Special Topics — Part I: Long-Term Functional Outcome of Epilepsy Surgery

Surgical Effects of Focus Resection for Patients With Intractable Epilepsy

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Abstract

Postoperative seizure-free outcome, psychiatric condition, intellectual function, and employment status were reviewed to demonstrate the usefulness of focus resection in 71 patients who underwent resective epilepsy surgery between 2000 and 2010 for the treatment of medication-resistant epilepsy. The psychiatric problems were assumed to be present only if the patient received psychotropic drug therapy. Seizure-free outcome was obtained in 53 (75%) patients. The patients were followed up for 2.0–12.0 years (mean 7.2 years) after surgery. Temporal lobe epilepsy (TLE), late seizure onset, short seizure duration, and magnetic resonance imaging lesions were all significantly associated with cessation of seizures. Psychotropic drug therapy was performed in 3 (4.2%) patients before surgery and in 12 (17.0%) patients at 2 years or later after surgery. TLE and preoperative psychotropic drugs were significantly associated with postoperative psychiatric problems. Among the 71 patients, 65 underwent full Wechsler Adult Intelligence Scale-Revised (WAIS-R) examinations both before and after surgery. The mean WAIS-R score was 82.5 ± 18.7 points for total intelligence quotient (IQ) preoperatively and 89.6 ± 20.3 points for total IQ postoperatively. Before surgery, 19 (27%) patients were engaged in full-time employment. After surgery, 2 patients lost and 9 patients newly entered full-time employment, so a total of 26 (37%) patients were engaged in full-time employment after surgery. Resective epilepsy surgery resulted in overall improvements in seizure control, intellectual functions, and employment status. However, patients with TLE had some risk of postoperative psychiatric disorder.

Key words: epilepsy surgery, seizure outcome, psychiatric problem, intellectual function, employment

Introduction

Our group previously reported that 35% of patients who underwent temporal lobe epilepsy (TLE) surgery achieved seizure-free status in the absence of medication and that a shorter duration from seizure onset to surgery was significantly related to successful withdrawal of postoperative antiepileptic drug (AED) treatment.¹⁰⁾ With this rate of postoperative AED discontinuation, we can inform patients contemplating surgery that TLE surgery has a moderate chance of achieving a seizure-free, off-drug out-

come; that is, of curing the epilepsy. We can also recommend early resective surgery after seizure onset for patients suffering from intractable TLE.

Although seizure-free off-drug outcome is the desirable goal after surgery, patients with medication-resistant epilepsy also suffer from various psychiatric, cognitive, memory, and social problems associated with their condition.^{1–6,9,11,13–15,17,19)} These problems have recently become a focus of interest, as intractable epilepsy is recognized as a chronic encephalopathy in which one seizure induces other seizures.⁷⁾ Therefore, we need to analyze the overall effects on the quality of life to demonstrate the benefits of surgery.

The present study reviewed the postoperative

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seizure-free outcome, psychiatric condition, intellectual function, and employment status in patients to demonstrate the usefulness of resective epilepsy surgery.

Materials and Methods

The study included 71 patients who underwent resective epilepsy surgery between 2000 and 2010 for the treatment of medication-resistant epilepsy. All patients were referred to our epilepsy outpatient clinic for surgical treatment. The patients were examined preoperatively by magnetic resonance (MR) imaging, fluorodeoxyglucose positron emission spectroscopy, serial electroencephalography (EEG), video-EEG monitoring, and neuropsychological testing. Thirty-two of the 71 patients underwent invasive electrocorticography (ECoG) monitoring to detect the epileptogenic areas preoperatively. All 71 patients were monitored using ECoG during the resection. The postoperative follow-up examinations were continued for at least 2 years.

Surgical outcome, postoperative psychiatric problems, intellectual function, and full-time employment were all analyzed. The following factors were also analyzed as potentially associated with postoperative seizure-free outcome: sex, age at operation, seizure duration, affected side, MR imaging lesions, TLE or non-TLE, intracranial electrodes, psychiatric problems, total intelligence quotient (IQ) score on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) test, and full-time employment. Table 1 shows the demographic and clinical characteristics of the 71 patients. The factors found to be associated with full-time employment, postoperative psychiatric disorders, and intellectual functions were then analyzed in addition to seizure-free out-

come in the same subjects.

