Surgical treatment of medically refractory epilepsy

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The last two decades have witnessed remarkable advances in the evaluation and treatment of patients with refractory epilepsy. We now understand the natural history of epilepsy and the causes of medical refractoriness better. The improvement in the localization of the seizure focus through the advances in technology such as digital EEG, structural and functional neuroimaging and stereotactic placement of invasive electrodes have facilitated the selection of ideal surgical candidates and thereby have improved postoperative outcome. A recent randomized, controlled trial confirmed that the seizure outcome is far superior in surgically-treated refractory temporal lobe epilepsy patients when compared to those continued on medical treatment. Today, surgical treatment is certainly a cost-effective option in carefully selected patients with medically refractory partial epilepsy. Developing countries should concentrate on selectively utilizing the recent advances to evolve cost-effective epilepsy surgery programs. It is encouraging to note that more neurology centers in India and other developing nations are currently developing facilities for epilepsy surgery.

EPILEPSY constitutes a major public health problem both in developing and developed countries[1,2]. As many as 70–80% of persons with newly-diagnosed epilepsy will eventually achieve remission, a majority of them within two years of the onset of epilepsy[3]. About 20–30% of persons developing epilepsy continue to exhibit chronic recurrent seizures despite optimal treatment with antiepileptic drugs (AEDs)[4]. Medically refractory epilepsy represents a challenge for both experimental and clinical researchers. The last two decades have witnessed remarkable advances in the evaluation and treatment of patients with refractory epilepsy[5]. Surgical treatment is an option in selected patients with medically refractory epilepsy[6].

During the last six years, the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala, has developed a comprehensive program for the evaluation and management of persons with medically refractory epilepsy through the R. Madhavan Nayar Center for Comprehensive Epilepsy Care. Three hundred and fifty patients have been operated for refractory epilepsy from March 1995 through June 2001. The book titled *Medically Refractory Epilepsy*, the first comprehensive largely Indian compilation on this subject[7], was published in 1999. *Epilepsia*, the official journal of the International League Against Epilepsy, has recently brought out a supplement on epilepsy surgery in developing countries[8]. In this essay, we intend to discuss the etiopathogenesis of medical refractoriness and elaborate on the evaluation and surgical treatment of persons with medically refractory epilepsy.

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Definition of refractory epilepsy

Refractoriness is inevitably an arbitrary decision. The spectrum of refractory epilepsies is wide, ranging from patients with only mild resistance to sub-optimal AED therapy to patients with long-standing disabling epilepsy unresponsive to treatment with several AEDs. The causes of pseudorefractoriness due to diagnostic error and inadequate treatment should be considered and excluded in every patient with a poorly-controlled seizure disorder. The diagnosis of epilepsy should be unequivocally established. Unresponsiveness to AEDs should not be due to inadequate dosage, inappropriate choice of drugs or drug combinations or due to poor compliance, or due to psychological or social factors. A frequent finding in refractory epilepsy is that, although many drugs have been used, none were given for sufficiently long periods, either alone or in proper combinations. Noncompliance is a common cause of pseudorefractoriness; as many as 30% to 50% of the patients with chronic epilepsy comply poorly with their prescribed medications and lifestyle modifications[9]. Effective doctor–patient communication and counseling have been shown to improve compliance[10,11].

Patients who continue to exhibit uncontrolled seizures or those who develop intolerable side effects that interfere with their quality of life, despite maximally tolerated trials of one or more AEDs are considered to have medically refractory epilepsy. For how long the patient should have uncontrolled seizures or what should be the frequency of seizures to designate intractability varies from patient to patient. Patient's expectation, the degree of disability due to seizures and AED toxicity, aversion to AED intake, and other factors such as employment, marriage and difficulty to obtain driv-

ing license have to be considered in the decision-making process. In general, patients who continue to exhibit one or more disabling seizures per month for a period of two years or more despite supervised trials (six months each), twice with a single AED and once with a combination of two AEDs are candidates for detailed evaluation in a comprehensive epilepsy care program[7]. Patients could also be surgically refractory because of the impossibility to localize or remove the epileptogenic area, or when surgery has failed to control the seizures.

