Prognostic Factors and Longitudinal Change in Long-Term Outcome of Frontal Lobe Epilepsy Surgery

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■ OBJECTIVE: **We aimed to investigate the possible predictive factors and longitudinal change in long-term surgical outcome after refractory frontal lobe epilepsy surgery.**

■ METHODS: **We retrospectively reviewed 82 patients who underwent frontal lobe resection. Invasive monitoring was performed in 43 patients. All patients were followed-up for a minimum of 3 years after surgery. Univariate and multivariate analyses were used to evaluate the predictors. The Kaplan-Meier survival curve showed the estimated probability of complete seizure freedom, and a favorable outcome was defined as Engel class I at the last follow-up.**

■ RESULTS: **The estimated probability of complete seizure freedom was 57.3% at 1 year postoperatively, 51.2% at 2 years, and 50.0% at 5 years. Factors predictive of worse long-term outcome were lack of a lesion in the frontal lobe on magnetic resonance imaging, generalized/nonlocalized ictal discharge, use of subdural grids, and acute postoperative seizure (APOS). After the surgery, 44 patients (53.7%) had seizures at any time during the first 2 years. Five of 44 patients had seizure freedom at the last follow-up. After a seizure-free period of at least 6 months, seizure recurred in 6 patients by 6 months to 1 year (early recurrence) and in 9 patients by 1—3 years (late recurrence). Eight of 43 (18.6%) seizure-free patients had discontinued drugs.**

■ CONCLUSIONS: **The overall seizure outcome after surgery changed most during the first 2 years. The presence of frontal focal lesions and ictal frontal rhythm predicted favorable outcome. However, APOS was predictive of early epilepsy recurrence.**

INTRODUCTION

Frontal lobe epilepsy (FLE) accounts for 6%—30% of surgical series of intractable focal epilepsies and is the second largest subgroup of refractory focal epilepsy.[1] However, postoperative seizure outcome after FLE surgery is less favorable than that following temporal lobectomy.[2] This difference may be because of the widespread seizure onset zone, rapid propagation, diverse clinical semiology, varying etiologies, and concerns about functional areas (eloquent cortex). In the last 20 years, long-term seizure-free rates after FLE surgery have ranged from 29% to 66%.[1-11] Because of the less favorable outcome of FLE surgery, the determination of the prognostic factors is important in predicting surgical outcome and identifying the spatial extension of surgery. Moreover, only a few studies have considered longitudinal aspects of recurrence such as the change in the rate of postoperative seizure freedom with time.[1,9,12,13]

The objectives of this study were to evaluate the surgical outcome in a cohort of patients with pure FLE and to correlate postoperative seizure outcome with age at operation, duration of epilepsy, and age at onset, clinical semiology, interictal and ictal electroencephalographic findings, magnetic resonance imaging (MRI), type of resection, and pathology. In particular, we aimed to present the longitudinal changes in the outcome of FLE surgery.

PATIENTS AND METHODS

Patients

We retrospectively studied 82 patients with intractable FLE epilepsy (49 men and 33 women) who underwent frontal lobe resection between January 2009 and September 2011 at Xuanwu Hospital, Capital Medical University. All patients had a minimum of 3 years of follow-up. Data collected included sex, age at seizure onset and at surgery, seizure semiology and frequency, presence of auras and of generalized tonic-clonic seizures, preoperative electroencephalograph (EEG) and MRI, side of surgery, date of

Key words
- Acute postoperative seizure
- Epilepsy surgery
- Frontal lobe epilepsy
- Seizure outcome

Abbreviations and Acronyms
APOS: Acute postoperative seizure
EEG: Electroencephalograph
FLE: Frontal lobe epilepsy
MCD: Malformation of cortical development
MRI: Magnetic resonance imaging

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seizure recurrence, postoperative EEG, and surgical pathology. The occurrence of acute postoperative seizure (APOS) as defined by seizures occurring within the first postoperative week was also recorded.

