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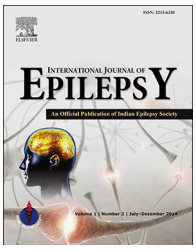

Original Article

Predictors of outcome of surgery in adults with mesial lesional temporal lobe epilepsy

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ABSTRACT

Background: We report the clinical characteristics and outcome of epilepsy surgery in adult patients with intractable epilepsy due to isolated lesional temporal lobe epilepsy (TLE).
Methods: Retrospective analysis of clinical and outcome characteristics in 47 consecutive adult patients with intractable epilepsy due to isolated lesional TLE who underwent epilepsy surgery from November 2009 to January 2015 was done to predictors of outcome.
Results: The mean age at surgery of the study population was 30.74 ± 10.85 years with 20 (43.5%) women. While the average age at onset of epilepsy was 20.12 ± 12.52 years, average duration of epilepsy was 10.78 ± 7.96 years. Favourable Engels outcome was observed in 39 (84.8%) of the patients. Findings on histopathology reported glioma in 24 (52.0%) of the patients. On comparing patients with favourable outcome ($n = 39$) with those with unfavourable outcome ($n = 7$), age at surgery was significantly higher in patients with unfavourable outcome (40.14 ± 11.69 years vs 29.05 ± 9.92 years; $p = 0.011$). Higher percentage of patients with unfavourable outcome scored poor on pre-surgical IQ tests (42.9% vs 7.7%; $p = 0.037$). On further analysis for predictors of outcome, age at surgery (β = 0.858; 95% CI 0.738–0.997) significantly predicts outcome (β = 1.166; 95% CI 0.931–1.461; $p = 0.182$), whereas pre-surgical poor IQ showed a trend towards being associated with unfavourable outcome (β = 0.079; 95% CI 0.005–1.287; $p = 0.075$).
Conclusion: Surgery for intractable epilepsy due to isolated lesional TLE has favourable outcome in vast majority (84.8%) of carefully selected patients. Age at surgery predicts outcome in these patients.

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1. Introduction

Epilepsy is a common neurological disorder with an estimated incidence of up to 1% of worldwide population.[1] Nearly 60% of all patients with epilepsy have focal seizures and with a majority of them affected by temporal lobe epilepsy (TLE).[2] Epilepsy is termed intractable when it is disabling and is not controlled with standard therapies. Despite major advances in therapeutics over years, one-third of patients with focal epilepsy become medically intractable.[2] The effects of chronic intractable epilepsy include cognitive and behavioural decline with increased rates of accidents.[3] Approximately half of the patients with intractable focal epilepsy can benefit from surgical treatment.[3] When carefully selected, epilepsy surgery improves quality of life and reduces costs of medical care[4] in 70–90% of the patients by controlling seizures.[5]

Structural lesions are reported in 30% of the surgical specimens resected in intractable TLE.[6] However, the structural lesion does not always localize the epileptogenic zone. Therefore, comprehensive pre-surgical evaluation involving clinical features, semiology, MRI brain for structural lesion and electrodiagnostics like electroencephalogram (EEG) are mandatory for a good post-surgical seizure control.[7] Bancaud and Talairach[8] in 1965 suggested an ''anatomo-electro-clinical'' correlation of pre-surgical evaluation in patients undergoing epilepsy surgery, which was developed further by their successors.[9] Since the goal of epilepsy surgery in patients with intractable TLE is seizure freedom, various surgical strategies like lesionectomy alone or in conjunction with removal of mesiotemporal structures are often performed.

Despite tailored pre-surgical assessment and favourable outcome, surgery for epilepsy remains under-used. This under-utilization of epilepsy surgery is perhaps due to lack of sufficient data from randomized clinical trials, fear of morbidity, increased confidence of physicians in new anti-epileptic drugs (AEDs) and vagal nerve stimulation.[10] However, Weise et al., in a randomized control study, showed that surgery is superior to prolonged medical management both in terms of efficacy and safety.[11] These findings reported from western population may have important implications in developing countries. Sastri et al. have reported excellent seizure-free outcome in a carefully selected cohort of Indian patients with mesiotemporal seizures with refractory epilepsy where the presence of dual pathology did not influence the outcome.[12]

Emphasis is often laid on mesiotemporal epilepsy[13] despite compelling evidence suggesting that 30–71% of the specimens from neuropathological series of patients undergoing surgery for TLE have focal lesions other than hippocampal sclerosis.[14,15] In the current study, we report the clinical characteristics and outcome of epilepsy surgery in 47 consecutive adult patients with intractable epilepsy due to isolated lesional TLE.