Patients who complained of psychiatric problems were referred to clinical psychologists. For the analyses, patients were assumed to have psychiatric problems only if they received drug therapy as follows: antipsychotic drugs olanzapine, risperidone, quetiapine fumarate, and aripiprazole, antidepressants sertraline hydrochloride, clobazepam, and clomipramine hydrochloride, and anti-anxiety drugs alprazolam, lorazepam, and bromazepam.

Correlations between the evaluated factors and seizure-free outcome, postoperative psychiatric disorders, intellectual function, and full-time employment were evaluated by either the t-test for continuous variables or the chi-square test for categorical variables. The factors with significant correlations were then analyzed using multiple logistic-regression analysis. Correlations were considered significant at $p < 0.05$.

Results

Seizure-free outcome was obtained in 53 (75%) patients. The patients were followed up for 2.0–12.0 years (mean 7.2 years) after surgery. Table 2 shows factors associated with seizure-free outcome. TLE, late seizure onset, short seizure duration, and MR imaging lesion were significantly associated with cessation of seizures. Multiple logistic-regression analysis demonstrated that short seizure duration and MR imaging lesions were the most important factors. Seizure freedom was achieved in 50 (82%) patients with MR imaging lesions versus only 3 (30%) patients without MR imaging lesions. The mean seizure duration was 11.2 years in patients with seizure-free outcome versus 20.3 years in patients with persistent seizures.

Table 1 Demographic and clinical characteristics of 71 patients who underwent focus resection

Variable	TLE (n = 57)	non-TLE (n = 14)	All (n = 71)
Sex, male:female	27:30	10:4	37:34
Age of seizure onset, mean $\pm$ SD (yrs)	17.4 $\pm$ 9.8	10.3 $\pm$ 6.6	16.0 $\pm$ 9.7
Age at operation, mean $\pm$ SD (yrs)	30.9 $\pm$ 12.1	23.0 $\pm$ 10.9	29.3 $\pm$ 11.8
Epilepsy duration, mean $\pm$ SD (yrs)	13.5 $\pm$ 12.5	13.4 $\pm$ 10.9	13.5 $\pm$ 12.1
Affected side, left:right	29:28	6:8	35:36
MR imaging lesion, yes:no	54:3	7:7	61:10
Intracranial electrodes, yes:no	21:3	11:3	32:39
Surgical outcome, Engel class I:II-IV	47:10	6:8	53:18
Psychiatric problems*, yes:no	12:45	0:14	12:59
TIQ score*, mean $\pm$ SD	92.0 $\pm$ 19.3 (n = 53)	78.8 $\pm$ 21.8 (n = 12)	89.6 $\pm$ 20.3 (n = 65)
Full-time employment*, yes:no	22:35	4:10	26:45

*Postoperation. MR: magnetic resonance, SD: standard deviation, TIQ: total intelligence quotient, TLE: temporal lobe epilepsy.

Table 2 Factors associated with seizure-free outcome

Factors	Univariate analysis	Number of patients or age	Multiple logistic-regression analysis
TLE	p = 0.004	TLE: 47/57 (82%), non-TLE: 6/14 (43%)	p = NS
Seizure onset, mean $\pm$ SD (yrs)	p = 0.024	free: 17.4 ± 9.6 , not-free: 12.0 ± 8.9	p = NS
Seizure duration, mean $\pm$ SD (yrs)	p = 0.007	free: 11.2 ± 9.5 , not-free: 20.3 ± 16.2	p = 0.015
MR imaging lesion	p = 0.001	lesional: 50/61 (82%), non-lesional: 3/10 (30%)	p = 0.030

MR: magnetic resonance, SD: standard deviation, TLE: temporal lobe epilepsy.

