Original article

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Nocturnal interictal epileptic discharges in adult Lennox-Gastaut syndrome: the effect of sleep stage and time of night

Emilia Sforza [1,2], Rima Mahdi [1], Frederic Roche [2], Malin Maeder [1], Giovanni Foletti [1]

[1] Institutions de Lavigny, Service d'épileptologie, Lavigny, Switzerland
[2] Service de physiologie clinique et de l'exercice, Pole NOL, CHU, Faculté de médecine J. Lisfranc, UJM et PRES Université de Lyon, Saint-Étienne, France

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ABSTRACT – *Aim*. Lennox-Gastaut syndrome (LGS) is characterized by interictal epileptiform discharges (IEDs) occurring during sleep. The aim of this study was to determine whether sleep influences not only the frequency of seizures and IEDs, but also the time-dependent evolution that may support the hypothesis of homeostatic influences on epileptic threshold.
Methods. Video polysomnography data from our database were reviewed to identify adult LGS patients with at least seven hours of nocturnal recording. Thirteen patients were identified and a second polysomnography was available for nine. The number, duration and index of IEDs, relative to total sleep, sleep stages, and time during the night, were calculated.
Results. The majority of IEDs occurred during non-rapid eye movement sleep, mainly in stage 2 and slow-wave sleep. Adjusting for time spent in each sleep stage, we found 45 IEDs/hour in stage 1, 123/hour in stage 2, 106/hour in slow-wave sleep, and 26/hour in rapid eye movement sleep. The temporal distribution of IEDs showed a significant rise in the first three hours of sleep, followed by a progressive decrease at the end of the night ($F=85.6$; $p<0.0001$).
Conclusions. Interictal epileptiform discharges occurrence in adult LGS is facilitated by non-rapid eye movement sleep with an evident effect of stage 2 and slow-wave sleep. The significant IED occurrence in the first part of the night and the subsequent decline suggests a link between epileptic threshold and homeostatic sleep mechanisms. The latter should be considered regarding choice of therapy.

Key words: Lennox-Gastaut syndrome, interictal epileptic discharges, sleep, sleep stages, sleep homeostasis

Correspondence:
Emilia Sforza
Service d'épileptologie,
Institutions de Lavigny,
Route du Vignoble,
1175 Lavigny,
Switzerland
<emilia.sforza@gmail.com>

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Lennox-Gastaut syndrome (LGS) is an uncommon and refractory epileptic encephalopathy of childhood with a peak onset at 3-5 years, and a prevalence of about 10% in those less than 15 years of age (Aicardi *et al*., 1992; Genton *et al*., 2000; Nabbout and Dulac, 2003). It may be caused by different structural, functional or genetic abnormalities, and the prognosis is poor (Beaumanoir and Blume, 2005). LGS is classified by the International League Against Epilepsy (Arzimanoglou *et al*., 2009) as a symptomatic generalized syndrome, characterized by the triad:

– different types of seizures (tonic, tonic-clonic, myoclonic, atonic, as well as atypical absences);

– typical electroencephalographic abnormalities (*i.e*. spikes and sharp waves, usually followed by a slow wave, distinguishable from background activity and lasting 5-20 mms, with runs of rapid spikes and polyspikes, and fast rhythms of ~10 Hz during sleep);

– learning disabilities and intellectual disability.

While extensive data exist in the literature on LGS in childhood, few data are available in adults. According to Ferlazzo and coworkers (Ferlazzo *et al*., 2010) in their study of 27 adults with LGS, tonic seizures remain the major seizure type occurring essentially during sleep, with atypical absences in 74% of cases. Moreover, interictal epileptiform discharges (IEDs) (Lüders and Noachtar, 2000) were found in 81% of cases. At follow-up, tonic seizures were still reported in 40% of the cases during wakefulness and in all cases during sleep, while IEDs were found only in 26% of patients. In another study (Rodriguez-Rodriguez *et al*., 2011), the authors followed adult LGS for 20 years and they found at the last examination a reduction in seizure frequency, with 33% having daily seizures, 17% weekly and 42% monthly on the same treatment.

While in children and adolescents it is well established that sleep activates IEDs and seizures during non-rapid eye movement sleep (NREM), particularly in stage 2 and slow-wave sleep (SWS) (Kotagal and Yardi, 2008; Matos *et al*., 2010), no extensive data have been reported in adults (Ferlazzo *et al*., 2010). Moreover, recent reports have described a possible circadian influence on. epileptic activity, either in an experimental model (Quigg *et al*., 2001) or in humans (Pavlova *et al*., 2004; Durazzo *et al*., 2008; Hofstra *et al*., 2009; Pavlova *et al*., 2009), suggesting that, independent of the sleep and/or awake state, circadian influences may affect the timing of seizures and IEDs.

