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Surgical Treatment in Refractory Epilepsy: Seizure Outcome Results Based on Invasive EEG Monitorization

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ABSTRACT

AIM: To discuss seizure outcomes of patients with invasive electroencephalography (EEG) monitorization (IEM) following their epilepsy surgery at our centre.

MATERIAL and METHODS: Forty-seven patients suffering from refractory epilepsy and who were evaluated by invasive EEG were included in this retrospective study at Istanbul Faculty of Medicine from 2003 to 2017. We examined the Video EEG and invasive EEG monitorization, cranial MRI, SPECT, PET and neuropsychological tests of all patients. Postoperative seizure outcome results were evaluated according to Engel classification. The factors affecting seizure outcomes were discussed.

RESULTS: Twenty-six of the patients were female (55.3%), 21 were male (44.7). The average age was 32.0 (± 12.4). Forty-three patients had surgery and the average age of these patients was 26,6 (±11.15). 38.3% of the patients had hippocampal sclerosis (HS), 23.4% had focal cortical dysplasia (FCD), 8.5% had a tumor, 14.9% had sequela lesion and 14.9% had unknown etiology. Postoperative seizure status according to the Engel classification showed that 81.6% of the patients were class I, 10.5% were class II, 2.6% were class III and 5.3% were class IV.

CONCLUSION: A significant relation was statistically determined between structural MRI lesion and favorable seizure outcome ($p<0.05$). The most frequent etiology was HS in our patients. Of the patients with Engel I, the averages of their ages, ages at onset of epilepsy and ages at surgery were lower than other groups, but the difference was not statistically significant ($p>0.05$). We argue that IEM is an essential examination for favorable outcomes for determining the epileptogenic zone and/or the proximity of the functional structures.

KEYWORDS: Epilepsy surgery, Refractory epilepsy, Invasive EEG monitoring, Outcome, Eloquent cortex

ABBREVIATIONS: **CSF:** Cerebrospinal fluid, **DNET:** Dysembryoplastic neuroepithelial tumor, **EEG:** Electroencephalography, **FCD:** Focal cortical dysplasia, **HS:** Hippocampal sclerosis, **IEM:** Invasive EEG monitorization, **MRI:** Magnetic resonance imaging, **PET:** Positron emission tomography, **SPECT:** Single-photon emission computed tomography, **VEM:** Video-EEG

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INTRODUCTION

Epilepsy surgery is an effective treatment option for refractory focal epilepsies (12). The effectiveness of surgery is related to many conditions, such as the type of epilepsy, underlying pathology, time to surgery and accurate identification of epileptogenic zones (10). Epileptogenic zone has been defined as that "area of cortex that is indispensable for the generation of epileptic seizures". The objective of the surgery is the complete resection or disconnection of the epileptogenic zone and elimination of the generation of clinical seizures (9). The review plan of epilepsy surgery candidates consists of clinical history, long-term video-EEG (VEM), neuroimaging and neurophysiological examinations (4,8). Effective use of magnetic resonance imaging (MRI) has led to identifying lesions in the brain (7). Each of these investigations provides useful and complementary information when determining the epileptogenic zone. With the advances in technology, it has become possible to identify the epileptogenic zone with more accuracy through invasive studies on patients with epilepsy over the years. Invasive EEG monitorization (IEM) is required to establish a seizure map in patients with non-localized, multifocal and non-concordant patterns in video EEG as well as neuroimaging and neuropsychological tests. It is also used to determine the boundaries of functional structures in patients to establish the relationship between the epileptogenic zone and the eloquent cortex (motor center, speech, and memory) (9). Indications for invasive EEG are shown in Table I (7). In this study, we aimed to discuss the seizure outcomes of patients who had had invasive EEG monitorization following their epilepsy surgery at our center.

