar findings [8,48–50]. However, the hypothesis that IEDs recorded in REM provides better localization than NREM sleep remains controversial. Sammaritano et al. found that localization of the primary epileptogenic area was more reliable in REM sleep and least reliable in NREM sleep [48]. On the contrary, Singh et al. found that discharges were fewer during REM sleep, they lost their sharp contour and were no more focal than those recorded during NREM sleep [50]. This study may have differed from ours and other studies since it included a heterogeneous population, with almost 1/3rd of patients having extratemporal lobe epilepsy; therefore, limiting comparisons.

Table 4
Patients characteristics which showed non-localizing IEDs in NREM sleep.

Gender	Age	Disease duration (years)	MRI side	Interictal IED	Ictal onset	Irritative zone	Symptomatogenic zone	NREM Side IED	REM Side IED	Post-surgical outcome[a]
F	46	10.5	L MTS	None	None	Non-local.	Non-local.	Bilat. T	LT	Not operated
F	46	36	R MTS	LT	RT	RT	RT	Bilat. T	None	Not operated
F	35	27	R MTS	RT	LT	Bilat T	LT	Bilat. T	Bilat. T	Not operated
M	32	30	L MTS	LT	Non-local.	LT	Non-local.	Bilat. T	LT	Not operated
F	42	26	L MTS	Bilat. T	LT	LT	LT	Bilat. T	None	Seizure free
M	30	27.6	R MTS	Bilat. T	LT	Bilat T	Bilat. T	Bilat. T	None	Not operated
F	30	15	R MTS	RT	RT	RT	RT	Bilat. T	Bilat. T	Seizure free
M	37	27	Bilat. MTS	None	RT	RT	RT	Bilat. T	RT	Not operated
M	26	15	L MTS	RT	LT	LT	LT	Bilat. T	Bilat. T	Wieser class 4
M	38	24	L MTS	LT	Bilat.	Bilat.	LT	Bilat. T	LT	Not operated
F	36	23	L MTS	LT	L MTS	LT	LT	Bilat. T	LT	Not operated
M	19	15	R MTS	RT	RT	RT	RT	Bilat. T	None	Wieser class 2

Bilat = bilateral; F = female; IED = interictal epileptic discharge; L = left; M = male; MRI = Magnetic Resonance Imaging; MTS = left mesial temporal sclerosis; Non-local = non-localizing; NREM = non-rapid eye movement sleep; R = right; REM = rapid eye movement sleep; T = temporal.
[a] Post-surgical outcome according to Wieser et al. [56], with follow-up >5 years.

Although we cannot make inferences about outcome due to the design of our study, previous reports demonstrated that analysis of sleep IEDs add prognostic data to epilepsy surgery evaluation. Malow et al. evaluated 24 patients with medically refractory TLE, and they noted that patients with unilateral NREM IEDs concordant with imaging studies who undergone surgery were more likely to be seizure free, demonstrating the localizing and prognostic value of IEDs recorded during NREM sleep. However, it is noteworthy that, sleep IEDs cannot be used in isolation to predict ictal-onset regions or surgical outcome and must be interpreted in combination with other data collected during presurgical evaluation [8].

In contrast to the literature, we did not find statistically significant correlation between spiking measures and epilepsy duration. Clemens et al., who conducted an EEG-PSG study in 38 TLE patients, found that spiking rates progressively increase with years spent with epilepsy [10]. Indeed, other studies on TLE patients showed that individuals with low spiking rates lived with the disease ten years less than patients with frequent IEDs [51]. The difference between previous studies and ours is that our patients had longer disease duration and younger age at epilepsy onset, which may have influenced the results. Also, TLE is a heterogeneous condition: even among patients with TLE-HS, there are different patterns of hippocampal neuronal cell loss [28] that might be influenced by epilepsy duration [52], age at epilepsy onset and the presence of an early preceding event, especially complex and prolonged febrile seizures [53]. Further investigation correlating clinical and neurophysiologic data with histopathological findings may help to clarify this issue.

Patients with seizures during PSG showed a statistically significant reduction in sleep efficiency, increased WASO (%), a higher number of awakenings and a nonsignificant tendency of decreased REM sleep. An earlier study reported that REM sleep was reduced when the seizure occurred during the night. Nocturnal seizures disrupted sleep by increasing awakenings and therefore reduced the sleep time and sleep efficiency. Furthermore, nocturnal seizures have a direct REM suppressant effect and increase the time to the first REM probably by affecting the circadian patterns responsible for this sleep stage [3].