Table 3 Patients receiving psychotropic drug therapy for psychiatric problems

Age (yrs)/ Sex	Side	Etiology	Type of drugs	Preoperative/postoperative psychotropic drug	Postoperative inpatient treatment	Outcome, Engel class/off drug
19/F	L	TLE	P	no/yes	yes	I/no
37/M	R	TLE	P	no/yes	yes	I/no
27/F	L	TLE	P	no/yes	yes	I/no
54/M	R	TLE	P	no/yes	yes	I/no
28/F	L	TLE	P, A	no/yes	yes	I/no
36/F	L	TLE	P	no/yes	yes	III/no
20/F	R	TLE	P, D, A	no/yes	yes	I/no
26/F	L	TLE	P	yes/yes	yes	III/no
42/F	R	TLE	A	no/yes	yes	III/no
45/M	L	TLE	P	no/yes	yes	II/no
35/M	R	TLE	D, A	yes/yes	yes	I/yes
30/M	L	TLE	D, A	yes/yes	no	I/no

A: anti-anxiolytics, D: anti-depressants, F: female, L: left, M: male, P: anti-psychotics, R: right, TLE: temporal lobe epilepsy.

Table 3 shows the characteristics of patients treated with psychotropic drugs. Psychotropic drug therapy was performed in 3 (4.2%) patients before surgery and in 12 (17.0%) patients at 2 or more years after surgery. All these patients had TLE. Eight of the 12 patients who received postoperative psychotropic therapy obtained seizure-free outcome. Two patients who underwent right temporal lobe resection needed inpatient treatment for postoperative psychiatric disorders. Antipsychotic drugs were administered in 9 patients, antidepressants in 3, and anti-anxiety agents in 5. TLE and treatment with preoperative psychotropic drugs were significantly associated with postoperative psychiatric problems (Table 4).

Full WAIS-R testing was performed both pre- and postoperatively in 65 of the 71 patients. The mean preoperative WAIS-R score was 84.4 ± 16.4 points for verbal IQ, 84.7 ± 18.9 for performance IQ, and 82.5 ± 18.7 points for total IQ. The score increased postoperatively to 88.9 ± 18.3 points for verbal IQ,

Table 4 Factors associated with psychiatric problems

Factors	Univariate analysis	Number of patients	Multiple logistic-regression analysis
TLE	p = 0.016	TLE: 12/57 (21%), non-TLE: 0/14 (0%)	p = 0.034
Preoperative psychotropic drug	p = 0.001	with: 3/3 (100%), without: 9/68 (13%)	p = 0.002

TLE: temporal lobe epilepsy.

93.5 ± 20.5 for performance IQ, and 89.6 ± 20.3 for total IQ. High postoperative total IQ score was significantly related to both short seizure duration and high preoperative total IQ score in both univariate analysis (p = 0.035, <0.0001) and multiple logistic-regression analysis (p = 0.033, <0.0001). Before surgery, 19 (27%) of 71 patients were engaged in full-time employment. After surgery, 2 patients lost and 9 patients newly entered full-time employment, so a

Table 5 Postoperative full-time employment

Factors	Univariate analysis	Postoperative full-time employment	Multiple logistic-regression analysis
Seizure onset, mean $\pm$ SD (yrs)	p = 0.0005	yes: 21.0 $\pm$ 10.3, no: 13.0 $\pm$ 8.0	p = NS
Preoperative full-time employment	p < 0.0001	yes: 17/26 (89%), no: 9/45 (65%)	p < 0.0001
Postoperative TIQ score, mean $\pm$ SD (65 cases)	p < 0.0001	yes: 101.1 $\pm$ 15.6, no: 81.9 $\pm$ 19.5	p = 0.015

SD: standard deviation, TIQ: total intelligence quotient.

total of 26 (37%) patients were engaged in full-time employment postoperatively. Late seizure onset, preoperative full-time employment, and high postoperative total IQ score were significantly associated with postoperative full-time employment (Table 5).