MATERIAL and METHODS

Forty-seven patients suffering from refractory epilepsy and who were evaluated by IEM were included in this retrospective study at Istanbul Faculty of Medicine from 2003 to 2017. We evaluated all patients with Video EEG monitoring, IEM, MRI, single-photon emission computed tomography (SPECT), positron emission tomography (PET) and neuropsychological tests. The evaluation parameters were age at surgery, age at onset of epilepsy, epilepsy duration, etiology, type of surgery, localization and related complications. Postoperative seizure outcomes of the first year were evaluated according to the Engel classification (4). Factors affecting the outcome were discussed.

Table I: Indications for Invasive EEG (Lhatoo, Kahane, & Lüders, 2018) (7)

1. MRI negative (particularly extratemporal) focal epilepsy
2. Dual or multiple epileptogenic pathologies
3. Suspected temporal plus epilepsy
4. Seizure recurrence after previous resective surgery
5. Proximity of putative epileptogenic zone to eloquent cortex
6. Complex malformation of cortical development
7. Discordant non-invasive presurgical evaluation information
8. Enablement of superselective surgeries (hippocampal transection, laser ablation)
9. Guiding surgical resection (acute electrocorticography)
10. Inconcordance in neuropsychological tests

The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki". It was approved by the Istanbul University, Istanbul Faculty of Medicine Ethics Committee at 14th-November-2014 (number=2014/1711).

Statistical Analysis

For statistical analyses, the IBM SPSS Statistics 24 package program was used. In this study, the descriptive statistics related to continuous variables were expressed with average, standard deviation, median, minimum and maximum values and the descriptive statistics related to categorical variables are expressed with numbers and percentages. When a normal distribution assumption could not be provided in analyzing the difference between two averages in the independent groups, the Mann-Whitney U test, which is a non-parametric method, was used. The relations between categorical variables were analyzed using the Chi-square test. The significance level was taken as 95% in the analyses and the results for p-value, which is equal to and lower than 0.05, were interpreted as statistically significant.

RESULTS

Patients

There were 26 (55.3%) female and 21 (44.7%) male patients, whose mean age at IEM was 32.0 (± 12.4) years. The total number of patients who had surgery was 43, and their mean age at surgery was 26.6 (± 11.15). The medical history of the patients showed that the mean age at epilepsy onset was 11.2 (± 9.38) years, and the mean duration of epilepsy was 15 (± 8.11) years. Although 89.4% of the patients were aged 16 and over, the findings showed that the age at onset of epilepsy was below 16 in 80.9% of the patients. 11.6% of the patients were operated on before the age of 16.

Twenty-one (44.8%) of the patients had temporal lobe epilepsy, and 18 (38.4%) of them had hippocampal sclerosis (HS). Nineteen (40.4%) had frontal lobe, four (8.5%) had occipital lobe and three (6.4%) had parietal lobe epilepsy. The focus was on the frontal region in 80% of patients below 16 years old. The focus was in the temporal region in 50% of the patients aged 16 and over and in the frontal region in 35.7% (Table II).

Hippocampal sclerosis was the most frequent etiology of epilepsy with 38.3%, focal cortical dysplasia (FCD) was second with 23.4%. The frequency of tumor was 8.5%, the sequelae lesion was 14.9% and the unknown etiology was 14.9% (Table III).

Preoperative Evaluation and Operation

All patients underwent VEM. The international 10–20 electrode system was used in all cases. Magnetic resonance imaging,