In all previous studies, a descriptive analysis of EEG abnormalities was reported without specific attention to number, duration or distribution. In this study, we examined a group of 13 adult LGS patients in which we quantified the number and duration of IEDs and seizures across the night, in order to obtain a more detailed analysis of the effect of sleep stage and timing during the night. Moreover, since night-to-night variability may occur, the analysis was performed in a subgroup of patients over two nights of recording to assess the reliability of our analysis.

Methods

Subjects

In this retrospective study, 13 LGS adults (four women and nine men; mean age: 30.6±2.4 years), monitored by the EEG service of the Lavigny Institution and followed for more than 15 years, were examined. Inclusion criteria consisted of the following:

– at least seven hours of sleep with diffuse epileptic activity during the night;

– LGS diagnosis based on clinical and EEG features;

– diagnosis consistently confirmed over at least two years of follow-up. All diagnoses were made according to the International League Against Epilepsy (ILAE) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Definition of interictal EEG abnormalities

Polysomnographies were collected by a digital polygraph (Nicolet, Neuroswiss, Switzerland). EEG was acquired from 19 electrodes placed in accordance with the 10-20 international system as a physical reference, with successive reconstruction of bipolar derivations. The low-pass filter was set at 70 Hz while the high-pass filter was set at 0.5 Hz, with sensitivity at 20 μV/mm. One electrooculogram channel, submental and deltoid electromyographies, electrocardiogram, oxygen saturation, and thoraco-abdominal movements were recorded.

The mean duration of nocturnal recording was 10.5±1.1 hours, starting at nine o'clock in the evening and stopping between eight and nine o'clock in the morning in order to record wakefulness before sleep and after final awakening. Each recording was scored following conventional rules for sleep staging (Rechtschaffen and Kales, 1968) and hypnogram, and respiratory analyses were also performed. The EEG for all patients was visually analysed and abnormalities were detected according to the systematic classification of EEG abnormalities previously published (Lüders and Noachtar, 2000), as IED sharp waves, spikes, polyspikes, and sharp-wave complexes; all were distinguished from background activity based on morphology and/or amplitude. The time point of the peak was noted for every epileptic spike or sharp wave. EEG events were counted, whether consisting of a single spike-wave complex or a burst of several spike-wave complexes (*figure 1*). IEDs were counted as a single discharge (or one event) when the interdischarge interval was <3 seconds. Discharges that were lateralized or

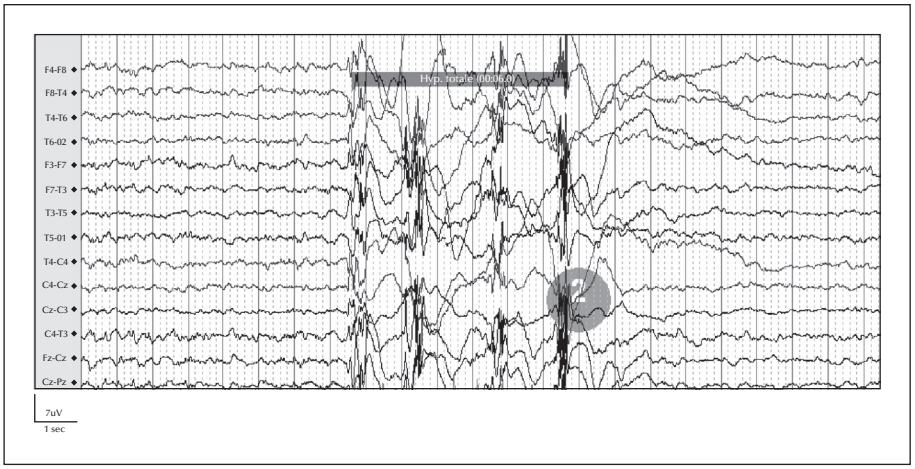

Figure 1. Example of a detected interictal epileptic discharge in stage 2 NREM sleep.

uncertain were excluded. Two experts (ES and RM) analysed the EEG, and only epileptic abnormalities that both observers agreed upon were included in the analysis. The interscore reliability was 88%. Two different IED parameters were analysed: (i) the absolute number of IEDs in each 30-second scoring period and their index (number/hour of sleep), as well as the mean duration for total sleep time and each sleep stage; (ii) the pooled number and duration of IEDs over 30-minute periods for the seven hours of sleep recorded for all patients, in order to evaluate evolution across the night. In order to assess for night-to-night variability, the same analysis was carried out in nine patients who had two recordings, at baseline and after 3-7 months, without change in therapy. The same criteria for detection were used at the second examination.