Presurgical Evaluation

All patients had prolonged video EEG monitoring with electrodes placed according to the International 10-20 system to record interictal and ictal scalp EEG using a video EEG monitoring system (Micromed, Treviso, Italy). Interictal epileptic discharges were classified as follows: ipsilateral frontal spikes, extrafrontal spikes, and generalized spikes. Ictal EEG patterns were categorized as follows: frontal, lateralized, and generalized.[1] Clinical seizure manifestations and the occurrence of multiple seizure types were recorded.[14] All patients had high-resolution MRI using a 1.5-T system (Siemens Magneton Vision [Siemens, Munich/ Erlangen, Germany]). Spin-echo T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences were obtained.

Results of the noninvasive evaluation were discussed to identify epileptogenic regions. An invasive evaluation was performed if all the noninvasive evaluation results were inconsistent or inconclusive. Before resective surgery, 43 patients underwent invasive monitoring with subdural electrodes or depth electrodes.

Surgical Procedure and Pathologic Subgroups

The area of resection was classified as involving orbito-polar, frontomedial, dorsolateral, and frontocentral areas. Intraoperative electrocorticography was performed in all patients during epilepsy surgery to guide surgical resections of the epileptogenic zone and to assess the completeness of the surgical resections. Pre- and intraoperative functional mappings were performed when appropriate.

All tissue sections from the cortical resection were routinely processed to obtain detailed pathologic diagnoses. Pathologic diagnoses were classified as malformations of cortical development (MCDs), Focal cortical dysplasia (FCD), tumor, scar lesions, tuberous sclerosis complex (TSC), nodular neuronal heterotopia, vascular lesions, gliosis, cystic lesion, infection, and nonspecific findings.

Outcome Classification

The postoperative seizure outcome was assessed according to Engel classification.[15] APOS was defined as seizure occurring within the first postoperative week. Seizure recurrence was defined as the occurrence of a seizure after a seizure-free period of at least 6 months. The recurrence of seizures between 6 months to 1 year or more than 1 year after the surgery was considered as early or late recurrence, respectively. Typically, patients are followed-up at 6 months, 1 year, and then yearly after surgery.

Statistical Analysis

Two patient groups consisting of seizure-free and non—seizure-free patients were formed. Descriptive statistics were used for each variable. The data were analyzed using the paired *t* test, Wilcoxon rank-sum test, χ^2 test, and Fisher exact test to compare seizure-free patients with those with recurrent seizures. Variables with a significance level of 5% on initial univariate analysis were then tested in a multivariate analysis. The Kaplan-Meier survival analysis was used to estimate the probability of remaining seizure free throughout the follow-up period.

Statistical analyses were performed using the SPSS 19.0 software package (IBM, Chicago, Illinois, USA). The significance level was set at 5% ($P < 0.05$).

Table 1. Demographic Data of the Patient Cohort

Item	Overall Group (N = 82)	Seizure Free (n = 43)	Non—Seizure Free (n = 39)	*P* Value
Male	49 (59.8)	25 (58.1)	24 (61.5)	0.754
Age at onset (years)	10.3 (0.2—45.9)	12.0 (0.2—45.9)	8.4 (0.2—24.8)	0.025
Age at surgery (years)	19.1 (2.5—54.8)	21.5 (3.7—48.9)	16.3 (2.5—54.8)	0.365
Epilepsy duration (years)	8.8 (0.1—34)	9.5 (0.1—34)	8.0 (1—30)	0.241
Follow-up time (months)	49.7 (36—68)	49.7 (36—68)	49.6 (37—66)	0.161
Preoperative seizure frequency per month	25 (1—900)	10 (1—900)	60 (1—600)	0.076
Preoperative auras present	32 (39.0)	20 (46.5)	12 (30.8)	0.144
Multiple clinical seizure types present	8 (9.8)	2 (4.7)	6 (15.4)	0.217
Predominant seizure type				
GTCS	20 (32.3)	12 (37.5)	8 (26.7)	0.089
Asymmetric tonic	8 (12.9)	1 (3.1)	7 (23.3)	
Hypermotor	13 (21.0)	6 (18.8)	7 (23.3)	
Dialeptic/automatism	15 (24.2)	9 (28.1)	6 (20.0)	
Other	6 (9.7)	4 (12.5)	2 (6.7)	

Values are mean (range), number of cases (%), or as otherwise indicated.
GTCS, Generalized tonic clonic seizure.

