Epilepsy Surgery in Pediatric Patients: A Single-Center Experience

Pediatric Hastalarda Epilepsi Cerrahisi Klinik Tecrübesi

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Summary

Objectives: Epilepsy surgery is one of the treatment options in pediatric patients with drug-resistant epilepsy. Our aim is to share demographic data, surgical outcome, possible surgical complications, and factors that affect surgical outcome in pediatric patients with drug-resistant epilepsy who were operated in our clinic.

Methods: In this retrospective study, 85 patients who were operated in Acıbadem Hospital Pediatric Epilepsy Surgery Clinic between years 2005 and 2017 were included. We investigated the influence of sex, age at seizure onset, side and frequency of seizures, time to surgery, type of epilepsy surgery, and histopathology on pediatric epilepsy surgery outcome. Surgical outcome was assessed by Engel classification system. Statistical analysis was performed with SPSS 20.0 software.

Results: There were 56 male (66%) and 29 female (34%) participants. Median of the age of seizure onset is 2 years (1 day–15 years). Median of age at operation is 6.2 years (3 months–16 years). Median of the duration of seizure until surgery is 3.2 years (3 months–15.5 years). Median follow-up is 5.6 years (3 months–13.5 years). There were permanent motor neurological deficits in 3 patients (3.5%). The best surgical outcome was achieved in patients with resective surgeries ($p<0.01$). Age at seizure onset was the most important factor that influences surgical outcome in our patients ($p<0.05$).

Conclusion: Epilepsy surgery is one of the safe and effective treatment options in pediatric patients with drug-resistant epilepsy.

Keywords: Drug-resistant; epilepsy; pediatric patients; surgery.

Özet

Amaç: İlaça dirençli epilepsi hastalığında epilepsi cerrahisi uygun olgularda etkili tedavi yöntemlerinden biridir. Bu çalışmadaki amacımız kliniğimizde epilepsi cerrahisi uygulanan çocukluk çağı ilaca dirençli epilepsi hastalarının demografik veri, ameliyat başarısı, olası cerrahi komplikasyonlar ve ameliyat başarısına etki eden faktörleri araştırmak ve çocukluk çağı epilepsi cerrahisi klinik tecrübemizi paylaşmaktır.

Gereç ve Yöntem: Bu geriye dönük çalışmaya kliniğimizde 2005–2017 yılları arasında ilaca dirençli epilepsi nedeni ile epilepsi cerrahisi yapılan 85 çocuk hasta dahil edilmiştir. Yaş, cinsiyet, nöbetin başlama yaşı, tarafı, sıklığı, nöbet başlangıcı ile ameliyat arasındaki zaman, epilepsi cerrahisi çeşidi ve histopatoloji değişkenleri ile cerrahi başarının arasındaki ilişki araştırılmıştır. Cerrahi başarı Engel sınıflaması ile ölçeklendirilmiştir. Veriler SPSS 20.0 programı ile analiz edilmiştir.

Bulgular: Araştırmaya dahi edilen hastalarının 56'sı (%66) erkek, 29'u (%34) kadındır. Nöbet başlama medyan yaşı ikidir (1 gün–15 yıl). Ameliyat zamanındaki medyan yaş 6.2'dir (3 ay–16 yıl). Nöbet başlangıcı ile cerrahi arasında geçen medyan yıl 3.2'dir (3 ay–15.5 yıl). Medyan takip süresi 5.6 yıldır (3 ay–13.5 yıl). Hastaların üçünde (%3.5) kalıcı motor kayıp gelişmiştir. En yüksek cerrahi başarı rezektif cerrahi yapılan hastalarda izlenmiştir ($p<0.01$). Ameliyat sonrası cerrahi başarıyı en çok etkileyen faktör nöbet başlama yaşıdır ($p<0.05$).

Sonuç: Epilepsi cerrahisi, doğru seçilmiş çocukluk çağı ilaca dirençli epilepsi hastalarında akılda tutulması gereken güvenli ve etkili tedavi seçeneklerinden biridir.

Anahtar sözcükler: İlaça dirençli; epilepsi; pediatrik hastalar; cerrahi.

