Original article

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# Spike frequency is dependent on epilepsy duration and seizure frequency in temporal lobe epilepsy

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**ABSTRACT –** *Objectives.* We wanted to investigate factors that are associated with frequency of interictal epileptiform discharges by investigating 303 patients with temporal lobe epilepsy (TLE). *Methods.* We included all patients who consecutively underwent the adult presurgical evaluation program at our center and who had intractable, medial TLE with complex partial seizures due to unilateral medial temporal lobe lesions. The interictal EEG samples were automatically recorded and stored on computer. The location and frequency of interictal epileptiform discharges were assessed by visual analysis of interictal EEG samples of 2-minute duration every hour. *Results.* There were 303 patients (aged 16-63) who met the inclusion criteria. The median interictal epileptiform discharge frequency was 15 IED/h, the median seizure frequency was 4 seizures/month. According to univariate analyses, we found that age at monitoring, epilepsy duration, and higher seizure frequency were associated with higher interictal epileptiform discharge frequency. In the logistic regression analysis, we found that higher seizure frequency ($p < 0.001$) and longer epilepsy duration ($p = 0.007$) were independently associated with higher spike frequency, while the age at monitoring was not. *Conclusions.* Seizure frequency and epilepsy duration (years of patient's life with seizure activity) were independently associated with IED frequency, suggesting that IED are modulated by seizures.

**Key words:** temporal lobe epilepsy, interictal discharges, seizure frequency, epilepsy duration, EEG

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Epilepsy is characterized by interictal and ictal functional disturbances. Not only the seizures, but also the interictal epileptiform discharges (IED) are associated with neuropsychiatric consequences. During IED, specific neuropsychological deficits called transient cognitive impairment (TCI) can be demonstrated (Aarts *et al.*, 1984). Some patients are clearly handicapped by TCI, and their functioning improves when the IED are suppressed by medication (Aarts *et al.*, 1984). In patients with Landau-Kleffner syndrome, the frequent IED disturb speech functions, resulting in long-term aphasia (Landau and Kleffner, 1957). Frequent IED may be partly responsible for atypical speech lateralization seen in every fourth patients with left-sided temporal lobe epilepsy (TLE) (Janszky *et al.*, 2003a). IED may have an influence on the memory lateralization (Janszky *et al.*, 2004). Thus, investigating the factors affecting IED is not only of theoretical importance, but may also have clinical relevance as understanding the evolution of interictal epileptogenesis may lead to the development of therapeutic interventions.

There is growing evidence that IED and seizures are not independent phenomena. Two recent studies investigated the relationship between IED and seizure frequency. Rosati *et al.* (2003) found that 31 TLE patients with rare IED (< 1 IED/h) showed a later age at seizure onset, lower monthly seizure frequency, lower incidence of secondarily generalized tonic-clonic seizures (SGTCS), lower incidence of hippocampal atrophy and no status epilepticus compared to 27 TLE patients with higher IED frequency. They did not perform a multivariate study and, thus, it is unknown whether the above-mentioned clinical features were associated with IED frequency independently. Clemens *et al.* (2005) investigated 38 TLE patients and found that higher IED frequency was associated with longer epilepsy duration and presence of SGTCS, but not with a higher seizure frequency or age at epilepsy onset.

In the present study, our aim was to determine which factors are associated with IED frequency by investigating 303 TLE patients. The large number of patients included in the present study allowed us to use a multivariate design and to test whether IED frequency is independently associated with seizure frequency, epilepsy duration, age at onset, generalized tonic-clonic seizures, or hippocampal sclerosis.

## Methods

### Patients

In this retrospective study, we included all patients who consecutively underwent the adult presurgical evaluation program at our center from 1993 to 2003 and who had intractable medial temporal lobe epilepsy with complex partial seizures due to unilateral medial temporal lobe lesions. Patients with dual pathology were excluded. Only patients who had long-term video-EEG and recorded seizures were included. In order to capture seizures, almost all patients underwent an antiepileptic drug reduction.

The data on the presence of generalized tonic-clonic seizures, duration of epilepsy, and seizure history were ascertained by questioning the patients and (in most cases) their relatives at admission to the presurgical unit. These data were taken by physicians blinded to goals of this study. Patients' previous medical charts were also reviewed. The seizure frequency was defined by the number of disabling seizures per month in the 1-year period before the monitoring during which spikes were counted. Non-disabling auras were not taken into consideration.

### EEG data

Patients underwent continuous video-scalp EEG monitoring lasting > 2 days. The electrodes were placed according to the 10-10 system. Their placement varied corresponding to the suspected epileptogenic region, but Fp1, F3, C3, P3, O1, AF7, FC5, CP5, F7, FT7, T7, TP7, P7, SP1, F9, FT9, T9, TP9 and homologous right-sided electrodes were always included. The interictal EEG samples were automatically recorded and stored on computer. The location and frequency of interictal epileptiform discharges were assessed by visual analysis of interictal EEG samples of 2-minute duration every hour. The EEG was analyzed in both bipolar and referential montages. The reference electrodes were the Cz and an extracranial electrode placed on the right shoulder. The EEG evaluation was made by electroencephalographers blinded to the objectives of this study and was supervised by one of the authors (A.E., R.S., M.H). In this study, we did not look at the impact of hyperventilation, sleep and different sleep stages, the effect of antiepileptic drug reduction, or seizure frequency during the monitoring period.

