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Surgery for "Long-term epilepsy associated tumors (LEATs)": Seizure outcome and its predictors

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ABSTRACT

Objectives: "Long-term epilepsy associated tumors (LEATs)" by definition are tumors primarily causing drug-resistant seizures for two years or more. They include low-grade glial and glioneuronal tumors with normal life expectancy. We studied a large cohort of patients with LEATs who underwent surgery through our epilepsy program.
Patients & methods: From 1998–2011, 105 patients with LEATs underwent surgery in our center. We utilized their data archived in a prospective registry to evaluate their electro-clinical-imaging characteristics affecting the long-term seizure outcome.
Results: Of 105 patients (age 3–50 years), mean age at surgery was 20 years and mean pre-surgical duration of epilepsy was 10.9 years. 66 (62.8%) had secondary generalized seizures. 82 had temporal tumors, 23 had extra temporal (13 frontal, 3 parietal, 2 occipital and 5 multilobar lesions) and four had associated hippocampal sclerosis. The interictal discharges and ictal onset were concordant to the lesion in 82 (78%) and 98 (93%) patients respectively. Lesionectomy and/or adjoining corticectomy or temporal lobectomy was done. Ganglioglioma was the most dominant pathological substrate in 61 (58%). During a mean follow-up of 7.5 years (range 3–16 years), 78/105 (74.2%) were seizure-free and 45 (57.4%) were totally off drugs. Secondary generalized seizures (p-0.02), temporal location of tumor (p-0.008) and spikes in third month post-operative EEG (p-0.03) caused unfavorable seizure outcome. A pre-surgical duration of epilepsy of more than 6.6 years caused less than optimal surgical outcome
Conclusions: Early surgery should be considered a priority in LEATs. Presence of secondary generalized seizures is the single most important predictor of a poor seizure outcome.

1. Introduction

The concept of "*long-term epilepsy associated tumor (LEAT)*" was introduced by Luyken et al. (2003) to denote tumors commonly encountered in surgical series of patients who have been investigated and treated for drug-resistant seizures for two years or more [1]. They differ from other primary brain tumors in that the patients manifest seizures at a young age, with epilepsy as the primary and only dominant symptom, their low growth potential and temporal lobe preponderance. It is now established that many of them exhibit similarities to focal cortical dysplasias (FCDs) in their cellular architecture and behavior. LEATs therefore strictly refer to low grade glial and glioneuronal tumors with refractory seizures [2–8] (Appendix A (Supplementary file). In studies which analyzed the pathologic findings in patients with drug resistant partial epilepsy, tumors constituted approximately 25–35% of the cases [3,9]. The incidence of epilepsy in these tumors varies between 30 and 100% and depends on the tumor type, with dysembryoplastic neuroepithelial tumor (DNETs) being the most epileptogenic (100%) [10]. Many, addressed the surgical treatment and outcome in tumor related chronic epilepsy [1,7,11–15]. Few including us earlier compiled ganglioglioma and dysembryoplastic neuroepithelial tumor alone since they are the most common and most epileptogenic [13,14,16].

We undertook this research with the following objectives: (1) to review the clinical, electroencephalographic (EEG), and radiological data of patients with LEATS who underwent surgery (2) to define the postoperative seizure outcome and factors that influence the

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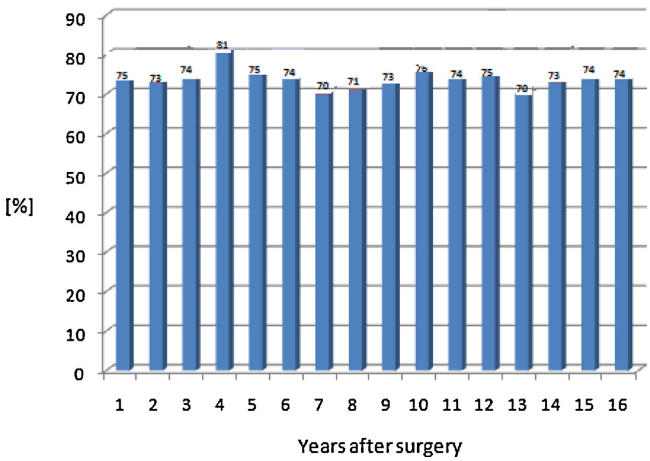

Fig. 1. Actuarial long-term seizure analysis from year to year from 1998 to 2011 showed a very stable number of patients (>70%) remaining seizure-free at all periods of follow-up for 14 years.

outcome. Most of the other series have combined all the tumors causing epilepsy with higher grades like WHO grade III with limited survival periods [1,15,17]. We have compared all the large series of LEATs in literature (Appendix B, Supplementary file).