Approval

The study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, China, according to the Declaration of Helsinki. Written informed consent was obtained from all patients and their relatives.

RESULTS

Clinical Data

Table 1 summarizes the patients' baseline clinical characteristics. Eighty-two consecutive patients (49 men and 33 women) fulfilled all the criteria and were analyzed. Age at the time of surgery was 19.1 ± 10.2 years (range, 2.5–54.8 years), and the mean duration of epilepsy was 8.8 ± 7.2 years (range, 0.1–34.0 years). Age at epilepsy onset was 10.3 ± 9.0 years (range, 0.2–45.9 years) for the entire patient cohort, which was significantly delayed in seizure-free patients (12.0 vs. 8.4 years, $P = 0.025$). The mean monthly seizure frequency was 25 seizures, and 8 patients (9.8%) had multiple clinical seizure types. Thirty-two patients (39.0%) had auras. The mean duration of follow-up was 49.7 ± 10.4 months (range, 36–68 months).

Table 2. EEG and Magnetic Resonance Imaging Characteristics of the Overall Group, with Comparison Between the Seizure-Free and Non–Seizure-Free Groups

Characteristics	Number of Cases	Seizure Free	Non–Seizure Free	*P* Value
Noninvasive EEG				
Interictal spikes	75	39	36	
Ipsilateral frontal spikes only				
Yes	22	13 (59)	9 (41)	0.428
No	53	26 (49)	27 (51)	
Extrafrontal spikes				
Present	48	25 (52)	23 (48)	0.985
Absent	27	14 (52)	13 (48)	
Generalized spikes				
Present	10	2 (20)	8 (80)	0.066
Absent	65	37 (57)	28 (43)	
Ictal rhythm				
Frontal	31	21 (68)	10 (32)	0.012
Lateralized	46	29 (63)	17 (37)	
Generalized	16	4 (25)	12 (75)	
Invasive EEG				
Seizure onset zones	37	16	21	
Lateral frontal	23	13 (57)	10 (43)	0.143
Mesial frontal	7	2 (29)	5 (71)	
Orbitofrontal	3	1 (33)	2 (67)	
Multifocal	4	0 (0)	4 (100)	
MRI characteristics	81	43 (53)	38 (47)	
Normal	28	12 (43)	16 (57)	0.027
Abnormal	53	31 (58)	22 (42)	
Frontal	36	25 (69)	11 (31)	
Multilobar	17	6 (35)	11 (65)	

Values are number of cases (%), number of cases, or as otherwise indicated.
MRI, magnetic resonance imaging; EEG, electroencephalograph.

EEG and MRI Findings

EEG and MRI characteristics are presented in Table 2. Interictal spikes were strictly frontal in 22 patients (29.3%), with generalized spikes in 10 patients (13.3%). Ictal frontal rhythms were recorded in 31 patients and were significantly recorded in seizure-free patients (48.8% vs. 25.6%, $P = 0.012$). A total of 52.4% of patients ($n = 43$) had intracranial EEG monitoring before resection. With invasive EEG recording, focal seizures were recorded in 33 patients (89.2%), and multifocal seizures were recorded in 4 patients (10.8%). A total of 65.4% of patients ($n = 53$) had abnormal MRI findings, and abnormal multilobar MRI was seen in 32.1% of patients ($n = 17$). Abnormal frontal MRI was significantly seen in seizure-free patients (58.1% vs. 28.2%, $P = 0.027$).