### MRI investigations

All patients had high-resolution MRI investigations. The examinations were made on 1.5 or 1.0 Tesla Siemens Magnetom MR machines (Siemens, Erlangen, Germany). Scout views with careful slides were used to avoid asymmetry, and then sagittal T1, axial T2 as well as coronal T1, T2 and proton density or FLAIR sequences perpendicular to the long axis of the hippocampus were made, giving adequate delineation of the temporal lobes.

### Statistical methods

The following variables were investigated as to whether they showed an association with the IED frequency: age, age at epilepsy onset, epilepsy duration, seizure frequency, presence of generalized tonic-clonic seizures, presence of hippocampal sclerosis. Because of the non-Gaussian distribution of seizure and IED frequencies, we divided these frequency data into 2 categories according to their median. For statistical analysis of categorical data, Chi-square and Fisher's exact tests were carried out. For continuous variables, independent sample t test or one-way ANOVA was performed. In order to independently establish the variables that are associated with higher spike frequency, a stepwise forward logistic regression analysis was designed for all variables with the exception of the age at onset. Age at onset was excluded because the duration of epilepsy was derived as the difference between age at monitoring and age at onset. Thus, for mathematical reasons only two of these three variables could be included into the logistic regression analysis. We have chosen the epilepsy duration and the age at monitoring because we expected that these variables might have had a greater influence on IED frequency than the age at onset. Two-tailed error probabilities smaller than $p < 0.05$ were considered to be significant.

## Results

There were 303 patients, 165 women and 138 men who met our inclusion criteria. The mean age of the patients was 33.5 years (range 16-63). The mean age at epilepsy onset was 12 years (range: 1-45). In 167 patients, the epileptogenic lesion was on the left side, while in the remaining 136 patients it was on the right. MRI revealed hippocampal sclerosis in 239, tumor in 53, cavernoma in 7, malformations of cortical development in 4 patients.

The median IED frequency was 15 IED/h (range 0-1800), the median seizure frequency was 4 seizures/month (range 0.33-300). *Figure 1* demonstrates the correlation between IED frequency and epilepsy duration. *Figure 2* shows the association between IED and seizure frequency. For the further analyses, we converted these variables into categorical variables according to their median. *Table 1* shows the association of IED frequency with the variables investigated. According to univariate analyses, we found that age at monitoring, epilepsy duration, and higher seizure frequency were associated with higher IED frequency, while the presence of generalized tonic-clonic seizures and hippocampal sclerosis on MRI were not.

In the logistic regression analysis, we found that the higher seizure frequency ($p < 0.001$) and longer epilepsy duration ($p = 0.007$) were independently associated with higher spike frequency, while the age at monitoring was not.

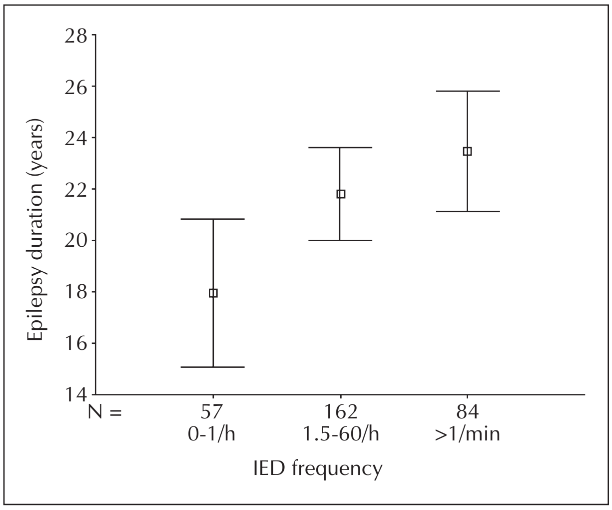


**Figure 1.** Higher IED frequency was associated with longer epilepsy duration. Because of non-Gaussian distributions of the variables, we categorized the variables. Considering the categorization of IED frequencies presented, one-way ANOVA after Bonferroni correction showed a significant difference in epilepsy duration between patients with ≤ 1 IED/h and patients with > 1 IED/min ($p = 0.013$). Error bar represents mean ± 2 SD.

## Discussion

There are many hypotheses about the relation between interictal and ictal epileptic activity. For many years it has been hypothesized that the temporal summation and spatial spread of IED may evolve to ictal discharges resulting in electroclinical seizures (Ralston, 1958). Recent studies however, indicate that there is no such causal relationship between IED and seizures, and interictal spiking does not increase prior to seizures (Katz *et al.*, 1991). IED may represent decreased seizure susceptibility (Engel and Ackermann, 1980), and may inhibit the expression of seizures (Librizzi and de Curtis, 2003). Jensen and Yaari (1988) demonstrated that seizures are independent of interictal spikes since after the chemical abolition of spike activity or after the disconnection of the spike-generating area from the seizure-generating area, seizures still occur.

