Relationship of Epileptic Discharges to Arousal Instability and Periodic Leg Movements in a Case of Nocturnal Frontal Lobe Epilepsy: A Stereo-EEG Study

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Abstract: We describe the case of a patient with nocturnal frontal lobe epilepsy, presenting with periodic leg movements during sleep and complaining of excessive daytime sleepiness. With the support of intracerebral electroencephalogram recordings and the corroboration of the postoperative outcome, periodic leg movements during sleep and excessive daytime sleepiness appeared to be associated to enhanced arousal instability induced by by recurrent epileptic discharges not detectable on scalp electroencephalogram.

Keywords: Periodic leg movements, nocturnal frontal lobe epilepsy, cyclic alternating pattern, arousal

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INTRODUCTION

PATIENTS AFFECTED BY NOCTURNAL FRONTAL LOBE EPILEPSY (NFLE) FREQUENTLY REPORT A POOR QUALITY OF SLEEP, FATIGUE, AND EXCESSIVE DAYTIME sleepiness.[1-3] This has been ascribed to the presence of recurrent seizures and motor episodes fragmenting sleep.[1-3] Indeed, apart from major seizures, patients with NFLE frequently present with a high number of minor motor events lasting 2 to 4 seconds, which can show a periodic recurrence in coincidence with arousal fluctuations during non-rapid eye movement (NREM) sleep.[1-3] The epileptic origin of these minor motor events has not been definitively proven, as they generally lack scalp electroencephalogram (EEG) epileptic correlates.[1-3]

The sleep of patients affected by NFLE and excessive daytime sleepiness is more unstable, as compared with patients with NFLE without sleep complaints, despite a similar number of motor episodes.[2] Such increased sleep instability is expressed by high values of the cyclic alternating pattern (CAP) rate, ie, the percentage ratio of CAP time to NREM sleep time.[2,4]

We describe the case of a patient affected by drug-resistant NFLE, complaining of excessive daytime sleepiness and presenting periodic leg movements during sleep (PLMS) not associated with scalp EEG abnormalities. Intracerebral EEG recordings (stereo-EEG) revealed the presence of recurrent epileptic discharges and permitted us to investigate the relationship among epileptic discharges, arousal instability, and PLMS.

Disclosure Statement
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Case report

A 24-year-old woman with no familial history of neurologic disorders had her first epileptic seizure at the age of 4 years. Ictal events occurred during both sleep and wakefulness and were characterized by sudden fear associated with terrified expression, intense palpitations, and diffuse piloerection. Symptoms could be followed by intense screaming, accompanied by the patient's tendency to grab people around her. Consciousness was preserved throughout the seizure. Over the years, seizures became sleep related (3-4 seizures per month). Different antiepileptic agents, in monotherapy or polytherapy, were administered, but no drug regimen resulted in satisfactory seizure control. When the patient was aged 20, the clinical and EEG features of the seizures were documented by a video-EEG recording in an epilepsy center in which the patient underwent also a brain magnetic resonance imaging examination. Analysis of video-EEG-recorded seizures suggested a left-frontal origin of the episodes supported by magnetic resonance imaging investigation that revealed the presence of a possible dysplastic lesion within the anterior part of the first circonvolution of the left frontal lobe. The patient was referred to our center for a presurgical assessment.

Presurgical Assessment

At the moment of evaluation, the patient was 22 years old. Seizure frequency was 5 to 6 episodes per month and occurred exclusively during sleep despite regular administration of carbamazepine 800 mg per day. Apart from epilepsy, the patient complained of nonrestorative sleep and severe daytime sleepiness, as measured by a score of 16 at the Epworth Sleepiness Scale (ESS).[5,6] No other specific symptoms that could be ascribed to other sleep disorders were reported by the patient.

No seizure was recorded during a first video-EEG investigation with scalp electrodes, but the analysis of sleep EEG revealed an extremely unstable sleep with periodic arousal fluctuations and the presence of PLMS occurring exclusively during NREM sleep. PLMS consisted of repetitive highly stereotyped leg movements that were 0.5 to 5 seconds in duration and were separated by an interval of 20 to 40 seconds. No definite epileptic discharges were recorded in association with PLMS.