Statistical analyses

Patient characteristics were summarized as mean±SD for continuous variables, and counts and percentages for categorical variables. Statistical significance for the first and second night was assessed using paired Student's t-test. The effect of time of night on IED density was analysed using ANOVA for repeated measures. All statistical analyses were conducted using the SPSS statistical software package (SPSS for Windows, version 12.0, SPSS, Chicago, IL). Significance was defined by a p value of ≤ 0.05.

Results

Patients

Thirteen patients, four women and nine men, aged 30.6±2.4 years, were examined. Epilepsy had started at a mean age of 5.4±0.6 years; all cases suffered from tonic, tonic-clonic or generalized seizures and atypical absences at the initial assessment, and women were on contraceptive treatment. During wakefulness, the EEG showed slow background activity at about 5-6 Hz with a low reactivity in all cases. In more severe cases (eight patients), spindle activity and K complexes during sleep were less evident in both hemispheres. Four subjects had a diagnosis of epileptic encephalopathy and three had pathological outcomes on MRI. For the other subjects, no data regarding the origin of epilepsy or MRI were available. All subjects had a moderate to severe intellectual deficit and severe epilepsy. At the time of EEG analysis, in all patients there was a reduction of tonic seizure frequency. All were on polytherapy, with four to seven drugs: valproic acid (nine cases), vigabatrin (one case), rufinamide (four cases), lamotrigine (11 cases), clobazam (11 cases), lacosamide (two cases), and levetiracetam (four cases). In patients who had two sleep studies, medication did not change between recordings.

Effect of sleep and sleep stage

Table 1 presents sleep variables and IED characteristics for all patients. At the first examination, all subjects showed disrupted sleep as indicated by the high number of awakenings and sleep stage changes, and low sleep efficiency. Sleep macrostructure showed increased light sleep (stages 1 and 2) and reduced SWS. When the number of seizures during sleep was considered, a mean of 3.5 tonic seizures was recorded in five patients with a mean duration of 8.8 seconds, all appearing in stage 2 sleep. With regard to IEDs, a sleep-dependent activation was identified, with a total mean IED index of 102±7.9 events per hour of sleep and a mean duration of 2.7±0.2 seconds. A greater number and index of IEDs were found during sleep stages 2 and SWS, with lower values in REM sleep ($p<0.001$).

For the nine patients examined twice (*table 2*), the data on sleep parameters and sleep-stage distribution of

Table 1. Sleep parameters and interictal epileptic discharge data of the total sample (mean±SD).

	Mean	SD
Age (years)	30.6	2.4
Men (%)	71%	-
Total sleep time (hours)	7.8	0.6
Sleep latency (minutes)	24.5	1.9
Sleep efficiency (%)	79.4	6.1
Awakenings (n)	25.5	2.0
Sleep state changes (n)	97.5	7.5
Sleep cycles (n)	3.0	0.2
Stage 1 (%)	9.5	0.7
Stage 2 (%)	72.1	5.5
Stage slow wave sleep (%)	4.6	0.4
Stage REM (%)	14.5	1.1
Seizures (n)	3.5	0.3
Seizures duration (seconds)	8.8	0.7
IED in total sleep (n)	805.3	61.9
IED duration in total sleep (seconds)	2.70	0.2
Index of IED in total sleep (n/h)	102.0	7.9
Index of IED in stage 1 (n/h)	45.7	3.5
Index of IED in stage 2 (n/h)	123.4	9.5
Index of IED in slow wave sleep (n/h)	105.9	26.5
Index of IED in stage REM (n/h)	26.5	2.0

IED: interictal epileptic discharges; REM: rapid eye movement sleep; n: number; n/h: number/hour.

IEDs did not reveal significant changes between nights, with the exception of a significant rise of total sleep time (p=0.04) in the second night.

Effect of time of night on IEDs

Figure 2 presents the time-of-night effect on IED number across seven hours of sleep at the first examination. ANOVA for repeated measures revealed that there was a significant time-of-night effect (p<0.0001), with the number of IEDs peaking during the first three hours of sleep and progressively declining across the night. In patients examined twice (*figure 3*), the same significant pattern was present without differences between nights.

