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Surgical outcome and predictive factors of epilepsy surgery in pediatric isolated focal cortical dysplasia

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ABSTRACT

Objective: Focal cortical dysplasia (FCD) is a common cause of medically intractable epilepsy in children. Epilepsy surgery has been a valuable treatment option to achieve seizure freedom in these intractable epilepsy patients. We aimed to present long-term surgical outcome, in relation to pathological severity, and to assess predictive factors of epilepsy surgery in pediatric isolated FCD.

Methods: We retrospectively analyzed the data of 58 children and adolescents, with FCD International League Against Epilepsy (ILAE) task force classification types I and II, who underwent resective epilepsy surgery and were followed for at least 2 years after surgery.

Results: The mean age at epilepsy onset was 4.3 years (0–14.2 years), and mean age at epilepsy surgery was 9.4 years (0.4–17.5 years). The mean duration of postoperative follow-up was 5.1 ± 2.6 years (2–12.4 years). Of 58 patients, 62% of patients achieved Engel class I at 2 years postoperatively, 58% at 5 years postoperatively, and 53% at the last follow up. Forty eight percent of our cohort successfully discontinued antiepileptic medication. Of 30 patients with seizure recurrence, 83% of seizures recurred within 2 years after surgery. We observed that FCD type IIb was significantly associated with a better surgical outcome. At fifth postoperative year, 88% of FCD IIb patients were seizure free compared with 21% of type I and 57% of type IIa patients ($P = 0.043$). By multivariate analysis, lesion on MRI ($P = 0.02$) and complete resection ($P < 0.01$) were the most important predictive factors for a seizure-free outcome.

Significance: Epilepsy surgery is highly effective; more than half of medically intractable epilepsy patients achieved seizure freedom after surgery. In addition, we found significant difference in surgical outcomes according to the ILAE task force classification. Lesion on MRI and complete resection were the most important predictive factors for favorable seizure outcome in isolated FCD patients.

1. Introduction

Focal cortical dysplasia (FCD) comprises a spectrum of developmental malformations, characterized by aberrant cortical architecture of the cerebral cortex (Taylor et al., 1971). It is the most common cause of medically intractable focal epilepsy in childhood. To improve the characterization of these clinicopathological entities, in 2011, an International League Against Epilepsy (ILAE) task force revised the classification system of FCD to isolated FCDs (FCD types I and II) and variants associated with other potentially epileptogenic lesions (FCD type III) (Blumcke et al., 2011). Approximately 50%–75% of intractable epilepsy patients have achieved seizure freedom after epilepsy surgery (Tassi et al., 2000; Sisodiya, 2000). Two large pediatric cohort series reported the surgical outcomes of pediatric FCD patients which included those with hippocampal sclerosis or benign tumor (Cossu et al., 2008; Krsek et al., 2009a). The surgical outcomes vary, depending on a

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cohort's age at surgery, pathology, and follow-up durations (Kim et al., 2011; Teutonico et al., 2013; Muhlebner et al., 2014). However, the data on the long-term surgical outcome of pediatric isolated FCDs (FCD types I and II) are limited.

The neuroimaging modalities for detecting dysplastic lesions have been greatly improved. But neither EEG nor MRI are sufficient for detecting FCD. Interictal and ictal abnormalities on scalp EEG are localized in 50%–68% of patients with cortical dysplasia (Raymond et al., 1995; Lerner et al., 2009). In addition, abnormal MRI scans are reported for 10%–54% of cortical dysplasia patients, and are more frequently seen in FCD type II patients than in type I patients (Krsek et al., 2009a). Fludeoxyglucose-positron emission tomography (FDG-PET), ictal single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) are often performed in MRI-negative patients; however, their sensitivities with regard to pathological severity were not significant.

To date, many researchers have analyzed the predictive factors associated with seizure outcome after surgery in FCD patients (Hader et al., 2004; Cossu et al., 2008; Kim et al., 2009; Krsek et al., 2009b; Phi et al., 2010). Complete resection is widely accepted to be the most important predictive factor for seizure freedom after surgery (Krsek et al., 2009b). A meta-analysis of predictors of seizure freedom found that, partial seizures, temporal location, detection by MRI, a type II Palmini histological classification, and complete resection were associated with higher rates of postoperative seizure control (Rowland et al., 2012). However, there is no consensus on the clinical and surgical variables associated with a good seizure outcome in patients with isolated FCD.

In this study, we aimed to present the surgical outcomes of a pediatric cohort with isolated FCD, with regard to seizure outcome, recurrence rate, and chance of tapering antiepileptic medication (AED) after surgery. We also evaluated the seizure outcomes according to pathological severity. In addition, we analyzed the predictive factors of seizure freedom after surgery.