Table II: Demographic Data of the Patients and Localization

	Localization n (%)				
	Temporal		Extra-temporal		
	Temporal	Temporal (HS)	Frontal	Occipital	Parietal
Age (years)					
0-16	0 (0.0)	0 (0.0)	4 (80.0)	1 (20.0)	0 (0.0)
16<	3 (7.1)	18 (42.9)	15 (35.7)	3 (7.1)	3 (7.1)
Gender					
Female	1 (3.8)	11 (42.3)	9 (34.6)	3 (11.5)	2 (7.7)
Male	2 (9.5)	7 (33.3)	10 (47.6)	1 (4.8)	1 (4.8)
Age at the onset of epilepsy (years)					
0-16	3 (7.9)	10 (26.3)	18 (47.4)	4 (10.5)	3 (7.9)
16<	0 (0.0)	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)
Age at the surgery (years)					
0-16	0 (0.0)	0 (0.0)	4 (80.0)	1 (20.0)	0 (0.0)
16<	3 (7.9)	16 (42.1)	13 (34.2)	3 (7.9)	3 (7.9)
Time to surgery	22.0 ± 9.5 (16-33)	16.2 ± 7.1 (5-33)	12.4 ± 8.2 (1-27)	15.5 ± 10.2 (3-28)	16.7 ± 8.1 (8-24)
	6.4	38.4	40.4	8.5	6.4

***HS:** *Hippocampal sclerosis.*

Table III: Etiology

Etiology	n (%)
HS	18 (38.3)
FCD	11 (23.4)
Unknown	7 (14.9)
Sequelae lesion	7 (14.9)
Tumor	4 (8.5)

***HS:** *hippocampal sclerosis*
****FCD:** *focal cortical dysplasia.*

Table IV: Engel's Classification

Engel	n (%)
I	31 (81.6)
II	4 (10.5)
III	1 (2.6)
IV	2 (5.3)

SPECT, PET and neuropsychological examination of all patients were evaluated. All patients underwent IEM based on the preoperative evaluation, suggesting a possible epileptogenic zone and a region of early spreading of the seizures. The eloquent cortex was also determined in the process.

Four of 47 cases (two HS, two unknown etiology) which were included in this study were not operated on because they had complete overlap with the eloquent cortex. In the other 43 cases, resection varied according to IEM results. Because of functional constraints, the resection could not include the whole epileptogenic zone in five patients (two FCD 1, two sequelae lesions, one unknown etiology) in whom seizures came from the dominant hemisphere and involved an eloquent cortex. Among our cases, surgery consisted of 34.2% (13) frontal area, 10.5% (4) occipital area, 7.9% (3) parietal area, and 18.5% (7) temporal area resection. In one patient (2.6%), multilobar resection was performed. In this study, 16 patients (42.1%) hypothalamic resection was performed with or without temporal resection.

Outcome

In the first year of operation, according to Engel's classification, the post-operative status of 38 patients showed that 31 patients were in class I (81.6%), four in class II (10.5%), one in class III (2.6%), and two in class IV (5.3%) (Table IV).

Additionally, four patients of FCD type 1 and four of FCD type 2 were Engel I, one of FCD 2 was Engel II. Thirteen of HS patients were Engel I, the other two patients were Engel II, and one patient was Engel IV. Five patients with sequelae lesions were classified as Engel I. The sequelae lesions of the patients were defined as a posttraumatic lesion in two patients, perinatal asphyxia in two patients, lesion following abscess surgery in one, lesion following hydatid cyst surgery in one and congenital ischemic lesion in one. Two patients with tumor (diffuse astrocytoma and glial tumor) were classified as Engel III and IV, whereas another two with dysembryoplastic neuroepithelial tumor (DNET) were classified as Engel I. Of the three patients with unknown etiologies, two were Engel I and one of them was Engel II.

As a result, 50% of the patients with tumor-related epilepsy were classified as Engel III and IV. On the other hand, no seizure

Table V: Engel's Classification According to Etiology

		Engel I	Engel II	Engel III-IV
Age (years)	0-16 (n=5)	4 (100.0)	0 (0.0)	0 (0.0)
	16< (n=42)	27 (79.4)	4 (11.8)	3 (8.8)
	Total (n=47)	**31**	**4**	**3**
Etiology	FCD I (n=6)	4 (100.0)	0 (0.0)	0 (0.0)
	FCD II (n=5)	4 (80.0)	1 (20.0)	0 (0.0)
	HS (n=18)	13 (81.3)	2 (12.5)	1 (6.2)
	Sequelae lesion (n=7)	5 (100.0)	0 (0.0)	0 (0.0)
	Tumor (diffuse astrocytoma +glial tumor +2DNET (n=4)	2 (50) (2DNET)	0 (0.0)	2 (50)
	Unknown (n=7)	3 (75.0)	1 (25.0)	0 (0.0)
	Total (n=47)	**31**	**4**	**3**

