Seizure Outcome in Adult Patients with Isolated Focal Cortical Dysplasia in Modern Era

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Abstract

Objective: Focal cortical dysplasia (FCD) is the most common cause of focal epilepsy in children and adults. The long-term seizure outcome has been reported in children, but very limited data are available for adults. The aim of this retrospective study is to provide long-term seizure outcome in adults with isolated FCD.

Methods: A total of 23 adult patients operated on type I and II FCD were included. Medical history, seizure semiology, and radiological features were reviewed from the patients' charts. Long-term seizure outcome was obtained with telephone interviews and last follow-up data available in archive.

Results: At the last follow-up, 16 patients (69.6%) were totally seizure free even without aura and 7 patients (30.4%) continued to have seizure. Both type I (75%) and type II FCD (63.7%) showed higher seizure-free rate, and no significant difference was found (p=0.6).

Conclusion: Surgery is safe and results in high seizure-free rate in adult patients with isolated FCD, but it is not enough because we cannot still explain why some patients continue to have seizure after complete removal of the dysplastic area.

Keywords: Epilepsy, cortical dysplasia, seizures, surgery

Modern Çağda Yetişkin Fokal Kortikal Displazi Hastalarının Nöbet Sonlanımı

Öz

Amaç: Fokal kortikal displazi (FKD) yetişkin ve çocuklardaki en sık görülen fokal epilepsi sebebidir. Uzun dönem nöbet akıbetleri çocuklarda raporlanmıştır ancak erişkin hastalar için etkin veriler oldukça sınırlıdır. Bu retrospektif çalışmadaki amaç erişkin izole FKD hastalarında uzun dönem nöbet sonuçlarının ortaya koyulmasıdır.

Yöntem: Toplamda 23 tip-1 ve tip-2 FKD hastası opere edilmiştir. Hastaların tıbbi öyküsü, nöbet semiyolojisi ve radyolojik özellikleri incelendi. Uzun dönem nöbet durumları hakkında bilgiler, hastalarla yapılan telefon görüşmeleri ve güncel arşiv bilgilerinden edinildi.

Bulgular: On altı hasta aurasız olarak tamamen nöbetsiz izlenmiştir, 7 hastanın nöbetleri devam etmektedir. Hem tip-1 hem de tip-2 FKD'de nöbetsizlik oranı daha yüksektir ve her ikisi arasında sonuçlarda anlamı fark bulunmamıştır.

Sonuç: İzole FKD hastalarında cerrahi güvenlidir ve yüksek nöbetsizlik oranı ile sonuçlanmıştır; ancak bazı hastalarda displastik alanın tamamen çıkarılması sonrasında hastaların hala neden nöbet geçirdiklerini açıklayamamamız nedeniyle cerrahi tamamen yeterli değilir.

Anahtar Kelimeler: Epilepsi, kortikal displazi, nöbet

Focal cortical dysplasia (FCD) is a common type of cortical developmental abnormality that can cause refractory epilepsy in both children and adults. This clinical entity was first described in detail by Taylor et al. [1] in 1970s, and the common malformations include neuronal heterotopias or dyslamination, large and bizarre pyramidal neurons in the cortex, and white matter with large balloon cells. With the introduction of modern imaging techniques and use of advanced surgical equipment such as neuronavigation, the detection, localization, and removal of FCD have become easy. Today, FCD is considered an important cause of medically refractory epilepsy, occurring in approximately 50% and 20% of children and adults with epilepsy, respectively [2, 3].

There are several classifications of FCD, but 2 classification systems have been widely accepted. In 2004, Palmini et al. [4] classified FCD into 2 types: type I (Ia and Ib) and type II (IIa and IIb). However, in 2011, the International League against Epilepsy revised the

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classification with adding of type III [5]. In this classification, types I and II (more severe form) are called isolated FCD because no additional pathological entity, such as hippocampal sclerosis, glioneuronal tumors, and ischemic injury, exists.

