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Long term outcome in patients not initially seizure free after resective epilepsy surgery

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ABSTRACT

Purpose: To assess the long-term seizure outcome and find predictors of outcome for patients who were not initially seizure free 6 months after epilepsy surgery.
Methods: We retrospectively reviewed all adult patients who underwent epilepsy surgery at the Epilepsy Center Bethel, between 1992 and 2003. There were 266 patients included in this analysis.
Results: Of the 266 patients who were included in this study, the probability of becoming seizure free was 12% (95%CI 8–16%) after 2 years, 19.5% (95%CI 15–24%) after 5 years and 34.7% (95%CI 28–41%) after 10 years. In patients who had auras only, the probability of being seizure free was 18.2% after 2 years, 25.5% after 5 years, and 39.1% after 10 years. In the multiregression analysis, the EEG carried out 2 years after surgery, a psychic aura, the frequency of postoperative focal seizures and hypermotor seizures predicted seizure remission in the long-term outcome.
Conclusions: The frequency and type of postoperative seizures are critical determinants for long-term outcome. Seizure semiology may be the clue to a precise diagnosis and long-term prognosis of epilepsy.
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1. Introduction

The main goal of epilepsy surgery is the long-term freedom from seizures.[1] In general, about 60% of patients with temporal lobe epilepsy and 25–40% of those with extratemporal epilepsy achieve long-term seizure freedom after epilepsy surgery.[2]

Currently, seizures persist or recur in 20–60% of patients following resective surgery for intractable partial epilepsy.[3–5] Most published studies were interested in evaluating the outcome in general[6] and/or in evaluating patients initially seizure free after epilepsy surgery.[7] Information regarding the course of patients who were not initially seizure free is scarce in the literature and predictors of the outcome are not known.[8,9]

The few studies reporting the outcome in those patients were older ones performed prior to the introduction of new anti-epileptic drugs (AEDs), were limited in the duration of follow-up, and reported only temporal lobe cases. Furthermore, the focus of these studies was on the early seizure recurrence in the first months after surgery and the results were gathered using limited statistic tools.[10–13]

More data concerning this group of patients is needed for several reasons. For one reason, there is a substantial number of patients who are not initially free of seizures. Secondly, it is important to know more about the dynamics of the course of seizures: i.e. the "running up" or "running down" after surgery, and thirdly, studying this group of patients helps to complete evaluation of the efficacy of epilepsy surgery.[14,15] Moreover, patients are concerned about whether seizures after epilepsy surgery will eventually be controlled in the long term and are in need of appropriate consultation.[16]

Our aim was to study the long-term seizure outcome among a large group of postsurgical patients who were not seizure free 6 months after surgery. We also intended to look at the relationship between postoperatively prescribed AEDs and the outcome.

1.1. Clinical materials and methods

We retrospectively reviewed the records of all adult patients (16 years and older) who underwent epilepsy surgery at the Epilepsy Center Bethel, Bielefeld, Germany, between May 1992 and May 2003. The preoperative protocol developed in the Bethel Epilepsy Center to identify patients for surgery has been published elsewhere Elsharkawy et al.[3,6,17]. We excluded patients who had

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Table 1
Patients' characteristics.

Variable	Temporal	Extratemporal	Total	Sig.
Mean age at surgery (yrs)	34.0 ± 10.7	28.9 ± 10.8	32.5 ± 11.0	0.001
Mean age at epilepsy onset (yrs)	12.1 ± 9.2	11.0 ± 9.7	11.7 ± 9.3	0.391
Mean of epilepsy duration (yrs)	22.2 ± 11.0	17.8 ± 10.0	21.0 ± 10.8	0.002
Mean duration of follow-up (yrs)	9.1 ± 3.0	8.9 ± 2.7	9.0 ±3.0	0.572
Predisposing factors in no. of patients				
Febrile convulsion	35 (18.2%)	2 (2.7%)	37 (13.9%)	0.000
History of head trauma	16 (8.3%)	12 (16.2%)	28 (10.5%)	0.059
History of meningitis	17 (8.9%)	7 (9.5%)	24 (9%)	0.541
Family history of epilepsy	8 (4.2%)	3 (4.1%)	11 (4.1%)	0.622
Pathological finding in no. of patients				
No pathology	1 (0.5%)	3 (4.1%)	4 (1.5%)	0.000
HS	116 (60.4%)	0	116 (43.6%)	
Tumor	39 (20.3%)	14 (18.9%)	53 (19.9%)	
FCD	10 (5.2%)	37 (50%)	47 (17.7%)	
Vascular	6 (3.1%)	5 (6.8%)	11 (4.1%)	
Inflammation	3 (1.6%)	5 (6.8%)	8 (3%)	
Gliosis	16 (8.3%)	8 (10.8%)	24 (9%)	
Other	0	2 (2.8%)	2 (0.8%)	

