Original article

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Epilepsy surgery in a developing country (Lebanon): ten years experience and predictors of outcome

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ABSTRACT – We present our 10-year experience and preoperative predictors of outcome in 93 adults and children who underwent epilepsy surgery at the American University of Beirut. Presurgical evaluation included video-EEG monitoring, MRI, neuropsychological assessment with invasive monitoring, and other tests (PET, SPECT, Wada). Surgeries included temporal (54%), extratemporal (22%), and multilobar resections (13%), hemispherectomy (4%), vagal nerve stimulation (6%), and corpus callosotomy (1%). Mesial temporal sclerosis was the most common aetiology (37%). After resective surgery, 70% had Engel class I, 9% class II, 14% class III, and 7% class IV. The number of antiepileptic drugs before surgery was the only preoperative factor associated with Engel class I (p=0.005). Despite the presence of financial and philanthropic aid, many patients could not be operated on for financial reasons. We conclude that advanced epilepsy presurgical workups, surgical procedures, and favourable outcomes, comparable to those of developed countries, are achievable in developing countries, but that issues of financial coverage remain to be addressed.

Key words: seizure, intractable epilepsy, epilepsy surgery, developing countries, cost-of-illness

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Epilepsy surgery is now broadly accepted as a treatment option for pharmacoresistant, localisation-related epilepsy. Almost 20% of patients with seizure disorders have intractable epilepsy and around half of these patients may be candidates for epilepsy surgery (Wass *et al.,* 1996; Engel, 2008). Surgery often results in seizure freedom and can improve or even normalise patients' quality of life (Aydemir *et al.,* 2004; Sabaz *et al.,* 2006; Mikati *et al.,* 2009, 2010). In 2003, the American Academy of Neurology (AAN) issued a practice parameter that recommended epilepsy surgery for the treatment of medically

intractable mesial temporal lobe epilepsy (Engel *et al.*, 2003). Despite increasing reports from Asia and Africa, this therapy remains much less available in developing countries, compared to developed countries (Wylie *et al.*, 1998; Salanova *et al.*, 1999; Williamson and Jobst, 2000; Mikati *et al.*, 2004; Chaudhry *et al.*, 2010; Mrabet khiari *et al.*, 2010; Chang and Huang, 2011; Jayalakshmi *et al.*, 2011).

Epilepsy affects approximately 50 million people in the world, of whom 80% are in the developing world and of these, 80-90% receive no treatment at all (World Health Organization, 2005). In these countries, epilepsy surgery was shown to be a cost-effective procedure when surgery candidates were properly identified and evaluated (Darazi and Mikati, 1997; Rao and Radhakrishnan, 2000), however, resources are limited for the majority of patients with refractory epilepsy (Asadi-Pooya and Sperling, 2008). Studies on epilepsy surgery in developing countries are scarce and strategies for the development of surgical treatment of patients with epilepsy in developing countries are needed (Asadi-Pooya and Sperling, 2008; Mikati *et al.*, 2008a; Boling *et al.*, 2009; Malekpour and Sharifi, 2009; Mrabet Khiari *et al.*, 2010; Chang and Huang, 2011; Jayalakshmi *et al.*, 2011).

The Adult and Pediatric Epilepsy Program at the American University of Beirut Medical Center (AUBMC) was launched in 1995. The program included clinical studies, invasive and non-invasive video-electroencephalographic (EEG) monitoring, epilepsy surgery, and basic science research. Epilepsy surgery was started in this program in 1997 and, since then, more than a 100 adult and paediatric patients have undergone resective epilepsy surgery or vagal nerve stimulation (VNS) implantation. In this study, we present our initial 10-year experience of 93 patients who underwent either resective epilepsy surgery or VNS from January 1997 to June 2007 with a follow-up period of at least one year. Our goal was to compare our findings, with respect to patient clinical characteristics, predictors of outcome, and other aspects, to those described in previous studies that have been predominantly reported from the West.

Materials and methods

A total of 512 adult and paediatric patients were admitted to the Epilepsy Monitoring Unit at the American University of Beirut Medical Center (AUBMC) from January 1996 to June 2006. Patients were of different Middle Eastern and North African nationalities. All patients were part of an epilepsy database (approved by the Institutional Review Board). Fifty-three adult patients and 40 paediatric patients underwent epilepsy surgery and were included in this study. Patients who underwent surgery came from Lebanon (77), Cyprus (5) Bahrain (3), Jordan (2), Iran (2), Syria (2), Egypt (1), and England (1).