Hopefully, previous surgical series reported that the seizure-free rate has increased up to 70% in patients operated with modern techniques [6-10]. The common notion is that the best predictor of a postoperative seizure-free status is the removal of entire lesion. However, the majority of previous surgical series included all types of FCD and had mixture of adults and children [6-14]. In this paper, we retrospectively analyzed only adult patients who were diagnosed with isolated FCD (types I and II), and all patients were operated by the same surgeon and followed up at least 1 year. The main goal of our study was to investigate the long-term seizure-free rate, even without aura, for isolated FCD adult patients who were evaluated and operated on with modern techniques.

Material and Methods

This is a retrospective study, and there are no data disclosing patients' identity in this study.

Patients

This study included 23 adult patients with proven isolated FCD who were operated on by the same surgeon between March 2010 and January 2018. The 23 patients were selected depending on our strict selection criteria as follows: patients who 1) were at least 18-year old, 2) were diagnosed with isolated FCD (types I and II), 3) had no previous epilepsy surgery, and 4) were followed up at least 1 year.

Presurgical evaluation

As in all epilepsy centers, every patient was evaluated in detail in our local epilepsy meetings. Basic measurements including detailed history, seizure semiology, head 1.5 T or 3.0 T (since 2015) magnetic resonance imaging (MRI) with epilepsy protocol, and video or scalp electro-encephalography (EEG) were taken. All patients were provided neuropsychological tests. If noninvasive studies provided inconsistent findings regarding lateralization and/or localization of the epileptogenic zone, invasive stereo-electroencephalography or depth electrode insertion was performed. If FCD was located on or close to any eloquent area, such as motor or speech cortices, functional MRI was performed. All patients, as routinely performed in our epilepsy center, underwent positron emission tomography to see additional hypometabolism, which could be the main seizure generator rather than FCD.

Resective surgery

After obtaining informed consent from the patients or next of kin, surgical procedures were performed. Our aim in resective surgery was to perform total removal as much as possible to get satisfactory seizure outcome. All surgical procedures were performed under the surgical microscope with neuronavigation. Subpial and/or endopial resection was performed with a cavitron ultrasonic surgical aspirator. If FCD was located on or close to the eloquent cortex, awake surgery with cortical electrical stimulation was performed.

Pathological diagnosis

Surgical specimens were sent to our pathological department, and after we performed the diagnosis, isolated type I and II FCD were chosen. Any lesion associated with FCD was excluded from the study.

Follow-up evaluation

MRI was performed in every patient within 24 hours of surgery to evaluate whether total removal was achieved. During hospital stay after surgery, close follow-up was performed to evaluate the occurrence of any surgery-related complication and of new neurological deficit. All the patients were on antiepileptic drug (AED), and within 1 week, they were discharged from the hospital.

Every patient was seen and evaluated regarding seizure outcome and AED use by the same epileptologist at regular intervals. We collected the long-term data by revising the follow-up charts, and the last seizure and medication outcomes were evaluated by telephone interview. Seizure outcome in this study was classified as "seizure-free" (Engel class Ia) and "not seizure-free" including auras (all other Engel classes).

Statistical analysis

We used a commercially available statistical software package Statistical Package for the Social Sciences version 22.00 (IBM SPSS Corp.; Armonk, NY, USA) for all the statistical analyses. The mean±standard deviations (±SDs) were calculated for each parameter. The independent samples test and chi-square tests were used for appropriate comparisons. Differences were considered statistically significant if the probability value was <0.05.

Results

General characteristics

Table 1 summarizes some clinical characteristics of the patients. Of the 23 patients, 14 (60.9%) were women, with a mean age of 27.2±7.5 (18-42) years. The mean age at seizure onset and duration of sei-

Table 1. Some clinical characteristics of the patients before and after surgery

Parameter	Before surgery	Follow-up	p
Mean age (years)	27.2±7.5		
Gender (M/F)	9/14		
Seizure onset (years)	7.6±10.1		
Mean duration (years)	17.5±10.6		
Frequency/month	165.7±254.9	10.4±13.4	0.008
Generalization (yes/no)	19/4	–/23	
Mean number of AED	2.82±0.98	2.27±1.12	0.1
FC (yes/no)	8/15		
DE (yes/no)	8/15		
Localization (right/left)	16/7		
Second surgery (yes/no)	4/19		
Deficit (yes/no)	2/21	*5/18	
Diagnosis (FCD I/ II)	12/11		
Mean follow-up (years)		5.52±2.8	
Seizure free (yes/no)		16/7	**0.06

