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Cyclic alternating pattern and interictal epileptiform discharges during morning sleep after sleep deprivation in temporal lobe epilepsy☆

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ABSTRACT

Purpose: Sleep deprivation (SD) increases the occurrence of interictal epileptiform discharges (IED) compared to basal EEG in temporal lobe epilepsy (TLE). In adults, EEG after SD is usually performed in the morning after SD. We aimed to evaluate whether morning sleep after SD bears additional IED-inducing effects compared with nocturnal physiological sleep, and whether changes in sleep stability (described by the cyclic alternating pattern-CAP) play a significant role.
Methods: Adult patients with TLE underwent in-lab night polysomnography (n-PSG) and, within 7 days from n-PSG, they underwent also a morning EEG after night SD (SD-EEG). We included only TLE patients in which both recordings showed IED. SD-EEG consisted of waking up patients at 2:00 AM and performing video EEG at 8:00 AM. For both recordings, we obtained the following markers for the first sleep cycle: IED/h (Spike Index, SI), sleep macrostructure, microstructure (NREM CAP rate; A1, A2 and A3 Indices), and SI association with CAP variables.
Results: The macrostructure of the first sleep cycle was similar in n-PSG and morning SD-EEG, whereas CAP rate and SI were significantly higher in SD-EEG. SI increase was selectively associated with CAP phases.
Conclusions: SD increases the instability of morning recovery sleep compared with n-PSG, and particularly enhances CAP A1 phases, which are associated with the majority of IED. Thus, higher instability of morning recovery sleep may account at least in part for the increased IED yield in SD-EEG in TLE patients.

1. Introduction

Electroencephalography (EEG) plays a fundamental role in the diagnosis of epilepsy. Interictal epileptiform discharges (IED), however, are not present in up to 40% of people with focal epilepsy [1]. Sleep deprivation (SD) significantly increases the likelihood of IED occurrence in morning EEG in these patients [2]. Relatively brief EEG recordings (2.5 h) after partial SD (6 h) can elicit IED in as much as 40% of patients with focal epilepsy and normal baseline EEG [3], similarly to what observed with more prolonged SD and morning EEG protocols [4,5].

The precise mechanisms underlying the increased diagnostic value of post-SD morning EEG are still a matter of debate [2]. Most of the IED observed during SD-EEG occur during sleep [3,6–10], and thus several Authors ascribed the diagnostic utility of SD-EEG to the mere induction of sleep. However, others claim that the activating potential of sleep occurring during the morning after nocturnal SD may be greater than that of sleep per se. Studies comparing patterns of physiological sleep and morning sleep after SD in patients with focal or generalized epilepsies support a higher efficacy of post-SD sleep in increasing the occurrence of IED [6,7,11]. Other authors, however, challenge this view [12,13].

Potentially, sleep instability and microstructural features may account at least in part for the enhanced provocative role of morning sleep post-SD compared with nocturnal sleep. Among markers of sleep instability, Cyclic Alternating Pattern (CAP) has recently gained considerable relevance. It is defined as a spontaneous and physiological rhythm of NREM sleep, characterized by EEG oscillations pointing to a condition of sustained sleep instability. The oscillatory patterns of CAP exhibit a 20–40 s periodicity, participate in the dynamic organization of sleep and consist of EEG arousal-related transient events (phase A

Abbreviations: AED, antiepileptic drug; CAP, cyclic alternating pattern; IED, interictal epileptiform discharges; nCAP, non-CAP periods; n-PSG, night polysomnography; SD, sleep deprivation; SD-EEG, sleep deprived EEG; SI, spike index; TLE, temporal lobe epilepsy.

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of the cycle) alternating with intervals of background activity (phase B). Three main EEG patterns have been described for phase A: predominant synchronized slow waves in subtype A1, predominant EEG fast rhythms in A3, and a combination of both in A2. CAP sequences are present in physiological NREM sleep, and the ratio of CAP time to NREM sleep time (CAP rate) has been proposed as a physiological marker of sleep instability [14–16].

As for IED occurrence during nocturnal NREM sleep, several authors have demonstrated their specific association with CAP, pointing to the potential involvement of specific CAP phases, mostly type A, both in focal and idiopathic generalized epilepsies [14,17–21], with the exception of benign childhood epilepsy with centro-temporal spikes [22]. The microstructural features of sleep after SD have been assessed only in few studies, which focused on healthy controls or patients with sleep disorders [23–26] and used different protocols for sleep deprivation and recovery.

Unexpectedly, despite long-standing evidence for an activating effect of SD in epilepsy patients, CAP features during morning recovery sleep after SD and their relation to IED occurrence have not been investigated yet.

In this retrospective study, we aimed to evaluate whether changes in sleep stability are implicated at least in part in the augmented diagnostic value of post-SD morning sleep compared with physiological nocturnal sleep in temporal lobe epilepsy (TLE). In particular, we analyzed in the same patients polysomnographic variables and IED in morning sleep occurring after SD and nocturnal sleep without SD. Since no more than one complete NREM/REM cycle is usually obtained for most patients during morning post-SD sleep, we compared its features with the first NREM/REM cycle of nocturnal sleep recordings.