A limitation of our study is that all patients were medically refractory epilepsy individuals taking high doses of AEMs in polytherapy which may disrupt sleep such as Phenobarbital and Clobazam, expected to increase sleep stage 2, reduce sleep stages 3 and REM, reduce WASO and sleep latency. AEMs are known to influence sleep structure, and it is often suggested that sleep problems in people with epilepsy are at least partly due to AEMs. However, it is difficult to draw firm conclusions on the effects of individual AEMs, since in most studies, individuals use a broad range of different AEMs and most are on polytherapy [54].

Table 5
Spiking rates (number of spikes in a sleep stage/time spend in each sleep stage) and their correlation with epilepsy duration, age at epilepsy onset, frequency of focal dyscognitive seizures and PDD/DDD.

	Spiking rate, mean spiking rate and relative spike density (mean ± standard deviation)	Epilepsy duration (years)		Age at epilepsy onset (years)		FDS frequency (per month)		PDD/DDD	
		R-Values	*p*-Values[a]	*R*-Values	*p*-Values[a]	*R*-Values	*p*-Values[a]	*R*-Values	*p*-Values[a]
Wake state	0.16 ± 0.64	−0.036	0.796	−0.166	0.226	−0.044	0.756	0.323	0.16
NREM1	0.31 ± 0.87	0.115	0.399	**−0.284**	**0.034**	**0.336**	**0.013**	0.011	0.938
NREM2	0.49 ± 1.01	0.104	0.447	−0.212	0.116	0.155	0.262	0.87	0.521
NREM3	0.82 ± 1.97	0.154	0.260	−0.196	0.150	0.142	0.309	0.157	0.252
REM	0.11 ± 0.34	0.187	0.172	**−0.291**	**0.031**	0.061	0.662	−0.024	0.864
Mean spiking	0.38 ± 0.72	0.155	0.253	**−0.294**	**0.028**	0.201	0.145	0.168	0.215
REL Wake	0.81 ± 1.59	−0.029	0.829	0.083	0.543	−0.132	0.342	−0.081	0.553
REL NREM1	0.48 ± 0.82	0.112	0.412	−0.091	0.506	0.198	0.152	−0.132	0.332
REL NREM2	1.33 ± 1.38	−0.056	0.683	0.029	0.831	−0.013	0.925	**−0.289**	**0.031**
REL NREM3	1.92 ± 1.60	0.070	0.609	−0.059	0.663	0.085	0.543	**0.419**	**0.001**
REL REM	0.16 ± 0.39	0.142	0.298	−0.253	0.060	0.068	0.626	0.005	0.972

FDS = focal dyscognitive seizures; NREM = Non Rapid Eye Movement sleep; PDD/DDD = prescribed daily dose/defined daily dose; REL = Relative Spike Density (spiking rate in a state/mean spiking rate determined for all sleep stages and wakefulness); REM = Rapid Eye Movement sleep;
[a] The "p" levels of significance were determined by Pearson's correlation test and a "p" value < 0.05 was considered to be statistically significant and they are indicated in bold type.

Unfortunately, due to patients' lack of collaboration, there were no baseline sleep log, so it is possible that patients were relatively sleep deprived on admission. To investigate whether there was sleep deprivation and minimize this effect, we interviewed patients at hospital admission for presurgical evaluation (VEEG) and we have registered how many hours the patient had slept the night before. PSG respiratory measures (apnea hypopnea index) were not included; it is possible that underdiagnosed sleep apnea was present in some patients, which could exacerbate baseline sleep disruption. Despite not being the ideal method, we recorded the desaturation index to control for this variable. Also, due to technical issues, limb movements (periodic limb movement index) could not be registered. At last, since PSG was performed on the first night of admission, the first night effect may have influenced some sleep parameters.

5. Conclusion

The present study evidences that a homogeneous group of drug-resistant patients with TLE-HS, with no known antecedent of sleep disorders, have disrupted sleep architecture characterized by sleep fragmentation, increased WASO and duration of NREM1 and 3 sleep, abnormal REM latency, reduced REM sleep; and higher rates of alpha-delta patterns, which were not observed among epilepsy patients previously. This disturbed sleep had an impact on daytime sleepiness as measured by self-reported sleep questionnaires. Furthermore, our findings support the hypothesis that processes related to NREM sleep, mainly deep NREM sleep, activate focal IEDs and also that IEDs recorded during sleep, particularly in REM stage, have higher localizing value.

Conflict of interest

The authors declare that they have no conflict of interest with respect to the work submitted in this article.

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[38] CAPES: Coordination of Improvement of Higher Education Personnel;
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