Sleep instability among adults with non-refractory temporal lobe epilepsy

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Sleep Instability in Adults with Non-Refractory Temporal Lobe Epilepsy

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Abstract

Purpose: The aim of this study was to analyze sleep instability using Cyclic Alternating Pattern (CAP) during NREM sleep in patients with non-refractory Temporal Lobe Epilepsy (TLE) compared to control subjects.

Material and Methods: Our sample comprised 13 patients who underwent a neuroimaging examination and were diagnosed with non-refractory TLE, and 13 normal subjects. The sleep parameters and CAP analyses were assessed according to international criteria. We used the Mann-Whitney U-test with a significance level of 5%.

Results: The age of our subjects were similar between patients and the control group (33.8 ± 8.5 y.o. *vs* 26.1 ± 9.2 y.o., respectively), and all of them showed normal sleep efficiency. Patients with non-refractory TLE showed an increase in the CAP rate and longer CAP time compared to the control group ($p < 0.001$). We found a higher arousal index during NREM sleep compared to normal controls (10.2 ± 2.9 *versus* 6.3 ± 1.7; $p = 0.001$, respectively). However, the arousal index during REM sleep was similar in both groups ($p=0.075$). A subgroup analysis performed on both genders showed no significant differences.

Conclusion: Patients with non-refractory TLE showed an increased in CAP rate and arousal index compared to normal control subjects. Sleep instability might be associated with epilepsy itself and may reflect the relationship between the epileptic foci and systems responsible for sleep maintenance and stability. CAP may serve as a useful marker of endogenous circadian rhythms in mild disorders. Further studies are required to elucidate the role of sleep instability in TLE.

Introduction

Temporal Lobe Epilepsy (TLE) is characterized by a number of clinical conditions or epileptic syndromes with partial complex seizures [1]. TLE is the most common epileptic syndrome in adults [2], and approximately 30% to 40% of these patients exhibit refractory seizures [3]. A relationship between refractory seizures and changes in the organization of sleep has been described in patients with TLE compared to normal controls [4,5]. Sleep and epilepsy exert a reciprocal effect [6-9]. Sleep stages modulate interictal and ictal epileptic phenomena: NREM sleep facilitates these phenomena, whereas REM sleep inhibits them [10]. Sleep may also cause important changes in interictal EEGs, particularly in terms of frequency, morphology, spatial distribution of epileptic discharges and seizure occurrence, also the thalamocortical and corticothalamic projections mediate a complex pattern of reciprocal interactions between thalamus and the cortex [11]. Interictal manifestations in the form of sharp-waves recorded in EEGs result from the depolarization and hyper polarization of cortical neurons [12]. In addition, processes relating to slow-wave sleep, including the progressive hyper polarization of thalamocortical neuronal projections may contribute to the activation of interictal epileptogenic discharges in partial epilepsy [13].

The Cyclic Alternating Pattern (CAP) is an EEG pattern expressed with periodic phasic activities in NREM sleep and is present in approximately 30% of NREM sleep in healthy adults [14]. These elements may occur during sleep as a physiological response to ambient or endogenous stimuli, resulting in patterns of CAP phases A and B and non-CAP (NCAP) during NREM sleep [15]. CAP is a pattern associated with sleep instability, where alternating between fragments with EEG phenomena relating to transitory activities (phase A) and a return to base, as well as the inhibitory activities of these events (phase B). CAP represents a powerful predisposing condition for the occurrence of nocturnal motor seizures, which arise in concomitance with phase A [16]. Phase A of the CAP has also been associated with activation of the autonomic system and phase B has been associated with its inhibition, resulting in a CAP cycle with a period of sleep instability and an NCAP cycle with stable sleep [17,18]. Various factors, such as stress, anxiety, humoral disorders, pain, drugs and/or ambient conditions may perturb sleep, thereby increasing its instability, which may be expressed as an increase in CAP rate in NREM sleep [19]. Most sleep disorders and ictal and/or interictal epileptic activity in EEGs are intimately associated with arousal during sleep and CAP cycles. Thus, the pathological events of sleep and sleep instability are interrelated. On the one hand, CAP is predisposed to the occurrence of pathological events of sleep, and on the other hand, these pathological events increase sleep instability [20].

