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Clinico-pathological factors influencing surgical outcome in drug resistant epilepsy secondary to mesial temporal sclerosis

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ABSTRACT

Background: Mesial temporal sclerosis (MTS) is the most common cause of drug resistant epilepsy amenable for surgical treatment and seizure control.
Methods: This study analyzed the outcome of patients with MTS following anterior temporal lobectomy and amygdalohippocampectomy (ATL-AH) over 10 years and correlated the electrophysiological and radiological factors with the post operative seizure outcome.
Results: Eighty seven patients were included in the study. Sixty seven (77.2%) patients had an Engel Class 1 outcome, 9 (11.4%) had Class 2 outcome. Engel's class 1 outcome was achieved in 89.9% at 1 year, while it reduced slightly to 81.9% at 2 years and 76.2% at 5 year follow up. Seventy seven (88.5%) patients had evidence of hippocampal sclerosis on histopathology. Dual pathology was observed in 19 of 77 specimens with hippocampal sclerosis, but did not influence the outcome. Factors associated with an unfavorable outcome included male gender ($p = 0.04$), and a higher frequency of pre-operative seizures ($p = 0.005$), whereas the presence of febrile seizures ($p = 0.048$) and loss of hippocampal neurons in CA4 region on histopathology ($p = 0.040$) were associated with favorable outcome. The effect of CA4 loss on outcome is probably influenced by neuronal loss in other subfields as well since isolated CA4 loss was rare. Abnormal post operative EEG at the end of 1 week was found to be a significant factor predicting unfavorable outcome ($p = 0.005$). On multivariate analysis, the pre-operative seizure frequency was the only significant factor affecting outcome.
Conclusions: The present study observed excellent seizure free outcome in a carefully selected cohort of patients with MTS with refractory epilepsy. The presence of dual pathology did not influence the outcome.

1. Introduction

The syndrome of mesial temporal sclerosis (MTS) is the most common indication for surgical treatment of refractory epilepsy [1]. The results of surgery in such patients are encouraging with over two thirds showing improvement in seizure control following resection. In India, about 450,000 patients will be potential candidates for epilepsy surgery [2]. Approximately 60–70% of these patients have MTS [2]. While several clinical studies report good outcomes in this cohort of patients with MTS, there is difficulty in comparing these studies due to variability in several parameters including duration of follow up, and temporal profile of seizure remission [3–23]. Literature abounds with several clinical studies evaluating outcome in these patients with MTS, but there is a paucity of studies that address pathological factors affecting outcome of surgery for temporal lobe epilepsy (TLE).

We reviewed all patients with medically refractory epilepsy secondary to MTS who were surgically treated at our center to identify the various clinical and pathological factors, if any, which influenced the outcome in this cohort.

2. Materials and methods

This retrospective study evaluated 87 patients who underwent surgical treatment for refractory epilepsy secondary to MTS between 1998 and 2008. They were recruited and underwent evaluation in the 'Refractory Epilepsy Clinic' at the National Institute of Mental Health and Neurosciences (NIMHANS) Bangalore, for drug resistant TLE. The study was approved by the institutional ethics committee.

The clinical data was collated after review of the medical records of the patients. This included the age of onset of epilepsy, duration and

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semiology, history of febrile convulsions, birth injury and family history of epilepsy. A comprehensive presurgical evaluation included serial 10–20 scalp EEG recording, video EEG for confirming the localization and the semiology of seizure, MRI with specific protocol for complex partial seizures along with volumetry in relevant cases, detailed neuropsychological evaluation and other routine blood hemogram and biochemistry.

All patients were discussed in the weekly epilepsy conference and a decision for surgery was made after reviewing the clinical, electrophysiological and imaging data. All patients were subjected to standard anterior temporal lobectomy with amygdalohippocampectomy. The presurgical evaluation and surgery were carried in accordance with an established protocol developed as part of a 'Comprehensive Epilepsy Surgical Program'. The pathological specimens were reviewed by the neuropathologist blinded to the clinical data. All patients underwent a post operative EEG 1 week following surgery.

Patients were followed up at the Refractory Epilepsy Clinic at 3 month intervals. EEG and psychometry were performed at the end of 1 year following surgery according to protocol. Post surgical outcome indicating the class of seizure freedom, change in the dose of antiepileptic drugs, cognitive/neuropsychological change (if any), follow up EEG and neuropsychological assessment were noted. Postoperative seizure outcome was assessed according to Engel's outcome scale. Patients were also contacted via mail or telephonic interviews and their current status with respect to seizure control and antiepileptic drug dosages was ascertained.

The pathological specimens were reviewed by the neuropathologist as per the protocol outlined below. The resected temporal lobe and hippocampus were collected en bloc, fresh from the operation theater. The specimen was oriented anatomically using the subpial surface as a marker for the superior aspect and sliced serially in the coronal plane. The slices were examined serially for any grossly visible lesion and the cortical ribbon thickness examined for variation in thickness or grossly evident dysplasia. The hippocampus was sliced serially in the coronal plane and examined for any gross deformity and shrinkage.

