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Predictors of Seizure Outcome after Repeat Pediatric Epilepsy Surgery: Reasons for Failure, Sex, Electrophysiology, and Temporal Lobe Surgery

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Abstract

Considering that seizure freedom is one of the most important goals in the treatment of epilepsy, repeat epilepsy surgery could be considered for patients who continue to experience drug-resistant seizures after epilepsy surgery. However, the chance of seizure freedom is reported to be below 50% after reoperation for failed epilepsy surgery. This study aimed to elucidate the predictive factors for seizure outcomes after repeat pediatric epilepsy surgery. In all, 39 pediatric patients who underwent repeat curative epilepsy surgery between 2008 and 2020 at our institution were retrospectively studied. The relationship between preoperative clinical factors and postoperative seizure freedom at the last follow-up was statistically evaluated. The mean age at the first surgery was 5.5 years (0–16). The etiology of epilepsy was malformation of cortical development in 33 patients. The average time to seizure recurrence after the first surgery was 6.4 months (range, 0–26 months). In all, 16 patients (41.0%) achieved seizure freedom after the second surgery. Seven patients underwent a third surgery, and three (42.9%) achieved seizure freedom. Overall, 19 patients achieved seizure freedom after repeat epilepsy surgery (48.7%). Female sex, surgical failure due to technical limitations, congruent electroencephalography (EEG) findings, lesional magnetic resonance imaging (MRI) and Rt-sided surgery were predictive of seizure freedom, and surgery limited to the temporal lobe was predictive of residual seizures, as determined in the multivariate analysis. The reoperation of failed epilepsy surgery is challenging. Consideration of the above predictive factors can be helpful in deciding whether to reoperate on pediatric patients whose initial surgical intervention failed.

Keywords: seizure outcome, focal cortical dysplasia, surgical failure, lobectomy

Introduction

Epilepsy surgery is an accepted treatment option for patients with drug-resistant epilepsy.[1] Long-term seizure freedom is achieved in 60%–80% of selected patients with surgically remediable etiologies, such as mesial temporal sclerosis and developmental tumors.[2,3] The chance of seizure freedom is reported to be as low as 50% for non-lesional epilepsy or extra-temporal surgery.[4,5] A certain fraction of the operated patients continue to experience drug-resistant seizures, which significantly impairs their quality of life. Further adjustment of anti-seizure medications and palliative surgery such as vagus nerve stimulation are usually considered for those patients.[6] Repeat resective surgery is another treatment option to control seizures, as seizure freedom is the most important outcome in patients with epilepsy that significantly improves quality of life and may decrease seizure-related mortality.[7,8]

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The current evidence on repeat epilepsy surgery remains limited. One systematic review revealed that the chance of seizure freedom was 47% after repeat epilepsy surgery and that congruent electrophysiology, lesional epilepsy, and the reasons for surgical failure were predictive of seizure freedom. The chance of seizure freedom is known to decrease following every subsequent resective epilepsy surgery.[9] The above evidences were mainly obtained from studies with adult patients. It is important for surgeons to identify the predictive factors for seizure outcomes when considering repeat interventions with limited efficacy. This retrospective study aimed to elucidate the predictive factors for seizure outcomes after repeat pediatric epilepsy surgery.

Materials and Methods

This was a retrospective descriptive study, and the manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10] This study was approved by the ethics committees at the National Center of Neurology and Psychiatry in Tokyo, Japan (No. A2018-049). The requirement for written informed consent was waived due to the retrospective design.

Patients

This study included 39 pediatric patients (<18 years of age) who underwent repeat epilepsy surgery for drug-resistant epilepsy between June 2008 and June 2020 at our institution with a minimum 1-year postoperative follow-up. Only curative epilepsy surgeries were included, and palliative procedures such as corpus callosotomy and vagus nerve stimulator implantation were excluded. A total of 323 curative epilepsy surgeries were performed for pediatric patients during this period. Among them, 48 procedures were performed as repeat epilepsy surgery, including 39 procedures as a second surgery, 7 procedures as a third surgery, and one procedure each as fourth and fifth surgeries. Adjustment of anti-seizure medication were generally attempted before the indications of repeat surgery were considered.

