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Original Article

Effect of valproate on the sleep microstructure of juvenile myoclonic epilepsy patients – a cross-sectional CAP based study

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ABSTRACT

Objective: Studies looking at the effect of anti-epileptic medications on sleep microstructure of patients with epilepsy are almost non-existent. The aim of this study was to compare sleep microstructural characteristics of drug-naïve juvenile myoclonic epilepsy (JME) patients with those on valproate (VPA) monotherapy.

Methods: Three age- ($p = 0.287$) and gender- ($p = 0.766$) matched groups ($N = 20$ in each group): (1) drug-naïve JME (mean age: 21.2 ± 4.06 years; M : F = 9:11); (2) JME on VPA (mean age: 21.85 ± 4.28 years; M : F = 11:9); (3) healthy controls (mean age: 23.2 ± 3.82 years; M : F = 9:11) underwent overnight polysomnography. Scoring and analysis of arousals American Sleep Disorders Association (ASDA, 2002), cyclic alternating pattern (CAP) (Terzano et al., 2002) parameters were performed. Comparison of arousal and CAP parameters was performed using one-way ANOVA, followed by pairwise comparisons using Fisher's LSD test ($p \leq 0.05$).

Results: Rapid eye movement (REM) arousal indices were higher in JME patients (Group 1 [$p = 0.002$] and Group 2 [$p < 0.001$]), whereas the overall and NREM arousal indices were comparable between the three groups. CAP rate was higher in JME patients as compared to controls ($p < 0.001$). Duration of phase A and its subtypes ($p < 0.001$) was reduced in drug-naïve patients as compared to VPA group and controls. Finally, percentage of phase A1 ($p = 0.003$) was decreased and A3 ($p = 0.045$) was increased in drug-naïve patients as compared to VPA group and controls.

Conclusions: We found significant alterations in REM arousal indices and several CAP parameters in JME patients. However, many of these alterations were not seen in the valproate group. This might indicate that anti-epileptic medications such as valproate may beneficially modulate arousal instability in JME patients, and hence promote sleep quality and continuity.

1. Introduction

The sleep quality in patients with epilepsy is frequently compromised by various factors interfering with the continuity of the sleep state. These factors lead to disruption of normal sleep architecture causing frequent arousals, awakenings, and stage shifts, and eventually manifesting as sleep disorders [1]. Most antiepileptic medications (AEDs), especially the conventional ones, might exacerbate sleep disorganization and further impair sleep quality in these patients on AEDs [2,3]. However, sodium valproic acid (VPA), a frequently used AED for most of the generalized epilepsy syndromes, is shown to have little or even no effect on sleep amount and macrostructure under therapeutic doses [4] and has sometimes been reported to improve sleep efficiency [5].

Although traditional visual sleep scoring provides a valuable description of the overall sleep macrostructure [6,7], it fails to provide information regarding electroencephalogram (EEG) frequency characteristics or rhythmicity that underlies sleep disturbances and needs to be addressed using sleep microstructural analysis [8]. Analysis of sleep microstructure using cyclic alternating pattern (CAP) can provide additional insights regarding the subtle beneficial or deleterious effects of VPA on sleep architecture in patients with epilepsy.

In this study, we hypothesized that there is probably an alteration in the pathophysiologic mechanisms regulating arousal patterns in patients with JME. Our aim was to compare the microstructural polysomnographic (PSG) characteristics in drug-naïve juvenile myoclonic epilepsy (JME) patients and those on valproate monotherapy, using Arousal and CAP analysis, which may highlight the role of VPA in causing alteration of arousal patterns in patients with epilepsy.

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2. Materials and methods

2.1. Patients

This is a cross-sectional, hospital-based, case-control study that was conducted at a tertiary neurology centre in south India from March 2010 to February 2013. The International League Against Epilepsy (ILAE) commission on Classification and Terminology (1989) defined JME (impulsive petit mal) as follows: "Impulsive petit mal appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. Often, there are generalized tonic-clonic seizures (GTCS) and, less often infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation [9]." Forty patients diagnosed with JME, 20 drug naïve (mean age: 21.2 ± 4.06 years; M : F = 9:11) and 20 on VPA monotherapy (mean age: 21.85 ± 4.28 years; M : F = 11:9), attending the neurological services and fulfilling the criteria for JME laid down by the ILAE commission [9] were recruited. Patients were excluded if: (1) they used any medications (other than VPA) known to affect sleep at study-entry; (2) they had history of drug or substance abuse of any degree; (3) they had abnormal brain imaging; (4) they had a primary sleep disorder; or (5) they reported any co-existing medical, psychiatric or surgical disorder known to affect sleep. Patients on VPA monotherapy were excluded if they were non-compliant or stopped medications during the period of the study. Twenty healthy controls (mean age: 23.2 ± 3.82 years; M : F = 9:11) consisting of friends/unrelated volunteers ($N = 14$) of the patients from similar educational and socioeconomic status and medical personnel (doctors = 3; medical technologists = 3) from the hospital on routine day duties (9.00 a.m.–4.30 p.m.) were also recruited, which were age ($p = 0.287$) and gender ($p = 0.766$) matched with patients. Controls were not related to patients and also did not have a 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 NIMHANS Comprehensive Sleep Disorders Questionnaire (NCSDQ) [10]. 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). A written informed consent was obtained from the study subjects and/or parents.

