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Absolute spike frequency and etiology predict the surgical outcome in epilepsy due to amygdala lesions

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Summary
Purpose: To identify surgical prognostic factors for temporal lobe epilepsy (TLE) due to amygdala lesions.
Methods: We included 42 patients (mean age: 31.4 ± 11) who underwent presurgical evaluation including long-term video-EEG and in whom the high-resolution MRI showed amygdala lesions without hippocampal abnormalities. All patients had apical temporal lobe resection without hippocampectomy. We distinguished patients with frequent spikes (spike frequency ≥ 60/h) and with non-frequent spikes (< 60 spikes/h).
Results: At the 2-year postoperative evaluation, 30 patients (71%) were seizure-free. The presence of infrequent spikes ($p = 0.013$), tumor on the MRI ($p = 0.027$), and no epilepsy history in the family ($p = 0.027$) were independently associated with 2-year seizure-free outcome. Of 33 patients with infrequent spikes, 79% became seizure-free, while of 9 patients with frequent spikes only 4 had a favorable surgical outcome (44%).
Conclusion: In TLE patients due to amygdala lesions, high spike frequency and family history of epilepsy predicted an unfavorable, while tumoral etiology a favorable outcome after apical temporal lobe resection without hippocampectomy. Seventy-one percent of patients with amygdalar epilepsy who underwent this novel type of epilepsy surgery became seizure-free. This is comparable with results of ''classical'' anterior temporal lobe resections where hippocampus is NOT spared. Moreover, the surgical outcome may be predictable.

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Introduction

Temporal lobe epilepsy (TLE) is the most common type of epilepsy requiring surgical treatment (Engel et al., 1997). The majority of patients with TLE have hippocampal sclerosis (HS) as a pathological abnormality underlying TLE (Engel et al., 1997). Surgical treatment of TLE including TLE with HS (TLE—HS) has a favorable prognosis, 60—70% of patients become seizure-free after ''standard'' anterior temporal lobe resection (McIntosh et al., 2001). Conversely, ca. one-third of patients have an unfavorable surgical outcome, thus, large amount of studies was conducted in order to look at predictive factors for surgical outcome in TLE. The most frequently reported predictors for favorable outcome of TLE surgery are unilateral temporal pathology (especially tumor) on MRI (Berkovic et al., 1995; Janszky et al., 2006; Schramm et al., 2001) and unilateral interictal epileptiform discharges (IED) (Schulz et al., 2000; Aull-Watschinger et al., 2008), epilepsy duration (Guldvog et al., 1994; Janszky et al., 2005), secondarily generalized tonic—clonic seizures SGTCS (Janszky et al., 2005), and preoperative seizure frequency (Clusmann et al., 2002; Aull-Watschinger et al., 2008).

Although TLE from a clinical point of view is a homogenous syndrome with typical auras, psychomotor seizures and EEG picture (Ebner, 1994), however, a variety of TLE subtypes exist according to the underlying etiology and localization of epileptologenic zone within the temporal lobe. These TLE subtypes may have different surgical prognosis (Janszky et al., 2006). Conversely, most studies investigating predictive factors for TLE surgery included patients with a variety of TLE subtypes (McIntosh et al., 2001). Because the majority of patients with TLE undergoing epilepsy surgery have TLE—HS (McIntosh et al., 2001), large multivariate studies investigating the surgical outcome in TLE include mostly (Berkovic et al., 1995) or exclusively (Janszky et al., 2005; Aull-Watschinger et al., 2008) TLE—HS patients, whereas other types of TLE patients make up only a small portion of these studies (McIntosh et al., 2001). This means that prognostic factors found in these studies can only be cautiously interpreted for TLE patients without HS. Three studies selectively investigated the surgical prognosis of non-hippocampal TLE patients without HS but all of these investigated neocortical TLE (Jung et al., 1999; Schramm et al., 2001; Janszky et al., 2006). Another study investigated predictors for surgical outcome in lesional mesial temporal lobe epilepsy and limited resections, but hippocampus was at least partially resected in all reported operations (Clusmann et al., 2004).

A recent study found that absolute spike frequency (independent of spike distribution) is a strong predictor for postoperative seizure control in patients with TLE—HS (Krendl et al., 2008). It is unknown whether this is true for epilepsy surgery in general or for surgery of other epilepsy syndromes than TLE—HS.