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Introduction

There are 50,000,000 people with epilepsy around the world. Median incidence of epilepsy in patients younger than 14 years of age is about 82/100,000. Nearly 60% of new cases are from developing countries including Turkey. A current number of children and adolescents with epilepsy in Europe are reaching to 1 million.^[1-3]

Antiepileptic drugs (AEDs) are first-line treatment options in patients with epilepsy. However, unfortunately, those drugs and ketogenic diet work only two-third of epileptic patients. Epilepsy which does not respond current AEDs is called as drug-resistant epilepsy.^[4] The International League Against Epilepsy (ILEA) makes more scientific definition of drug-resistant epilepsy as “a failure of adequate trials of two tolerated, appropriately chosen, and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.”^[5]

Drug-resistant epilepsy has detrimental effects on developing brain during childhood in terms of mental and motor development. For this reason, there is a increasing consensus about epilepsy surgery to treat pediatric patients with drug-resistant epilepsy.

In this study, we aimed to share the clinical data of 85 pediatric patients with drug-resistant epilepsy who were operated in our clinic between years 2005 and 2017 and to analyze long-term outcome of epilepsy surgery in this study group.

Materials and Methods

In this retrospective study, we reviewed the medical data of 85 pediatric patients with drug-resistant epilepsy who were operated on at Acibadem Hospital Pediatric Epilepsy Surgery Clinic between 2005 and 2017. This study was approved by the medical ethical committee of Acibadem University Faculty of Medicine.

Pre-surgical patient evaluation

All drug-resistant epilepsy patients had neurological examination and at least 48-h, 21 channel video electroencephalogram (EEG) monitoring with at least 3 ictal recordings. All the patients had 3 Tesla magnetic resonance imaging (MRI) including sagittal and axial section turbo spin echo (TSE) T2-weighted imaging, coronal section fat-sat TSE T2-weighted diffusion, sagittal section three-dimensional

(3D) Turbo-FLAIR T2 with reconstructions, sagittal section 3D turbo flash T1 with reconstructions, and axial section 3D susceptibility-weighted imaging and diffusion tensor imaging tractography (Fig. 1).

All patients were evaluated by a clinical pediatric psychologist working with the pediatric neurosurgery team. After all data were collected for each patient, pediatric epilepsy surgery team which includes two pediatric neurosurgeons, a pediatric epileptologist, a neuroradiologist, and a clinical pediatric psychologist discusses the patients in a conference to decide if they benefit from epilepsy surgery or not. In patients without a clear epileptic zone, additional nuclear medicine evaluations such as single-photon emission computerized tomography (SPECT) and positron-emission tomography (PET) were also performed (Fig. 2).

Surgery

All patients had tailored microsurgical resection of the epileptic zone and/or lesions such as tumor, cortical tuber, and in-

Fig. 1. (a) Three-dimensional reconstruction of cranial magnetic resonance imaging (MRI) of a patient with epilepsy and mass lesion (arrows), (b) Functional MRI of the same patient shows close proximity of mass lesion and motor cortex (arrows), (c) In another patient with drug-resistant epilepsy, two-dimensional reconstruction of cerebral cortex provides clinicians to see whole cerebral cortex in horizontal plane. Red circle indicates the region of polymicrogyria. (d) Another patient with focal cortical dysplasia. Fiber tractography shows the relationship of dysplastic cortex (arrows) with corticospinal tracts.

fact zone. We also performed multiple subpial transections (MSTs) in a few patients who have the extension of epileptic networks to the motor cortex in order not to risk the eloquent cortex. Electrocorticography (ECoG) was performed in all patients with resective surgery, during pre-resection and

Fig. 2. (a) Axial T2-weighted section of a patient with drug-resistant epilepsy which shows suspicious lesion on left mesial frontal lobe. (b) Positron-emission tomography (PET)-computerized tomography of the same lesion shows hypermetabolism which confirms the lesion as an epileptic focus (suspected seizure during PET scan).

Fig. 3. A patient with right-sided invasive subdural grid implantation surgery. (a) Subdural electrodes are directly placed on the cerebral cortex. (b) Cables of grids exit through skin edges. (c) Lateral skull X-ray shows electrodes on right hemisphere. (d) Lateral skull X-ray shows electrodes on right hemisphere with markers on them which localizes epileptic network. Pink dots designates interictal discharges, whereas dark blue circle and rectangle localize ictal discharges.

post-resection period intraoperatively. We also performed invasive EEG recording with subdural grid electrodes in patients with ill-defined epileptogenic zones and in whom it is hard to decide surgical strategy besides all detailed radiological and neurophysiological investigations (Figs. 3–7).

Post-operative follow-up

Each patient stayed in pediatric neurosurgical intensive care

Fig. 4. (a) Video electroencephalogram (EEG) laboratory. (b) Continuous EEG recording in a patient who had invasive subdural grid implantation.