Discussion

The present study found that patients with TLE had a significantly higher seizure-free rate compared with patients with epilepsy in other lobes. According to a review combining systemic review and meta-analytical techniques,¹⁹⁾ long-term seizure outcome was the best in patients with TLE, second-best in patients with parietal and occipital lobe epilepsy, and worst in patients with frontal lobe epilepsy, suggesting that long-term seizure freedom was consistently lower after non-TLE surgery.

The present study also shows that MR imaging lesions are significantly associated with postoperative seizure freedom. The overall odds ratio of seizure freedom after surgery was two to three times higher in the presence of a lesion on MR imaging.²⁰⁾ Hippocampal sclerosis in patients with TLE^{8,12)} and detection of cortical dysplasia on MR imaging¹⁶⁾ were also significant predictors of good surgical outcome. Evidence from previous reports agrees with our own finding that TLE and MR imaging lesions are important predictors of seizure freedom.^{8,12,16,19,20)}

We also found that the seizure duration and age at seizure onset were significantly related to seizure-free outcome. Several studies have reported the significance of factors related to the timing of surgery, especially in patients with TLE. Age at surgery and duration of epilepsy both had significant effects on seizure cessation in univariate analysis.^{4,8,12)} Short seizure duration was an important factor for seizure-free, off-drug outcome in patients with TLE.¹⁰⁾ However, a regression analysis found none of these timing-related factors had any effect on outcome or age, and no association was found between seizure

onset and postoperative seizure recurrence.¹²⁾ In our series, we found no significant association between seizure onset and postoperative seizure cessation by regression analysis. Different results on the predictive factors related to the timing of surgery and seizure-free outcome are still being reported.

Twelve (17.0%) of the 71 patients required postoperative psychotropic therapy in the present study, of whom 10 patients responded well. Two of these patients had also received psychotropic drugs preoperatively. Postoperative psychiatric problems were found in 21% of patients with TLE, similar to those rates reported in previous reviews.^{5,9)} In one study,¹⁾ 18% of patients developed de novo psychopathology following TLE surgery. However, the surgical effect on psychiatric impairment is still under discussion. Surgical patients were observed to be much less likely to experience de novo depression or anxiety than medical treatment controls at 12-month follow-up examination.¹⁵⁾

The present and previous findings have implicated TLE and presurgical psychiatric history as important risk factors for postoperative psychiatric problems.^{1,5,9,14)} In contrast to the present results, some earlier studies identified poor seizure outcome and surgical side as strong predictive factors.^{1,2,15)} The findings of the types of postoperative disorders have also varied: earlier papers more commonly report milder psychiatric issues⁹⁾ and transient mood disorders such emotional lability and depression,⁵⁾ whereas we predominately observed conditions requiring treatment with antipsychotic drugs. The follow-up period and patient selection criteria might partly explain these discrepancies, as our subgroup of patients with postoperative psychiatric disorders was limited to patients who received psychotropic drugs 2 or more years after the surgery.

The mean postoperative WAIS-R score was slightly higher than the mean preoperative score. After surgery, 37% of patients were engaged in full-time employment, which represented an increase of about 10% compared to the preoperative rate. High

postoperative IQ score was significantly associated with high preoperative IQ score and short seizure duration. Full-time employment was associated with high postoperative total IQ score and full-time employment before the operation.

Significant increase in IQ was found in a surgical group more than 5 years after temporal lobe resection compared to a non-surgical group.¹⁷⁾ In this pediatric series, postoperative cessation of AEDs was associated with significant increase in IQ scores. Rather than focusing on the IQ score per se, we looked at IQ-related factors that we considered more advantageous for obtaining full-time employment.

Several TLE studies evaluating post-surgical psychosocial outcomes have demonstrated that long-term employment status was improved after surgery.^{3,6,13,18)} Employment and other components of the psychosocial long-term outcome showed no dramatic changes over the years and did not depend on seizure freedom.³⁾ This conclusion is compatible with our own observation that seizure outcome was not a predictive factor for employment. We understand that the social conditions required for employment are unique in our area, a dense metropolis with a highly developed transportation system. Our study suggests that a high IQ score and preoperative employment status are important predictors of full-time employment after surgery.