Values are represented as mean±standard deviation, unless noted otherwise. *Three patients had a new neurological deficit after surgery. **No statistically significant difference was noted regarding seizure outcome rate between seizure-free and non–seizure-free patients. AED: antiepileptic drug; DE: depth electrode; FC: febrile convulsion; FCD: focal cortical dysplasia

zure were 7.6±10.1 (1-39) years and 17.5±10.6 (1-38) years, respectively. The mean follow-up period was 5.52±2.8 (1-9) years. From the medical history of the patients, we noted that febrile convulsion was seen in 8 (34.8%), and 7 patients (30.4%) had head trauma. Most patients (19 patients; 82.6%) had secondary generalized tonic-clonic seizures before surgery. The preoperative MRI showed that FCD was located on the right side in 16 patients (69.6%) and left side in 7 patients (30.4%). On the left side, FCD was located parietooccipital in 1, temporal in 2, frontal in 2, and parietal in 2 patients. On the right side, the location was as follows: frontotemporal in 1, parietooccipital in 2, parietal in 3, temporal in 4, and frontal in 6 patients. In 8 patients (34.8%), depth electrode was inserted because of ambiguous data obtained from noninvasive studies. Histopathologic diagnosis showed type I FCD and type II FCD in 12 (52.1%) and 11 (47.8%) patients, respectively.

A total of 4 patients (17.4%) underwent second surgery because of either incomplete removal or continuous seizure. In 3 of the 4 patients, FCD was located on the parietal lobe close to the central area. After the second surgery, seizure frequency/month significantly decreased, but seizure continued although total removal was achieved in 3 patients and all were on AED. Of the 3 patients with parietal lobe FCD, 1 patient had hemiparesis at the last follow-up after the second surgery. In the remaining 1 patient who underwent second surgery, FCD was on the right prefrontal cortex close to the motor area, and the patients had hemiparesis on the left side before the first surgery. Because of continuous seizure, second surgery was performed. Seizure frequency/month significantly decreased, and the patient still is on AED. On the head MRI after the second surgery, complete excision of the FCD was noted and hemiparesis did not recover.

Medication outcome

Before surgery, all patients were on AED and 21 patients (91.3%) were on polytherapy. The mean number of AED before surgery was 2.82±0.98 (1-5). At the last follow-up, we noted that 5 patients (21.7%) were drug free and 13 patients (56.5%) were on polytherapy. The mean number of AED at the last follow-up was 2.27±1.12 (1-5). The difference regarding the mean AED use before and after surgery was not significant (p=0.1; chi-square test). At the last follow-up, the number of AED was increased in 2 and decreased in 10 patients. The number was the same in 6 patients. Short-

ly, at the last follow-up, a total of 18 patients (78.2%) were still using AED.

Seizure outcome

Mean seizure frequency/month before and at the last follow-up were 165.7±254.9 (1-900) and 10.4±13.4 (1-30), respectively, and the difference was significant (p=0.008). Generalized tonic-clonic seizure was seen in 19 patients (82.6%) before surgery; however, no generalized seizure was noted at the last follow-up. Sixteen patients (69.6%) were totally seizure free even without aura (Engel class Ia). Seven patients (30.4%) continued to have seizure. Of the 7 patients who were not seizure free, 4 underwent second surgery and detailed information was given above. One of the common findings in these 7 patients was that all had secondary generalization and the majority of the FCD was on or close to the eloquent cortex. In the remaining 3 patients, FCD was on the right parietooccipital in 1, right frontal in 1, and right temporal lobe in 1. The seizure frequency decreased after surgery and all were on AED. Regarding the type of FCD, 9 patients (9/12; 75%) with type I FCD and 7 patients (7/11; 63.7%) with type II FCD were seizure free.