Table 3. Surgical Factors with Comparison Between the Seizure-Free and Non–Seizure-Free Groups

Predictor	Overall Group (N = 82)	Seizure Free (n = 43)	Non–Seizure Free (n = 39)	*P* Value
Use of invasive electrodes				
Yes	43 (52)	16 (37)	27 (69)	0.004
No	39 (48)	27 (63)	12 (31)	
Side of surgery				
Left	47 (59)	23 (55)	24 (63)	0.446
Right	33 (41)	19 (45)	14 (37)	
Both sides	2 (2.4)	1 (1.2)	1 (1.2)	
Localization of resected area	81	42	39	
Orbito-polar	8 (10)	2 (5)	6 (15)	0.234
Frontomedial	14 (17)	5 (12)	9 (23)	
Dorsolateral	30 (37)	19 (45)	11 (28)	
Frontocentral	6 (7)	3 (7)	3 (8)	
Total lobectomy	23 (28)	13 (31)	10 (26)	
APOS				
Present	13 (16)	0 (0)	13 (34)	<0.0001
Absent	69 (84)	43 (100)	26 (66)	

Values are number of cases (%), number of cases, or as otherwise indicated.
APOS, acute postoperative seizure.

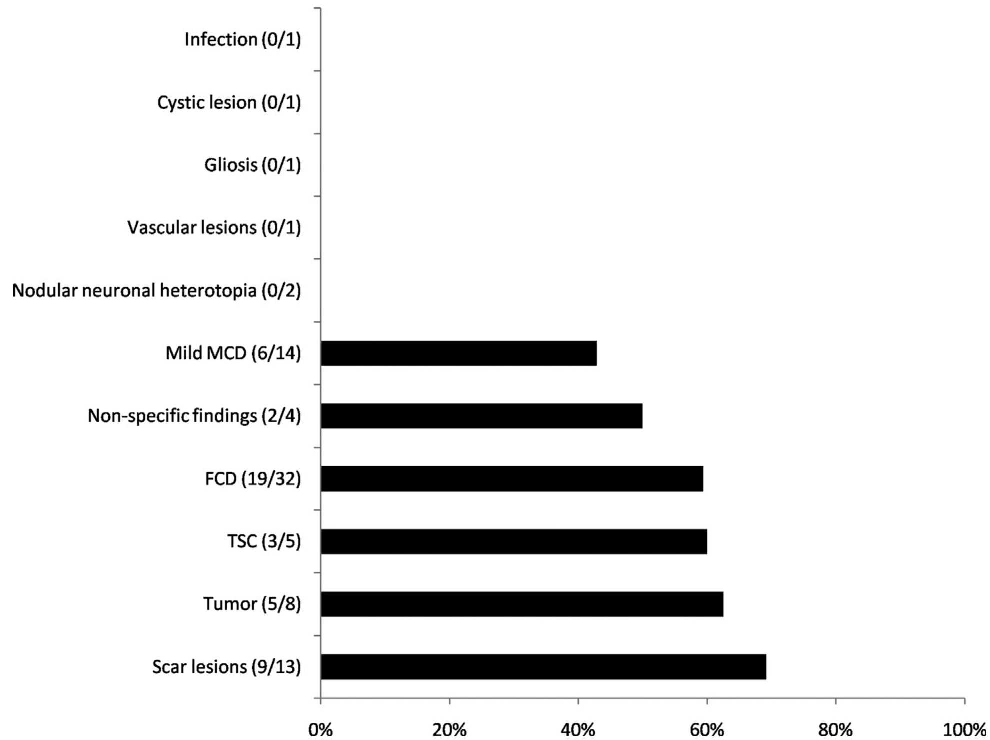

Figure 1. Proportion of seizure-free patients in relation to histopathologic diagnoses. FCD, focal cortical dysplasia, MCD, malformation of cortical development. TSC, tuberous sclerosis complex.

Surgical Data and Histopathologic Findings

Surgery was performed in all patients: 47 procedures were performed on the left side, 33 procedures were performed on the right side, and 2 patients had surgery on both sides. The interventions were located in the following regions: orbito-polar (n = 8), frontomedial (n = 14), dorsolateral (n = 30), frontocentral (n = 6), and total lobectomy (n = 23). In the seizure-free group, fewer patients underwent invasive EEG monitoring (37.2% vs. 69.2%, $P = 0.004$) and no patients had APOS (0% vs. 33.3%, $P < 0.0001$).

Surgical factors between the seizure-free patients and the non—seizure-free patients are summarized in Table 3.