Typically, epileptic phenomena are sensitive to the duration of the arousal response level [20]. The CAP/NCAP modality affects the epileptiform activity and distribution of discharges in epilepsy lesions that grow during phase A of CAP [21]. Due to vigilance fluctuations, the presence of muscle tonus and activation of the autonomous system, CAP represents a favorable condition for the occurrence of generalized discharges, lesion foci and motor seizures. All of these changes are strongly connected with phase A, which is a phase of activation during the CAP cycle. In contrast, phase B is related to the inhibition of this phenomenon in patients with epilepsy [15]. The effect of the CAP, particularly in phase A, on secondary bisynchronous discharges, suggests a crucial integration between thalamocortical circuits, modulation of disorders and the mechanisms/regulators of epileptic generalization. Epileptiform activity in the lesion foci is regulated by mechanisms responsible for controlling the epileptic response and synchronization of EEG during sleep [21]. Analysis of sleep on the basis of CAP parameters provides a sensitive means to explore the connection between EEG dynamic events and epileptic phenomena [20]. Furthermore, analyses of CAP parameters have shown changes in primary generalized epilepsies and an absence of regulation in epileptiform activity by CAP and NCAP periods in benign infant partial epilepsies. However, the effect of CAP in temporal lobe epilepsies still remains unclear. The aim of this study was to analyze CAP expression in non-refractory TLE compared to a control group.

Material and Methods

Sample description

This study included 13 patients (7 females and 6 males) between the ages of 23 and 49 years (mean age = 33.8 ± 8.5 years old) who met the diagnostic criteria for non-refractory TLE without primary sleep disorder (Table 1). The control group consisted of 13 healthy volunteers (5 females and 8 males) between the ages of 19 and 53 years (mean age = 26.1 ± 9.25 years) who did not display any evidence of systematic, neurological or Sleep Disorders (SD). All of the patients were subject to a clinical neurological evaluation, as well as a polysomnographic and neuroimaging examination. The inclusion criteria included a clinical history compatible with a partial seizure complex according to the ILAE classification of an epileptic seizure [22], the presence of focal discharge over temporal regions, a seizure-free period for at least four weeks prior to the study and lack of participation in polytherapy. The exclusion criteria included the presence of an SD on Polysomnography (PSG), such as sleep-related respiratory disorders, sleep movement disorders and insomnia. A signed consent form was obtained from all of the subjects and volunteers, and the study was approved by the local ethics committee [23].

Sleep conventional scoring

Polysomnograms were obtained using a digital system and were subsequently analyzed using analysis software that was an integral component of the instrument. The technical characteristics of the biological signal acquisition included the following: impedance of entrance: >500 MOhm, common mode rejection >100 dB, interference between channels <0.5%, measurement scale of 0.2 mkV up to 5.0V, internal noise (with a gain constant x 20,000) 10 nV. All of the signals were sampled at a frequency of 512 Hz. For the EEG recordings, a gain constant of x10,000 was used, and the filter was set at 0.1 to 120 Hz. The EEG recording was acquired from 20 electrodes (FP1, FP2, F3, F4, F7, F8, T3, T4, T5, T6, P3, P4, O1, O2, FZ, CZ, PZ) in patients with TLE and 12 electrodes (F3, F4, T3, T4, P3, P4, O1, O2, FZ, CZ, PZ) in the control group. The electrodes were positioned on the scalp using electrolytic paste according to the "10-20" international electrode placement system, as recommended by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) [24], with reference to M1/M2. Computerized reconstruction of bipolar and average reference derivations was available. Throughout the entire night, polysomnographic recordings of the following parameters were performed: EEG, electromyogram, electro-oculogram, electrocardiogram, nasal airflow, thoracic and abdominal respiratory effort, transcutaneous oximetry and snoring [25].

