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Original Article

Effect of carbamazepine on the sleep microstructure of temporal lobe epilepsy patients: a cyclic alternating pattern-based study

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ABSTRACT

Background: Studies looking at the effect of anti-epileptic drugs on the sleep microstructure of patients with epilepsy are scarce. The aim of this study was to compare the sleep microstructural characteristics of drug-naive temporal lobe epilepsy (TLE) patients and those on carbamazepine (CBZ) monotherapy.
Methods: Three age-matched ($p = 0.286$) and sex-matched ($p = 0.398$) groups were studied: drug-naive TLE (n = 20); TLE on CBZ (n = 20); and healthy controls (n = 40). All groups underwent overnight polysomnography. Scoring and analysis of arousals and cyclic alternating pattern (CAP) parameters were performed. Comparison of arousal parameters and CAP parameters was performed using either one-way analysis of variance or the Kruskal–Wallis test, followed by pairwise comparisons ($p \leq 0.05$).
Results: Rapid eye movement (REM) arousal indices and overall CAP rates were higher in patients with TLE (group 1, $p < 0.001$; group 2, $p < 0.001$) compared to controls. Furthermore, the overall CAP rate was higher in patients on CBZ. The CAP cycle/sequences indices (group 1, $p < 0.001$; group 2, $p < 0.001$) were higher, and conversely, the average duration of CAP cycles/sequences (group 1, $p = 0.018$; group 2, $p = 0.003$) was lower in patients with TLE. Finally, an increase in A2 percentage was noted in patients with TLE (group 1, $p = 0.011$; group 2, $p = 0.011$).
Conclusion: We found significant alterations in REM arousal indices and CAP parameters in patients with TLE as compared to controls. Moreover, many of these CAP alterations were greater in patients on CBZ. These findings suggest that anti-epileptic drugs such as CBZ may augment arousal instability in patients with TLE, and hence worsen sleep quality and continuity.

1. Introduction

Poor nighttime sleep quality accompanied by excessive sleepiness during the day is a common accompaniment with epilepsy [1,2]. It is quite common to come across patients with epilepsy who have either a single underlying sleep disorder or a combination of various sleep disorders [3,4]. Anti-epileptic drugs (AEDs) are significant contributors to sleep problems in patients with epilepsy, irrespective of their mechanism of action [5,6]. Carbamazepine (CBZ) is a commonly used AED to treat patients with partial epilepsy and is known to have variable effects on sleep architecture [7,8]. Polysomnographic (PSG) studies have shown increased numbers of stage shifts, reduced rapid eye movement (REM) sleep, and increased REM sleep fragmentation, and these effects were almost completely reversed after chronic treatment [8].

Although traditional visual sleep scoring provides a valuable description of the overall sleep architecture [9,10], it fails to provide information regarding electroencephalographic (EEG) frequency characteristics or rhythmicity that underlie sleep disturbances, and needs to be addressed using sleep microstructural analysis [11]. Analysis of sleep microstructure can provide additional insights regarding the subtle beneficial or deleterious effects of CBZ on sleep architecture in patients with epilepsy.

The aim of this study was to compare the microstructural polysomnographic (PSG) characteristics in drug-naive temporal lobe epilepsy (TLE) patients and those on carbamazepine monotherapy, using arousal and cyclic alternating pattern (CAP) analysis, which

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may highlight the role of CBZ in causing alteration of arousal patterns in patients with epilepsy.

2. Methods

2.1. Patients

This is a cross-sectional, hospital-based, case-control study that was conducted at a tertiary neurology center in southern India from March 2013 to February 2015. According to International League Against Epilepsy (ILAE) classification of epilepsy and epileptic syndromes (1989) [12], TLE is characterized by retained consciousness and the presence of unusual sensations which may be amnestic, such as déjà vu (a feeling of familiarity), jamais vu (a feeling of unfamiliarity), a specific single or a set of memories, amnesia, auditory (such as a sound or tune), gustatory (such as a taste), or olfactory (such as a smell that is not physically present). This is usually followed by motionless staring, automatic movements of the hands or mouth, altered ability to respond to others, unusual speech, or unusual behaviors. In some people, seizures may spread to involve the whole of the brain, and if this happens it is called a secondarily generalized seizure. Forty patients diagnosed with TLE, 20 drug-naive (mean age: 24.15 ± 9.92 years; male:female = 13:7) and 20 on CBZ monotherapy (mean age: 25.85 ± 6.54 years; male:female = 9:11), attending the neurological services and fulfilling the criteria for TLE laid down by the ILAE commission [12] were recruited. Patients were excluded if they used any medications (other than CBZ) known to affect sleep at study-entry, had a history of drug or substance abuse of any degree, had a primary sleep disorder, or reported any coexisting medical, psychiatric, or surgical disorder known to affect sleep. Patients on CBZ monotherapy were excluded if they were noncompliant or stopped medications during the period of the study. A total of 40 healthy controls (mean age: 23.85 ± 4.91 years; male:female = 24:16) consisting of friends/unrelated volunteers (n = 28) of the patients from similar educational and socioeconomic status and medical personnel (six doctors and six medical technologists) of the hospital on routine day duties (9:00 a.m.–4:30 p.m.) were also recruited, which were age (p = 0.286), sex (p = 0.398), and body mass index (BMI) (p = 0.154) matched with patients. Controls were not related to patients and also did not have family history of seizures or any other medical or neurological illness. All subjects were screened for underlying sleep disorders such as sleep-disordered breathing, periodic limb movement disorders, narcolepsy, insomnia, restless legs syndrome, and parasomnias using the National Institute of Mental Health and Neurosciences (NIMHANS) Comprehensive Sleep Disorders Questionnaire (NCSDQ) [13]. All subjects were ≥12 years of age in view of their participation in the evaluation and completing the sleep questionnaires. Ethical approval for the study was obtained from the Institute Ethics Committee (IEC). Written informed consent was obtained from the study subjects and/or parents.