Surgical complications

Complication directly related to surgery was noted in only 1 patient (4.3%) who was operated on the right frontal (premotor) FCD. Extensive resection, from the precentral sulcus to the frontal pole, was performed. Hydrocephalus developed, and the ventriculoperitoneal shunt was inserted after the second surgery. The patient tolerated the shunt well and was discharged from the hospital without any other clinical problem. Regarding the neurological deficits after surgery, new neurological deficits developed in 3 patients (13%) because of the location of FCD. One patient showed left hemiparesis after resection of FCD on the premotor area close to the central sulcus. One showed right hemiparesis after resection of the left parietal area close to the postcentral sulcus and the last one had paresis on the right upper extremity after resection of the right parietal cortex. All 3 patients recovered completely from said paresis and were deficit-free at the last follow up.

Discussion

Epilepsy surgery series has demonstrated that FCD is a common cause of focal epilepsy not only in children but also in adults [6-14]. Surgical removal of dysplastic area is the most promising treatment to achieve favorable seizure outcome and seizure freedom after surgery has been reported to be as low as 50% or as high as 80% in different series [6-14]. It is clear that success of surgery in terms of seizure outcome depends on advanced development in imaging, neurophysiological studies, and surgical equipment such as neuronavigation [15].

Studies have shown that MRI negativity is more common in type I FCD, and complete removal is sometimes impossible [16]. However, type II FCD is more severe and generally visible on MRI [16]. Thus, compete removal is possible, which explains why in some clinical reports, the seizure-free rate is higher in this type of FCD [7, 14, 16].

In this report, we could include only a limited number of because of our strict inclusion criteria, such as including only adults with isolated FCD. We underline that reports regarding the surgical outcome of FCD operated with the use of modern equipment in modern era from developing countries are scarce [8] and wanted to report our seizure and medication outcomes in adults from a developing country.

Seizure outcome

The present results showed that surgery in isolated FCD resulted in favorable seizure outcome, as suggested by previous reports [6-16]. No generalized tonic-clonic seizures after surgery were noted, and seizure frequency was significantly decreased. The overall seizure-free rate was found to be almost 70%, and both type I and type II FCD benefited surgery and showed a high rate of seizure freeness. Closeness to the eloquent area prevented us to perform complete excision in 7 patients (30.4%), and thus, all had seizures after surgery. Even after second surgery performed in 4 patients, we could not achieve seizure freedom although seizure frequency had decreased significantly.

Seizure outcome from our report is comparable to that reported previous studies, most of which included children, reported during the last 10 years. In 149 patients (of which 144 were children), Krsek et al. [11] reported that overall seizure freedom was achieved in 70% of patients who had complete resection. They underlined that 8% of patients whose resections were complete showed no improvement in seizure frequency, supporting the concept of intrinsic epileptogenicity of dysplastic lesions. Kim et al. [12] reported predictors of surgical outcome in 166 patients, including both children and adults, with isolated FCD and mild malformations of cortical development (mMCD). They found that type II FCD showed a higher seizure-free rate than type I FCD, and complete resection and severe histopathologic type were associated with good seizure outcome; however, the presence of generalized tonic-clonic seizures was a predictor of poor seizure outcome. Fauser et al. [6] reported 211 children and adults undergoing epilepsy surgery for FCD. However,

they included all types of FCD and found that FCD types did not correlate with seizure control and 5 years after surgery, the seizure-free rate was 60%. According to the authors, favorable seizure outcome was stable in almost 80% of patients. Jin et al. [8] reported long-term seizure outcome of 120 patients with all types of FCD. Five years after surgery, almost 70% of patients were seizure free, and incomplete resection was associated with unfavorable outcome. Veersema et al. [10] found that almost 50% of 88 patients operated on FCD had seizures since surgery, and incomplete resection and mMCD were associated with unfavorable seizure outcome. Choi et al. [9] found the seizure-free rate as 58% at the 5th year of surgery in 58 children with proven FCD, and type II FCD showed a higher rate of seizure freedom compared with other types. Among the surgical variables, complete resection was the only positive prognostic factor for seizure freeness.