Fig. 5. (a) Axial section T2-weighted magnetic resonance imaging (MRI) of a child with drug-resistant epilepsy revealed left temporal tumor (arrow), (b) Intraoperative electrocorticography of the patient. (c) Post-operative axial section T2-weighted MRI of the patient shows complete removal of the lesion.

Fig. 6. (a) A tuberous sclerosis complex (TSC) patient with facial angiofibromas on the forehead (white arrows) and adenoma sebaceum on the nasal region (black arrows). (b) Axial section T2-weighted magnetic resonance imaging of the patient reveals a big left frontal cortical tuber and several small tubers on both hemispheres. (c) Intraoperative ultrasonographic appearance of the cortical tuber on left frontal region. (d) Axial section computerized tomography scan of the patient obtained just after removal of left frontal cortical tuber which was supposed to cause seizures after through epilepsy evaluation (electrocorticography). Please note hyperdense calcified subependymal nodules around lateral ventricles, which are pathognomonic for TSC patients.

unit for 24 h and 3–4 days in the patient ward afterward, depending on the clinical condition of the patient. All patients continued their AEDs with the same doses just after the surgery. Each of them was evaluated by both pediatric neurosurgeon and pediatric epileptologist every 3 months in post-operative year 1, every 6 months in post-operative year 2, and yearly thereafter. All patients had control EEG recordings starting from 3 months after the surgery. Drug dose adjustments were performed according to the EEG results by the pediatric epileptologist.

Evaluation of outcome and statistical analysis

Seizure outcome was evaluated according to Engel's classification.^[6] Statistical analysis was performed with SPSS 20. Variables evaluated in the statistical analysis were age, sex, age of seizure onset, side of epilepsy surgery (right-left),

Fig. 7. (a) Multiple subpial transection needle. (b) A patient who had cortical dysplasia involving occipital, parietal, and frontal lobes with the involvement of the motor cortex (area between dotted lines). Arrows show borders of occipital and parietal lobectomy. Motor cortex was not resected, instead multiple subpial transections within and around the motor cortex was performed (arrowheads).

Fig. 8. Epilepsy surgery numbers by years in our clinic.

duration of epilepsy till surgery, seizure frequency, type of surgery, and histopathologic results.

Results

All patients in the study group were operated only once in our institution. Patients who were previously operated in other institutions were excluded from the study. The total number of patients in the study group was 85 (56 [66%] males and 29 [34%] females). Figure 8 shows the epilepsy surgery numbers by years in our clinic.

Median age at seizure onset was 2 years (1 day–15 years). Median age of patients at the time of operation was 6.2 years (3 months–16 years). Median duration of seizure (timeline between seizure onset and operation) was 3.2 years (3 months–15.5 years). All patients still had seizures despite adequate trials of two tolerated, appropriately chosen AED (whether as monotherapy or in combination).

Table 1. Demographics

Total number of patients	n=85
Gender	
Male	n=56 (66%)
Female	n=29 (34%)
Median age at seizure onset	2 years (range: 1 day–15 years)
Median age at surgery	6.2 years (range: 3 months–16 years)
Median duration of seizure	3.2 years (range: 3 months–15.5 years)
Seizure frequency	
Daily	61 (72%) patients
Weekly	18 (21%) patients
Monthly	6 (7%) patients
Median follow-up	5.6 years (range 3 months–13.5 years)

Seizure frequency before surgery was daily (>30 seizures/month) in 61 patients (72%), weekly (5–30 seizures/month) in 18 patients (21%), and monthly (1–4 seizures/month) in 6 patients (7%) (Table 1).

In 82 patients (96.5%), MRI showed anatomical and structural changes. Only in 3 patients (3.5%), brain MRIs were completely normal. Since MRI evaluation was radiologist dependent and it is very hard to eliminate interobserver variability, MRI evaluations were not included in the statistical analysis in this study. In 76 patients (89.5%), routine radiological evaluation and scalp EEG recordings were satisfactory for surgical decision. 63 patients (74.2%) had resective epilepsy surgery including 31 patients with lobectomies and 32 patients with lesionectomies. Four patients with lobectomies also had additional MST during the same surgical session. Eighteen patients (21.2%) had disconnective epilepsy surgery including 11 patients with functional hemispherotomy, 5 patients with hypothalamic hamartoma (HH) disconnection, and 2 patients with callosotomy. Four patients had functional (vagal nerve stimulator implantation) epilepsy surgery. Table 2 details the surgery types.