2.2. Sleep questionnaire assessment

Validated sleep questionnaires including the Epworth Sleepiness Scale (ESS) to assess daytime somnolence [14] and the Pittsburgh Sleep Quality Index (PSQI) to assess nighttime sleep quality [15] were administered to all of the study subjects. The NIMHANS Comprehensive Sleep disorder questionnaire (NCSDQ) was administered to rule out various sleep disorders [16].

2.3. Polysomnography

Overnight PSG recording was performed (Sleepscan Vision Collection Software, version 7.11.01, Bio-Logic Systems Corp., Mundelein, IL, USA) after obtaining a written informed consent from all participants using standard protocols. The parameters recorded included (1) an eight-channel EEG using bi-hemispheric referential montage (F7-A2, C3-A2, T3-A2, O1-A2, and F8-A1, C4-A1, T4-A1, O2-A1): sensitivity 7 μV/mm, high-pass filter 0.3 Hz, low-pass filter 35 Hz, (2) two-channel electro-oculogram (EOG) for eye movements, sensitivity 10 μV/mm, high-pass filter 0.3 Hz, low-pass filter 35 Hz, (3) electromyogram (EMG) from the sub-mentalis and right tibialis anterior muscle: sensitivity 3 μV/mm and 20 μV/mm respectively, low-pass filter 0.3 Hz, low-pass filter 100 Hz, (4) electrocardiogram (ECG): sensitivity 20 μV/mm, low-pass filter 0.5 Hz, low-pass filter 35-Hz, (5) body position monitor, and (6) respiratory events: oro-nasal airflow using thermistor (sensitivity 7 μV/mm, high-pass filter 0.5 Hz, low-pass filter 15 Hz), chest and abdominal wall movements using strain gauge (sensitivity 10 μV/mm, high-pass filter 0.5 Hz, low-pass filter 15 Hz), snore (sensitivity 2 μV/mm, low-pass filter 10 Hz, low-pass filter 100 Hz), and arterial oxygen saturation (sensitivity 7 μV/mm, low-pass filter 70 Hz). All channels were sampled at 256 Hz; electrode impedance was kept at less than 5000 Ω, and a notch filter of 50 Hz was applied to remove noise artifact caused by electrical power lines. The subjects were allowed to fall asleep spontaneously, and the recording was continued until their spontaneous awakening in the morning. All subjects reported a comfortable, undisturbed, and refreshing sleep.

2.3.1. Analysis of sleep macrostructure

Sleep was scored visually in 30-s epochs using standard criteria [17]. The conventional PSG parameters studied included total time in bed (TIB) (minutes), total sleep time (TST) (minutes), sleep latency (minutes), rapid eye movement (REM) latency (minutes), sleep efficiency (%), wake after sleep onset (WASO) (minutes), as well as percentage of non-REM (N1, N2, N3) and REM stages. Visual analysis of the chin EMG tone during REM was performed in both patients and controls. Periodic limb movement (PLM) as well as apnea–hypopnea indices (AHI) were also assessed.

2.3.2. Analysis of sleep microstructure

Sleep microstructure evaluation included detection of the arousals and CAP analysis.

2.3.2.1. Detection and analysis of arousals. The number of arousals occurring during the entire period of sleep, as well as that during each of the various sleep stages, were computed. An arousal was defined as an abrupt shift in EEG frequency, including alpha, theta and/or frequencies higher than 16 Hz (but not spindles) lasting at least three seconds, with at least 10 s of stable sleep preceding the change. Scoring an arousal in REM sleep mandated an additional increase in chin EMG tone for at least one second. Complete awakening from sleep was not counted as an arousal. An arousal could be accompanied by an increase in EMG activity, heart rate, and/or body movements [18].

2.3.2.2. Cyclic alternating pattern (CAP) analysis. CAP analysis was performed manually as per the criteria provided by Terzano et al. [19]. A CAP sequence was composed of a succession of CAP cycles comprising a phase A and the following phase B, which is the interval between two consecutive phases A. CAP sequences have no upper limits for duration and number of CAP cycles. Conversely, the lower limit to define a CAP sequence requires at least two consecutive CAP cycles. Therefore, the CAP sequence is defined as three or more A phases separated from each other by at least two seconds and no more than 60 s. All CAP sequences begin with a phase A and end with a phase B. Each phase of CAP may vary from 2 to 60 s in duration. Accordingly, a phase A is scored within a CAP sequence only if it precedes and/or follows another phase A up to