Analysis of sleep architecture

Sleep was visually staged according to the standard American Academy of Sleep Medicine (AASM) criteria [26,27]. The following parameters were analyzed: time in bed, sleep period time, Total

Table 1: Clinical characteristics of patients with non-refractory temporal lobe epilepsy.

Subject	Age(Years)	Gender	Etiology	EEG	MRI	AED
1	35	F	S	RT	Hippocampal sclerosis	OXC, VPA
2	37	M	C	RT	Normal	CBZ, PHT
3	49	M	C	LT	Normal	CBZ, VPA
4	44	F	C	LT	Normal	CBZ, OXBZ
5	18	F	S	LT	Temporal arachnoid cyst	CBZ, VPA
6	26	F	C	LT	Normal	CBZ
7	40	M	C	LT	Normal	CBZ
8	34	M	C	RLT	Normal	OXC, PHT
9	29	F	C	RT	Normal	CBZ
10	33	M	S	RT	Hippocampal sclerosis	OXC
11	23	F	C	LT	Normal	VPA, BZD
12	39	F	C	RT	Normal	CBZ
13	33	M	C	RT	Normal	BZD

S -symptomatic epilepsy; C - cryptogenic epilepsy; RT, right temporal, LT, left temporal; RLT, right and left temporal.

Sleep Time (TST), wake after sleep onset, sleep onset latency, REM latency, number of stage shifts, sleep efficiency, percentage of TST spent in sleep stages N1 (N1%), N2 (N2%), N3 (N3%) and REM sleep (REM%).

Analysis of arousal events

Arousal events were scored in NREM and REM sleep according to the ASDA scoring guidelines: NREM sleep was characterized by an abrupt shift in the EEG frequency, which included theta, alpha and/or frequencies greater than 16 Hz (but not spindles) with duration of 3 to 15 sec, with or without an increase in submental tonus. In REM sleep, arousal was determined when sleep was accompanied by an increase in submental tonus. The following variable values were analyzed: number of arousals, number of arousals in NREM sleep, number of arousals in REM sleep, total duration of arousals in REM sleep, arousal index, arousal index in NREM sleep and arousal index in REM sleep.

Visual analysis of CAP

Visual scoring, registration and classification of CAP events were performed in accordance with the parameters previously described by Terzano and colleagues [28]. The CAP was defined as a pattern of EEG during NREM sleep phase, consistent with phases A and B; their sum was termed the CAP cycle. Two consecutive CAP cycles were necessary to define a CAP sequence. The last phase A was not included in the duration of the CAP sequence and was used to define the end of the second sequence cycle. Phase A of the CAP was characterized by phasic events (abrupt changes in frequency and amplitude in relation to basal activity) of the periodic nature of NREM sleep with a duration of 2 to 60 sec, which characterizes phase B. The amplitude of the phasic events should be 1/3 greater than the amplitude of the basal activity, which was visualized at 2 sec before and after the appropriate phasic event. Phase A of the CAP may include delta bursts, vertex sharp transients, K-complex sequences with or without spindles, polyphasic bursts, K-alpha, intermittent alpha and EEG arousals [28]. The following parameters of the CAP in NREM were analyzed in this study: the mean duration of phases A and B, CAP time, CAP rate, all parameters in NREM. The CAP rate was defined as the percentage ratio of total CAP time to total NREM sleep time (CAP time/NREM Sleep time).

Our study was performed using visual scoring of CAP after a previous scoring of sleep in accordance with international criteria [24,25]. CAP events were registered according to the criteria [28]. Moreover, the CAP was analyzed in all of the channels with monopolar derivation with references to M1/M2, including 13 channels (F3, C3, P3, T3, O1, F4, C4, P4, T4, O2, Fz, Cz and Pz) that were submental to EMG, EOG and ECG. The derivations were mounted considering that delta bursts exhibit major expression in frontal and temporal derivation, sharp-waves of the vertex and K-complexes in the central derivations and alpha frequency in the parieto-occipital regions [28]. The CAP events were registered by two independent researchers who were blind to the clinical conditions of the subjects.