Mean ± standard deviation, HS, hippocampal sclerosis; FCD, focal cortical dysplasia.

previous epilepsy surgery outside our clinic and patients who had malignant tumors or who were reoperated on for malignant tumors. This left 639 patients who were included. Of these, 373 (58%) were categorized as completely seizure free (without aura) and 266 (42%) as not seizure free at the 6-month follow-up examination. Out of the 266 patients who still had seizures, 55 patients (20.7%) had auras only.

1.2. Patient characteristics

Our analysis included 266 patients (146 (55%) males and 120 (45%) females). The mean age in years at surgery was 32.5 ± 11 (range 16–61 for temporal lobe epilepsy patients and 16–59 for extratemporal). The mean age of epilepsy onset was 11.7 ± 9.3 (range 0–53 for temporal and 0–51 for extratemporal). The mean duration of epilepsy was 21 ± 10.8 years (range 2–57 years for temporal and 1–57 years for extratemporal). The mean duration of follow-up was 9 ± 3 years (range 5–16 years for temporal and 5–14 years for extratemporal). Patient characteristics, predisposing factors and neuropathologic findings are summarized in Table 1.

1.3. Surgical procedure and postoperative evaluation

In this study, 74 patients (27.8%) had extratemporal resections: 37 (13.9%) underwent frontal lobe surgery, and 34 (12.8%) had posterior cortical epilepsy, 3 (1.1%) submitted to multilobar resections. There were 192 patients (72.2%) who underwent temporal lobe epilepsy surgery, 145 (54.5%) of them had mesial resection and 47 (17.7%) had lateral temporal lobe resection.

Our surgical procedures for temporal and extratemporal resections have been published elsewhere.[6,17] Eleven patients in this study had additional MSTs (multiple subpial transsections). Invasive monitoring in the form of subdural electrodes was used on 42 (15.8%) patients(39 (92.9%) extratemporal lobe and 3 (7.1%) temporal).

1.4. Outcome evaluation

At the first follow-up examination 6 months after surgery, outcome was evaluated using Engel's classification.[4] All patients were then reclassified into two groups determined by whether they were completely seizure free or not. For this study, all patients who were not completely seizure free were included.

In subsequent follow-up examinations 2, 5 and 10 years after surgery, patients were defined as seizure free if they had absolutely no seizures, including auras, for at least one year before the follow-up examination. Patients in remission were patients who not only became seizure free but maintained seizure freedom during the entire period of follow-up. Seizure types were classified according to the semiological seizure classification suggested by Luders et al.[18] AEDs were evaluated 6 months and 2 years postsurgically. Depending on the seizure situation and the serum levels of AEDs, they were replaced by other AEDs or the dosage was modified. Patients whose AEDs were replaced by other ones were seen every 3–6 months. In our study, 95 patients (35.7%) had such AED modifications or replacements after surgery within the follow-up period.

Post-operative MRI evaluation revealed that 173 (65%) had complete resection of preoperative lesions and 93 (35%) had incomplete resections, and in 5 of the patients, there was a lesion in the functional area. Postoperative EEG was carried out at the 6-month and 2-year follow-up examinations. Seizure semiology was re-evaluated 6 months and 2 years after surgery. In this anaylsis 17 (6.4%) had new seizure semiology during the first 2 years. Postoperative seizure frequency was evaluated during the first 6 months after surgery. For details of numbers and frequency, see Table 4.

1.5. Statistical analysis

Kaplan–Meier methods were used to estimate the probability of patients remaining seizure free as a function of time. Univariate analysis was used to detect factors affecting the long-term outcome. A stepwise logistic multivariate regression model was

Table 2
Seizure outcome.

Variables	Seizure free	In remission	Not seizure free	Total no. of patients
All patients				
2 years	32 (12%)	24 (9%)	234 (88%)	266
5 years	52 (19.5%)	41 (15.4%)	214 (80.5)	266
10 years	69 (34.7%)	56 (28.1%)	130 (65.3)	199
Patients who had auras only				
2 years	10 (18.2%)	9 (16.4%)	45 (81.1%)	55
5 years	14 (25.5%)	12 (21.8%)	41 (74.5%)	55
10 years	18 (39.1%)	14 (30.4%)	28 (60.9%)	46
Patients with other forms of seizures				
2 years	22 (10.4%)	15 (7.1%)	189 (89.6%)	211
5 years	38 (18%)	29 (13.7%)	173 (82.0%)	211
10 years	51 (33.3%)	42 (27.5%)	102 (68.6%)	153

Table 3
Multivariate analysis: variables showing predictors for seizure remission.