A comprehensive pre-surgical evaluation, including 3.0-T magnetic resonance imaging and long-term video-electroencephalography (EEG) monitoring, was performed in all patients before surgery. At least one of the following additional examinations was performed before repeat surgery in all except two cases who had apparent residual lesions on MRI: Magnetoencephalography (MEG), ictal single-photon emission computed tomography (SPECT), or fluorodeoxyglucose positron emission tomography (FDG-PET). Among 48 presurgical evaluations before repeat surgeries, MEG, ictal SPECT, and FDG-PET were performed in 41 (85.4%), 30 (62.5%), and 31 (64.9%) occasions, respectively. Surgical indications were determined at the patient management conference attended by neurologists, pediatric neurologists, neurosurgeons, and certified epileptologists. Repeat surgery was generally indicated when localizing information was concordant between two or more modalities of evaluation.

Seizure outcome

Postoperative follow-up of the patients for evaluation was achieved through outpatient visits or at admission. The same anti-seizure medication as before surgery was generally continued for 1 year postoperatively. Postoperative seizure outcome was assessed using the International League Against Epilepsy (ILAE) classification.[11]

Data collection

Candidate patients were first identified from the National Center of Neurology and Psychiatry Neurosurgical database. The following data were retrospectively collected from medical records: date of surgery, side and type of surgery, intracranial EEG evaluation, histopathological diagnosis of surgical specimen, etiology of epilepsy, age of epilepsy onset, date of seizure recurrence, MRI findings, reasons for surgical failure, and postoperative seizure outcome at the last follow-up.

The etiology of epilepsy was determined based on the histopathological diagnosis, neuroimaging findings, and other clinical information at the initial surgery. The reasons for surgical failure were determined based on the clinical course of the patients and patient management discussions that occurred before the repeat surgeries. The timing of seizure recurrence was classified as acute postoperative when the drug-resistant seizures recurred within 1 week after surgery. Postoperative seizure outcome was categorized as seizure freedom (ILAE class 1) or no seizure freedom at the last follow-up.

Statistical analysis

Univariate analysis

Descriptive statistics were used to summarize the patient characteristics. The above clinical data were categorized, and Fisher's exact test was used to examine the association with postoperative seizure freedom.

Multivariate analysis

Logistic LASSO regression analysis (logistic regression with L1 regularization) was used to identify clinical predictors for postoperative seizure freedom.[12,13] Because L1-regularized regression shrinks unnecessary coefficients strictly to zero, it allows for feature selection without any handmade threshold parameters, such as the significance level. The following preoperative clinical variables were included in the regression analysis: sex, side of surgery, etiology of malformation of cortical development, reasons for surgical failure, acute seizure recurrence, location of surgery limited to the temporal lobe, lobar or larger surgery, intracranial EEG evaluation, lesional MRI, and congruent EEG findings as categorical variables; age at surgery, duration of epilepsy, age at onset, and time to seizure recurrence were included as integer values. The hyperparameter of the logistic LASSO model was determined by leave-one-out cross-validation (LOOCV).

The predictive ability of the logistic LASSO regression model was evaluated by drawing a receiver operating characteristic (ROC) curve. The area under the ROC curve was calculated.

R version 4.0.0 (The R Foundation for Statistical Computing) and the glmnet package version 4.1.2 were used for statistical analysis. Statistical significance was accepted at $p < 0.05$.