Histologic examinations were performed in all cases. Of all patients with histologic results, 39.0% involved FCD, 17.1% involved mild MCD, 15.9% involved scar lesions, 9.8% involved tumors (ganglioglioma: n = 2; oligodendroglioma: n = 1; dysembryoplastic neuroepithelial tumor: n = 1; mixed neuronal-glial tumor: n = 4), and 6.1% involved TSC. A total of 62.5% of the patients (5/8) with tumor and 52.8% of the patients (28/53) with MCD were seizure free after the operation (Figure 1).

Multivariate Analysis

On initial univariate screening, 4 variables correlated with seizure recurence: lack of a lesion in the frontal lobe on MRI, generalized/nonlocalized ictal discharge, use of subdural grids, and APOS. These variables were tested with multivariate analysis. The results showed that these 4 variables did not retain their significance as independent predictors of surgical outcome ($P > 0.05$).

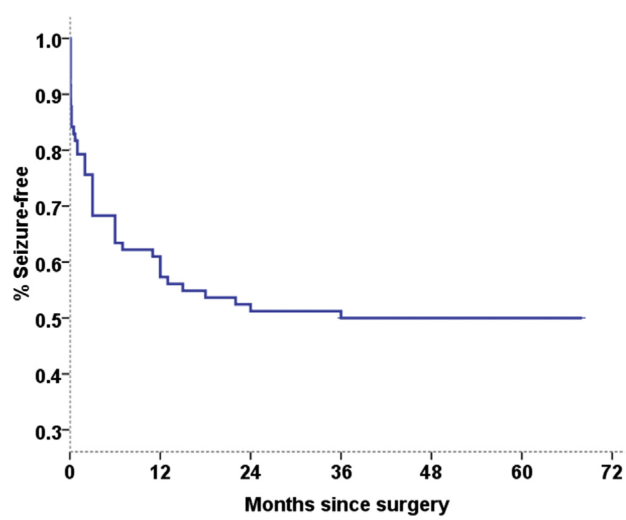

Figure 2. Survival analysis illustrating the chances of postoperative seizure freedom after frontal lobectomy.

Table 4. Engel Classification of the Overall Cohort at 1, 2, and 5 Years After Frontal Lobectomy

Engel Classification	6 Months (N = 82)	1 Year (N = 82)	2 Years (N = 82)	3 Years (N = 82)	4 Years (n = 42)	5 Years (n = 27)
Engel class I	55 (67)	49 (60)	44 (54)	44 (54)	22 (52)	14 (52)
Engel class II	5 (6)	9 (11)	9 (11)	9 (11)	6 (14)	4 (15)
Engel class III	6 (7)	8 (10)	10 (12)	10 (12)	3 (7)	2 (7)
Engel class IV	16 (20)	16 (20)	19 (23)	19 (23)	11 (26)	7 (26)

Values are number of cases (%).

Overall Recurrence

The Kaplan-Meier survival curve is shown in Figure 2. The chance of being seizure free varied widely with postoperative time. The chance of seizure freedom is 57.3% within the first 1 year, and then decreased to 51.2% at 2 years postoperatively. The rate of seizure freedom was 50% at 3 years postoperatively.

Table 4 shows the outcome using the Engel classification at 1, 2, and 5 years postoperatively. At 1 year postoperatively, 49 patients were completely seizure free and 17 patients had a significant improvement (Engel class II: n = 9, Engel class III: n = 8). Moreover, 52.4% of patients had a seizure-free outcome at the last follow-up (mean, 49.7 ± 10.4 months). Subgroup analysis was performed according to the pathology difference. For patients with MCD, the seizure-free rate was 67% at 6 months, 63% at 1 year, 54% at 2 years, and 56% at 5 years. For patients with tumor, the seizure-free rate was 75% at 6 months, 75% at 1 year, 63% at 2 years, and 67% at 5 years. Patients with MCD showed worse seizure-free outcome than patients with tumor.