Variable	Sig.	HR	95%CI
2-Year EEG	0.044	4.70	1.1–20.9
Hypermotor seizures	0.034	2.70	1.1–7.1
Frequency of postoperative focal seizures	0.002	4.60	1.7–12.0
Psychic aura	0.003	0.235	0.09–0.61

Table 4
Variables of interest in the analysis.

Variable	No. of Patients (%)
Type of surgery	
Temporal	192 (72.2%)
Extratemporal	74 (27.8%)
Gender	
Male	146 (54.9%)
Female	120 (45.1%)
Interictal spike and sharp waves	
Yes	235 (88.3%)
No	31 (11.7%)
Unilateral spike and sharp waves	
Yes	142 (53.4%)
No	124 (46.6%)
Bilateral spikes and sharp waves	
Yes	93 (35%)
No	173 (65%)
Presence of EEG seizure ictal rhythm	
Yes	249 (93.6%)
No	17 (6.4%)
Unilateral EEG seizure pattern	
Yes	157 (59%)
No	109 (41%)
Hemispheric EEG seizure pattern	
Yes	92 (34.6%)
No	174 (65.4%)
Presence of aura	
Yes	217 (81.6%)
No	49 (18.4%)
Somatosensory aura	
Yes	40 (15%)
No	226 (85%)
Abdominal aura	
Yes	101 (38%)
No	165 (62%)
Psychic aura	
Yes	46 (17.3%)
No	220 (82.7%)
Unspecific aura	
Yes	41 (15.4%)
No	225 (84.6%)
Visual aura	
Yes	22 (8.3%)
No	244 (91.7%)
Vegetative aura	
Yes	16 (6%)
No	250 (94%)
Psychomotor seizure	
Yes	198 (74.4%)
No	68 (25.6%)
Tonic seizure	
Yes	43 (16.2%)
No	223 (83.8%)
Hypermotor seizure	
Yes	39 (14.7)
No	227 (85.3)
Versive seizure	
Yes	26 (9.8%)
No	240 (90.2%)
Absence seizure	
Yes	23 (8.6%)
No	243 (91.4%)
Generalized tonic-clonic	
Yes	119 (44.7%)
No	147 (55.3%)
History of febrile convulsion	
Yes	37 (13.9%)
No	229 (86.1%)
History of head trauma	
Yes	28 (10.5%)
No	238 (89.5%)
History of meningitis	
Yes	24 (9%)
No	242 (91%)
Family history of epilepsy	
Yes	11 (4.1%)
No	255 (95.9)
Site of epilepsy surgery	
Temporal	
Mesial temporal	145 (54.5)
Lateral temporal	47 (17.7%)
Frontal	37 (13.9%)
PCEs	34 (12.8%)
Multilobar	3 (1.1%)
Side	
Right	142 (53.4%)
Lift	124 (46.6%)
Postoperative MRI	
Complete resection	173 (65%)
Incomplete resection	93 (35%)
Invasive monitoring	
Yes	42 (15.8%)
No	224 (84.2%)
Postoperative EEG 6 months	
With IED	76 (28.6%)
Without IED	190 (71.4%)
Postoperative EEG 2 years	
With IED	76 (28.6%)
Without IED	190 (71.4)
Postoperative focal seizure frequency	
3 or fewer	106 (39.8%)
Between 4 and 10	31 (11.7%)
More than 10	129 (48.5)
Postoperative GTCS frequency	
3 or fewer	245 (92.1%)
More than 3	21 (7.9)
Postoperative seizure semiology	
No change	249 (93.6%)
New seizure semiology	17 (6.4%)
Postoperative AEDs	
No change	161 (60.5%)
Changed	95 (35.7%)
No treatment	10 (3.8%)

PCE, posterior cortical epilepsy; IED, interictal epileptiform discharges; AED(s), anti-epilepsy drug(s).