2. Methods

2.1. Patient population

From November 2009 to January 2015, a total of 288 TLE surgeries were done in adults at Krishna Institute of Medical Sciences, Secunderabad, a tertiary referral care centre with a dedicated Epilepsy Surgery Program. Of the 288 TLE surgeries performed during the study period, lesionectomy for isolated temporal lobe lesions was done in 49 patients. Two patients were excluded due to loss of follow-up, resulting in 47 patients who formed the study population.

2.2. Pre-surgical evaluation

Pre-surgical evaluation and surgery were performed after the necessary consent of the patient and/or the parent was obtained. The pre-surgical evaluation included variables such as age, gender, aetiology, semiology, age of onset of epilepsy, type and frequency of seizures, febrile convulsions and clinical findings of neurological examination.

Imaging of brain was done with 1.5 and/or 3Tesla MRI. All the patients underwent prolonged video-EEG (VEEG) monitoring and at least two seizures were recorded. Inter-ictal spikes were grouped as unilateral (>75% on the ipsilateral side of the imaging abnormality) and bilateral/multifocal. The ictal EEG patterns were classified as follows: focal—activity maximal at a single electrode with no more than two contiguous electrodes within 80–100% of the maximal activity; regional—activity involving electrodes overlying a single lobe having a 2:1 or greater amplitude predominance than that seen over other regions of the same hemisphere; hemispherical—lateralized activity involving multiple electrodes over multiple lobes of a single hemisphere having a 2:1 or greater amplitude predominance than that seen over the contralateral hemisphere; generalized—activity involving multiple electrodes over both cerebral hemispheres having a less than 2:1 amplitude predominance of one side over other. Ictal single photon emission computed tomography (SPECT) and inter-ictal fluorodeoxy-D-glucose positron emission tomography (FDG PET) were performed in selected patients.

Neuropsychological tests done were: tests for intelligence, complex figure test for visual memory, Rey auditory verbal learning test for verbal memory, block design test for visuospatial functions, visuoconstructional test, object assembly test for visual integration and montreal handedness test. For quality of life, QOLIE-31 was used; psychiatric and behavioural disorders were assessed according to clinical interview and diagnosed with reference to ICD-10 classification for mental and behavioural disorders.

2.3. Surgery

All the patients underwent lesionectomy guided by electrocorticography (ECoG). Reduction of more than 80% of spikes during intra-operative ECoG was considered adequate to decide the extent of resection during surgery. Resection of the mesial structures, namely hippocampus, amygdale, uncus and para hippocampal gyrus, was done if these structures were involved by the lesion. The entire surgical specimen was reviewed by a pathologist trained in epilepsy pathology. In addition to routine stains, immunohistochemistry (IHC) was performed as required.

2.4. Post-surgical evaluation and outcome

Data on post-surgical clinical course included acute post-operative seizures (APOS), memory disturbances, visual field defects, motor weakness and the number of AEDs required at follow-up. Furthermore, patients at last follow-up were assigned into two categories of Engels[16] classification (favourable and unfavourable) based on post-operative seizure status. Engels Class I and IIA were classified as favourable outcome and the rest as unfavourable outcome.

2.5. Statistical analysis

After confirming the homogeneity of the data, the study population was divided into two groups based on outcome. All continuous variables are expressed as mean ± standard deviation and the differences between continuous variables were analysed using independent student *t*-test. Categorical data are presented as frequency or percentages and the difference for categorical variables was analysed using chi-square test. Variables that were significantly different between the groups were included in a logistic regression model to help evaluate predictors of outcome. A $p \leq 0.05$ was considered significant. All data analysis was done using statistical package for social sciences (SPSS) version 17.0 for windows, IBM Computers, New York, USA.