Presurgical evaluation

All patients were evaluated by one epileptologist (MAM) and operated on by one epilepsy surgeon (YGC). The evaluation included a complete clinical assessment, a neurological examination, non-invasive long-term video-EEG monitoring, magnetic resonance imaging (MRI), and neuropsychological assessment. Some patients received subdural electrode monitoring (36.6%), [^{18}F] deoxy-glucose positron emission tomography (PET) (10.8%), single-photon emission computed tomography (SPECT) (23.7%), or intracarotid amobarbital procedure (Wada) (43%) tests, as required. Patients were required to be non-responsive to at least three antiepileptic drugs (AEDs), with no anticipated adverse consequences of surgery and an anticipated preserved ability of the remaining brain to carry out normal function. Patients who had a clearly delineated epileptogenic zone underwent resective surgery. Those who did not qualify for resective surgery were considered for VNS or corpus callosotomy.

The EEG, seizure semiology, neurological examination, and neuroimaging were used to help identify the epileptogenic zone in all patients for resective surgery. Patient test results were discussed in an epilepsy surgery conference (with an epileptologist, epilepsy surgeon, neuroradiologist, neuropsychologist, and neurologists). The chance of seizure freedom was estimated based on the findings and presence or absence of previously reported prognostic factors in the literature (hippocampal atrophy on presurgical MRI, epileptic EEG arising from the site of resection, imaging localisation, a known underlying aetiology, history of febrile seizures in patients with MTS, partial seizures only, absence of a history of generalised tonic-clonic [GTC; except those associated with drug withdrawal in hospital or on initial presentation of epilepsy], focal abnormality on neuroimaging, and lack of use of invasive monitoring). When the estimate for postsurgical seizure freedom was around 60% or higher, resective surgery was recommended.

Surgical procedures

The surgical procedures which were performed included: temporal resection, extratemporal resection, multilobar resections, hemispherectomy, corpus

callosotomy, and VNS. Awake craniotomy, intraoperative cortical stimulation, corticography, and somatosensory evoked potentials (SSEPs) were performed, as required. Stereotactic surgery using a navigational system was also performed on some patients, as required.

Seizure outcome assessment

Data were collected from follow-up visits and completed or confirmed by telephone interview, as required, and then entered sequentially into the data base. The data included: presurgical evaluation procedures, dates of surgery, age at epilepsy onset, age at surgery, pre- and postsurgical seizure frequency, type of seizures, type of surgery, number of AEDs before and after surgery, and aetiology of epilepsy. Classification of the outcome was based on the system proposed by Engel and collaborators. Outcomes involving no seizures, auras only, or generalised convulsion with drug withdrawal only were classified as class I. Class II included rare disabling seizures or nocturnal seizures only. Class III represented outcomes with worthwhile improvement and class IV involved outcome with no worthwhile improvement (Engel, 1987).

The Pearson χ^2 and Independent t-test were used for statistical comparisons. Binary logistic regression was used for multivariate analysis. The results of our paediatric patients were reported previously (Mikati *et al.*, 2008b).

Results

Type of surgery

Of the total 93 patients, 50 patients underwent temporal resection (53.8%), 20 underwent extratemporal resection (21.5%), 12 patients underwent multilobar resection (12.9%), and four underwent hemispherectomy (4.3%). Six patients also underwent the VNS procedure (6.5%) and one patient underwent corpus callosotomy (1.1%).

Patient data

Patient data including gender, mean age at epilepsy onset, mean time from epilepsy onset to surgery, age at surgery, and mean follow-up time following surgery are summarised in *table 1*. Three of the 93 patients, one of whom underwent callosotomy, were lost during follow-up.

Seizure frequency before surgery ranged from 1 seizure/month to 1,905 seizures/month.

Table 1. Patient data.

Characteristics	Data
Gender *n* (%)	
male	42 (45.2)
female	51 (54.8)
Mean age at epilepsy onset (years)	8.98
Temporal resection	9.13
Extratemporal resection	8.49
Multilobar resection	12.99
Hemispherectomy	5.40
VNS	4.67
Corpus Callosotomy	3
Mean time from epilepsy onset to surgery (years)	14.11
Mean age at surgery (years)	23.09
Age at surgery (years)	
Temporal resection	24.66
Extratemporal resection	21.01
Multilobar resection	27.5
Hemispherectomy	9.25
VNS	17
Corpus Callosotomy	25
Mean follow-up time following (years)	
Resective surgery	4.84
VNS	2.23

Patients were of different nationalities: Lebanese (433), Cypriot (22), Syrian (15), Bahrainis (14), Jordanian (7), Iranian (5), Palestinian (4), Kuwaiti (3), English (1), Saudi Arabian (1), Egyptian (1), Pakistani (1), Yemeni (1), Brazilian (1), Moroccan (1), Qatari (1), and United Arab Emirates (1).