**FCD: Focal cortical dysplasia. **HS: Hippocampal sclerosis. ***DNET: Dysembryoplastic neuroepithelial tumour.*

was observed after surgery in all patients with FCD I, sequelae lesion and DNET (Table V). Furthermore, in all patients below the age of 16, no seizure was observed after surgery.

In one patient with FCD type I, seizures significantly decreased in the first year after the operation. However, Lennox-Gastaut syndrome developed afterwards; however, there was no relation between the operation and this situation. One patient with HS was Engel Ic with simple partial seizures, but these were not disabling after the surgery, yet the seizures increased after taking a blow to the head during a fight.

Data Analysis

Of the patients with Engel I, the averages of their ages, ages at onset of epilepsy and ages at surgery were lower than the patients in the group with Engel II, III and IV, but the difference was not statistically significant ($p>0.05$). There was no statistically significant difference between the duration of epilepsy and the post-operative seizure outcome ($p>0.05$).

The relation between preoperative evaluations (MRI, VEM and PET/SPECT findings) and the seizure outcome was analyzed. A statistically significant relation was determined between distinct lesions on MRI and seizure outcome ($p<0.05$). It was seen that the seizure outcome was better in patients who had lesions on MRI. However, no statistically significant relation was found between VEM and PET/SPECT findings and the seizure outcome ($p<0.05$).

"Switch of" Phenomena

"Switch of" findings were detected in VEM of six patients. In one of the patients, the lesion could not be completely resected because of the closeness of the epileptogenic zone to the speech center. The other five patients were HS, and their epileptogenic zone was resected in the light of IEM. The post-operative status in four patients was Engel I and in 1 it was Engel II.

Complications

The post-operation complications were analyzed. Meningitis was seen in two cases (4%). One case (2%) had transient aphasia and one case (2%) had right homonymous hemianopsia after the operation. Two patients died, one in three months and the other in six months following the operation. The epilepsy etiology of one of these patients was not determined, and the other had sequelae lesions. The reasons for death could not be determined in this study.

DISCUSSION

This retrospective study revealed the indispensable role of IEM in presurgical evaluation when non-invasive presurgical evaluation information was discordant and/or the epileptogenic zone was in close proximity to the eloquent cortex. With IEM, the epileptogenic zone was identified successfully in most patients and the chance for a positive outcome was improved. In this study, we showed that 31 patients were in class I (81.6%) after surgery, according to Engel's classification. Mapping the functional area also reduces the rate of neurological complications after resective surgery, especially in patients whose epileptogenic zone is close to the eloquent cortex.

However, we determined that there are several other factors affecting favorable post-surgical outcomes. In a meta-analysis, it was reported that the early age of surgery or early age at onset of epilepsy in patients with temporal lobe epilepsy influenced the post-operation seizure outcome in a positive way (12). In our patient group, the mean age at surgery was 26.6 (±11.15) and the onset of epilepsy in most cases was early childhood. The averages of ages, ages at onset of epilepsy and ages at the surgery in patients with Engel I were lower than those in the group with Engel II, III and IV. This finding was remarkable although there was no statistical relation between age of patients, age at onset of epilepsy, age at surgery, duration of epilepsy and seizure outcome.

Etiology also affects the outcome. The most common etiology in this study was HS, and the second one was FCD. Sequelae lesions and unknown etiology followed these and the rarest etiology was tumors. According to the literature, HS is the most common indication for epilepsy surgery (12). The variety in methods of investigation causes sampling bias in each study (1). However, there is a growing rate of FCD in the field of epilepsy surgery, up to 25% (14).