Table 2: Sleep parameters in patients with temporal lobe epilepsy and control subjects.

	TLE (n=13)	Controls (n=13)	P-value
Age	33.8 ± 8,5	26.1 ± 9.25	
F:M	7:06	5:08	
Time in bed (min)	432.7 ± 22.4	442.5 ± 17.1	0.22
Total sleep time (min)	390.7 ± 16.6	400.3 ± 19.8	0.195
Sleep on set latency (min)	5.8 ± 2.4*	14.,2 ± 7.6	0.002
REM latency (min)	90.4 ± 26.9	95.9 ± 39	0.682
Stage shifts	91.1 ± 25.7*	68.2 ± 12.8	0.008
Wake after sleep onset (min)	26.2 ± 14.7	21.9 ± 10.2	0.812
Sleep efficiency (%)	90.4 ± 2.9	90.6 ± 2.7	0.395
N1%	5.46 ± 3	4.38 ± 1.3	0.249
N2 %	57.1 ± 6.2	55 ± 4	0.321
N 3 %	15,6±3,4	18,6± 2,5	0.148
REM %	21.9 ± 3,7	21.9 ± 2.4	1
Arousals (n)	66.5 ± 20*	41.8 ± 9	0.001
Arousals in NREM sleep (n)	52.9 ± 19.6*	31 ± 9.5	0.002
Arousals in REM sleep (n)	13.6 ± 5.6	10.8 ± 3.7	0.14
Arousals total duration (sec)	549.1 ± 170.3*	357.2 ± 88.5	0.002
Arousal index /TST (n/h)	10.2 ± 2.9*	6.3 ± 1.7	0.001
Arousal index /NREM (n/h)	10.3 ± 3.4*	6 ± 2	0.001
Arousal index /REM (n/h)	9.7 ± 3.8	7.4 ± 2.4	0.075
Apnea/hypopnea index (n/h)	< 5	< 5	NS
Periodic limb movements (n/h)	< 5	< 5	NS

TLE - Temporal Lobe Epilepsy; TST: Total Sleep Time; N1%, N2%, N3%, REM% - percentage of TST spent in sleep stages N1, N2, N3 and REM; n - number; n/h - number per hour; NS - not significant.
Data are presented as the mean ± SD; Student's t-test with P<0.05.

Statistical analysis

The measures of central tendency resulting from the measures of dispersion were calculated. The two groups were compared using the Student t-test and confirmed using the Mann-Whitney U-test in cases of data asymmetry. The level of significance was established as 5%.

Results

All of the subjects in this study exhibited normal sleep efficiency. The sleep parameters were significantly different between patients with non-refractory TLE and the control group (Table 2). Patients with non-refractory TLE demonstrated a smaller sleep latency, increase in sleep stage shift, greater number of arousals, greater number of arousals in NREM sleep, longer total duration of arousals, longer total duration of arousals in NREM sleep, increase in arousal index and increase in arousal index in NREM sleep (Table 2). The CAP

Table 3: CAP parameters in patients with non-refractory temporal lobe epilepsy.

	TLE (n=13)	Controls (n=13)	P-value
CAP rate (%)	44.02 ± 5.23*	31.83 ± 3	< 0,001
CAP time (min)	133.77 ± 15.56*	99.38 ± 9.6	< 0,001
Phase A (sec)	9.27 ± 1.15	8.7 ± 0.61	0.131
Phase B (sec)	22.92 ± 1.71	21.54 ± 1.78	0.054

CAP, cyclic alternating pattern; TLE - temporal lobe epilepsy; Data are presented as the mean ± SD; Student's t-test with P < 0.01.