We chose to address patients with TLE because: a) it is the most represented type of focal epilepsy in adult patients, b) sleep EEG per se shows more frequent IED compared with wake EEG in TLE (see, among others, [27–29]) and c) the highest IED incidence after SD in subjects with normal routine EEG has been documented for patients with complex partial seizures [4,30,31].

We hypothesized that sleep occurring in the morning in adult patients (as currently performed in most Epilepsy Centers) would exhibit a significantly increased instability, which may be linked at least in part to the higher occurrence of IEDs in this diagnostic test.

2. Methods

2.1. Population and clinical evaluation

We retrospectively selected patients with TLE evaluated at the Epilepsy Center of the Neurology Unit of the Pisa University-Hospital, who: a) underwent both nocturnal in-lab polysomnography (n-PSG) and SD-EEG within no more than seven days during their clinical work-up; b) exhibited a complete NREM/REM cycle in both n-PSG and SD-EEG; c) showed IEDs both in n-PSG and SD-EEG; d) did not experience any clear epileptic seizures within 72 h preceding the recordings; e) did not show a periodic leg movements index or an apnea-hypopnea index >15 (see below); f) were not diagnosed with concomitant psychiatric illnesses, nor were assuming any psychotropic drugs (including antidepressants, anxiolytics, hypnotics, antipsychotics) apart from antiepileptic drugs (AEDs). All the patients underwent 1.5 T brain MRI and images were routinely re-evaluated at our Center. Thirteen patients were retrospectively included in the study (mean age 44.3 ± 16.3 years; 7F, 6M) from an initial population of 126 consecutive subjects submitted to n-PSG monitoring and SD-EEG at Neurology Unit of the University of Pisa. Mean seizure frequency for the two months preceding the recordings was 3.8 ± 1.1. Further details regarding demographic and clinical characteristics are reported in Table 1.

Epilepsy diagnosis was based on semiology, clinical history, neuroimaging and EEG findings, according with ILAE recommendations [32–34].

This retrospective study complies with the Declaration of Helsinki and was approved by our Institutional Review Board. All the subjects included in the study had given their consent for the analysis of their clinical data for research purposes and for publication in scientific journals.

2.2. Night polysomnography and SD-EEG recording

In-lab n-PSG and SD-EEG recordings were conducted using the same protocol for all the subjects. Nocturnal-PSG was performed from 11 pm to 7 am in the EEG-Sleep Center of the University of Pisa according to standard procedures [35]. The SD-EEG protocol consisted of instructing the patient to wake up at 2:00 AM and to remain awake until morning EEG recording, without the use of stimulating substances. EEG recording was performed from 8:00 AM to 10:30 AM in the EEG-Sleep Center (see [3] for details).

All n-PSG and SD-EEG recordings were acquired using digital EEG polygraphy (BElite, EBNeuro, Florence). Nineteen collodium-applied scalp electrodes were placed according to the 10–20 system; electrocardiogram, chin electromyogram, and electrooculogram were included using additional skin surface electrodes. Patients were allowed to sleep without external influence in a quiet dark room. Concomitant video-recording was performed during the SD-EEG and n-PSG; a thermistor for nasal and oral airflow, thoracic and abdominal respiratory effort strain gauges, finger pulse oximeter, digital microphone, and left and right tibialis anterior EMG were included in the n-PSG.

Table 1
Demographics and clinical characteristics.

Subject	Age (years)	Sex	Seizure types	Etiology	Seizures/month	Antiepileptic drugs
#1	34	F	CPS, SGTCS	Right MTS	3	LTG, TPM
#2	31	M	CPS, SGTCS	Right MTS	5	TPM
#3	33	M	CPS, SGTCS	Right temporal lobe cavernous hemangioma	5	LEV, OXC, PGB
#4	45	M	CPS	Cryptogenic (left temporal lobe focus)	4	GBP, TPM
#5	58	F	CPS, SGTCS	Right MTS	3	CBZ, OXC, VPA
#6	76	M	CPS	Left temporal lobe post-ischemic gliosis	6	PB
#7	53	F	CPS, SGTCS	Left MTS	3	LEV, OXC, TPM
#8	31	M	CPS, SGTCS	Cryptogenic (left temporal lobe focus)	2	CBZ
#9	44	F	CPS, SGTCS	Left temporal lobe post-ischemic gliosis	4	OXC, TPM
#10	23	F	CPS	Cryptogenic (right temporal lobe focus)	3	CBZ
#11	30	F	CPS, SGTCS	Cryptogenic (right temporal lobe focus)	3	/
#12	70	M	CPS, SGTCS	Cryptogenic (left temporal lobe focus)	4	/
#13	48	F	CPS, SGTCS	left MTS	4	LEV, LTG, TPM

CPS = complex partial seizures; SGTCS = secondarily generalized tonic-clonic seizures MTS = mesial temporal lobe sclerosis. CBZ = Carbamazepine; GBP = Gabapentin; LEV = Levetiracetam; LTG = Lamotrigine; OCX = Oxcarbazepine; PGB = Pregabalin; PB = Phenobarbital; TPM = Topiramate; VPA = Valproic acid.