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Original Article

Effects of antiepileptic treatment on sleep and seizures in nocturnal frontal lobe epilepsy

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ABSTRACT

Objective: To study the effects of antiepileptic treatment on sleep parameters and video-polysomnography (VPSG) seizures in nocturnal frontal lobe epilepsy (NFLE).
Methods: Twenty patients with a clinical and VPSG diagnosis of NFLE (baseline polysomnography [PSG]) underwent a clinical follow-up and performed a second VPSG after effective antiepileptic treatment lasting for at least 6 months. Conventional sleep measures, cyclic alternating pattern (CAP) parameters, and objective VPSG seizures were assessed in NFLE patients before and after treatment and were compared with the results of 20 age- and gender-matched control subjects.
Results: Antiepileptic treatment determined a partial reduction of objective VPSG seizures of approximately 25% compared to baseline condition. Alterations of most conventional sleep measures recovered normal values, but nonrapid eye movement (NREM) sleep instability remained pathologically enhanced (CAP rate, +26% compared to controls) and was associated with persistence of daytime sleepiness.
Conclusions: Residual epileptic events and high levels of unstable NREM sleep can define a sort of objective resistance of both seizures and disturbed arousal system to the therapeutic purpose of the antiepileptic drugs in NFLE. This finding could determine the need for new therapeutic options in this particular form of epilepsy.

1. Introduction

Nocturnal frontal lobe epilepsy (NFLE) is a particular form of partial epilepsy in which seizures characterized by bizarre motor behaviors or sustained dystonic postures appear almost exclusively during sleep. The clinical spectrum of NFLE comprises distinct paroxysmal sleep-related attacks of variable duration and increased complexity [1–6], ranging from minor motor events (MMEs) [1,6–12] to major attacks (MAs) [1,5,13]. MAs are constituted by: (1) paroxysmal arousals, characterized by brief simple motor phenomena and similar to a sudden arousal recurring several times per night; (2) asymmetric tonic seizures, suggesting the involvement of the frontal mesial area; (3) hyperkinetic seizures, characterized by more complex motor pattern with violent behavior, vocalization, screaming, fearful and repetitive movements of the trunk and limbs; and (4) prolonged episodes such as the epileptic nocturnal wandering, which can mimic sleepwalking episodes [13].

MMEs are brief (2–4 s) stereotyped movements involving the limbs, the axial musculature, or the head [1,6–12]. Although MMEs often are not clearly qualified as a kind of seizure in NFLE, a well-established association of MMEs to epileptic discharges and fluctuations of arousal activity has been proven in NFLE patients [8,10,12,14]. To the extent that these stereotyped brief motor phenomena are a motor component of an arousal triggered by epileptic discharges, the possibility that MMEs could be considered of epileptic origin appears plausible [10].

Few patients exhibit only one type of seizure; however, different seizures usually are likely to overlap in the same patient, and the briefest episodes are the initial fragment of more prolonged attacks [7].

According to the International Classification of Sleep Disorders [15], nocturnal video-polysomnography (VPSG) is the main investigative tool for a sleep-related epilepsy, in which interictal and ictal epileptic discharges confirm the clinical diagnosis. On the other hand, a normal electroencephalogram (EEG) does not rule out a diagnosis of epilepsy in NFLE (15). Moreover, most of the clinical manifestations of NFLE mimic the motor behavior patterns of arousal-related parasomnias, and differentiating nocturnal frontal seizures from nonepileptic paroxysmal motor phenomena may be arduous [16–22]. The lack of internationally shared interpretation criteria make the diagnosis of NFLE mostly reliant on clinical

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history and VPSG recording of behavioral seizures, suggesting a frontal lobe involvement [16,20].

Clinical manifestations of NFLE are strongly influenced by circadian sleep-wake alternation and by physiologic components of sleep structure. Regardless of their semiology, the majority of NFLE seizures arise during nonrapid eye movement (NREM) sleep and are followed by a sudden transition to a more superficial stage or a frank awakening [1–3]. The epileptic fragmentation of the first part of the night can produce a significant sleep disruption with a consequent increase of wake after sleep onset (WASO) and rapid eye movement (REM) sleep latency but without alterations of slow-wave sleep (SWS), which even increases [23]. Moreover, the temporal development of epileptic events across sleep period seems to be modulated by the homeostatic process of deep NREM sleep [23]. The cyclic alternating pattern (CAP), the marker of unstable NREM sleep [24], plays a primary role in the activation of epileptic events in NFLE patients [23,25].

During CAP, the sleep process swings from periods of activation (phase A), characterized by NREM sleep-phasic events and periods of deactivation (phase B), characterized by paucity or disappearance of phasic events. In contrast, noncyclic alternating pattern (NCAP) consists of a rhythmic and stable EEG background and is the expression of sustained sleep stability. The arrangement of NREM sleep into CAP and NCAP allows identification of three neurophysiologic conditions (phase A, phase B, and NCAP), each exerting a specific modulatory influence on a number of epileptic events occurring in NREM sleep [26–32].