In our cohort, according to post-operative seizure outcomes, 81.3% of hippocampal sclerosis cases, 100% of FCD I cases and 80% of FCD II cases had no seizure after surgery. The worst result of seizure outcome was in the tumor group, with 50%. There are many studies related to seizure outcomes. It is observed that seizure freedom varies from 48% and 84% in HS patients (1) and 60–80% in FCD patients (6). According to the literature, for epilepsy surgery, the most important prognostic factors are full resection of the lesion, finding structural lesion visible on MRI or determining epileptogenic zone by intracranial EEG (3,6). In tumor cases, because the invasive feature of the lesion makes the borders of the lesion unclear, difficulties and impossibilities arise in the full resection of tumors. In tumor patients, it may not be possible to determine the borders of lesions sufficiently even when it is evaluated by invasive exploration. We were able to show that this is also true for structural lesions in MRI, which gave a good seizure outcome. The determination of the lesion's borders results in full extraction of the epileptogenic zone and increases the success rate of the operation (6,15). However, no significant relation was found between video EEG and PET/SPECT results and the seizure outcome.

Steinhoff et al. were first to define the unusual ictal propagation pattern called 'switch of lateralization'. The pattern is considered bilateral epileptogenicity and yields unsuccessful results with epilepsy surgery (13). However, this may not always be true. The determination of the epileptogenic zone with the pre-operative examinations increases the rate of a favorable outcome with additional examinations. Finding a 'switch of lateralization' pattern does not always lead to a poor prognosis (11). In our patients, seizure freedom was seen in four of five "switch of" patients. As opposed to most literature, we are able to say that this pattern is not always related to poor prognosis. However, it is important to note that our patients were investigated using IEM and yet 'switch of lateralization' was detected in a small number of patients.

The metabolic complications seen in patients who have had epilepsy surgery are cerebrospinal fluid (CSF) leakage, infection, deep vein thrombosis/pulmonary embolism, pneumonia, intracranial hematoma, metabolic disorders. The neurological complications vary depending on the region where the lesion is extracted. Cranial nerve disorders, dysphasia, memory dysfunctions, hemiparesis, psychiatric disorders, hemianopsia, epilepsy, and death may be seen (5). In our study, the most frequent complication after surgery was meningitis. Also, one patient had temporary aphasia and one patient had hemianopsia. It was not proven that the deaths of the two cases were related to the surgery.

In one case with FCD type I, Lennox-Gastaut syndrome developed after surgery and worsened clinically. However, it was not associated with surgery. On the other hand, there are studies reporting that accompanying focal lesions may be seen in severe epileptic encephalopathy cases, such as Lennox-Gastaut and a good prognosis, may be seen with epilepsy surgery (2,16). In one of our patients, seizures increased with head trauma after surgery. It was found worthy of discussing among the factors affecting seizure outcome.

CONCLUSION

Our study revealed the indispensable role of IEM in the presurgical evaluation. With IEM, the epileptogenic zone is identified successfully in most patients, and the chance for a favorable outcome was improved. In our study, the findings showed that the seizure outcome is related to the structural MRI lesions. The most frequent etiology in our patient group is HS. It is thought that "switch of" finding is not always related to poor prognosis. It is emphasized that the most frequent complication after the operation is meningitis and situations, such as subsequent disorders and head trauma, could affect seizure outcome. In the preoperative examination, when an opinion is needed to determine the epileptogenic zone and the functional structures, we argue that IEM is an essential analysis.

AUTHORSHIP CONTRIBUTION

Study conception and design: ZMG, NGS, CG

Data collection: ZMG, NGS, BK, GG, FSE, BTG, SV, AS, AA, YA, NB, BB, AS, ATC, AG, CG

Analysis and interpretation of results: ZMG, NGS, CG, UAC

Draft manuscript preparation: ZMG, NGS, CG

All authors (ZMG, NGS, BK, GG, FSE, BTG, SV, AS, AA, YA, NB, BB, AS, ATC, AG, UAC, CG) reviewed the results and approved the final version of the manuscript.

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