3. Results

The mean age at surgery of the study population was 30.74 ± 10.85 years with 20 (43.5%) women. While the average age at onset of epilepsy was 20.12 ± 12.52 years, average duration of epilepsy was 10.78 ± 7.96 years and mean number of AEDs was 3.84 ± 1.87. Co-existing developmental delays were observed in 16 (34.8%) patients. While 3 (6.5%) patients presented with febrile convulsions, 13 (28.3%) reported aura. The clinical and demographic characteristics of the study population are summarized in Table 1. The inter-ictal spikes were unilateral in 39, bilateral in 6 and contralateral in 2 patients. Ictal EEG onset was lateralized in 39 patients while generalized in 5 and contralateral ictal EEG onset was noted in 3 patients. Resection of mesial temporal structures with lesionectomy was performed in 12 patients while isolated lesionectomy was done in the rest. Findings on histopathology reported low grade glioma (LGG) in 12 (25.5%) of the patients, followed by FCDs in eight (17.0%), cavernoma in six, gliosis in five, ganglioglioma in four and DNET in three patients, as summarized in Fig. 1. Favourable Engels outcome was observed in 39 (82.9%), with Engels outcome I observed in 35 and IIA observed in four patients, whereas in eight patients with unfavourable Engel's outcome, IIB and III grade were observed in four patients each.

3.1. Clinical characteristics

On comparing patients with favourable outcome ($n = 39$) with those with unfavourable outcome ($n = 8$), age at surgery was significantly higher in patients with unfavourable outcome (40.14 ± 11.69 years vs 29.05 ± 9.92 years; $p = 0.011$). There was no difference between the groups for number of women (28.6% vs 46.2%; $p = 0.446$). Similarly, there were no differences between the groups for those with a clear cut aura before the seizure (14.3% vs 30.8%; $p = 0.654$). However, higher percentage of patients with unfavourable outcome scored poor on pre-surgical IQ tests (42.9% vs 7.7%; $p = 0.037$). On the contrary, there were no differences between the groups for number of patients with concordant inter-ictal EEG (85.7% vs 84.6%; $p = 1.000$) and ictal EEG (100.0% vs 79.5%; $p = 0.325$). The differences between groups for pre-surgical clinical and demographic characteristics are summarized in Table 2.

3.2. Clinical course and outcome

At the last follow-up, 39 (82.9%) patients had Engel's favourable outcome. Two (4.3%) patients had transient hemiplegia post-surgery which recovered during subsequent follow-up. Post-surgery visual field defects were observed in 13 (28.3%) patients. One patient had symptomatic hemianopia in the immediate post-surgery period and improved by 1 year, while all other patients had asymptomatic quadrantanopia which was noted immediately post-surgery, persisting even at one year follow-up. Acute post-operative seizures were reported in 3 (6.5%) patients and memory disturbances were observed in one each. The average number of AEDs required post-surgery follow-up at last follow-up was 2.39 ± 0.75. On comparing patients with favourable outcome with those with unfavourable outcome, there were no differences between the groups for post-surgery APOS (0.0% vs 7.7%; $p = 1.000$), as summarized in Table 2. Among 20 patients who underwent lesionectomy alone, seventeen (85.0%) patients had favourable Engel's outcome, similar to rest of the patients (81.5%) who underwent lesionectomy with ATLAH.

Table 1 – Demographic and clinical characteristics of the study population ($n = 47$).

S. No.	Variable	Frequency/mean ± SD
1	Age at surgery in years (range)	30.74 ± 10.85 (19–61)
2	Age of onset of epilepsy in years (range)	20.10 ± 12.52 (1–62)
3	Duration of epilepsy in years (range)	10.78 ± 7.96 (0–38)
4	Number of women (%)	20 (43.5%)
5	Family history of epilepsy (%)	5 (10.9%)
6	History of childhood insult (%)	2 (4.3%)
7	Co-existing developmental delay (%)	16 (34.8%)
8	Febrile convulsions (%)	3 (6.5%)
9	Aura (%)	13 (28.3%)
10	Secondary generalized seizures (%)	17 (37.0%)
11	IQ < 75 (%)	6 (13.0%)
12	Co-existing psychiatric disorders (%)	21 (45.7%)
13	History of status epilepticus (%)	2 (4.3%)
14	Average number of AEDs prior to surgery (range)	3.84 ± 1.87 (1–6)