In NFLE patients, CAP is a powerful triggering condition for the occurrence of both ictal and interictal epileptic events that arise in concomitance with phase A. In turn epileptic manifestations act as a subcontinuous sleep disturbance that induces a significant increase of sleep instability [23]. This enhancement of unstable NREM sleep together with the alterations of conventional sleep measures can define distinctive polysomnography (PSG) features in NFLE patients [23] and can be responsible for the poor sleep quality and the excessive daytime sleepiness, which has already been described in these patients [3,9,17,23,33].

In approximately two out of three NFLE patients, carbamazepine (CBZ) [1,4,11] and topiramate (TPM) [34] were reported to reduce nocturnal seizures in frequency and complexity, while the remaining patients, who commonly had a higher seizure frequency, seemed to be drug resistant [2]. Because of the almost exclusive recurrence of seizures during sleep, NFLE patients often are scarcely aware of the presence, complexity, and frequency of attacks. Moreover, a reliable description of epileptic motor events occurring during the night often are difficult to collect from a witness or sleep partner, as observers may be absent, or if present, not fully awake or reliable [16]. Lastly, MMEs often are difficult to be clearly qualified.

For these reasons, nocturnal video-EEG features and PSG metrics can provide objective data of the effects of antiepileptic therapy, especially on minor seizures and sleep parameters. In our study, we compare the conventional sleep measures and CAP parameters of 20 healthy subjects with the measures of 20 NFLE controls before and after effective antiepileptic therapy of at least 6 months' duration. VPSG epileptic seizures of NFLE patients before and after treatment also are analyzed.

2. Methods

2.1. Subjects

Among all patients who received a VPSG diagnosis of NFLE according to previous studies [1,6,23,35], 20 consecutive patients (12 men and eight women; mean age, 32 ± 12 y) were selected from the database of the Sleep Disorder Centre of Parma based on certain criteria: (1) antiepileptic therapy prescribed for at least 6 months, which was effective in the control of seizures as ascertained by seizure diaries based on subjective patient's report and partner's report. Only seizure-free patients (disappearance of reported seizures since starting antiepileptic treatment) and responders (reduction of $\geqslant$50% of seizures) were included in the study. Nonresponder patients (NFLE patients showing reduction of <50% of reported seizures or no improvement or worsening of their seizure control, despite taking the maximum tolerated dose) were excluded from the study; (2) an obstructive apnea–hypopnea index <5 per hour and periodic limb movements (PLM) index <15 per hour of sleep in diagnostic VPSG, to exclude an increase of CAP rate and arousals induced by respiratory events or PLM disorder; and (3) the exclusion of coexisting neurologic, medical, or psychiatric disorders known to affect sleep architecture.

At time of enrollment, all NFLE patients underwent a clinical evaluation of daytime sleepiness using the Epworth sleepiness scale and a second VPSG study during antiepileptic treatment. All 20 NFLE patients who met the inclusion criteria and had an obstructive apnea–hypopnea index <5 per hour and also had a PLM index <15 per hour during the second VPSG were finally suitable for sleep analysis.

Conventional sleep measures and CAP parameters of the selected NFLE subjects were analyzed before (group A) and after (group B) antiepileptic treatment and were compared with the measures of 20 age- and gender-matched healthy control subjects (12 men and eight women; mean age, 33 ± 8 y) who were paid volunteers and free of psychiatric, neurologic, or medical disorders (group C).

The absolute number and distribution of VPSG epileptic seizures of NFLE subjects before and after treatment also were compared. Both NFLE subjects and control subjects gave informed consent to perform the study and underwent a nocturnal PSG in a video-monitored sound proof (Leq < 35 dB) laboratory. In the week preceding the PSG recording, all subjects completed a sleep log to determine the personal sleep-wake profile and refrained from alcohol or caffeine consumption and central nervous system drugs other than the prescribed antiepileptic treatment.

2.2. Video-sleep recordings

Sleep was recorded from a C3/A2 or a C4/A1 derivation integrated by bihemispheric bipolar montages (Fp1-F3, F3-C3, C3-P3, P3-O1 and Fp2-F4, F4-C4, C4-P4, P4-O2) used to optimize the detection of focal or generalized epileptic abnormalities. A calibration of 50 μV/cm was used for all the EEG channels with a time constant of 0.1 s and a high frequency filter in the 30-Hz range. The total recording time for all recordings was 500 min. Eye movements, electrocardiogram, and chin and tibialis muscles electromyography also were recorded together with oxygen saturation, thoracoabdominal motion, and oronasal flow to exclude sleep apnea syndrome and PLM disorder. Video recording was performed using an infrared camera associated to an audio trace recorder both integrated in EEG acquisition system and synchronized to EEG recording.

2.3. VPSG data analysis

2.3.1. Conventional sleep variables and sleep cycles

For conventional sleep measures visual assessment was based on 30-s epochs [36] and was accomplished by a trained scorer blind to the subjects' conditions. Conventional sleep variables that were measured included, total sleep time, sleep latency, sleep efficiency (SE), WASO, total duration and percentage of all NREM sleep stages (stage 1, stage 2 [S2], stage 3, and stage 4), REM sleep, and REM latency. Stage 3 and stage 4 NREM sleep stages were referred together as SWS.