Most recently, a new surgical technique was introduced in those TLE patients where there is no hippocampal abnormalities (Elsharkawy et al., 2010; Gyimesi et al., 2009) called apical temporal lobe resection without hippocampectomy (aTLRwHC) in epilepsy patients with temporal epileptogenic lesions other than hippocampal sclerosis. This surgical procedure was developed to perform surgery in those patients who had no hippocampal abnormalities on MRI in order to spare hippocampal cognitive functions. Thus, one of the goals of the present study was to investigate the possibility for prediction of this surgical procedure in a well-definitive TLE subtype, namely TLE due to amygdala lesions.

In the present study we aimed at (1) identifying surgical prognostic factors in a TLE due to amygdala lesions where apical temporal lobe resection without hippocampectomy was performed (2) testing whether the absolute spike frequency — a newly described prognostic factor for epilepsy surgery — has a prognostic value in other epilepsy than TLE—HS.

Methods

Patient selection

For this study we included all drug-resistant TLE patients who (1) underwent presurgical evaluation including long-term video-EEG and high-resolution MRI, (2) had amygdala lesion without hippocampal abnormalities according to the MRI (3) had apical temporal lobe resection without hippocampectomy between 2001 and 2007, and (4) with 2-year postoperative follow-up.

Data collection

The following variables were investigated: (1) age at operation, (2) sex, (3) duration of epilepsy, (4) seizure frequency, (5) presence of SGTCS, (6) epilepsy risk factors, (7) presence of unilateral IED, (8) absolute spike frequency, (9) Type of lesion according to the MRI examination and (10) Extension of the lesion beyond the borders of the amygdala. The first 6 clinical variables were ascertained by asking the patients and (in most cases) their relatives at admission to the presurgical unit. This history was taken by physicians blinded to goals of this study. Patients' previous medical charts were also reviewed.

MRI data

MRI pictures in most patients were made by a Siemens Magnetom Impact 1.5-T scanner, and included T1-weighted three-dimensional volume, proton density, FLAIR, and T2-weighted images. All MRI was re-evaluated for this study by one of the authors (F.G.W.) who was blinded to clinical data, in order to (1) confirm the presence of amygdala lesion, (2) the absence of hippocampal alterations, and (3) to categorize the type of the lesion seen on the MRI.

EEG data

The data on EEG were determined by non-invasive continuous video-EEG monitoring. A 32—64 channel EEG recording was used, electrodes were placed according to 10—10 systems, the number of electrodes and their placement varied individually taking consideration of the suspected epileptogenic region and side. However, Fp1, F3, C3, P3, O1, AF7, FC5, CP5, F7, FT7, T7, TP7, P7, F9, FT9, T9, TP9 and homologous right-sided electrodes were always used. In cases of suspicion on non-temporal epilepsy, other electrodes were placed, but the scalp over the temporal lobe was always covered using the above-mentioned electrodes. In 15 patients sphenoidal electrodes were also used. The location and frequency of IED were assessed by visual analysis of interictal EEG samples of 2-min duration every hour. Those interictal samples which were recorded within an hour before or after the seizures were not evaluated. Unilateral IED were defined if at least 90% of spikes appeared over one temporal lobe.

According to Krendl et al. (2008), we distinguished patients with frequent spikes (with absolute spike frequency $\geq$ 60/h) and with non-frequent spikes (< 60 spikes/h).

Selection of variables

The above mentioned variables were chosen according to their presumed importance in presurgical evaluation or if they were previously reported as a predictive factor for TLE surgery. The results of psychiatric, neuropsychological, and sociological assessments were not included.

Surgical procedure

All patients had apical temporal lobe resection without hippocampectomy. The details about surgical technique, patient selection and surgical results are described elsewhere (Elsharkawy et al., 2010; Gyimesi et al., 2009). Briefly, the resection starts from the temporal pole followed by a complete resection of the amygdala, uncus and the most anterior part of the parahippocampal gyrus. Thus, the hippocampus remains spared during the surgery.

Outcome assessment and postoperative examinations

Outcome was assessed 2 years after the operation. We only evaluated seizure outcome, while psychiatric, social and neuropsychological outcome was ignored. For this study, we divided the patients into two categories according to the 2-year outcome: with seizure-free or non-seizure-free outcome. Patients with non-disabling auras without other seizures were considered to be seizure-free.

Statistical methods

Logistic regression analysis was used to assess the prognostic importance of the clinical variables. Odds ratios (OR) were calculated for being seizure-free at 2 years after the operation. Two-tailed error probabilities smaller than $p < 0.05$ were considered to be significant.