Patterns of seizure remission and relapse in the total cohort were stratified into 5 groups (Table 5). Thirty-eight patients (46.3%) were seizure free since surgery, and 44 patients (53.7%) had seizures at any time after surgery. Most seizures occurred during the first 24 months after the operation. For the 44 patients, the Engel classification at last follow-up was class I in 5 patients (11.4%), class II in 10 patients (22.7%), class III in 9 patients (20.5%), and class IV in 20 patients (45.5%). Therefore, although seizure occurred after surgery at any time, 54.5% of patients had significant improvement at last follow-up.

Recurrence was defined as a seizure that occurred after a seizure-free period of at least 6 months.[15] A total of 18.3% of the patients (n = 15) had seizures after 6 months after the operation. Early recurrences (more than 6 months to 1 year) occurred in 6 patients, and 9 patients had late recurrence (more than 1 year). Among the patients with late recurrence, 6 patients had seizure recurrence during the second year after operation. After 2 years, the changes in seizure outcome became negligible, and seizures recurred in 3 patients within 3 years. The seizure outcome after recurrence is shown in Table 6.

DISCUSSION

Seizure Outcome and Seizure Patterns Since Surgery

The purpose of this article is to review the clinical characteristics and treatment results in a series of patients treated surgically for refractory FLE. We hoped to gain further insights into FLE and to examine the features that might offer the greatest chance of surgical success. Because of the high rate of patients lost to follow-up, we did not include patients from 2001 to 2009 in this study. The long-term rate of seizure freedom (50% at 3 years or longer of follow-up) is similar to that of many recently published reports,[11] and somewhat better than a recent meta-analysis, where 45.1% of patients undergoing FLE surgery were seizure free at 2 years or more.[2] In a longitudinal study of FLE surgery, the prevalence of seizure freedom decreased from 55.7% in the first postoperative year to 45.1% in the third year.[1] Seizure outcome after frontal surgery is somewhat worse than outcomes after temporal lobectomy.[16,17] The probable explanation is that the extent of brain tissue resection is restrained because of the proximity to the eloquent cortex. After the surgery, the patterns of seizure recurrence are different. In our cohort, almost half of the patients had absolute seizure freedom at some stage, and a quarter of the patients had initial seizure freedom then relapse, or seizure initially then terminal remission. Usually, the change of seizures occurred during the first 2 years. In a study of temporal surgery,[18] people who were seizure free for any 1 year had a 90% probability of having no seizures in the next year, and those with 2 successive years of seizure freedom had a 94% chance of seizure freedom in the subsequent year.

Predictors of Outcome

We identified 4 predictors of outcome. Factors that either reflect poor visualization of the epileptogenic zone (MRI negative) or generalized/nonlocalized ictal pattern make a complete removal of epileptogenic zone difficult and hence characterize the patients at the highest risk of recurrence. Use of subdural grids is another unfavorable predictor. The occurrence of APOS may represent an

Table 5. Patterns of Seizure Remission and Relapse After Surgery

Seizure Outcome	Number of Patients (%)	Mean Duration of Follow-Up (months)
Seizure free since surgery	38 (46.3)	48.8
Never seizure free	25 (30.5)	49.2
Initial seizure freedom then relapse	14 (17.1)	50.9
Seizure freedom with transient relapse and then terminal remission	3 (3.7)	56.0
Seizure initially and then terminal remission	2 (2.4)	54.5

Table 6. Engel Classification of the Patients with Recurrence

Pathological Subtype	Recurrence	Number of Patients	Engel Class I	Engel Class II	Engel Class III	Engel Class IV
Total	Early	6	2	2	0	2
	Late	9	1	4	1	3
MCD	Early	4	1	2	0	1
	Late	4	1	1	0	2
Tumor	Early	0	0	0	0	0
	Late	1	0	0	0	1
Others	Early	2	1	0	0	1
	Late	4	0	2	1	1

MCD, malformation of cortical development.

immediate postoperative correlation of residual epileptogenicity after an incomplete resection. These predictors were similar to a U.S./European series.[1,9]

Imaging Predictors. In our series, patients with positive MRI lesion did have favorable outcome after surgery, which is consistent with the results in the current literature.[1,12,19] There is a highly significant correlation between the MRI-visible lesion and the seizure onset zone in FLE. However, the surgical outcome of focal cortical dysplasia is no better than that of other pathologies. This may explain the better outcome in patients with tumor than in patients with MCD. In our study, 62% of patients with tumor etiology and 52% patients with MCD were seizure free after resection at last follow-up. The study of Chung et al.[20] demonstrated that 68.8% of frontal lobe MCD cases actually had normal imaging, and this was the only variable predictive of a poor outcome. One possible reason for the relatively poor outcome in patients with MCD may be a greater extent of the malformation outside the resection site.