Results

Patient characteristics

The clinical characteristics are summarized in Table 1. The first surgery was performed before the age of three in 14 (35.9%) patients. The main seizure types were tonic seizure in 16, focal impaired awareness seizure in 13, epileptic spasm in 5, clonic seizure in 3, and focal to bilateral tonic-clonic seizure (FBTCS) in 2 patients. Five patients had FBTCS as a part of their habitual seizures. The majority of the patients had daily seizures before the first surgery. Five and one patient had a previous history of West syndrome and Ohtahara syndrome, respectively. The average interval between the first surgery and seizure recurrence was 6.4 months. Acute postoperative seizure recurrence was observed in 14 patients (35.9%). The type of first surgery included focal resection in 28, frontal lobectomy in 2, temporal lobectomy in 2, posterior quadrant disconnection in 3, other multilobar resection/disconnection in 3, and vertical hemispherotomy in 1 patient. The most frequent location of surgery was the frontal lobe. The etiology of epilepsy was malformation of cortical development in 33 patients (84.6%).

Table 1 Clinical characteristics of the 39 patients

Female sex, n (%)	22 (56.4)
Age at epilepsy onset, mean (range), years	2.0 (0–11)
Age at first surgery, mean (range), years	5.5 (0–16)
Duration of epilepsy, mean (range), years	3.8 (0.1–16)
Daily seizures, n (%)	33 (84.6%)
Time to seizure recurrence after the first surgery, mean (range), months	6.4 (0–26)
Interval between seizure recurrence and the second surgery, mean (range), months	16.7 (1–90)
Side of the first surgery, n (%)	
Left	23 (59.0%)
Cerebral location included in the first surgery, n	
Frontal	17
Temporal	10
Parietal	11
Occipital	8
Central	3
Insula	3
Type of the first surgery, n	
Focal cortical resection	25
Lesionectomy	3
Lobectomy	4
Multilobar resection/disconnection	6
Hemispherotomy	1
Etiology of epilepsy, n	
FCD type IIa	12
FCD type IIb	6
FCD type I	2
Cortical dysplasia, not othewise specified	7
Hemimegalencephaly	2
Polymicrogyria	2
Tuberous sclerosis complex	2
Tumor	3
Hippocampal sclerosis	1
Rasmussen encephalitis	1
Trauma	1

FCD: focal cortical dysplasia.

Seizure outcome

The postoperative course after repeat surgery is summarized in Fig. 1. In all, 16 patients achieved seizure freedom after the second surgery (41.0%). Among the remaining 23 patients, seven patients underwent the third surgery, and three of them

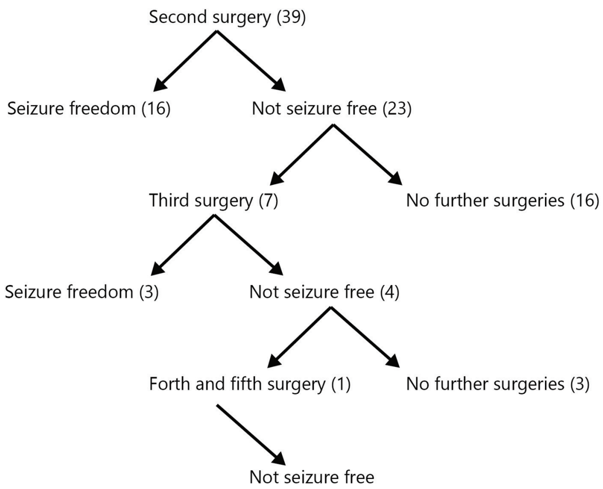

Fig. 1 Seizure outcome after successive surgeries in the 39 patients who underwent repeat epilepsy surgery. The number of patients is shown in parentheses.

achieved seizure freedom (42.9%). One patient underwent the fourth and fifth surgeries, but their seizures did not improve (ILAE class 5). Overall, 19 patients achieved seizure freedom after repeat surgeries (48.7%). The postoperative seizure outcomes were ILAE class 2 in 1, class 3 in 2, class 4 in 10, and class 5 in 7 patients. The mean follow-up period after the last surgery was 54.2 ± 34.0 months (12–132).