All patients who underwent resective surgery and one VNS patient had partial epilepsy, the remaining VNS patients (5 of 6) and the corpus callosotomy patient had Lennox-Gastaut syndrome with GTC, absence, myoclonic, and atonic seizures.

Causes of epilepsy

Mesial temporal sclerosis (MTS) was the most common epilepsy aetiology (36.6%), followed by tumours (23.7%; astrocytoma, dysembryoplastic neuroepithelial tumour, glioma, xanthoastrocytoma, hypothalamic hamartoma, oligodendroglioma, and ganglioglioma), malformations of cortical development (MCD) (9.7%), gliosis (8.6%), and vascular malformations (7.5%). Other aetiologies (7.6%) included stroke, Rasmussen encephalitis, undetermined congenital syndrome, and "ruling out" of cortical dysplasia. Epilepsy aetiology based on the type of resective surgery is summarised in *table 2*. There was no relationship between

Table 2. Epilepsy aetiology and type of resective surgery.

Cause of epilepsy (%) / type of surgery	Temporal resection (*n*=50)	Extratemporal resection (*n*=20)	Multilobar resection (*n*=12)
Mesial temporal sclerosis (MTS)	64	35	16.7
Tumours*	24	30	33.3
Malformations of cortical development	0	0	16.7
Gliosis	2	15	25
Vascular malformations	8	15	
Other aetiologies†	0	5	8.3
MTS + glioma	2	0	0

*tumours included astrocytoma, dysembryoplastic neuroepithelial tumour, glioma, xanthoastrocytoma, hypothalamic hamartoma, oligodendroglioma, and ganglioglioma.
†Other aetiologies (7.6%) included stroke, Rasmussen encephalitis, undetermined congenital syndrome, and "ruling out" of cortical dysplasia.

the presence of tumour, as aetiology of epilepsy, and type of resective surgery (Pearson χ^2 *p* value =0.604).

Surgery outcome

Mean seizure frequency significantly decreased from 143.55 seizures/month before resective surgery to 5.79 seizures/month following resective surgery (paired t-test *p* value=0.000, power=0.00, *n*=84). There was a significant decrease in the number of AEDs following resective surgery (2.45 *vs* 1.37, paired t-test *p* value=0.000, power=1.000, *n*=84).

Following resective surgery, 63 of 84 patients (75%) had an Engel class I outcome; 44 of 84 patients (52.4%) were completely seizure-free (Engel class IA), seven patients (8.3%) had only auras (Engel class IB), 11 patients (13.1%) had some disabling seizures after surgery but were seizure-free for at least two years (Engel class IC), and 1 patient (1.2%) had only a generalised convulsion upon AED withdrawal (Engel class ID). One patient (1.2%) was initially free of disabling seizures but now has infrequent seizures (Engel class IIA), 4 patients (4.8%) had infrequent disabling seizures (Engel class IIB), one patient (1.2%) had more frequent disabling seizures after surgery, but less frequent seizures for at least two years (Engel class IIC), and 2 patients (2.4%) had nocturnal seizures only (Engel class IID). Eight patients (9.5%) had worthwhile seizure reduction (Engel class IIIA), 2 patients (2.4%) had prolonged seizure-free intervals amounting to greater than half the follow-up period but not less than two years (Engel class IIIB), 2 patients (2.4%) had a significant seizure reduction (Engel class IVA), and 1 patient (1.2%) had an increase in seizure frequency (Engel class IVB). The resective surgery outcome and the preoperative prognostic indicators discussed in the following section are summarised in *table 3*.

Predictors of outcome

For patients undergoing resective surgery (focal, multifocal or hemispherectomy), outcome, defined as percent of patients with Engel class I, did not correlate with any of the following variables: age at onset of epilepsy, age at surgery, type of surgery, presence of tumour as the aetiology, and preoperative seizure frequency. The number of AEDs before surgery was the only preoperative factor associated with Engel class I outcome (Independent t-test *p* value=0.005, power=0.804); patients with Engel class I outcome were taking less AEDs than patients with Engel class II, III, and IV outcome (*table 3*).