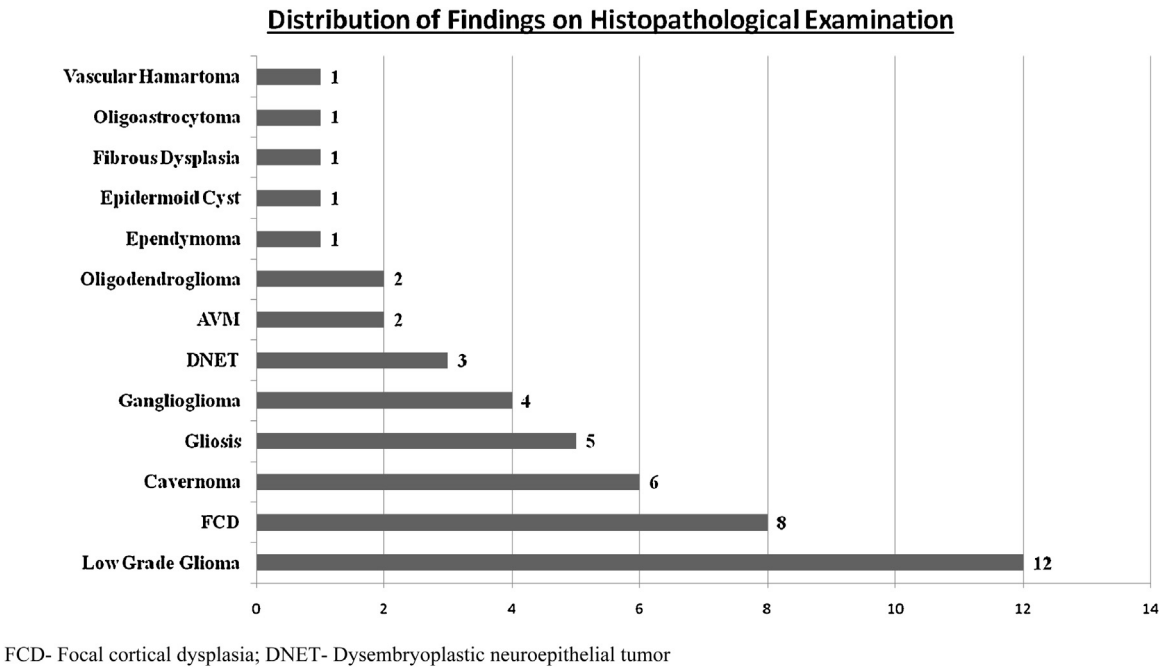

Fig. 1 – Findings on histopathology ($n = 47$). FCD, focal cortical dysplasia; DNET, dysembryoplastic neuroepithelial tumour.

On further analysis for predictors of outcome, age at surgery ($\beta = 0.858$; 95% CI 0.738–0.997) significantly predicts unfavourable outcome, whereas pre-surgical poor IQ showed a trend towards being associated with unfavourable outcome ($\beta = 0.079$; 95% CI 0.005–1.287; $p = 0.075$).

4. Discussion

In the current study, we report our single centre experience of TLE surgeries on isolated lesions. Our observations are

Table 2 – Comparison between study population with favourable outcome ($n = 39$) vs unfavourable outcome ($n = 8$).

S. No.	Variable	Unfavourable outcome ($n = 8$)	Favourable outcome ($n = 39$)	P value
1	Age at surgery (years)	40.14 ± 11.69	29.05 ± 9.92	0.011
2	Age of onset of epilepsy (years)	23.71 ± 14.08	19.45 ± 12.31	0.413
3	Duration of epilepsy (years)	16.61 ± 11.45	9.73 ± 6.85	0.034
4	Duration of epilepsy >10 years (%)	6 (85.7%)	14 (35.9%)	0.033
5	Women (%)	2 (28.6%)	18 (46.2)	0.446
6	Family history of epilepsy (%)	1 (14.3%)	4 (10.3%)	1.000
7	History of childhood insult (%)	1 (14.3%)	1 (2.6%)	0.284
8	Co-existing developmental delay (%)	2 (28.6%)	14 (35.9%)	1.000
9	Febrile convulsions (%)	0 (0.0%)	3 (7.7%)	1.000
10	Aura (%)	1 (14.3%)	12 (30.8%)	0.654
11	Secondary generalized seizures (%)	3 (42.9%)	14 (35.9%)	1.000
12	IQ < 75 (%)	3 (42.9%)	3 (7.7%)	0.037
13	Co-existing psychiatric disorders (%)	2 (28.6%)	19 (48.7%)	0.428
14	History of status epilepticus (%)	0 (0.0%)	2 (5.1%)	1.000
15	Number of AEDs pre-surgery (%)	3.29 ± 1.11	3.95 ± 1.52	0.281
16	Glioma on histopathology (%)	2 (28.6%)	22 (56.4%)	0.234
17	Gliosis on histopathology (%)	0 (0.0%)	3 (7.7%)	1.000
18	Cavernoma histopathology (%)	1 (14.3%)	6 (15.4%)	1.000
19	FCD on histopathology (%)	3 (42.9%)	6 (15.4%)	0.123
20	Dysembryoplastic neuroepithelial tumour on histopathology (%)	1 (14.3%)	2 (5.9%)	0.398
21	Post-surgery visual field defect at 1 year (<quadrantanopia) (%)	0 (0.0%)	13 (33.3%)	0.166
22	Post-surgery transient hemiparesis (%)	0 (0.0%)	2 (5.2%)	1.000
23	Acute post-operative seizures (%)	0 (0.0%)	3 (7.7%)	1.000
24	Number of AEDs post-surgery (%)	2.43 ± 0.53	2.38 ± 0.79	0.874