Reasons for surgical failure

The reasons for surgical failure were roughly divided into technical limitations in surgery (n = 6) and diagnostic limitations in the identification of the epileptogenic zone (n = 33). Technical limitations included incomplete disconnection during hemispherotomy (n = 1) or during posterior quadrant disconnection (n = 2), and residual epileptogenic lesion that was recognized postoperatively on MRI (n = 3).

Diagnostic limitations were further categorized into larger epileptogenic zones (n = 30), mislocalization of the epileptogenic zone (n = 2), and the emergence of a new epileptogenic zone (n = 1). The larger epileptogenic zones were classified as such because the epileptogenic zone was suspected from repeat evaluation in the same or contiguous area to the first diagnosis, and the second surgery was performed in the area next to the first surgery. This occurred in the near eloquent area in six cases. Mislocalization was determined based on minimum improvement after the first surgery and if the second surgery was performed in an area distant from the first surgery. The emergence of a new epileptogenic zone was observed in a patient with a tuberous sclerosis complex. The left occipital tuber became epileptogenic 7 years after the removal of the right central tuber in this patient.

Univariate analysis

Table 2 summarizes the univariate analysis of postoperative seizure freedom after repeat surgeries. Female sex, congruent EEG findings, and surgical failure due to technical limitations were associated with postoperative seizure outcomes (p <0.05).

Multivariate analysis

Logistic LASSO analysis revealed that six clinical factors were expected to be predictive of postoperative seizure outcome: female sex, surgical failure due to technical limitations, surgery limited to the temporal lobe, congruent EEG findings, lesional MRI, and Rt-sided surgery. The estimated coefficients are presented in Table 3. Female sex, surgical failure due to technical limitations, congruent EEG findings, lesional MRI, and Rt-sided surgery were predictive of seizure freedom. Surgery limited to the temporal lobe was predictive of residual seizures. This result was consistent with the univariate analysis. The coefficients of lesional MRI and Rt-sided surgery were small compared with other factors, suggesting minor contribution to the outcome.

The ROC curve of the regression model is shown in Fig. 2. The area under the ROC curve was 0.91, suggesting sufficient performance as a predictive model.

Discussion

This institutional retrospective study of repeat pediatric epilepsy surgery revealed that the chance of seizure freedom was 41.0% after the second surgery and 42.9% after the third surgery. Cumulatively, 48.7% of patients achieved seizure freedom after repeat epilepsy surgery. Female sex, surgical failure due to technical limitations, first surgery limited to the temporal lobe, congruent EEG findings, lesional MRI, and Rt-sided surgery were predictive of postoperative seizure outcome in the multivariate analysis. The contribution of the first four factors was larger than the others based on the magnitude of the coefficients (Table 3).

The postoperative seizure outcome after repeat epilepsy surgery was below 50%. The chance of seizure freedom after repeat surgery was 48.7% at the last follow-up in this study. This figure is in line with those of previous studies. One meta-analysis including 782 patients from 36 studies reported that the overall rate of an Engel I outcome after repeat resective epilepsy surgery was 47%.[14)]

Table 2 Univariate analysis of variables for seizure freedom after repeat epilepsy surgery

Variables	Seizure freedom (n = 19)	Not seizure freedom (n = 20)	*p*-value
Sex			0.01
Female	15	7	
Male	4	13	
Age of epilepsy onset			0.205
<1 year	12	8	
1 year or older	7	12	
Age at surgery			1
<3 years	7	7	
3 years or older	12	13	
Duration of epilepsy			0.748
<2 years	8	7	
2 years or greater	11	13	
MRI			0.082
Lesional	16	11	
Non-lesional	3	9	
EEG			0.031
Congruent	17	11	
Incongruent	2	9	
Intracranial EEG evaluation			1
Performed	6	7	
Not performed	13	13	
Side of first surgery			0.523
Left	10	13	
Right	9	7	
Extent of first surgery			0.301
Lobar or larger	7	4	
Focal	12	16	
Location of first surgery			0.106
Limited to temporal lobe	0	4	
Including extra-temporal	19	16	
Reason for surgical failure			0.008
Technical limitation	6	0	
Diagnostic limitation	13	20	
Time to seizure recurrence			0.32
Acute (<1 week)	5	9	
Chronic	14	11	
Interval between seizure recurrence and the second surgery			0.751
<6 months	9	8	
6 months or greater	10	12	

EEG: electroencephalography.