2.2. Clinical evaluation

All patients underwent a structured evaluation, including a detailed clinical, family and treatment history, neurological examination, 21-channel digital EEG recording using the international 10–20 system of electrode placement, brain imaging (magnetic resonance imaging, MRI), and other investigations when indicated. The mean age at onset of illness was 16.2 ± 4.04 years in Group 1 and 14.05 ± 4.29 years in Group 2. The average duration of illness was 5.0 ± 4.1 years in Group 1 and 6.9 ± 4.73 years in Group 2. All patients had myoclonic jerks, five of them (three in Group 1 and two in Group 2) not developing any other type of seizures till the time of the study. The mean duration ($p = 0.186$) and frequency ($p = 0.684$) of myoclonus in Group 1 (5.0 ± 4.1 years; 7.05 ± 1.96/day) and Group 2 (6.9 ± 4.73 years; 6.75 ± 2.61/day) was comparable. Except for five patients (three [15%] Group 1 and two [10%] Group 2), the rest had GTCS during the course of their illness. It was preceded by a series of myoclonic jerks (heralding myoclonus) in 8/17 (47.1%) in Group 1 and 3/18 (16.66%) in Group 2. The mean duration ($p = 0.181$) and frequency ($p = 0.688$) of GTCS in Group 1 (4.01 ± 4.65 years; 2.29 ± 1.89/month) and Group 2 (6.19 ± 5.05 years; 2.06 ± 1.55/month) were comparable. Only one patient had status epilepticus (Group 1: 0/20 [0%]; Group 2: 1/20 [5%]; $p = 0.311$) at any time during their disease course and three patients (Group 1: 1/20 [5%]; Group 2: 2/20 [10%]; $p = 0.548$) had features suggestive of absence attacks. Five patients (Group 1: 3/20 [15%]; Group 2: 2/20 [10%; $p = 0.633$) had a history of typical febrile seizures.

2.3. Sleep questionnaire assessment

Validated sleep questionnaires including Epworth Sleepiness Scale (ESS) to assess daytime somnolence [11] and Pittsburgh Sleep Quality Index (PSQI) to assess night-time sleep quality [12] were administered to all the study subjects. NCSDQ was administered to rule out various sleep disorders [13].

2.4. Polysomnography

Overnight PSG recording was done (Sleepscan Vision Collection Software, version 7.11.01, Biologic Systems Corp, 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, low-pass filter 0.3 Hz, high-pass filter 35 Hz; (2) two-channel electro-oculogram (EOG): for eye movements, sensitivity 10 μV/mm, low-pass filter 0.3 Hz, high-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, high-pass filter 100 Hz; (4) electrocardiogram (ECG): sensitivity 20 μV/mm, low-pass filter 0.5 Hz, high-pass filter 35 Hz; (5) body position monitor; and (6) respiratory events: oro-nasal airflow using thermistor (sensitivity 7 μV/mm, low-pass filter 0.5 Hz, high-pass filter 15 Hz), chest and abdominal wall movements using strain gauge (sensitivity 10 μV/mm, low-pass filter 0.5 Hz, high-pass filter 15 Hz), snore (sensitivity 2 μV/mm, low-pass filter 10 Hz, high-pass filter 100 Hz), and arterial oxygen saturation (sensitivity 7 μV/mm, high-pass filter 70 Hz). All channels were sampled at 256 Hz; electrode impedance was kept 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. None of the subjects had generalized seizures within the last 2 weeks of the PSG recording.

2.4.1. Analysis of sleep macrostructure

Sleep was scored visually in 30-s epochs using standard criteria [14]. The conventional PSG parameters studied included: total time in bed (TIB, min), total sleep time (TST, min), sleep latency (min), rapid eye movement (REM) latency (min), sleep efficiency (%), wake after sleep onset (WASO) (min), 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.

2.4.2. Analysis of sleep microstructure

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

2.4.2.1. 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, was computed according to the standard ASDA criteria [15]. The following arousal parameters were measured: arousal index (number of arousals per hour of sleep), NREM arousal index (number of arousals per hour of NREM sleep), and REM arousal index (number of arousals per hour of REM sleep).