Concurrent ECoG was performed in every patient who had resective epilepsy surgery. In 9 patients (9.5%), invasive EEG recording with subdural grid electrodes was performed. Among those patients, 5 patients had subsequent unilobar resections including 2 patients with frontal lobectomy, 2 patients with temporal lobectomy, and 1 patient with occipital lobectomy, and 4 patients had multilobar (all had temporo-occipital) resections. Within functional hemispherotomy group, 4 patients had Sturge-Weber syn-

drome, 5 patients had hemispheric infarcts, and 2 patients had Rasmussen's encephalitis. Eight patients (9.4%) had neurocutaneous syndromes, 4 patients were diagnosed with Sturge-Weber syndrome, all of whom had functional hemispherotomy, and 4 patients were diagnosed with tuberous sclerosis complex all of whom had cortical tuber excision.

There were no early and late surgical complications such as epidural, subdural, intraparenchymal hematoma or surgical infections. Nine patients (11%) developed temporary motor neurological deficits such as central facial paresis, monoparesis, or hemiparesis just after the surgery. Seven of them were within resective surgery group and 2 of them were within functional hemispherotomy group. The longest period for resolution of deficits was 9 months after the surgery. Permanent motor neurological deficits occurred in 3 patients (3.5%) all in patients who had functional hemispherotomy. Indeed, all of the hemispherotomy patients had moderate hemiparesis before surgery, two of them had an increase in hemiparesis, and one patient had contralateral visual field defect.

Histopathological reports were available for 61 of 85 patients. They revealed focal cortical dysplasia in 25 patients (41%), low grade tumor (including dysembryoplastic neuroepithelial tumors, ganglioglioma, and astrocytoma) in 20 patients (32.8%), HH in 7 patients (11.5%), and other pathologies such as cortical tuber, cavernoma, and pial angiomatosis in 9 patients (14.7%).

Our study group has post-operative median follow-up of 5.6 years (3 months–13.5 years).

Table 2. Surgery types

Resective surgery	Disconnective surgery	Functional surgery	Sum
Unilobar resection, n=23 (27.1%)			
Temporal lobectomy, n=17			
Frontal lobectomy, n=5	Callosotomy, n=2 (2.4%)	VNS implantation, n=4 (4.7%)	
Occipital lobectomy, n=1			
Multilobar resection, n=8 (9.4%)	Functional hemispherotomy, n=11 (12.9%)		
Lesionectomy, n=32 (37.6%)	Hypothalamic hamartoma, n=5 (5.9%)		
Sum, n=63 (74.1%)	n=18 (21.2%)	n=4 (4.7%)	n=85 (100%)

VNS: Vagal nerve stimulator.

Table 3. Epilepsy surgery outcome according to surgery types

Type of surgery	Engel classification				Total
	I	II	III	IV	
Resective surgery, n (%)					
Lesionectomy	23 (71.9)	5 (15.6)	3 (9.4)	1 (3.1)	32 (100)
Unilobar resection	16 (69.6)	3 (13)	2 (8.7)	2 (8.7)	23 (100)
Multilobar resection	3 (37.5)	2 (25)	3 (37.5)	0 (0)	8 (100)
Disconnective surgery, n (%)					
Callosotomy	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)
Functional hemispherotomy	7 (63.6)	2 (18.2)	1 (9.1)	1 (9.1)	11 (100)
Hypothalamic hamartoma disconnection	4 (80)	0 (0)	0 (0)	1 (20)	5 (100)
Functional surgery, n (%)					
Vagal nerve stimulator implantation	0 (0)	0 (0)	2 (50)	2 (50)	4 (100)
Total					(p<0.01)

Seizure outcome evaluation yielded that there were 53 patients (62.4%) with Engel class 1, 14 patients (16.5%) in Engel class 2, 11 patients (12.9%) in Engel class 3, and 7 patients (8.2%) in Engel class 4. The pediatric epileptologist discontinued all AED in 22 patients (26%) and reduced either the dose or the number of drugs in 38 patients (44.6%). Statistical analysis revealed that there is no influence of sex, histopathology, age at surgery, duration of epilepsy until surgery, side of epilepsy surgery, or seizure frequency on surgical outcome. On the other hand, resective surgery patients had the highest rate of seizure control, with lesionectomies having the best results, followed by unilobar resections ($p<0.01$) (Table 3). Patients who had seizures at earlier ages had poorer seizure control in comparison to the ones who had seizures at older ages ($p<0.05$). Patients who had seizures in early ages more likely to have focal cortical dysplasia in comparison to older patients ($p<0.05$).