Table 3 Clinical variables with non-zero coefficients estimated with Logistic LASSO

Explanatory variable	Estimate
Female sex	1.104
Reason for surgical failure: technical limitation	1.997
Congruent EEG findings	1.176
Surgery limited to the temporal lobe	−0.92
Rt-sided surgery	0.262
Lesional MRI	0.076

EEG: electroencephalography, MRI: magnetic resonance imaging.

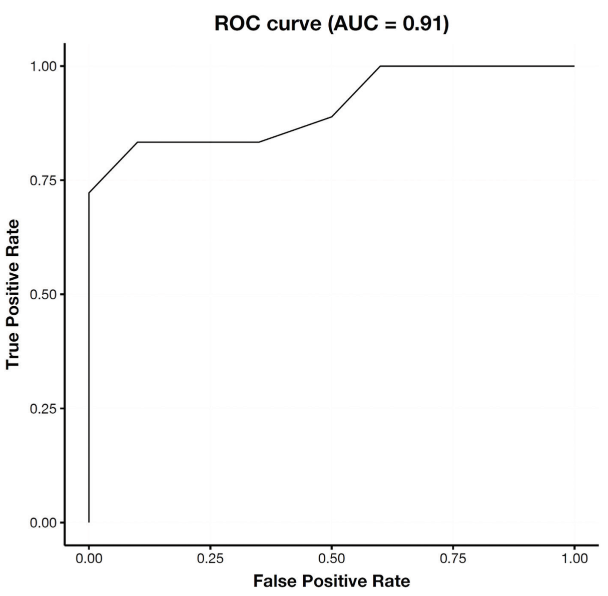

Fig. 2 ROC curve of the logistic Lasso regression model for predicting postoperative seizure freedom. ROC: receiver operating characteristic.

The largest retrospective study from Cleveland Clinic showed that 42% of the patients with one prior surgery and 33% of those with two or more prior surgeries had Engel I outcomes 2 years after repeat surgery, suggesting that the chance of seizure freedom decreases after every subsequent surgery.[9] Reoperation for failed epilepsy surgery is challenging, although a successful outcome is expected in a certain proportion of patients. Repeat epilepsy surgery should be carefully performed in selected patients. Advanced neuroimaging studies play an important role in identifying the residual epileptogenic zone. The majority of our patients underwent MEG, ictal SPECT, and FDG-PET in the repeat presurgical evaluation.

Predictive factors for seizure freedom after repeat epilepsy surgery were similar to those for the initial surgery. Congruent electrophysiological findings and lesional pathology were reported from the meta-analysis as predictive of better outcomes.[14] Tumors, cysts, and vascular malformations were categorized as lesional pathologies, but focal cortical dysplasia (FCD) and hippocampal sclerosis were not included in that meta-analysis. The initial pathology of FCD and mesial temporal sclerosis was associated with poor seizure outcome after repeat epilepsy surgery.[15] Lesional MRI at the initial surgery was predictive of seizure outcome in our study, but the majority of our patients had cortical dysplasia. FCD and other malformations of cortical development can be categorized as lesional in some studies.[16,17] Abnormal MRI findings prior to the initial surgery showed trends related to seizure freedom; however, they were not predictive in multivariate analyses.[9,14] In contrast, congruent EEG findings are frequently reported as predictors of seizure freedom.[14,17–19] The presence of remote, multifocal, or generalized epileptiform discharges is indicative of poor seizure outcomes.[14,18,20]