Magnitude of the problem

The magnitude of the problem of refractory epilepsy in most of the developing countries, including India, is unknown. Epidemiological studies from India[12–14] have revealed that epilepsy occurs with a prevalence rate of ~ 5/1000 and incidence of ~ 50/100,000/year. Assuming that 20% of patients with active epilepsy would be resistant to AED treatment, among the nearly one billion population of India, there would be about one million people with medically refractory epilepsy. There will be nearly 30,000 medically refractory epilepsy patients in Kerala (30 million population), of them, 600 patients will be residing in the city of Thiruvananthapuram (600,000 population). Nearly half of the patients with refractory epilepsy would be potential candidates for epilepsy surgery. There will be over 300 potential candidates for epilepsy surgery in the Thiruvananthapuram city itself, to which about 30 new patients will be added every year.

Causes of medical refractoriness

Epilepsy is a collection of syndromes and conditions of widely variable prognosis[3,15]. Evidence from multiple sources regarding the natural history of epilepsy in humans has repeatedly demonstrated that in most cases the occurrence of seizures itself does not influence the long-term outcome of epilepsy[3,16]. It is the underlying epileptic syndrome that primarily determines the prognosis. AED therapy, although very effective in controlling seizures, probably does not prevent the development of chronic epilepsy[17].

Certain factors are well-known predictors of resistance to AED treatment such as onset in infancy, organic brain damage (mental retardation and neurological signs), seizure type(s) (tonic, atonic and myoclonic seizures), multiple seizure types, high seizure frequency, long duration of uncontrolled seizures, failure of past AED treatments and an abnormal electroencephalogram (EEG). Most of these factors are especially relevant in predicting the prognosis of childhood epilepsy syndromes[18].

Surgically remediable lesional epilepsy syndromes

A recent advance in the treatment for epilepsy is the recognition that among the medically refractory patients is identifiable subgroups, which have surgically remediable syndromes[4,5,7] (Table 1). These syndromes have a well-defined pathophysiology and natural history, can be usually identified by noninvasive diagnostic methods, and are resistant to AED therapy, but have a high rate of surgical cure[5].

Temporal lobe epilepsy is the commonest form of localization-related epilepsy and nearly 80% of epilepsy surgery involves the temporal lobe[6,7]. In a recent study of 2200 tertiary referral center-based epilepsy patients, aged 16 years and older, among the 74% of the patients who had localization-related epilepsies, 66% had temporal lobe epilepsy[19]. The International Classification of Epilepsies and Epilepsy Syndromes[15] distinguishes between mesio-basal (mesial) temporal lobe epilepsy and lateral (neocortical) temporal lobe epilepsy. Mesial temporal lobe epilepsy, the form of temporal lobe epilepsy associated with mesial temporal lobe sclerosis (Figure 1), is the most medically refractory surgically remediable lesional adult epilepsy syndrome[4,19]. Among the first 100 consecutive temporal lobe epilepsy patients who underwent temporal lobectomy in SCTIMST for medically refractory epilepsy, histopathological evidence for mesial temporal lobe sclerosis was detected in 79% of the specimens[20].

Low-grade neoplasms such as ganglioglioma (Figure 2) and dysembryoplastic neroepithelial tumour, vascular malformations, and focal cortical dysplasias are other lesions associated with refractory partial seizures[21]. In endemic areas for cysticercosis, calcified cysticercous granulomas as a cause for refractory partial epilepsy are not uncommonly encountered[22].

Table 1. Surgically remediable lesional epilepsy syndromes

Mesial temporal lobe epilepsy
(Temporal lobe epilepsy associated with hippocampal atrophy/ sclerosis)
Benign neoplasms
Ganglioglioma
Dysembryoplastic neuroepithelial tumour
Low-grade astrocytoma
Oligodendroglioma
Developmental lesions
Glioneuronal hamartoma
Focal cortical dysplasias
Other focal lesions
Vascular malformations
Atrophic scars
Rasmussen's encephalitis