Representative samples from the hippocampus and temporal lobectomy specimen were processed for paraffin embedding and histological sectioning. Two to three micrometer thick sections were stained with hematoxylin–eosin, cresyl violet and Luxol Fast blue (for myelin) and immunohistochemistry with antibodies to delineate neuronal (NeuN, 1:50, Millipore USA and phosphorylated neurofilament, 1:100, Nova Castra Labs, USA) and Glial alterations (GFAP, 1:500, Nova Castra labs, USA).

The histological sections were evaluated for dentate gyrus alterations, degree of neuronal loss in various subfields (CA1–4) of Ammon's horn, and astrocytosis and graded in accordance with Blumcke's grading system [24]. The temporal lobe was examined for the presence of cortical dysplasia or other dual pathology and classified in accordance with recent ILAE classification [24,25].

The clinical, electrophysiological, radiological and histopathological data was tabulated and correlated with seizure outcome to evaluate their effect, if any. Results were subjected to statistical analysis using SPSS v15.0. The statistical tests used were the Pearson's chi square, Mann–Whitney *U* test (non parametric data), and Student's *t* test (parametric data) for univariate analysis. Multivariate analysis was done using a binomial logistic regression model.

3. Results

3.1. Demographic, clinical and presurgical evaluation data

The age of the patients at the time of surgery ranged from 10 years to 49 years (mean age of 26.4 ± 8.68). Most of the patients belonged to the age group between 11 and 30 years. The male to female ratio was 1.35:1. Thirty seven patients (42.5%) had history of febrile seizures in their childhood, while four patients (4.6%) had history of perinatal insult (hypoxic-ischemic events at birth—2, neonatal jaundice—1, maternal febrile illness—1). Family history of seizure disorder in first degree relatives was recorded in 3 patients (3.4%). Cognitive decline on preoperative testing was noted in 9.2% ($n = 8$) of patients and concomitant psychiatric disorders on treatment were present in 3 patients (3.4%).

The age at seizure onset ranged from 1 to 29 years (mean 10.57 ± 6.0 years) with over half developing seizures in the first decade of life. The duration of seizures at the time of surgical intervention ranged from 2 years to 36 years (mean 15.68 ± 7.75 years, median 16 years). Seizure semiology was complex partial seizures in 55 (63.2%) and with secondary generalization in 32 patients. In 28 (32.2%) patients, there was a change in ictal semiology from initial generalized seizures to complex partial seizures during the course of the illness. Patients had been on treatment for varying periods of time prior to referral for surgery (range: 2–36 years, mean 15.68 ± 7.75 years) and received a minimum of two antiepileptic drugs. Most of the patients were on three or more antiepileptic drugs at the time of surgery, 47.1% had a seizure frequency of 1–3/month, 42.5% had seizure frequency of 1–6/week while 9.2% of patients had more than one seizure per day.

MRI and EEG data were concordant with the side of lateralization in 80 patients (92.0%). Of the seven patients with discordance, three underwent ictal and inter ictal SPECT to determine lateralization, while four underwent surgery according to the side of MRI lateralization. The results of presurgical evaluation and their utility in deciding the side of surgery is shown in Supplementary Table ST1.

Forty one patients underwent left sided surgery (47.1%) and 46 underwent right sided surgery. Intraoperative electrocorticography was performed in 21 patients (24.1%). Postoperative seizures were noted in 8 patients (9.2%) within the first week of surgery. There was no procedure related mortality in this series.

3.2. Pathology

Hippocampal sclerosis of varying degrees was detected in 77 of 87 patients. On application of Blumcke's grading system, MTS Type 1a was the most common (55.2%) (Fig. 1B), followed by MTS Type 2 (17.2%) (Fig. 1D), and MTS Type 1b (12.6%) (Fig. 1C) while Type 3 (3.4%) was the least common. In 10 patients (11.5%), no neuronal loss was detected in the hippocampus (Blumcke's grade 0) (Fig. 1A).

Evaluation of the dentate gyrus also revealed a spectrum of changes, ranging from normal (Fig. 2A) to patchy loss of neurons in 28 patients (32.1%) (Fig. 2B), ischemic change in 21 (24.1%), laminar duplication in eight (Fig. 2D), while two patients had meganeurons in the midst of normal granule cells. Granule cell dispersal of varying degrees was observed in 21 patients (24.6%) (Fig. 2C).Interestingly among the 77 cases of hippocampal sclerosis, additional pathological changes (dual pathology) were noted in the temporal lobe in 19 patients (24.68%), and included cortical laminar disorganization ($n = 5$) (Fig. 2F), cortical ectopia ($n = 4$), granule cell ectopia ($n = 1$) (Fig. 2G), and malformations of cortical development ($n = 8$). Neoplasm was detected only in one case in the form of dysembryoblastic neuroepithelial tumor (Fig. 3A–D).

In patients without evidence of hippocampal sclerosis (Blumcke's grade 0), the ischemic changes were noted in the hippocampal pyramidal neurons as well as in the temporal cortex. In four cases, scattered neurons were seen in the temporal while matter, indicating microdysgenesis.

3.3. Follow up and outcome

The overall follow up ranged from 0.3 to 129 months (median—37 months) post surgery. Three patients were lost for follow up immediately after discharge and 33 patients (38%) had a follow up of over 5 years.