Female sex is a possible predictive factor for better seizure outcomes after repeat epilepsy surgery. Sex differences have been reported in the electrophysiological and metabolic presentation of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE).[21] However, sex has never been raised as a factor related to postoperative outcome after epilepsy surgery.[22,23] Interestingly, one recent study found female sex to be a predictive factor for seizure freedom after "repeat" epilepsy surgery.[9] Sex is considered an inherent biological marker of surgical refractoriness, together with the tendency for secondary generalization. Men tend to have more secondarily generalized tonic-clonic seizures than women with MTLE.[24] One study with a two-hit rat model of MTLE showed that males were more vulnerable to epileptogenesis than females.[25] Thus, sex may be a biological factor for epileptogenesis after surgical intervention.

First surgery limited to the temporal lobe was associated with worse seizure outcomes in this study. No consistent relationships were found between the location of surgery and outcome in the previous studies, partly due to the different patient populations studied.[9,16,20] Temporal lobe surgery is most frequent in studies that include adult patients.[9,16] A meta-analysis of repeat epilepsy surgery found a nonsignificant relationship between temporal lobe surgery and better outcomes.[14] Our study focused on pediatric epilepsy surgery. The most frequent surgical location was the frontal lobe, and the majority of surgeries included the extra-temporal region in this study. Part of the failure after temporal lobe surgery is attributed to the epileptogenic foci in the extra-temporal limbic system, the so-called "temporal-plus epilepsy."[26] We have reported that postoperative seizure outcomes were paradoxically worse in patients who underwent invasive presurgical exploration limited to the temporal lobe.[27]

Reasons for failure of initial surgery are important predictors of seizure outcomes after repeat surgery. However, reasons for failure are difficult to formulate; this is because a retrospective review of the records may not have the information for which to correctly infer the reason; additionally, there could be multiple reasons behind the failure. Resection is especially reserved for surgeries close to functionally important areas. Whether a reason is a technically incomplete resection or an inaccurate estimation of the epileptogenic zone can be difficult to determine in these cases. "Surgery-related" factors for failed initial surgery, which include extension of the epileptogenic zone into functional areas, missed lesions, incomplete resections, lesional recurrences, and improperly categorized epileptogenic areas, were reported to be predictors of seizure freedom after repeat epilepsy surgery.[14] This is in comparison to "disease-related" factors, which include emergence of a new epileptogenic zone and diffuse or bilateral epileptogenic zones. Repeat surgery for the cases with technical limitations such as obvious residual lesions and incomplete disconnection during hemispherotomy/posterior quadrantic disconnections warranted postoperative seizure freedom in this study. It is important to check if the planned surgery was performed completely when the seizures recur.

Rt-sided surgery was predictive of seizure freedom in this study, although the contribution may be small. This is partly explained by the fact that a more reserved surgery would be performed on the dominant hemisphere, or that a more radical surgery would be performed on the non-dominant hemisphere.

A retrospective study design with a relatively small number of subjects provided only low-level evidence in this study. Statistical comparison was performed mostly on two categorical variables, and the study might not have sufficient power to detect other meaningful factors. Our study only included pediatric patients, reflecting the characteristics of our institution. Careful interpretation is necessary to generalize our findings.

Conclusions

Seizure freedom was observed in 48.7% of patients after repeat epilepsy surgery, in line with previous observational studies. Female sex, surgical failure due to technical limitations, congruent EEG findings, lesional MRI, and Rt-sided surgery were predictive of postoperative seizure freedom, and first surgery limited to the temporal lobe was predictive of unfavorable outcomes. The reoperation of failed epilepsy surgery is challenging. Consideration of the above predictive factors can be helpful in deciding whether to reoperate on pediatric patients whose initial surgical intervention failed.

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Conflicts of Interest Disclosure

All authors have no conflict of interest and have registered online self-reported COI disclosure statement forms through the Japan Neurosurgical Society members' website.

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