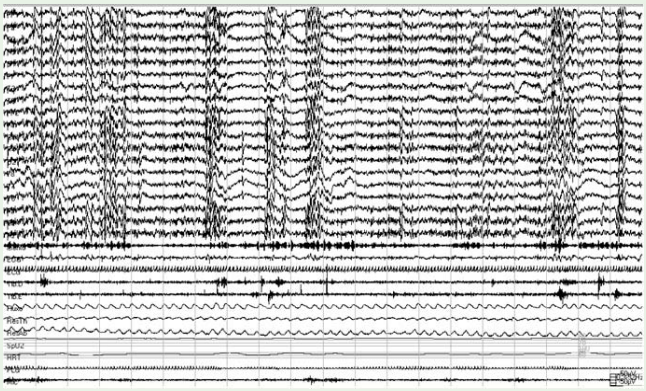

Figure 1: This figure shows a patient (33 years old) with 38.8% of CAP rate and epileptic discharges in the right temporal region during N2 stage of NREM sleep.

expression between the groups also showed significant differences, particularly in the CAP rate ($p < 0.001$). The patients with TLE had an increased CAP rate and longer duration of CAP time compared to the control group. The duration of phases A and B did not significantly differ (Table 3), and we did not identify differences between genders. The figure 1 showed an example of CAP event in stage N2 of NREM sleep in a patient with non refractory TLE.

Discussion

Our results showed that patients with non-refractory TLE had an increase in the expression of the CAP rate and the duration of the CAP was longer compared to the control group. Interestingly, there was no difference in the average duration of phases A and B between the two groups. The CAP modulation in patients with TLE needs to be further clarified [29]. Until recently, there have been few studies related to lesions, refractory epilepsy and/or ictal EEG. Terzano et al [21] observed an increase in the expression of the CAP rate in patients (mean age: 27 years) with frontal and temporal lesion epilepsy compared to the control group (53% *versus* 31%). The epileptiform activity in TLE more commonly occurred in NREM compared to REM without significant differences in the frequency of this activity during CAP and NCAP period, suggesting that CAP may be a neurophysiological oscillator that modulates the expression of epileptiform activity in TLE [30].

The expression of the CAP rate in patients with TLE varies between 30% and 53% among studies [21,31]. Arun kumar et al [31] analyzed the sleep microstructure in 8 patients with TLE (between the ages of 22 and 50 years). In this study, CAP rate was 30%, which was not significantly higher than the control subjects (respectively 23%), without variability in the CAP rate from one night to another in stages 1-2 and 3-4 of NREM sleep. This study suggested the absence of modulation of the CAP in TLE [31]. However, changes in sleep microstructure were described in patients with TLE and refractory FLE, demonstrating a frequent association between "epileptic complex-K" and arousal responses [32]. These controversial data were most likely dependent on protocols and/or patient selection. In a study conducted by Arun kumar et al [31], there was no description of the clinical characteristics of the patients. Our results indicated a CAP rate (44%) that was lower than those observed in a study by Terzano et al [21] in patients with frontotemporal lesion epilepsy. Our findings suggested that there was sleep instability in patients with TLE. These results were consistent with the data currently in the literature on sleep instability, which is commonly observed in patients with epilepsy in the absence of nocturnal seizures [17].