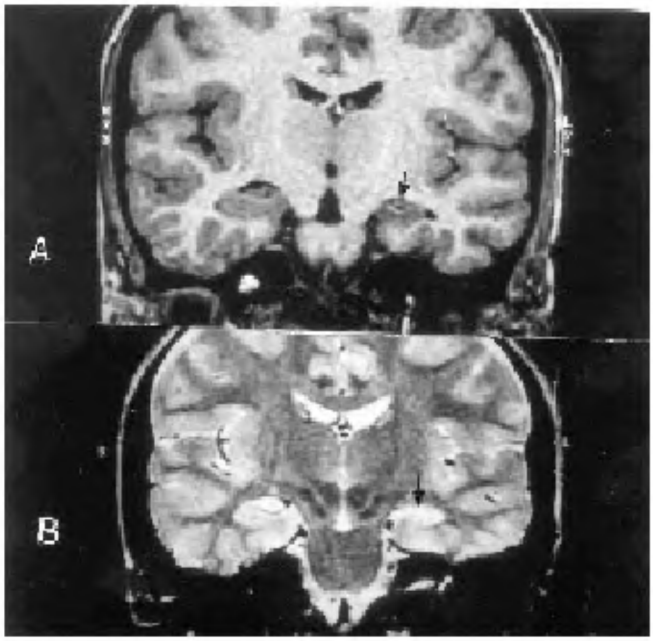

Figure 1. MRI in a patient with left hippocampal atrophy and sclerosis (pathologically confirmed after anterior temporal lobectomy and amygdalohippocampectomy) shows (arrows): (A) small hippocampus in T_1-weighted sequence, and (B) increased signal in T_2-weighted sequence.

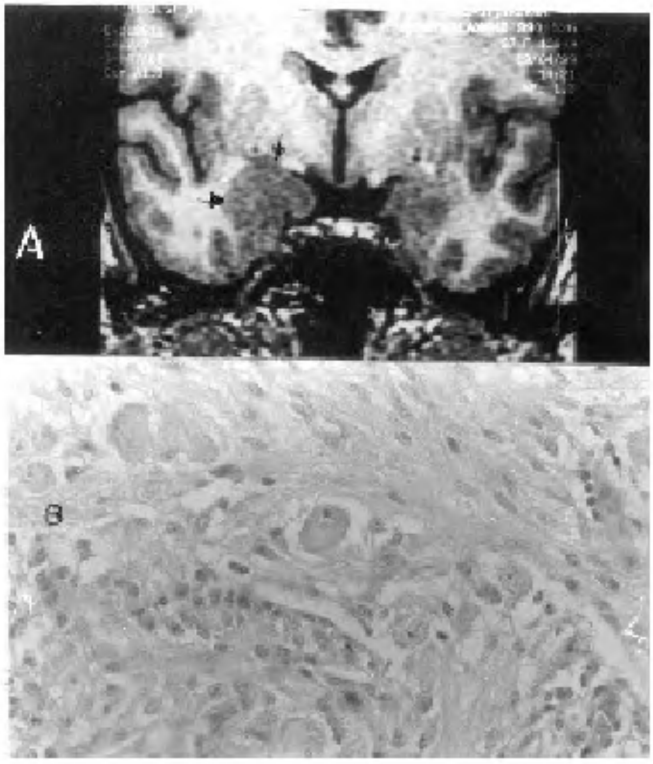

Figure 2. Pathologically confirmed ganglioglioma in a patient with medically refractory temporal lobe epilepsy shows: (A) the neoplasm (arrows) involving right medial temporal region in T_1-weighted coronal MRI sequence; and (B) admixture of well differentiated neoplastic ganglionic cells and astrocytes (H&E × 200).

Identification of medically refractory epilepsy

Surgical treatment of epilepsy should not be considered as the last resort after all combinations of AEDs have been tried. With 10 commonly used AEDs (phenobarbitone, primidone, phenytoin, carbamazepine, valproate, clonazepam, clobazam, gabapentin, lamotrigine and topiramate), there are 45 different two-drug and 36 different three-drug combinations to which a patient with refractory epilepsy may be exhibited to; the trials with all of them will require the whole lifetime of the patient to complete. Complete freedom from seizures without AED side effects should be the ultimate objective of AED therapy, but only less than 5% of patients with chronic active epilepsy have been rendered seizure-free even by the addition of new AEDs[23,24], and only less than one-quarter of patients with chronic partial epilepsy are likely to continue therapy with new AEDs beyond five years[25].

The natural history studies of epilepsy have shown that most of the patients who are destined to achieve satisfactory seizure control will do so within two years of the onset of epilepsy[3,16]. Continuing frequent seizures during childhood, adolescence and early adult life can produce devastating psychosocial, familial, educational and occupational sequel. Once the lifestyle gets fixed, surgical treatment undertaken to successfully terminate the seizures may not have any significant influence on the quality of life of the individual[26,27]. Because of these reasons, more emphasis is recently being placed on early referral for epilepsy surgery[28]. If after two years of appropriate trials with AEDs, the patient is medically refractory, referral to a comprehensive epilepsy program should be considered.