Discussion

In this study, we aimed to quantify EEG abnormalities in adult LGS patients during sleep and at specific time points during the night. The first finding is that our quantitative analysis confirmed previous studies (Sammaritano *et al*., 1991; Terzano *et al*., 1991; Shouse *et al*., 2000; Kotagal and Yardi, 2008; Matos *et al*., 2010; Ferlazzo *et al*., 2010), showing a greater number of IEDs during NREM sleep, in particular in stage 2 and SWS, inducing alterations in sleep quality and duration. The strong relationship between epileptic events and SWS suggests a role of inductive mechanisms, either a state of hyperexcitability during NREM sleep or hypersynchrony. In support of a role of hypersynchrony, EEG-fMRI studies (Siniatchkin *et al*., 2011; Pillay *et al*., 2013) suggest that the brainstem, centromedian and anterior thalamus induce phases of activation and deactivation, generating IEDs. During NREM sleep, the reduction of inputs from the brainstem reticular area induces a progressive hyperpolarization and synchronization of the thalamo-cortical circuits that may facilitate hypersynchronous pathological discharges in humans and under experimental conditions (Steriade *et al*., 1994).

The second and new finding of our study is the temporal IED distribution across the night, showing a peak firing in the first 2-3 hours of sleep, followed by a progressive decline in the last part of the night. To explain this effect, two different mechanisms have been proposed; either a circadian or a homeostatic sleep effect. When we consider the evolution of IEDs over time in *figures 2 and 3*, the peaking of IED frequency at the beginning of the night and the subsequent progressive decline mirror the nocturnal changes of sleep homeostatic processes. This hypothesis is supported by the analysis of slow-wave activity (SWA) (Achermann *et al*., 1993), a marker of sleep depth, that peaks at the start of sleep and progressively declines as a function of time of night. Although we did not perform a spectral EEG analysis, the build-up of IED density during the first three hours of sleep and the progressive decline in the second part support the role of sleep homeostatic influences on epileptic threshold.

This last finding may have clinical implications. Firstly, the need for at least one nocturnal sleep study to assess the time-of-night effect in adult LGS patients. Secondly, if there is a time-of-night effect, a clinician may choose the best treatment (*i.e.* increased dose of antiepileptic medication before sleep or long-lasting benzodiazepines) to reduce IED peaking and the associated clinical consequences. This suggestion, however, needs to be confirmed in large populations.

Table 2. Sleep parameters and interictal epileptic discharge data of nine patients over two nights of video-EEG recordings (mean±SD).

	First night	Second night	*p*
Age (years)	29.2 (7.4)	29.5 (7.0)	ns
Total sleep time (hours)	7.4 (1.3)	8.6 (1.5)	0.04
Sleep latency (minutes)	28.9 (16.4)	26.2 (14.4)	ns
Sleep efficiency (%)	80.1 (12.2)	79.5 (12.2)	ns
Awakenings (n)	24.2 (17.1)	27.0 (10.9)	ns
Sleep state changes (n)	89.1 (56.1)	98.8 (33.9)	ns
Sleep cycles (n)	2.9 (0.9)	3.2 (1.5)	ns
Stage 1 (%)	9.1 (6.5)	9.1 (5.0)	ns
Stage 2 (%)	72.3 (14.1)	74.6 (8.4)	ns
Stage slow-wave sleep (%)	6.3 (11.1)	2.2 (3.6)	ns
Stage REM (%)	13.1 (6.7)	14.0 (7.8)	ns
Seizures (n)	13.9 (17.7)	13.0 (8.9)	ns
Seizure duration (seconds)	10.1 (9.8)	6.7 (4.0)	ns
IED in total sleep (n)	902.3 (429.0)	1029 (668.8)	ns
IED total duration in total sleep (seconds)	2.6 (1.5)	2.6 (1.2)	ns
Index of IED in total sleep (n/h))	116.3 (48.6)	112.4 (53.7)	ns
Index of IED in stage 1 (n/h)	52.1 (36.3)	49.2 (31.5)	ns
Index of IED in stage 2 (n/h)	137.9 (53.0)	135.0 (54.4)	ns
Index of IED in slow wave sleep (n/h)	115.5 (88.7)	125.5 (98.6)	ns
Index of IED in stage REM (n/h)	26.6 (32.9)	30.6 (28.1)	ns

IED: interictal epileptic discharges; REM: rapid eye movement sleep; *p*: paired Student's *t*-test; n: number; n/h: number/hour; ns: not significant.