Table 1—Polysomnographic Parameters and Epworth Sleepiness Scale Score Before and After Corticectomy

	PRE	SEEG	POST
TRT	450,0	440,0	460,0
TST	410,0	390,0	435,0
SE%	91,00	89,00	95,00
1 NREM	48,8	51,5	20,9
2 NREM	165,2	169,3	165,7
3+4 NREM	87,3	71,0	142,2
REM	69,3	66,7	84,0
WASO	39,4	31,6	22,2
1 NREM %	11,9	13,2	4,8
2 NREM %	40,3	43,4	38,1
3+4 NREM %	21,3	18,2	32,7
REM%	16,9	17,1	19,3
WASO%	9,6	8,1	5,1
PLMI	33,0	36,0	9,0
CAP rate, %	80,0	83,0	32,0
ESS score	16,0	16,0	6,0

PRE refers to presurgical scalp video electroencephalogram (EEG) investigation; SEEG, stereo-EEG investigation; POST, 6 months follow-up video-EEG investigation; TRT, total recording time; TST, total sleep time; SE%, sleep efficiency; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; WASO, wake after sleep onset; PLMI, periodic leg movement index; CAP rate%, percentage ratio of total cyclic alternating pattern (CAP) time in NREM sleep to total NREM sleep time; ESS, Epworth Sleepiness Scale.

Conventional sleep measures (macrostructure) revealed an increase of stage 1 and a decrease of slow-wave sleep. Arousal instability as assessed by CAP scoring criteria[4] revealed an extremely high CAP rate of 80% (age-matched normal values: 32%).[7] The periodic leg movements index was 33 per hour (Table 1).

One month later, the patient underwent an individualized investigation[8] with 9 stereotactically implanted intracerebral multilead electrodes for a careful definition of the epileptogenic zone for surgical purposes (stereo-EEG)(Figure 1). A postimplantation magnetic resonance imaging study was obtained in order to confirm the actual position of each single electrode. Two EEG scalp electrodes (C4-O2) were applied on the scalp to allow scoring of conventional sleep measures. The clinical conditions were unchanged. The ESS score was still 16. Pharmacologic treatment was unmodified.

Four days after the implantation of intracerebral electrodes, nocturnal video-stereo-EEG recording confirmed the presence of an extremely unstable sleep with only minor changes in macrostructural sleep parameters, as compared with the previous video-EEG investigation. The CAP rate was 83%, and the periodic limb movement index was 36 per hour (Table 1). Sleep stereo-EEG analysis revealed the presence of periodically recurrent (every 20-40 seconds) epileptic discharges within the intralesional recording derivations (first circonvolution of the left frontal lobe). A total of 440 epileptic discharges were recorded, 99% of which occurred in relationship with an A phase of CAP. Ninety-seven percent of PLMS occurred within an A phase; 83% of PLMS occurred immediately after an epileptic discharge, and this associa-