Presurgical evaluation

Comprehensive epilepsy care organization

A major challenge in the management of patients with refractory epilepsy is how to address the medical and psychosocial issues together. These patients often require a multidisciplinary approach for a systematic and comprehensive diagnostic and therapeutic evaluation. Psychogenic nonepileptic seizures are frequently seen at epilepsy centers, where they represent approximately 20% of patients referred for refractory seizures[29]. Furthermore, a combination of epileptic and psychogenic seizures may occur in about 10% of patients[30]. It is often necessary to consult psychologists, psychiatrists and social workers to participate in the evaluation. The neurologists, neurosurgeons, radiologists, psychologists, psychiatrists and medico-social workers constitute an organized team of the comprehensive epilepsy care program[7].

Objectives of presurgical evaluation

The goals of the presurgical evaluation are: (1) to establish the diagnosis of epileptic seizures and to exclude nonepileptic behavioral events; (2) to define the electroclinical syndrome; (3) to delineate the lesion(s) responsible for the seizure(s); (4) to select ideal surgical candidates with optimal electro-clinical-radiological correlation; and (5) to ensure that surgery will not result in disabling neuropsychological deficits.

Principles of presurgical evaluation

The rate of success of epilepsy surgery depends upon the accurate localization of the *epileptogenic zone*, which is defined as the area necessary and sufficient for initiating seizures, and whose removal or disconnection is necessary for abolition of seizures[5]. Since the epileptogenic zone cannot be reliably defined preoperatively, selection of ideal candidates for epilepsy surgery requires a multimodal approach by careful correlation between clinical (symptomatogenic and hypofunctional zones), neuropsychological (hypofunctional zone), interictal scalp EEG (irritative zone), structural magnetic resonance imaging (MRI) (lesional zone), ictal video-scalp EEG (ictal onset zone), interictal positron emission tomography (PET) (hypofunctional zone), and ictal single photon emission computed tomography (SPECT) (ictal onset zone) data[5].

Noninvasive strategy. Today, a majority of patients can be selected for anterior temporal lobectomy, the commonest epilepsy surgery performed all over the world, based on the results of noninvasive methods such as scalp EEG, video-EEG, MRI and neuropsychological findings[5,6,31,32]. In MRI, hippocampal sclerosis is characterized by decreased hippocampal size on T_1-weighted images and increased signal on T_2-weighted (Figure 1) and fluid-attenuated inversion recovery (FLAIR) images[33,34]. A protocol for evaluation of patients with medically refractory epilepsy used in the comprehensive epilepsy program of SCTIMST, Trivandrum, is provided in Table 2. Concordance of MRI and scalp EEG abnormalities (Figure 3) correlates with an excellent postoperative seizure outcome[35,36]. The contraindications for epilepsy surgery are summarized in Table 3.

Noninvasive mapping procedures such as SPECT, PET, functional MRI (fMRI) and magnetic resonance spectroscopy (MRS) and magnetoencephalography (MEG) may provide information complementary to that provided by EEG, video-EEG and MRI[5]. Periictal SPECT studies are obtained by injecting the radiotracer during (ictal) or soon after (postictal) the seizure activity, which necessitates correlation with the patient's EEG activity preceding, during, and after the injection of the radio-

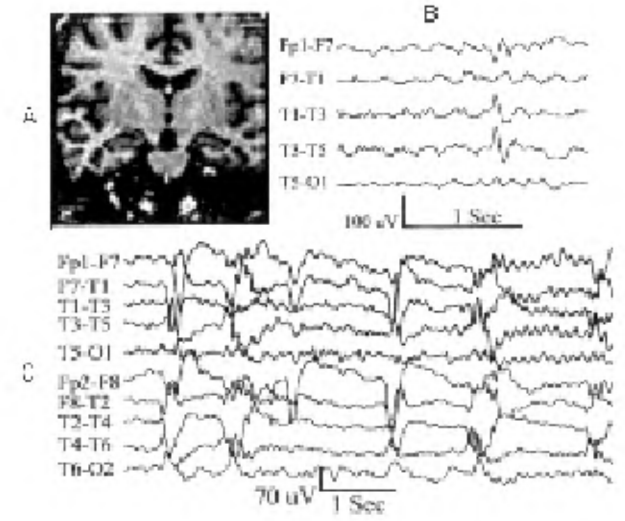

Figure 3. MRI-EEG correlation in a patient with medically refractory temporal lobe epilepsy. (A) Small left hippocampus on T_1-weighted coronal MRI sequence, (B) Left anterior temporal spike discharges, and (C) Rhythmic left temporal EEG activity and chewing artifacts during the seizure.