Significant association was detected between the outcome measures seizure freedom (Engel class I outcome) and number of AEDs following resective surgery (independent t-test *p* value=0.000, power=0.986). This finding was expected since both seizure freedom and the number of AEDs following surgery are measures of outcome.

Financial aspects

Most of the patients who were evaluated as outpatients and who qualified for inpatient evaluation for epilepsy surgery could not be admitted for financial reasons (about a quarter of those who were medically eligible were admitted). This occurred despite the presence

Table 3. Resective surgery outcome and potential preoperative prognostic indicators.

	Free of disabling seizures (Engel class I) (*n*=63)	Persistent seizures (Engel class II, III, or IV) (*n*=21)	*p* value	Power
Number of AEDs before surgery	2.29	2.95	0.005	0.80
Age at epilepsy onset (years)	9.62	7.92	0.514	0.13
Age at surgery (years)	22.58	25.52	0.379	0.14
Seizure frequency before resective surgery (per month)	139.71	155.07	0.858	0.05
Tumour presence (%)	76.2	23.8	1.000	0.05
Type of surgery (temporal) (%)	77.1	22.9	0.621	0.09

of substantial financial and philanthropic aid. Patients were often denied coverage by their third party payers due to the presumed "congenital" nature of epilepsy or other financial reasons.

Discussion

This study reports our initial 10-year experience of epilepsy surgery, both resective surgery and VNS, in a tertiary referral centre in Lebanon. Our seizure freedom outcome (Engel class I) following resective surgery was similar to that reported in series from the West, such as the study by Khoury *et al*. (2005) who reported Engel class I outcome in 68.21% of patients with a mean age of 32±10 years (range: 11-56 years), two years after surgery.

Temporal resection was the most frequently performed procedure (53.8%) at our centre. It was also reported to be the most common procedure in the studies of Hildebrandt *et al*. (2005) and Eriksson *et al*. (1999), who stated that 74% and 54% of their patients had temporal resection, respectively. We also found that the highest percentage of seizure-free patients (defined as Engel class I) occurred after temporal resection. Similarly, Hildebrandt *et al*. (2005) reported the greatest seizure freedom in patients with temporal resection (64%). However, Eriksson *et al*. (1999) reported hemispherectomy as the procedure with the highest percentage of seizure-free patients (75%).

In comparison to data of series from other developing countries, our seizure freedom outcome was better than that reported in one series of 17 patients in India, where excellent seizure outcome (seizure-free or having only auras) was reported in seven patients (41%) following anterior temporal lobectomy (ATL) (Sylaja *et al*., 2004), but similar to that reported (64.1%) in another larger series of 87 children from the same country (Jayalakshmi *et al*., 2011). The outcome of seizure freedom reported here was also similar to that reported in Uganda, where 6 of 10 patients were seizure-free following surgery from intractable temporal epilepsy (Boling *et al*., 2009) and lower than that reported in Chile, where 15 of 17 patients (88.24%) had Engel class I outcome (Campos *et al*., 2000). Obviously, such comparisons are limited by selection criteria and referral patterns which are likely to differ between different centres in different countries.

In our study, MTS was the most common aetiology in patients having epilepsy surgery. Eriksson *et al*. (1999) found that the majority of patients included in their study had at least one type of atrophic-gliotic lesion (84.2 and 74.4% for children and adults, respectively) and reported parenchymal malformation in 56.1% of children and 23.1% of adults. Similar to us, Hildebrandt *et al*. (2005) reported hippocampal sclerosis as the most common aetiology (48%), followed by tumours (22%), and focal cortical dysplasia (16%). Wyllie *et al*. (1998) found tumours to be the most common cause (37%), followed by cortical dysplasia (26%), hippocampal sclerosis (15%), and other aetiologies (22%) in children and adolescents who had undergone resective surgery.

In our study, the number of AEDs before surgery was the only presurgical variable that was negatively associated with seizure freedom (Engel class I outcome). This is a relatively novel prognostic indicator and is worth noting. The most likely reason for this association is that the more refractory the epilepsy, the greater the number of AEDs likely to be used before surgery and the less likely the response will be to surgery due to the severity of the condition. In the study of Alfstad *et al*. (2011), univariate analysis indicated that, of the preoperative factors, a high number of AEDs (≥6) used prior to surgery and

female gender predicted long-term poor seizure outcome after epilepsy surgery. However, significance in the multivariate analysis was only retained with gender.