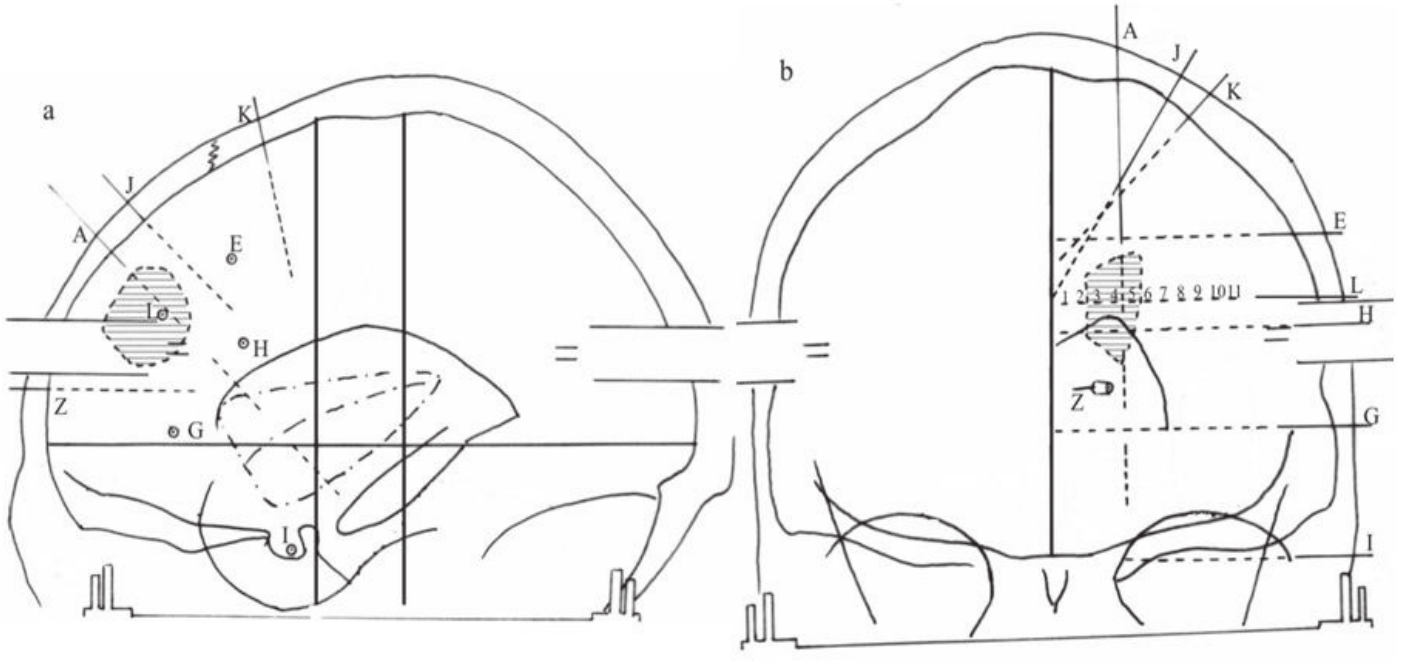

Figure 1—Left lateral (a) and frontal (b) views of the stereotactic scheme of the electrodes implantation for the stereo electroencephalogram (SEEG) investigation. Electrodes are indicated as dotted circles or lines and labeled with upper-case letters. Each semirigid electrode has a diameter of 0.8 mm and comprises 10 to 15 leads of 2-mm length, 1.5 mm apart. The lesion, as documented by hyperintensity on T2-weighted fluid-attenuated inversion recovery sequences on magnetic resonance imaging, has been incorporated in the stereotactic scheme, and it is indicated as a shaded area. The brain structures covered by each electrode are (from external to internal contacts): electrode A (15 contacts): superior frontal gyrus, lesion, amygdala; electrode I (10 contacts): temporal pole; electrode G (13 contacts): inferior frontal gyrus, cingulated gyrus; electrode Z (10 contacts): frontal pole, cingulated gyrus; electrode L (13 contacts): middle frontal gyrus, lesion, mesial frontal cortex (for this electrode, each single contact has been labeled with a number); electrode H (14 contacts): inferior frontal gyrus, cingulated gyrus; electrode J (9 contacts): superior frontal gyrus, mesial frontal cortex; electrode E (12 contacts): middle frontal gyrus, mesial frontal cortex; electrode K (10 contacts): Superior frontal gyrus, mesial frontal cortex.