Discussion

Epilepsy surgery for children was accepted as an extreme procedure and reserved only for children with life-threatening and debilitating epilepsy syndromes until the mid-nineteens.^[7,8] Today, this concept is totally changed because it became obvious that epilepsy within developing brain interferes with neuronal migration and neuroplasticity, results in memory, learning problems, and speech problems, and consequently results in mental motor retardation.^[9–11] Drug-resistant epilepsy patients use a combination of AEDs with high doses which may also negatively influence the metabolic functions of the growing child. Epilepsy surgery for children and adults has encouraging results today. For this reason, patients with drug-resistant epilepsy are recommended to be evaluated for epilepsy surgery regardless of their age.^[12–14]

The ILEA proposed criteria for the evaluation of pediatric epilepsy surgery candidates and structure of epilepsy

surgery units. MRI with epilepsy protocol and functional imaging, neuropsychological evaluation, interictal scalp EEG recording, video EEG recording and, in selected patients, invasive EEG recording with subdural grid electrodes are recommended. They also recommend evaluation of all pediatric surgical candidates in a multidisciplinary team including pediatric neurologist, pediatric neurosurgeon, neuroradiologist, and neuropsychologist.^[12]

In our clinic, we strictly follow these recommendations. Our pediatric epilepsy surgery team has all members that ILEA recommends and all patients have at least 48-h video EEG recording, 3 Tesla cranial MRI with epilepsy protocol, functional MRI, MR tractography imaging as a routine, and PET-CT and ictal SPECT as needed.

In our study group, patients who had seizures starting at earlier ages had poorer seizure outcomes after surgery. This result is concordant with the literature.^[15,16] This supports the theory that developing brain and neural networks are more vulnerable to epileptic discharges. It is hypothesized that, if a developing neuronal network gets an impact, this may trigger the development of new abnormal neuronal networks which end up with wider epileptic networks and more intractable epilepsy.^[17,18]

We observed the highest seizure control rates in patients who had resective surgeries. Patients with lesionectomies had the best seizure outcome, followed by patients who had unilobar resections and multilobar resections. These findings are also concordant with the results of other studies in the literature.^[15,19–21] Our study did not show any influence of sex, histopathology, age at surgery, duration of epilepsy till surgery, side of epilepsy surgery, and seizure frequency on the post-operative epilepsy outcome. There are many papers in literature about the predictors of seizure outcome, but many of them have conflicting results regarding sex, age at surgery, duration of epilepsy till surgery, side of epilepsy, and seizure frequency. Some of studies found several of these variables as predictors of post-operative epilepsy outcome in very homogeneous small cohorts, and some of them did not. For example, seizure frequency is a predictor of epilepsy outcome after surgery in temporal lobectomy patients, whereas it is not in ones with frontal lobectomy.^[22]

It is well accepted that patients with tumoral lesions have better post-operative seizure outcomes than patients with other pathologies.^[23,24] In our study, although patients

with tumoral lesions seem to have better post-operative epilepsy outcomes in comparison to patients with other pathologies, this correlation did not reach a statistical significance. This result may be because of the small number of patient cohort.

Epilepsy surgery in pediatric patients is a safe and efficient treatment with low morbidity and mortality.^[22,25–27] In our study group, only three patients (3.5%) had permanent neurological deficit, all of whom after hemispherotomy surgery. There was no mortality in our study group.

Although satisfactory post-operative epilepsy outcome regardless of antiepileptic treatment is the main aim of pediatric epilepsy surgery, the hope for tapering the doses or totally discontinuation of AEDs is highly encouraging. The burden of antiepileptic treatment both on the growing child's physiology and on the economy of countries is very high.^[28,29] In this study group, our epilepsy surgery team achieved total discontinuation of AEDs in 22 patients (26%), and decreased the doses of AEDs in 38 patients (44.6%).

Limitations

Our limitations are the small number of the study group, limited number of available neuropsychological test results, and absence of visual field examinations performed on each patient.

Conclusion

Epilepsy surgery is a safe and effective treatment option in patients with drug-resistant epilepsy. Patients who had resective surgery have better post-operative epilepsy outcome. Age of epilepsy onset is a good predictor of post-operative epilepsy outcome.

Ethics Committee Approval

This study was approved by Acibadem University Faculty of Medicine Medical Research Ethical committee.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: B.T., M.M.Ö.; Design: B.T., M.M.Ö.; Supervision: M.M.Ö.; Materials: B.T., M.M.Ö., U.I.; Data collection &/or processing: B.T., M.M.Ö., U.I.; Analysis and/or interpretation: B.T., M.M.Ö.; Literature search: B.T.; Writing: B.T.; Critical review: M.M.Ö.

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