Ferrillo et al [33] described the important role of EEG synchronization in the modulation of interictal epileptiform abnormalities using spectral analysis of EEG frequencies in patients with partial epilepsy. It is known that the CAP interacts with EEG synchronization in all sleep stages [34]. The epileptiform phenomena were activated by processes of epileptiform oscillations with an increase in sleep synchronization [35,36] and/or in the conditions of cortical diffused excitability [37,38]. The progression of different stages of NREM sleep resulted in the balanced function of the arousal systems and maintenance of sleep. This balance was responsible for the promotion of cortical arousal and sleep via slow oscillations of <1 Hz, which was regulated by ultra-slow oscillations (0.002-0.02 Hz) [39]. These oscillations were expressed as cerebral bioelectric activity using the CAP14 and internally resulted from the confluence of different rhythms, as a consequence of the interaction between different physiological subsystems affected by reciprocal intrinsic connection [40]. Similarly, in the absence of nocturnal seizures, sleep fragmentation and diurnal excessive somnolence might increase due to sleep instability, which results from epileptic discharges [40]. Moreover, the bidirectional effect between the CAP and epileptiform activity has been discussed, and the interrelationship of these phenomena may involve the predisposition of the CAP to the occurrence of epileptiform events, as well as an increase in sleep instability caused by pathological events [41,42]. Sleep instability may also cause changes in the expression of the NREM/REM cycle, independent from the EEG patterns at every stage of NREM sleep [43-47]. Furthermore, Terzano et al. [2005] [40] suggested that the sleep microstructure may also modulate the expression of ictal discharges. The lesion epileptiform activity most likely suffers from a dual regulation via the control of mechanisms responsible for the arousal and synchronization of EEG during sleep [21,29].

We found changes in the parameters of sleep fragmentation compared to the control group. Markers of sleep fragmentation were higher than the control group, indicating an increase in the number of stage shifts, number of arousals and number of arousal indices in NREM and REM sleep (Table 2). Our data were consistent with previous reports on sleep fragmentation in patients with TLE [32,46,47].Yu-Dan et al. (2013) previously showed that there was an association between epileptic form discharges and the sleep cycle in 200 patients with epilepsy [48]. This association was particularly higher in cases of temporal lobe epilepsy. In addition, these patients demonstrated longer mean sleep time during lighter sleep stages [48]. This data might explain the cognitive dysfunction and daytime symptoms observed in some patient cases, even though the seizures were under control. There was also an intra-sleep condition consisting of highly fluctuating vigilance, which constitutes the real substrate for the occurrence of epileptic seizures [49]. Moreover, conditions during sleep can change according to sleep structure, as has been described for nocturnal frontal lobe epilepsy, where the first cycle represents a powerful predisposing condition for the occurrence of nocturnal seizures [50]. Children and adults with mild sleep disorder breathing showed an increase in CAP rate [51,52] Various factors, such as surgery stress, anxiety, humoral disorders, pain, drugs and /

or ambient conditions may perturb sleep, [53-55] thereby increasing its instability, which may be expressed as an increase in CAP rate in NREM sleep.

Anti-Epileptic Drugs (AEDs) may alter sleep structure, contributing to sleep fragmentation and instability, or may cause a stabilizing effect on sleep, consistent with drugs and applied therapeutic schemes [56-58]. In our study, all of the subjects epileptic syndromes were under control, as determined by a clinical evaluation and the absence of seizures for at least 4 weeks after the sleep evaluation. Moreover, none of our patients were treated with polytherapy AED schemes. The real effect of the epileptic foci on sleep was most likely dependent on several factors, including epileptical syndrome, distribution of seizures in the wake sleep cycle, combination of AED and sleep comorbidities (such as disordered sleep breathing, sleep deprivation and individual sleep variations in biological rhythms). According to some authors, CAP is associated with surges of sympathetic nervous system activity, heightened baro reflex sensitivity, an increase in blood pressure and vasoconstriction, particularly unstable heart rhythm and breathing [54]. These changes in the rhythms during sleep can explain how sleep disorders may change the endogenous circadian rhythms, and may increase the morbidly and mortality in all age spans. CAP is a very sensitive measure and can provide early information on repercussions of circadian rhythm sleep disorder. We found an application of CAP analyses in non-refractory epileptic patients. Probably, CAP is useful to detect early changes in mild sleep disorders. In conclusion, our data showed an increase in sleep instability due to changes in the expression of CAP rate in patients with non-refractory TLE. Sleep instability in patients with TLE might also be associated with epilepsy itself and may reflect the relationship between the epileptic foci and systems responsible for sleep maintenance and stability. The number of participants in our study was low this may be a limitation in drawing conclusions. Further studies are needed to evaluate the influence of sleep instability in pathophysiological processes in epileptic patients.

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