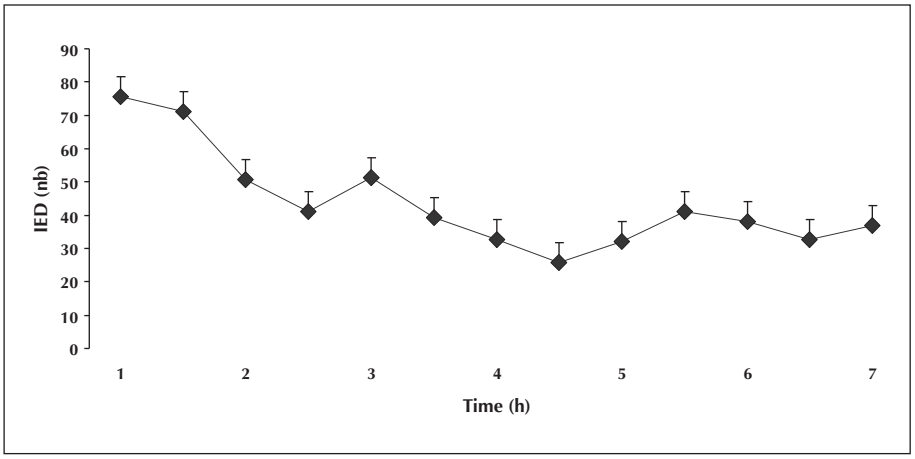

Figure 2. Sleep-related temporal distribution of interictal epileptic discharges in all patients.

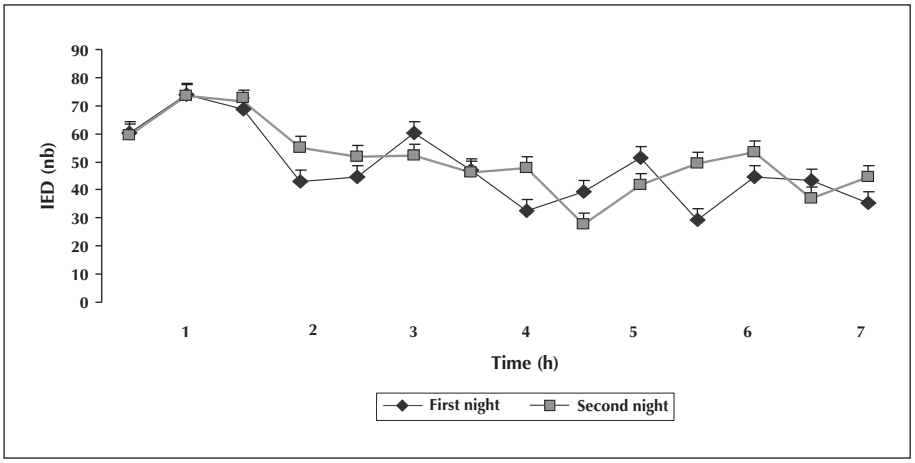

Figure 3. Evolution of interictal epileptic discharges during the first and second night for the nine patients examined twice.

Strengths and limitations

The strengths of our study include:
– a polysomnographic study allowing analysis of sleep structure and associated sleep disorders;
– a long duration of analysis that enabled examination of not only EEG during wakefulness but also the effects of sleep stage and time of night on IED frequency.
The latter point should be stressed since an analysis limited to NREM and REM sleep may limit the understating of physiopathological mechanisms. A significant limitation is the small number of patients, restricting thorough statistical inference, to affirm any robust effect of sleep/awake state and time of night on IED frequency. In addition, spectral EEG analysis was not performed, which could have better supported the association between the build-up of SWA and the peaking of IEDs at the beginning of the night. Moreover, the presence of high IED density in LGS patients is expected to induce a high number of artefacts on EEG recordings, precluding correct EEG spectral analysis. Finally, the effect of medication was difficult to establish in patients on polytherapy. Of the drugs known to increase IED density and seizures, two patients were on lacosamide and one was on vigabatrin, however, this effect was not confirmed in these patients.

Conclusions

Our study on adult LGS patients demonstrates a clear effect of sleep stages and time-of-night effect on the nocturnal evolution of epileptiform discharges across the night, with the first effect related to hypersynchronization more than hyperexcitability, and the second effect probably related to homeostatic sleep processes on epileptic threshold. These data stress the need to perform polysomnography at baseline and to use medication during the first hours of sleep in order to reduce IED density and the associated influence on attentional, motor, sensory, and cognitive dysfunctions (Overvliet *et al*., 2010). Further studies on large populations are needed to confirm our data in adult LGS patients. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) The sleep stage effect on interictal epileptic discharges in Lennox-Gastaut syndrome is unknown?
A. True
B. False

(2) The time-of-night effect on interictal discharges might suggest which mechanism?
A. Circadian
B. Homeostatic
C. Both

(3) What is the interest to perform a nocturnal sleep study in Lennox-Gastaut syndrome?
A. Scientific interest only
B. To determine efficacy of treatment through the night
C. Understating the mechanisms underlining interictal discharges in order to choose the best treatment

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".