Resective epilepsy surgery showed overall improvement in seizure-free rate, intellectual function, and employment status. However, patients with TLE face some risk of postoperative psychiatric disorder.

Conflicts of Interest Disclosure

There are no conflicts of interest for all authors. Taketoshi Maehara and Motoki Inaji who are members of the JNS have registered on-line Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

- 1) Cleary RA, Thompson PJ, Fox Z, Foong J: Predictors of psychiatric and seizure outcome following temporal lobe epilepsy surgery. *Epilepsia* 53: 1705–1712, 2012
- 2) Derry PA, Rose KJ, McLachlan RS: Moderators of the effect of preoperative emotional adjustment on postoperative depression after surgery for temporal lobe epilepsy. *Epilepsia* 41: 177–185, 2000
- 3) Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, Baulac M: Long-term prognosis and psychosocial outcomes after surgery for MTLE. *Epilepsia* 47: 2115–2124, 2006
- 4) Ficker DM, So EL, Mosewich RK, Radhakrishnan K, Cascino GD, Sharbrough FW: Improvement and deterioration of seizure control during the postsurgical course of epilepsy surgery patients. *Epilepsia* 40: 62–67, 1999
- 5) Foong J, Flugel D: Psychiatric outcome of surgery for temporal lobe epilepsy and presurgical considerations. *Epilepsy Res* 75: 84–96, 2007
- 6) Hamiwka L, Macrodimitris S, Tellez-Zenteno JF, Metcalfe A, Wiebe S, Kwon CS, Jette N: Social outcomes after temporal or extratemporal epilepsy surgery: a systematic review. *Epilepsia* 52: 870–879, 2011
- 7) Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, Seiffert E, Heinemann U, Friedman A: TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. *Brain* 130: 535–547, 2007
- 8) Jeong SW, Lee SK, Hong KS, Kim KK, Chung CK, Kim H: Prognostic factors for the surgery for mesial temporal lobe epilepsy: longitudinal analysis. *Epilepsia* 46: 1273–1279, 2005
- 9) Macrodimitris S, Sherman EM, Forde S, Tellez-Zenteno JF, Metcalfe A, Hernandez-Ronquillo L, Wiebe S, Jette N: Psychiatric outcomes of epilepsy surgery: a systematic review. *Epilepsia* 52: 880–890, 2011
- 10) Maehara T, Ohno K: Preoperative factors associated with antiepileptic drug withdrawal following surgery for intractable temporal lobe epilepsy. *Neurol Med Chir (Tokyo)* 51: 344–348, 2011
- 11) Malmgren K, Starmark JE, Ekstedt G, Rosen H, Sjöberg-Larsson C: Nonorganic and organic psychiatric disorders in patients after epilepsy surgery. *Epilepsy Behav* 3: 67–75, 2002
- 12) McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF: Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 127: 2018–2030, 2004
- 13) Paglioli E, Palmini A, da Costa JC, Portuguese M, Martinez JV, Calcagnotto ME, Hoefel JR, Raupp S, Barbosa-Coutinho L: Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. *Epilepsia* 45: 1383–1391, 2004
- 14) Quigg M, Broshek DK, Heidal-Schiltz S, Maedgen JW, Bertram EH 3rd: Depression in intractable partial epilepsy varies by laterality of focus and surgery. *Epilepsia* 44: 419–424, 2003
- 15) Reuber M, Andersen B, Elger CE, Helmstaedter C: Depression and anxiety before and after temporal lobe epilepsy surgery. *Seizure* 13: 129–135, 2004
- 16) Rowland NC, Englot DJ, Cage TA, Sughrue ME, Barbaro NM, Chang EF: A meta-analysis of predictors of seizure freedom in the surgical management of focal cortical dysplasia. *J Neurosurg* 116: 1035–1041, 2012
- 17) Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T: Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology* 76: 1330–1337, 2011

- 18) Tellez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S: Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain* 130: 334–345, 2007
- 19) Tellez-Zenteno JF, Dhar R, Wiebe S: Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 128: 1188–1198, 2005
- 20) Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S: Surgical outcomes in lesional and

non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res* 89: 310–318, 2010

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