2. Patients and methods

From March 1998 through March 2011, 105 patients with LEATs underwent surgery at our tertiary referral center for epilepsy care where, in the last one decade around 1600 resective surgeries were done. We selected patients whose surgical pathology revealed tumor as the substrate and is one among LEATs, who had drug-resistant seizures and have completed $\geq$3 years of postoperative follow-up. Institute Ethics Committee approved the study. We have described the details of our presurgical evaluation protocol including video-EEG earlier [18]. Neuropsychological test results were classified into concordant (when it was concordant to the side of the lesion resected) discordant or diffuse (when it was contralateral or diffuse to the lesion side). Any co-existing major or minor psychiatric illness was classified according to DSM-IV Axis I based on a structured clinical interview.

Two expert Neuroradiologists (CKD & BT) reviewed all preoperative MRI films to delineate the site, size, extent of tumor, contrast enhancement, calcification, cystic changes, mass effect, and associated hippocampal atrophy or sclerosis (MTS/HS) and dysplastic changes. We used collateral sulcus as the boundary between the medial and lateral location of the tumor in the temporal lobe. In extra temporal location, the tumors were noted to be either confined to one of the lobes (frontal, parietal or occipital) or multilobar when it extended beyond one lobe. A post-operative MRI was done for all patients after surgery at various periods of follow-up. Per-operative electrocorticography (ECoG) was performed in all patients except 12 of them. Post excision ECoG results were classified as (1) no or rare residual spikes and (2) persistent spiking (if the difference from pre resection ECoG spiking was less than 70% 3) inconclusive, when pre-resection ECoG had no spikes.

All surgeries were undertaken under general anesthesia by trained Neurosurgeons (MA&GV). When the lesion is confined to the limits of the collateral sulcus i.e. in the mesial temporal lobe, a lesionectomy encompassing amygdalohippocampectomy was undertaken. If lesion was in the language dominant hemisphere, functional MRI and/or Wada test was done to ascertain memory reserve on the opposite hemisphere. If lesion extended into mesial and lateral temporal region, a standard anterior temporal lobectomy with amygdalo hippocampectomy (ATL) was performed with 5–5.5 cm and 6–7 cm of lateral neocortical resection respectively on left and right sides. If the lesion was confined to the temporal neocortex or extra temporal locations in a single lobe, a lesionectomy alone was performed. We defined "completeness of resection" as complete removal of lesion as noted in post-operative MRI.

2.1. Pathological examination

Four-micrometer-thick histologic sections were generated from 10% formalin fixed, paraffin-embedded tissue and stained with hematoxylin and eosin (H&E) by a trained neuropathologist (NR). Special stains such as Cresyl violet, Bodian and Luxol fast blue-hematoxylin eosin and immunohistochemical stains such as Neurofilament protein (NFP), synaptophysin, epithelial membrane antigen(EMA), glial fibrillary acid protein (GFAP), Neu N, chromogranin (Novacastra, Newcastle upon Tyne,UK;1:100 dilution) etc were used regularly as and when indicated. Malformations of cortical development and FCD were noted and classified [19,20].

2.2. Outcome assessment

The following variables were assessed according to their importance in presurgical evaluation of refractory epilepsy-age at surgery, age at onset of habitual seizures, duration of epilepsy prior to surgery, history of initial precipitating injury (febrile seizures, meningoencephalitis or status epilepticus), secondary generalized seizures, concordant interictal epileptiform discharges (IEDs, >75% on the side of MRI abnormality/resected lobe), presence of spikes in post resection ECoG, discordant or diffuse neuropsychological variables, associated psychiatric co-morbidity, pathology, and presence of spikes in post-operative EEGs.

Patients were regularly followed up at 3 and 12 months after surgery and at yearly intervals thereafter. We categorized the post-operative seizure outcome as "excellent" if the patient remained seizure-free at all times of follow-up with or without antiepileptic drugs (AEDs), "good outcome" if they have gone into remission with or without AEDs in the last 2 years of follow-up ("favorable outcome") and the rest as "unfavorable outcome". The excellent and good outcome group was considered together for analysis as "seizure-free (category-1)" and the second group with relapse of any type of seizure as "treatment (surgical) failure"(category-2), this is as per the latest definition put forth by the Adhoc Task force of the ILAE Commission for any form of intervention for epilepsy [21]. Our protocol of tapering AEDs following surgery is as follows: all of them receive full dose of AEDs for 3 months following surgery. If the patient is remaining seizure-free and the post operative EEG is also normal, we start tapering the drugs-the second or third add-on drug is tapered first followed by reviewing the patient at the end of one year and yearly thereafter during which a planned, gradual withdrawal of one drug at a time is done based on the above said criteria of seizure freedom and normal EEG. A final discontinuation is tailored according to the individual patient.

3. Statistical methods

Quantitative data are summarized as mean ± standard deviation (SD). Categorical data are summarized as proportions and 95% confidence intervals. Pearson's Chi-square test, Fisher's exact test and Student's t-test were used to evaluate the statistical significance of the association of different clinical, EEG, MRI and histological characteristics with the seizure outcome at last follow-up. Continuous variables were analyzed by *t* test and categorical variables by Chi square test or Fisher's exact test. The level of statistical significance was set at p value < 0.05. Univariate logistic regression analysis was used to assess the prognostic importance of each of the above variables. The factors which attained significance in the univariate