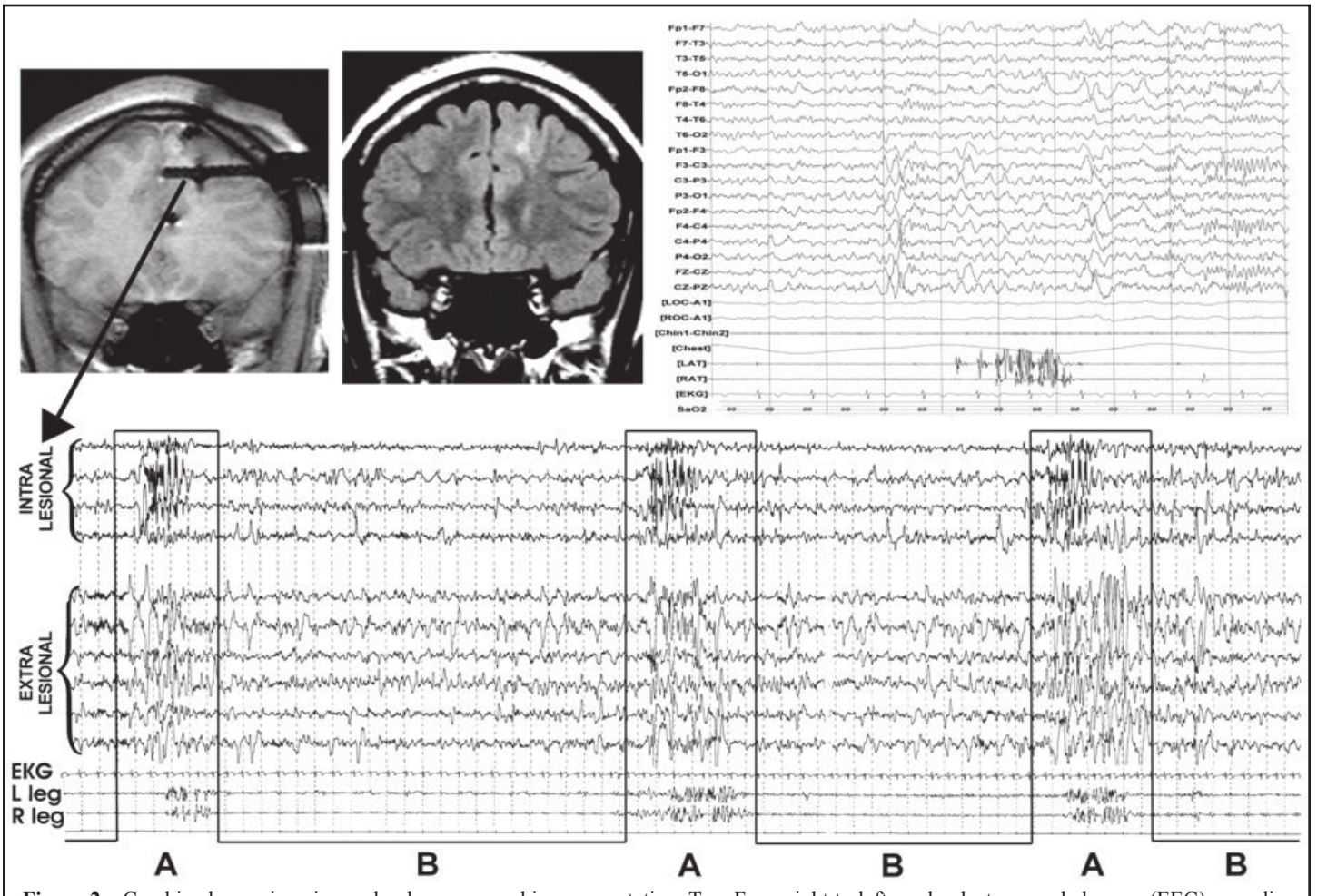

Figure 2—Combined neuroimaging and polysomnographic representation. Top. From right to left: scalp electroencephalogram (EEG) recording during stage 2 non-rapid eye movement sleep. Bilateral leg movements (LAT and RAT: left and right tibialis anterior muscles) not associated with clear-cut epileptic discharges. Coronal magnetic resonance imaging (MRI) sections showing a cortical dysplasia within the left superior frontal gyrus. Coronal MRI section after the electrodes' implantation showing 1 of the electrodes sampling the lesion (electrode labeled as L in figure 1). Bottom. Stereo-EEG recording: each EEG trace is a bipolar derivation from contiguous contacts. Four derivations record the intralesional activity (intralesional: contacts 1 to 5 in Figure 1b) from the mesial contacts of the electrode L (arrow). Six derivations record from outside the lesion (extralesional; contacts 5 to 11 in Figure 1b), same electrode. Notice the periodic recurrence of epileptic discharges associated with bilateral periodic leg movements linked to A phases of cyclic alternating pattern (CAP). Epileptiform activity and the A phases of CAP preceded the onset of periodic leg movements during sleep.

tion always occurred within an A phase of CAP (Figure 2). During the following nights, we recorded 1 seizure originating from the same derivations in which the periodic epileptic discharges were observed and spreading after a few seconds to the orbitary and temporal cortex. The first clinical symptom was a sudden head elevation followed by intense screaming and agitated movements of the arms without loss of contact.

The patient underwent a left frontal lesionectomy and corticectomy. Histopathologic examination of the resected cortex disclosed a Taylor dysplasia of the anterior part of the superior frontal gyrus.