Results

There were 42 patients who met inclusion criteria. The mean age of the patients was 31.4 $\pm$ 11 years). The age at epilepsy onset ranged from 1 to 56 years. The duration of epilepsy ranged from 1 to 26 years. There were 18 women and 24 men. All patients had psychomotor (complex partial seizures), but 32 patients had also SGTCS. Regarding epilepsy risk factors, 6 patients had epilepsy in the family (among the first-grade relatives), 4 patients had a history of perinatal asphyxia, 1 patient had meningoencephalitis in childhood and another three had a history of significant head trauma before starting epilepsy. Only 4 patients had bilateral IED, in the remaining 38 patients IED appeared unilaterally, on the side of the operation. There were 9 patients with frequent spikes (with absolute spike frequency $\geq$ 60/h) and 33 with non-frequent spikes (< 60 spikes/h). Patients with non-frequent spikes had 6.9 $\pm$ 8.3 spikes/h (median: 3 spikes/h), while patients with frequent spikes had 162 $\pm$ 140 spikes/h (median:120).

The epileptogenic lesion according to MRI examination was tumor in 19, cavernoma in 5, dysgenesis in 4 patients. In the remaining 14 patients, the epileptogenic lesion seen on the MRI could not be unambiguously categorized. In 20 patients the resection was on the right, while in the other 22 patients it was on the left side.

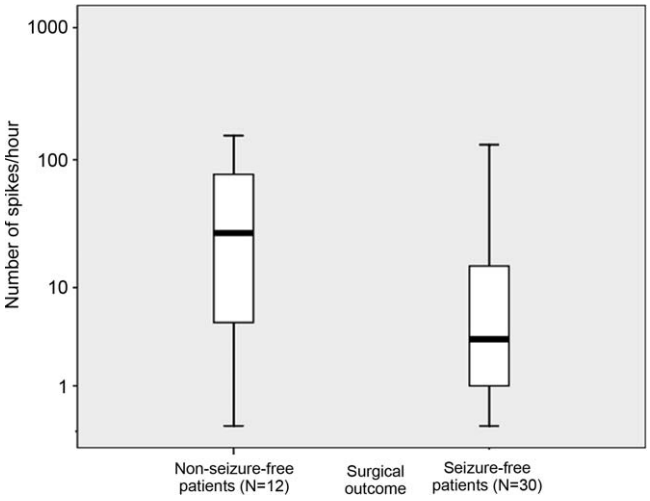

Fig. 1 Association between spike frequency and the surgical outcome. The frequency of interictal epileptiform discharges (spikes) is associated with the surgical outcome even if we consider it as a continuous variable. The Mann—Whitney test showed that the difference between the two groups is significant ($p = 0.034$): larger spike frequency predicts an unfavorable postoperative outcome. Please note that the *Y* axis is logarithmically scaled due to non-Gaussian distribution of the spike frequency.

At the 2-year postoperative evaluation 30 patients (71%) were seizure free.

Table 1 shows the characteristics of the patient population and the difference between seizure-free and non-seizure-free patients.

Because results of the histological examination was available only postoperatively, we did not include these data in searching presurgical predictor factors. Histological results revealed tumor in 18 cases (9 ganglioma, 7 dysembryoplastic neuroepithelial tumors, 2 astrocytoma), dysgenesis in 9 cases (3 polymicrogyria/schizencephalia, 6 focal cortical dysplasia) cavernoma in 3 cases, postencephalitis gliosis in 1, non-specific gliosis in 6 cases, and no pathological alterations in 5 cases.

In those 14 patients where the lesion seen on MRI could not be unambiguously categorized, 1 patient had dysembryoplastic neuroepithelial tumor, 2 patients had dysgenesis, 6 had non-specific gliosis, and in 5 cases no pathological alterations were found.

Logistic regression revealed that the presence of infrequent spikes ($p = 0.013$, OR for seizure-free outcome = 25, 95% Confidence Intervals for OR [95%CI]: 1.92—250) tumor on the MRI ($p = 0.027$, OR for seizure-free outcome = 14.2, 95%CI: 1.35—142) no epilepsy history in the family ($p = 0.27$, OR for seizure-free outcome = 22.9, 95%CI: 1.43—369) were independently associated with 2-year seizure-free outcome. The other variables presented in the methods section were not.

Of 33 patients with infrequent spikes 79% became seizure free, while of 9 patients with frequent spikes only 4 had a favorable surgical outcome (44%). Fig. 1 demonstrates the difference in spike frequency in seizure-free vs. non-

Table 1 Clinical characteristics of seizure-free and non-seizure-free patients.