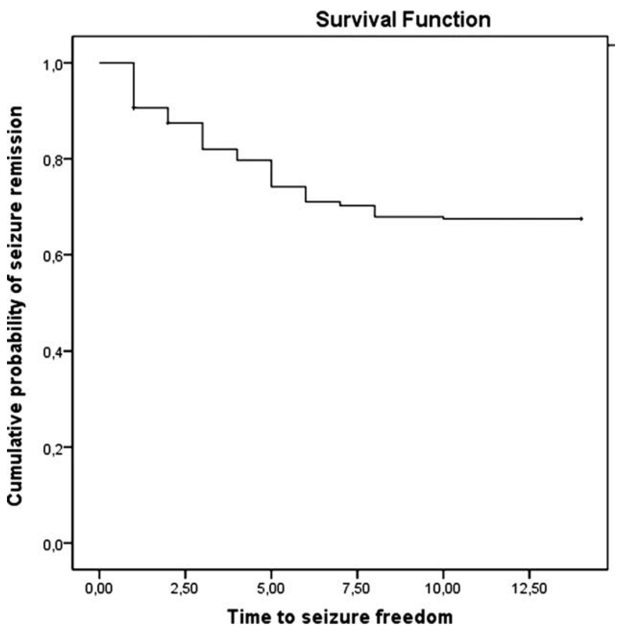
used to estimate the hazard ratios with 95% confidence intervals (CIs) for each risk factor. Variables of interest in this analysis were preoperative, operative and postoperative factors. These variables are summarized in Tables 1–4.

2. Results

2.1. Seizure outcome

Of 266 patients who were included in this study, 32 patients (12%) became free of seizures by the 2-year follow-up examination, 52 (19.5%) within 5 years, and 69 (34.7%) within 10 years. The statistical probability of becoming seizure free was 12% (95%CI 8–16%) at 2 years, 19.5% (95%CI 15–24%) at 5 years and 34.7% (95%CI 28–41%) at 10 years. From 69 patients who were seizure free at the 10-year follow-up examination, 56 patients were in remission and 13 patients showed an intermittent course between seizure freedom and relapse during the whole period of follow-up.

Of the 266 patients who were included in this study, 55 (20.7%) had auras only at the 6-month follow-up. The probability of being seizure free, defined as Engel's class 1A, for this group of patients was 18.2% (95%CI 9–30%) at 2 years, 25.5% (95%CI 15–38%) at 5 years, and



Graph 1. Kaplan–Meier graph showing the probability of remission after epilepsy surgery.

39.1% (95% CI 26–53%) at 10 years of follow-up. The numbers and percentage at each time point are summarized in Table 2.

The group of temporal lobe surgery patients presented a higher rate of persistent aura. A total of 16 patients had persistent auras during the entire follow-up period; 15 of them were temporal lobe surgery patients. Over time, 12 temporal lobe patients had a relapse of seizures.

The Kaplan–Meier curve shows that seizure freedom mostly occurred in the first 5 years after surgery (Graph 1).

2.2. AED outcome

In our study, 10 (3.8%) patients had not been taking AEDs for at least one year before each of the follow-up examinations, 95 (35.7%) had changes made to the preoperative AEDs either by adding new AEDs or by modifying the dosage of AEDs, and 33 of the patients took different AEDs. The most frequently used add-on AEDs after surgery in our group were levetiracetam and lamotrigin. It is interesting to note that most of the seizure-free patients in the long-term outcome were taking the same AED as preoperatively, namely only 17 (24.6%) had drug changes but 52 (75.4%) were on the preoperative medications. Univariate analysis showed that postoperative AEDs changes was correlated to seizure remssion outcome ($p = 0.015$, HR 2.60 (95% CI 1.20–5.50).

2.3. Multivariate analysis

Using multivariate analysis we found that hypermotor seizure, 2-year EEG, frequency of postoperative focal seizures and psychic aura independently predict seizure remission in the long-term outcome.

In patients with auras only, preoperative GTCS were found to predict short- and long-term outcome ($p = 0.008$, HR 0.11 (95%CI 0.02–0.56). Preoperative tonic seizures predicted running up of seizures ($p = 0.004$, HR 0.14 (95%CI 0.03–0.52).

3. Discussion

Patients who have seizures after surgery experience significant disappointment and a sense of "failure".[19] Consequently, they are especially eager to hear from the medical team what their prognosis is. Our study presents predictive factors for the long-term outcome (<5 years) in that group of patients.