consistent with studies previously reported in western population where higher age at surgery was predictive of unfavourable outcome in these patients.

There are few studies about clinical outcome in patients undergoing surgery for lesional mesial TLE which is a different clinical entity from mesial temporal sclerosis (MTS).[17,18] The reported incidence of lesional mesial TLE is up to 38% of all TLE.[19,20] Variations in the reported frequencies may be due to differences in patient selection.[21] Mesiotemporal lesions is also a less recognized subgroup of TLE where Hennessy et al described only five (6.3%) of the eighty specimens available.[19] In the current study, we observed mesiotemporal lesions in 49 (17.0%) of the 288 patients who underwent surgery for TLE. The reported lower incidence of lesional mesial TLE patients in the current study may be due to our inclusion criteria where only patients with refractory epilepsy due to mesial temporal lesions and who underwent surgery were included; there may be others who did not undergo surgery due to well-controlled epilepsy or socio-economic constraints. Though desirable, it was not the aim of the current study to understand the differences in the prevalence of TLE.

In our study population, only three patients (6.5%) presented with history of febrile convulsions; this is similar to 6.8% reported by Clusmann et al.,[22] who attributed the lower prevalence to differences in subtypes of TLE. The mean age of onset of seizure of 20 years in our study is similar to that previously reported by studies on patients with TLE.[19,22] Furthermore, Clusmann et al.[22] reported that age greater than ten years at onset of seizures is associated with outcome. In the current study, we report that age at onset predicts outcome. This may be attributed to our findings that more number of patients with unfavourable outcome had duration of seizure greater than ten years. Similarly, we also report that a higher percentage of patients with unfavourable outcome have scored poor on pre-surgical IQ assessment. However, poor pre-surgical IQ was not a predictor of outcome probably due to a small study population.

In the current study, no difference was noted for outcome between different histopathological diagnoses. It is widely accepted that success rate for malformations like cortical dysplasias is lower than other aetiologies because of the widespread changes observed in the architecture of the cortex in patients with dysplasias.[23] In the current study, though not statistically significant, three of the seven patients with unfavourable outcome were diagnosed on FCDs. The favourable outcome (84.8%) in the current study is similar to the 86.5% reported by Clusmann et al.[22] There is very little literature on outcome of TLE lesional surgery from studies done exclusively in patients with lesional mesial TLE. Comparison of success rates with the existing studies is difficult due to variations in methods of patient selection, outcome scales used and duration of follow-up.[22] Favourable outcome reported in 2 out 3 patients with DNET in the current study is similar to the 12 out of 16 patients reported by Raymond et al.[24]

4.1. *Strengths and limitations*

The current study is one of the very few done on exclusive patients with lesional mesial TLE who have undergone epilepsy surgery in India. Caution must be executed in the interpretation of the findings and most of the statistical analysis is univariate in a small study population. Future randomized studies may be required to evaluate the clinical applicability and consistency of our findings. Though randomized trials are desirable, lesional mesial TLE is relatively small subgroup of TLE patients. Encouragingly, surgical procedures applied in our study appeared to be safe with results comparable to international reports.

5. Conclusion

Surgery for intractable epilepsy due to isolated lesional TLE has favourable outcome in vast majority (84.8%) of carefully selected patients. Age at surgery is a predictor of outcome in these patients.

Author contribution

Sita Jayalakshmi – Study design and critical review of manuscript, Sudhindra Vooturi – Data analysis, Rammohan Vadapalli – Data collection and review, Shanmukhi Somayajula – Data collection, manuscript writing and review, Sailaja Madigubba – Data collection and manuscript writing, Manas Panigrahi – Study design and critical review of manuscript.

Conflicts of interest

The author has none to declare.

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