Electrophysiologic Predictors. As previously reported, generalized scalp EEG abnormalities were predictors of seizure recurrence,[21] and localized ictal EEG was an independent predictor of being seizure free.[22] In our study, patients with ictal frontal rhythm tended to have a favorable outcome. This is in accordance with the findings of Boesebeck et al.,[23] who found that the lack of extralesional or generalized seizure patterns has a correlation with a favorable seizure outcome. Worrell et al.[24] observed that the scalp EEG pattern of focal ictal β discharge at seizure onset predicts excellent seizure control after surgical resection. However, the discharge was present in only approximately 25% of either lesional or nonlesional FLE patients who underwent surgical treatment. Bautista et al.[25] showed that the type of discharge is more likely to be associated with convexity location than with medial location of the frontal lobe. In another study of frontal lobe cases, focal frontal ictal β discharge did not show the aforementioned association.[24] An intracranial EEG study showed that rapid spread of seizure discharges predicts ongoing seizures after frontal lobe surgery.[26] This is probably explained by the extensive epileptic tissue beyond the actual seizure onset zone and more widely distributed pathology in cortical and subcortical structures.[27]

Intracranial EEG monitoring helps to define the ictal onset zone and to map the cortical function.[28] Intracranial EEG was performed when other diagnostic modalities were inconclusive or incongruent. In our cohort, most of the patients with normal MRI underwent intracranial EEG monitoring. However, the group had unfavorable surgical prognosis. This is consistent with a recent report showing that intracranial EEG had a negative prognostic significance in FLE.[21]

Postoperative Predictors. Previous investigations assessing the predictive value of APOS, which predominantly included individuals after temporal lobectomy, showed worse outcomes. The early seizure recurrence is mainly driven by inaccurate localization or incomplete resection of an epilepsy focus. Patients who had bilateral MRI abnormalities, invasive EEG monitoring, and postoperative EEG abnormalities tended to have early postoperative TLE recurrence.[17] Previous studies have found APOS to occur in 16%–29% of patients with FLE.[1,13] Tigaran et al.[29] first assessed the prognostic importance of APOS after FLE surgery. However, Tigaran et al. found that patients with FLE who had APOS had a seizure-free outcome similar to that of individuals without APOS. This is contrary to our finding that APOS predicts seizure recurrence. Their results may not have reached statistical significance because of the relatively small sample size. In our series, APOS occurred in 13 patients (16%), of whom 12 (92%) developed persistent seizures (class III: $n = 3$; class IV: $n = 9$). Some earlier studies have shown that APOS is associated with worse outcomes after frontal surgery.[1,13] Data on APOS after temporal lobectomy could apply after surgery for FLE, where epileptogenic tissues are even more diffuse. In this study, we did not address whether the type of APOS was similar to the habitual seizures. One reason is that video EEG monitoring is not performed after surgery, and the personnel may not have the experience to classify seizure type. Therefore, it is difficult to determine the relation between the APOS and the habitual seizure.

Limitations

There are several limitations in this study. Major limitations include the small sample size and the retrospective monocenter study. In addition, some patients had magnetoencephalography and positron emission tomography results. Further investigation will be carried out to evaluate the localization value of magnetoencephalography and positron emission tomography. Another limitation is that a multivariate analysis did not show the independence and significance of the predictors. Finally, not all patients were followed through 5 years.

CONCLUSIONS

The overall seizure freedom of FLE surgery is favorable. Individual seizure status changes most up to 2 years after surgery. Ideal surgical candidates are those who have MRI and electrophysiologic evidence of epileptogenicity restricted to the frontal lobe. These results may have important implications for patients counseling and postoperative discontinuation of anticonvulsant medications.

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