We found that, in patients who had seizures within the first 6 months, 34.7% were seizure free and 28.1% reached remission within the long-term follow-up. Seizure outcome within the first 2 years shapes long-term outcome after surgery. Long-term prediction reliability of seizure outcome 2 years after surgery has been proven in previous studies.[6,17] Our study confirms this reliability, also among patients who were not seizure free within the first 6 months after surgery. However, data available in the literature for this group of patients showed a great difference in the rate of seizure freedom, ranging between no seizure freedom and 55.7%.[10–13,15]

The older studies reported poorer outcome. This poorer outcome could be attributed to the old preoperative evaluation protocol and seizure localization methods. Patients were evaluated using a low resolution MRI, during which subtle lesions may have been missed. Moreover, only classical AEDs were used postoperatively.[20] There are, however, several studies that reported better results than ours,[10–13] but comparisons are difficult due to the variations in the seizure outcome definitions, different patient groups, the variations in AED treatment protocols, and different follow-up periods.[1,10–13,15] Our results may be seen as more reliable as we investigated a large number of patients who underwent advanced and similar preoperative diagnostic studies, had relatively uniform surgical procedures at a single institution, and a relatively long follow-up period. Moreover, newer AEDs that have become available over the years were administered to our patients postoperatively.

Seizure freedom in patients who were not initially seizure free after surgery might be explained by a reduction in the size and extent of the epileptogenic zone, which may lead to it gradually losing the ability to generate seizures and enhance the patient's response to AEDs.[21]The dynamic nature of the epileptogenic zone may play a role, as indeed, spontaneous progressive extension and shrinking of the epileptogenic zone over time have been observed.[22,15,23] Moreover, individual variations in the degree of epileptogenicity and the epileptogenic profiles may differ between one patient and another.[21]

3.1. Outcome predictors

The EEG carried out 2 years after surgery, a psychic aura, the frequency of postoperative focal seizures and hypermotor seizures were predictors of seizure remission in the long-term outcome.

This suggests that patients who had IED in the 2-year postoperative EEG will most probably never enjoy remission but may have seizure freedom at some point in the postsurgical course. This result seems logical as the presence of IED on EEG correlates strongly with the diagnosis of epilepsy.[1,21] However, the converse is not true. Therefore, IED on a single routine EEG 2 years after surgery strongly indicates the presence of an active residual epileptogenic zone or neural epileptic network rebuild, which in most cases leads to relapse. Several previous studies reported a strong predictive value of postoperative EEG in temporal and extratemporal lobe epilepsy.[14,24–26,27]

3.2. Clinical seizure semiology

It is worth noting that seizure semiology (psychic auras, hypermotor seizures and GTCS) were predictors of seizure remission. In a recent study, hypermotor seizures were semiologically reanalyzed, and the authors found that hypermotor seizures could be differentiated into two clinical groups, the ventromesial frontal cortex and the mesial premotor cortex, based on their seizure origin namely, either.[28]

The absence of a history of GTCS seizures predicted remission in patients who had auras only. It has been reported that the absence of generalized tonic-clonic seizures was the sole predictor of seizure remission after temporal epilepsy surgery.[29]

The absence of a psychic aura was a slight predictor of seizure remission. The available data may indicate that the occurrence of psychic auras involves a large neural network, including neocortical and limbic structures.[30] Furthermore, patients who have auras with psychic content are likely to have a higher rate of depression.[31] It has been reported that postoperative depression is concomitant with poor seizure outcome.[32] Psychic auras have also been correlated with poor outcome in extratemporal studies.[3,33,34] In general, the nature of psychic auras and their association with the seizure focus has received relatively little attention and so remains less well understood.[35]

3.3. AEDs and change from pharmacoresistance to pharmacosensitivity

According to our data, administered AEDs (either in original postsurgical form or with changes) was *correlated* with *seizure* remission in long-term outcome. Although AED changes played an important role in obtaining seizure freedom, most patients in remission were on the same AEDs which were taken before surgery. The beneficial role of AEDs after temporal lobe resection, especially levetiracetam that was administered or added on after failed epilepsy surgery, has been proven in several studies.[10] It has been documented that no advantage or disadvantage exists for prescribing drugs with different mechanisms of action or using drugs with possible neuroprotective effects after temporal lobectomy.[36]

This could be explained by the fact that epilepsy surgery transforms pharmacoresistant to pharmacosensitive epilepsy.[37,38] Hence the response either to the preoperative AEDs or to newly added AEDs improves.

4. Conclusion

Our results showed that about 30% of patients who were not seizure free within the first 6 months after surgery eventually achieved seizure freedom or remission. The central finding in our study was that frequency and type of postoperative seizures are a critical determinant for long-term outcome. Seizure semiology may be the clue to a precise diagnosis and long-term prognosis of epilepsy. Our data is especially valuable for counseling and providing medical care for patients who experience seizure recurrence within the first 6 months after surgery.

Disclosure

The authors report no conflicts of interest.

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