	Mean (SD) in seizure-free patients 2 years after surgery	Mean (SD) in non-seizure-free patients 2 years after surgery	Significance level[a]
	N = 30	*N* = 12	
Age (year)	31.4 (11)	31.3 (12)	NS
Epilepsy duration (year)	11.1 (8)	10.3 (7)	NS
	N (%) in seizure-free patients	*N* (%) in non-seizure-free patients	Significance level
Men	6 (50)	18 (60)	NS
>1 seizure/week	13 (43)	8 (67)	NS
Presence of generalized tonic—clonic seizures	22 (73)	10 (83)	NS
Perinatal asphyxia/injury	4 (13)	0 (0)	NS
Epilepsy in the family	3 (10)	3 (25)	$p = 0.027$
Traumatic brain injury	2 (7)	1 (8)	NS
Uncategorized lesion on MRI	8 (26)	6 (30)	NS
Tumor on MRI	16 (53)	3 (25)	$p = 0.027$
Lesion extended into structures boarding amygdala on MRI	8 (26)	3 (25)	NS
Bilateral spikes on MRI	3 (10)	1 (8)	NS
Low spike frequency (< 60/h)	26 (86)	7 (58)	$p = 0.013$

[a] Significance level of difference was calculated by the logistic regression analysis

seizure-free patients is also present even if we consider it as a continuous variable. Table 2 shows the characteristics of patients with frequent spikes. Due to small number of patients, we could not perform multivariate statistics and the Fisher's exact test for categorical and Mann—Whitney test for continuous variables showed no differences between seizure-free and non-seizure groups in this subpopulation.

Of 19 patients with tumor on the MRI 84% became seizure free, while only 60% of patients without a tumor on the MRI achieved seizure freedom. Of 6 patients with family history of epilepsy, 3 (50%) became seizure free, while of 36 patients without positive family history the seizure freedom occurred in 75%.

There may be a theoretical possibility that spike frequency may also depend on the electrode placement, we checked whether spike frequency or surgical outcome is related to the usage of sphenoidal electrodes. Usage of sphenoidal electrodes did not influence whether the patient belonged to the group with frequent spiking or not. Of 15 patients in whom sphenoidal electrodes were used, 13 belonged to the group with infrequent spiking (87%), while of the remaining 27 patients, 20 had infrequent spiking (74%).

Table 2 Clinical characteristics of patients with high spike frequency.

	Mean (SD) in seizure-free patients 2 years after surgery	Mean (SD) in non-seizure-free patients 2 years after surgery
	N = 4	*N* = 5
Age (y)	30.2 (8)	27.6 (16)
Epilepsy duration (y)	6.8 (6)	9.6 (7)
	Seizure-free patients	Non-seizure-free patients
Men	1	3
>1 seizure/week	2	4
Presence of generalized tonic—clonic seizures	1	3
Perinatal asphyxia/injury	0	0
Epilepsy in the family	0	0
Traumatic brain injury	0	0
Uncategorized lesion on MRI	1	1
Tumor on MRI	3	2
Lesion extended into structures boarding amygdala on MRI	2	2
Bilateral spikes on MRI	0	0

This difference was statistically not significant ($p = 0.45$, Fisher's exact test). Of 15 patients in whom sphenoidal electrodes were used, 11 became seizure 2 years after the operation (73%), while of the remaining 27 patients, 19 became seizure-free according to the 2-year postoperative evaluation (70%, $p = 1.0$, Fisher's exact test).

Discussion

We evaluated the prognostic factors for outcome of TLE surgery due to amygdala lesions. The main findings of our study are: (1) high spike frequency and (2) family history of epilepsy predicts an unfavorable, while (3) tumoral etiology predicts a good surgical outcome.

Determination of prognostic factors for epilepsy surgery is of important influence when counseling our patients in everyday practice. In addition, the identification of prognostic factors may improve general understanding of the pathophysiology of surgical failure and of spatial extension of the epileptogenic zone.

A recent study found that absolute spike frequency (independent of spike distribution) is a strong predictor for postoperative seizure control in patients with TLE—HS (Krendl et al., 2008). One of the potential limitations of that study is that some frequently described surgical predictors were not controlled (for example epilepsy duration or SGTCS). Moreover, there are some data that spike frequency may reflect the lifetime number of seizures (Janszky et al., 2005b), but the predictive value of the usual seizure frequency was not investigated by Krendl et al., only the number of seizures during the actual presurgical monitoring period. Conversely, some earlier studies suggested that low seizure frequency was associated with better postoperative outcome (Clusmann et al., 2002; Aull-Watschinger et al., 2008). Because our statistical model was controlled for monthly seizure frequency and epilepsy duration, our results are in agreement with the conclusion of the study conducted by Krendl et al. (2008): the association between absolute spike frequency and postoperative outcome does not reflect the seizure frequency or total number of seizures. Thus, our study not only confirmed this observation but also demonstrated that the association between spike frequency is an independent predictor for surgical outcome and this association is valid in another epilepsy syndrome than TLE—HS and is true for an epilepsy syndrome with a different lesion than HS.