Similar to our study, other studies did not find an association between seizure outcome following surgery and age at surgery (Armon *et al.*, 1996; Khoury *et al.*, 2005), tumour on MRI, preoperative seizure frequency (Khoury *et al.*, 2005), or type of surgery (Armon *et al.*, 1996). However, other studies identified different prognostic factors associated with epilepsy surgery outcome. The presence of MTS based on postsurgical pathological analysis, a known underlying aetiology, and partial seizures only were identified as predictors of good outcome (seizure-free for one year since discharge) and when combined together, it was possible to predict a seizure freedom of almost 100% after temporal and extratemporal surgery with these three factors (Berg *et al.*, 1998). Age of $\leq$5 years and presence of MTS on MRI were associated with rare seizures ($\leq$2 per year) after ATL, while preoperative seizure frequency of $\geq$20 seizures/month was associated with frequent seizures ($\geq$12 per year) in patients after non-ATL surgery (Khoury *et al.*, 2005). Antecedent history of febrile seizures, strictly unilateral anterior temporal interictal epileptiform discharges, and a concordant type 1 ictal EEG pattern were reported as predictors of excellent outcome (seizure-free or having only auras) following ATL (Sylaja *et al.*, 2004). Spencer *et al.* (2005) found that absence of GTC seizures and presence of hippocampal atrophy on presurgical MRI were associated with a two-year remission following medial temporal lobe resection. Daniel and Chandy (1999) found that intellectual disability, focal EEG abnormality restricted to the area planned for resection, and post-excision electrocorticography predicted good outcome (Engel class I and II) in patients with temporal lobectomy, hemispherectomy, and multifocal surgery. Armon *et al.* (1996) reported that the percentage of epileptiform EEG abnormalities arising from the site of resection and either imaging localisation or lack of use of invasive monitoring were significant predictors of seizure freedom including auras, at two years after temporal or extratemporal epilepsy surgery. Elsharkawy *et al.* (2008) reported that the presence of well-circumscribed lesions (neoplastic, vascular and cystic lesions) on preoperative MRI predicted a positive outcome (Engel class I outcome) after extratemporal resection. Binder *et al.* (2008) found that early age at epilepsy manifestation and shorter epilepsy duration were predictive of good outcomes (Engel class I and II), while shorter epilepsy duration and female gender were associated with Engel class I outcome following occipital lobe epilepsy surgery. Ferrier *et al.* (1999) reported that the presence of focal abnormality on neuroimaging was associated with Engel class I or II outcome, whereas contralateral head version was associated with Engel class III or IV outcome following frontal lobe epilepsy surgery.

The fact that the previously described prognostic factors were used for patient selection of candidacy for epilepsy combined with the potential presence of a ceiling effect (most of our patients had multiple good prognostic factors) could potentially account for our failure to replicate the previous results regarding prognostic factors since there was little variability of these factors in our patients.

Costs of epilepsy surgery

In Lebanon, the break-even time after epilepsy surgery has been estimated to be at five years. After five years of follow-up, the total average cost for an epilepsy resective surgical procedure in 1996 was 22,000 USD, whereas the total average cost of drug therapy without surgery was 29,000 USD (Darazi and Mikati, 1997). This difference becomes much larger over longer periods, as more patients become seizure-free after epilepsy surgery while the medically treated patients continue to require expensive care.

However, because the costs of epilepsy surgery have to be provided within a short period of time rather than over several years, many patients find they cannot afford the cost of presurgical evaluation and surgery. In Lebanon, as in most countries in the world, the costs of epilepsy surgery exceed the financial capabilities of most of the patients. It has been our experience in Lebanon that neither insurance companies nor governmental organisations readily cover the costs of the presurgical evaluation or epilepsy surgery. The apparent reasons why patients are not given financial coverage by their third party payers are: 1) the erroneous presumption that epilepsy is a congenital disorder; this presumption is used to deny patients coverage on the pretext that their policy excludes congenital disorders; 2) the higher short-term costs of epilepsy surgery relative to the initial costs of drugs; and 3) the neglect of the fact that there are increased costs associated with ongoing intractable epilepsy when surgery is not implemented (employment and quality of life). Because third party payers are concerned with the immediate costs, financial coverage for epilepsy surgery and workup is denied in order to save money. However, as discussed above, in the long term and with continued drug therapy, epilepsy surgery is more cost effective than drug therapy. Continued efforts to raise awareness about the nature of epilepsy and the cost effectiveness of epilepsy surgery compared to drug therapy should hopefully convince governments and insurance companies to better cover epilepsy surgery costs. □

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