Our results are comparable to the above recent studies that surgery has beneficial effects on seizure outcome, and the majority of our patients were seizure free at the last follow-up. However, our series included only adult patients, and interpretation of the data from comparing the series including children should be considered carefully. We underline that the seizure-free rate in adults after surgery for isolated FCD is as higher as in children, and surgery should be the first option for treatment. In this report, patients who were not seizure free had incomplete resection at first surgery due to mainly closeness of FCD to the eloquent area. Although we could not perform statistical analysis whether complete resection was associated with seizure freeness, it seems that complete resection is important to get favorable seizure outcome. Second surgery with complete resection significantly decreased seizure frequency in our 4 patients, but none of them was seizure free, supporting the current literature that second surgery does not increase the rate of seizure freeness [17, 18].

Medication outcome

Out report showed that surgery did not cause significant decrease in the number of AED use at the last follow-up. The number of patients on polytherapy decreased from 21 (91.3%) to 13 (56.5%) at the last follow-up, and only 5 patients (21.7%) were drug free. At the last follow-up, 18 patients (78.2%) were still using AED, and the majority (11 patients) were seizure free. In the recent literature, a few surgical series mentioned AED outcome [6, 11]. However, our results are comparable to the limited number of previously reported studies that [6, 11] almost 30% to 50% of patients undergoing surgery for FCD were drug free at the last follow-up. Almost all reports that mentioned AED use after surgery underlined that the number of patients on polytherapy decreased at the long-term follow-up [6, 11]. Data from a recent study indicated that 16% of seizure-free patients remained on monotherapy and a further 16% were still on polytherapy [6]. The current literature including the present data suggested that there is still a relatively high percentage of seizure-free patients who remained on AED at the long-term follow-up. We think that several reasons may be responsible for this high percentage of patients who are still on AED. One may be that persistent spiking on EEG after surgery renders the physicians to stop AED. In other seizure-free patients, there may not be an indication for AED but the patients' wishes may become more important. Thus, before reduction or cessation of AED, every case should be considered carefully and individually, with consideration of patients' wishes and electrophysiological findings.

Safety of surgery

Our results in line with the previous surgical series [3, 19] supported the concept that surgery of epilepsy is safe. In our patient series, there was no mortality, and surgical morbidity was seen in only 1 patient (4.3%). In the literature, almost 9% surgical mortality rate was reported [9]. Intracerebral hematoma and infections including meningitis, wound, and bone flap infections were the main complications reported after surgery of FCD [9]. Regarding neurological deficits, our results supported the previous data that the main neurological complication in patients undergoing surgery on FCD was contralateral weakness on the extremities [3, 9, 19]. In this series, 3 patients (13%) showed new neurologic deficits after surgery. It is clear that in some patients with FCD extending to the motor cortex, weakness on the contralateral extremities is expected. Thus, patients or next of kin should be informed in detail about neurological deficits after surgery. This report does not contain cognitive complications.

Depending on the recent studies reported in modern era and our own experience, we speculate that we still need further studies that should focus on seizure network and molecular events that cause propagation of seizure. In FCD, one of the most important issues is returning of seizure after extended resection of the dysplastic area. The answer to the question "why some patients have seizure despite extensive surgery?" is that we have lack of understanding of epilepsy pathogenesis; thus, a better understanding of the pathogenesis of epilepsy in FCD is of utmost importance to provide successful treatment. We still do not know what we should do in FCDs extending to or located on any of the functional or eloquent cerebral cortices, which is the main cause of incomplete excision of the dysplastic lesion.

Study limitations

The readers should be aware of the limitations in this study. We are aware of 2 important limitations. First, this a retrospective study that we cannot completely avoid bias in collecting and interpreting the data. The second one is that rather small or inadequate number of adult patients was included, which prevented us to perform other statistical analyses.

Modern epilepsy surgery with modern equipment is performed by multidisciplinary teams in Turkey for the recent 10 years. Our data revealed that seizure outcome or seizure-free rate in our study is comparable to that reported in developed countries. Surgery is safe and results in high seizure-free rate in adult patients with isolated FCD, but it is not enough because we do not have enough data for understanding the pathophysiological or molecular mechanisms underlying the seizure in FCD.

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