2. Methods

2.1. Patients

This was a retrospective study of patients with a postoperative histological diagnosis of FCD types I and II who had undergone resective epilepsy surgery at Seoul National University Children's Hospital from January 2004 to December 2013. All patients were younger than 18 years at surgery, and had been followed for at least 2 years after surgery. We excluded patients with other potentially epileptogenic lesions (FCD type III), such as hippocampal sclerosis, benign brain tumors, vascular malformations, ischemic changes, and the sequelae of meningoencephalitis. A total of 58 patients were included for analysis. A comprehensive review of their medical records included the following: (1) demographics (gender, age at seizure onset, duration of epilepsy, age at epilepsy surgery, presence of intellectual disability); (2) epilepsy details (seizure burden, history of febrile convulsion, number of antiepileptic medications); (3) interictal scalp electroencephalography (EEG) and, when needed, ictal video-EEG monitoring or intracranial EEG monitoring; (4) brain MRI. Additional data including FDG-PET, ictal SPECT, and MEG studies were collected.

2.2. EEG and neuroimaging studies

All patients underwent preoperative scalp EEG according to the International 10–20 system of electrodes. Video-EEG monitoring was recorded in 51 patients and intracranial EEG monitoring with subdural and depth electrodes was performed in 41 patients. We considered intracranial EEG monitoring when noninvasive investigations failed to localize the extent of the epileptogenic zone, or suggested wide involvement of extra-lesional areas, or the epileptogenic zone involved highly eloquent areas. In the latter cases, we performed functional mapping with intracranial electrical stimulation to identify the primary motor, somatosensory, and language areas. Interictal epileptiform discharges and ictal EEG patterns were classified as either localized (exclusively over a single lobe or in two contiguous areas) or not-localized (e.g., multilobar or hemispheric, or generalized). All patients underwent brain MRI with 1.5- or 3-T epilepsy protocols, including axial and sagittal T1-weighted, axial and coronal T2-weighted, oblique coronal T2-weighted, and fluid-attenuated inversion recovery (FLAIR) perpendicular to the long axis of both hippocampi. The MRI characteristics of FCD lesions include hyperintensities of the cortex and subcortical white matter on T2-weighted and FLAIR imaging, blurring of the gray-white matter, and sulcal or gyral abnormalities. FDG-PET was performed in 51 patients to detect hypometabolic regions of the brain. Ictal SPECT was performed in 20 patients during video-EEG monitoring. MEG was performed in 14 patients. We defined "localized" as confinement of a hypometabolic or hyperperfused area to a regional lobe.

2.3. Surgery and pathology

The surgical plan was decided based on the available data collected during presurgical assessment. Complete resection was defined as complete removal of the lesion as confirmed by postoperative MRI. In MRI-negative cases, the resection of a presumed epileptogenic zone on intracranial EEG monitoring was considered to be complete resection. The diagnosis of pathological cortical dysplasia was based on the ILAE classification (Blumcke et al., 2011).

2.4. Outcome definition

Postoperative seizure outcome was classified according to Engel as follows (Engel and Rasmussen, 1993): (class Ia) completely seizure-free since surgery, (I) seizure free or auras only or convulsions with antiepileptic medication discontinuation only, (II) rare disabling seizures (< 2 seizures/year or $\geq 90\%$ seizure reduction), (III) worthwhile seizure reduction (reduction of seizure frequency $\geq 75\%$), (IV) no worthwhile improvement (reduction of seizure frequency $< 75\%$).

2.5. Statistical analysis

The Statistical Package for the Social Sciences, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis. Descriptive statistics were used for data expressed as means ($\pm$ SD) and percentages. Categorical data were evaluated by the chi-square or Fisher's exact test, and continuous data were evaluated by the Student' *t*-test or the one-way analysis of variance (ANOVA). Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. To evaluate the effect of variables on postoperative seizure outcome, variables with a P value < 0.1 on univariate analysis were included in a multivariate Cox proportional hazards regression analysis. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical data

Of the 58 FCD patients, 30 were female and 28 were male. Age at seizure onset, age at epilepsy surgery, and duration of epilepsy to surgery are described on Table 1. The mean follow-up duration was 7.6 $\pm$ 3.9 years (range: 2.2–20.1 years). The postoperative follow-up duration ranged from 2 to 12.4 years (mean 5.1 $\pm$ 2.6 years). On average, patients took 2.5 AED prior to surgery. A history of febrile convulsions was present in 11 children (19%). According to the ILAE classification, 9 patients were FCD IIa and 15 were FCD IIb. We observed that age at seizure onset and surgery, seizure frequency, nor intellectual disability were not significantly different between FCD type I and II.