The exact reason why frequent spiking is associated with an unfavorable surgical outcome is not clear. The detection of spikes on scalp-EEG requires involvement of the temporal neocortex, because spikes generated in the mesiotemporal regions cannot be detected on the scalp-EEG, only if they propagate to necortex (Clemens et al., 2003). Thus, the epileptic activity in patients with spikes visible on the scalp-EEG never remains confined to mesial temporal compartments but also involves the structurally non-altered temporal neocortex. Thus, Krendl et al. (2008) hypothesized that the frequent spiking represents an extended irritative zone which zone may not be resected during the surgery. Our findings are in agreement with this hypothesis.

The absolute spike frequency represents the spike frequency detected over the whole neocortex. Thus, absolute spike frequency depends not only on interictal epileptic activity of circumscribed neuron populations but also on a summation of regions generating spikes: the larger area is involved in the spike generation the higher the spike frequency is. In our previous study we suggested that spikes are generated in those brain areas which are involved by the preceding seizures. Thus, we hypothesized that spike generation may be influenced by the seizure activity (seizure generation and propagation), and may not be independent signs of epileptogenicity (Janszky et al., 2001). Consequently, the absolute spike frequency may also depend on seizure activity: the area where the seizure is generated and the regions which are involved during seizure spread. Previous studies suggest that widespread seizure propagation is a prognostic factor for unfavorable outcome in TLE surgery (Schulz et al., 2000; Janszky et al., 2006).

In the present study, we found that tumor on the MRI was associated with seizure-free outcome. Previous studies (Schramm et al., 2001; Hennessy et al., 2001; Janszky et al., 2006) also found that one of the positive predictors for surgery of lesional TLE surgery is a tumoral etiology (Schramm et al., 2001; Janszky et al., 2006). The association of tumoral etiology and the favorable seizure-free outcome can be explained that tumors represent a well-circumscribed epileptogenic lesion which is visible during the operation.

In this study we found that positive family history for epilepsy was associated with an unfavorable outcome. Although we cannot fully explain this association, we might hypothesize that in these patients there may be an inherited susceptibility for a lower seizure threshold which susceptibility may affect not only a circumscribed area but the whole brain or a more extended brain region beyond the amygdala and temporal pole which is removed by the surgical technique used in the present study. Another possibility is that some of these patients had familial mesial temporal lobe epilepsy. Presence of hippocampal abnormalities is not always detectable by MRI in this syndrome (Kobayashi et al., 2003), thus — in our cases — we might not recognize that the hippocampus is a part of the epileptogenic region which was not resected by the surgical procedure used in our study.

One of the limitations of the present study is that we could include only a relatively low number of patients, which may result in a limited statistical power. Thus, some infrequent clinical phenomena might had no chance of reaching statistical significance because they did not occur at a high enough frequency to reach statistical significance. For example, only 4 patients had bilateral IED which were frequently found as a poor prognostic factor in other studies assessing surgical predictors in different epilepsy types (Schulz et al., 2000; Aull-Watschinger et al., 2008), although there are other well-powered studies which also failed to demonstrate the predictive value of a unilateral spike focus (Jeong et al., 1999; Hennessy et al., 2001; Clusmann et al., 2002; Janszky et al., 2005).

Another limitation may be that measuring spike frequency may face some methodological difficulties: (i) spike frequency may depend on the placements of the scalp electrodes, however, in our study the scalp over the temporal lobe was always covered by a standard electrode arsenal and using sphenoidal electrodes did not influence the spike frequency or surgical outcome. (ii) Spike frequency is

influenced by sleep—wake cycle, epilepsy duration, seizure frequency and the timing from the last seizure (Gotman and Koffler, 1990; Janszky et al., 2005b). Although spikes appeared within on our after a seizure were excluded from calculating spike frequency, we could not control all of these confounding factors. (iii) We evaluated EEG samples of 2-min duration every hour which may not reflect the true spike frequency and a continuous measure of spikes might have been a more appropriate method.

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