Some recent studies suggest that IED are generated by seizures and this IED-inducing effect of seizures lasts for a long time:

1) *Seizures promptly increase the IED frequency.* Gotman and Maciani (1985) found that IED frequency is highest immediately after the seizures.

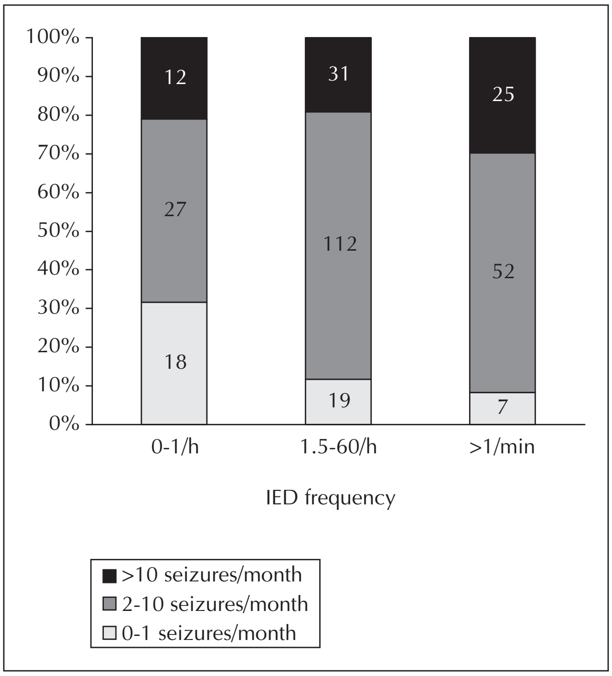


**Figure 2.** Higher IED frequency was associated with higher seizure frequency. Because of non-Gaussian distributions of the variables, we categorized the variables. Taking into account the categorizations presented, this association was highly significant ($p < 0.001$).

**Table 1.** Association of higher spike (IED) frequency with clinical variables.

| | Patents with higher spike frequency (> 15 IED/h) n = 154 | Patients with lower spike frequency (≤ 15/h) n = 149 | p value |
|---|---|---|---|
| Age (y) [a] | 35 ± 10 | 32 ± 10 | 0.015 |
| Age at epilepsy onset (y) [a] | 11.7 ± 9 | 12.3 ± 9 | 0.57 |
| Epilepsy duration (y) [a] | 23.3 ± 11 | 19.8 ± 11 | 0.007 |
| Higher seizure frequency (> 4/month) | 93 (60%) | 54 (36%) | 0.001 |
| Presence of generalized tonic-clonic seizures | 81 (53%) | 85 (57%) | 0.49 |
| Hippocampal sclerosis on MRI | 125 (81%) | 114 (77%) | 0.32 |

[a] mean ± SD.

2) *The region of the seizure activity is identical to the subsequent IED activity.* One of our previous studies found that the lateralization of spikes is influenced by the lateralization of the onset of the preceding seizure, if the seizure activity involves only one hemisphere. In seizures with contralateral propagation, we did not find a correlation between the localization of seizure onset and the postictal spike distribution (Janszky *et al.*, 2001). However, the study revealed that lateralized seizures without any contralateral involvement only led to a change in the *degree* of ipsilateral spiking, whereas as a rule, the *presence* of contralateral spikes did not completely disappear (Janszky *et al.*, 2001). This may raise the possibility that spikes provide information not only about the *directly* preceding seizure but that they also depend on other seizures preceding them. Thus, there would be not only an acute effect of seizures but also a chronic effect which influences IED frequency.

3) *After cessation of seizures following epilepsy surgery, the IED usually disappear but not always, especially if the preoperative IED frequency was high.* Persistence of IED after epilepsy surgery is associated with an unfavorable postoperative outcome (Godoy *et al.*, 1992). In our previous study however, we found that not only the postoperative seizures but also the preoperative IED frequency were independently associated with persistent postoperative IED (Janszky *et al.*, 2003b). This suggests that IED depend on acute ictal (persistent postoperative seizures) and chronic interictal (preoperative IED frequency) factors. Considering our results however, this chronic interictal factor was also generated by preceding seizures that had appeared many years before, as patients with 2-year seizure-freedom may also have postoperative IED (Janszky *et al.*, 2003b).

4) *In the present study, we found that seizure frequency and epilepsy duration (such as years of patient's life with seizure activity) were independently associated with IED frequency.*

One of the main limitations of the present study is that IED frequency may considerably vary depending on the sleep-wake cycle, antiepileptic drug levels, and the recent occurrence of seizures and that we did not control these variables. However, there is no reason to believe that these factors are correlated with the factors that we evaluated. □

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