Postsurgical Assessment

Six months later, the patient was admitted to our hospital for a clinical and video-EEG examination during sleep. Treatment was still carbamazepine 800 mg per day. After the operation, she was seizure free and reported a remarkable improvement of sleep quality and daytime sleepiness. The ESS score was 6. Sleep-macrostructure parameters revealed an increase of slow-wave sleep and a reduction of stage 1 sleep. There was an impressive drop of arousal fluctuations, with a CAP rate of 32% and a periodic limb movement index of 9 per hour (Table 1). One year after the operation, the patient is still seizure free, and the ESS score value is 6.

DISCUSSION

CAP is an endogenous rhythm of NREM sleep recurring with a periodicity of 20 to 40 seconds. It is composed of a repetitive biphasic pattern in which collectives of K complexes, delta bursts, and arousals (Phase A) periodically interrupt the tonic theta/delta activities of sleep (phase B). The phase A of CAP reflects a condition of transient activation, while phase B translates an inhibitory potential. The phase A of CAP acts as a gate through which pathologic events occur more easily.[9] This gating effect has been observed in a number of sleep disturbances, including PLMS[10] and both ictal and interictal sleep-related epileptic manifestations.[11] CAP is extremely sensitive to perturbing conditions. Any disturbing factor administered during NREM sleep induces a poststimulus CAP sequence that can persist for minutes.[9] This explains why any condition of disturbed sleep causes an increase in the CAP rate.

PLMS occur in a wide variety of sleep disorders[12] and are also reported in epileptic patients.[13] The primary cause of PLMS seems to be related to an excessive excitability of the spinal cord triggered periodically by state-dependent sleep-related factors located at a supraspinal level.[14,15] In particular, it has been shown that PLMS are heralded by an activation of heart rate and a production of delta activity, as assessed by both the visual analysis of CAP[10] and automatic analysis.[16,17]

Our patient, before the operation, complained of nonrestorative sleep and excessive daytime sleepiness without any complaint ascribable to other sleep disorders. The level of sleepiness was assessed by applying the ESS, a validated questionnaire that measures the general level of daytime sleepiness. Perhaps integrative information could have been provided by objective measures of sleep propensity; however, a score of 16 at the ESS is highly indicative of excessive sleepiness.[5,6]

The first video-EEG study revealed a high sleep instability and the presence of PLMS in the absence of clear-cut epileptic discharges. The stereo-EEG investigation confirmed the presence of an extremely elevated CAP rate and showed an association among the occurrence of phase A of CAP, epileptic discharges, and PLMS. A possible explanation could be that PLMS induce sleep instability that in turn facilitates the occurrence of epileptic discharges. However, stereo-EEG recording showed that PLMS always occurred after the epileptic discharges within an A phase. Moreover, after the operation, the patient became seizure free, her sleep recovered the physiologic values of CAP rate, and the periodic limb movement index showed a dramatic reduction. This suggests that PLMS were not the direct cause of sleep instability but that the periodic epileptic discharges, not detectable on scalp EEG, played the primary role in the mechanism inducing arousal instability. In the sequence of events, arousals were due to epileptiform discharges that were permissive for PLMS. In other words, epileptic abnormalities acted as a nonspecific internal trigger able to increase arousal fluctuations, which facilitated the occurrence of PLMS and resulted in excessive daytime sleepiness.

The coexistence of PLMS, parasomnia, and other sleep disorders has been observed in several patients with NFLE.[1] It is interesting to note that, in our patient, a relatively high periodic limb movement index (9/hour) persisted after surgery, indicating the presence of a comorbid sleep disorder that was enhanced by the epileptic discharges. In our patient, PLMS were phenomena not directly induced by epileptic discharges occurring within a cerebral area not involved in motor control. Indeed, the dysplastic lesion was identified in the anterior part of the first circonvolution of the left frontal lobe. A different pathophysiology can be evoked when periodic epileptic discharges during sleep arise from a motor cerebral area. In this case, sleep is disturbed by the occurrence of multiple minor ictal motor events, the features of which may vary in relation to the involved motor region. This alternative pathophysiologic mechanism is supported by the description of a patient with NFLE and excessive daytime sleepiness in whom periodic motor phenomena during sleep were directly induced by brief epileptic discharges occurring within the supplementary motor area.[3] In both conditions, arousal instability represents the permissive background for the manifestation of epileptic activity and motor events during sleep.[18]

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