Table 3. Contraindications for epilepsy surgery

Absolute
Primary generalized epilepsy
Minor seizures that do not impair the quality of life
Relative
Progressive medical or neurologic disorder
Active psychosis, not related to peri-ictal period
Behavioral problems that impair rehabilitation
IQ < 70 (for local resective surgery only)
Poor memory function in hemisphere contralateral to the epileptic focus

IQ, intelligence quotient

Table 2. SCTIMST noninvasive protocol for evaluation of patients with refractory epilepsy

Review the history, past AED treatments, seizure frequency and EEGs
Medical and neurological examination
16-channel awake and sleep scalp EEG recording
Neuropsychological evaluation
Psycho-social evaluation
Psychiatric evaluation
Visual field testing
MRI with protocol for hippocampal volume and sclerosis
Ictal video-scalp EEG recording (3–5 days)
Intracarotid amobarbital (Wada) testing for language and memory distribution

AED, antiepileptic drug; EEG, electroencephalogram; MRI, magnetic resonance imaging; SCTIMST, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala.

tracer[37,38]. In addition, when neurosurgical procedures are planned in neocortical sensory, motor and speech areas, functional mapping is performed to circumscribe the areas of resection in order to avoid an unacceptable neurological deficit postsurgically. In developing countries, fMRI, MRS and SPECT can be utilized in a cost-effective manner in the presurgical evaluation.

The advent of whole-head MEG systems represents a major breakthrough because simultaneous recording from the entire brain and correlation of MEG and EEG findings has become possible[39,40]. Simultaneous MEG and invasive EEG recordings indicate that epileptic activity restricted to mesial temporal structures cannot be reliably detected on MEG, while in neocortical temporal lobe epilepsy, MEG appears to be more sensitive than scalp EEG[39,40]. Magnetic source imaging (combined processing of MEG and MRI data) and coregistration of EEG, MEG and MRI may further reduce the need for invasive recordings in presurgical evaluation.

The ability to detect subtle perfusion abnormalities or blood oxygen-level dependent (BOLD) effects related to the occurrence of EEG events has resulted in EEG-functional MRI correlation strategies[41]. Several groups are currently experimenting with interictal EEG-related BOLD images[41,42].

Neuropsychological evaluation. Neuropsychologic evaluation has long been an integral part of the presurgical workup of patients with refractory epilepsy. In the past, neuropsychologic assessment assumed a diagnostic role in helping to lateralize and localize the seizure focus. After the advent of modern electrophysiologic and neuroimaging techniques, neuropsychology no longer has a major role in the lateralization or localization of seizure focus. However, neuropsychological assessment is the best single means of quantifying the cognitive abilities and psychosocial status of a person. The information obtained through neuropsychological testing helps in counseling patients about potential risk of postoperative memory impairment[43]. Assessment of the effect of epilepsy on the psychosocial status and quality of life of the patient is an important part of present-day neuropsychological evaluation[44].

The Wada test is used to temporarily anesthetize each hemisphere in turn by intracarotid injection of amobarbital, in order to determine the language and memory abilities supported by the nonanesthetized hemisphere[45]. Wada test is undertaken prior to amygdalohippocampectomy to localize the distribution of language and memory function between the two hemispheres and thereby to predict the postoperative language and memory outcome. While language assessment during Wada test is simple and straightforward, interpretation of memory deficit is complex and requires a carefully designed protocol. Furthermore, amobarbital is not freely available in developing countries; methohexital[46] and propofol[47] are used instead of amobarbital. Noninvasive evaluation with fMRI, PET and MEG may largely obviate the need of Wada test in the future.

Invasive evaluation

Patients may require invasive monitoring when the results of noninvasive methods such as scalp EEG, video-EEG and MRI are conflicting. Placing sphenoidal electrodes under fluoroscopy directly below the foramen ovale may result in a better detection of interictal and ictal epileptiform activity of mesial-basal-temporal origin[48]. In selected patients with presumed mesial temporal lobe epilepsy with sparse interictal epileptiform discharges or poorly defined ictal EEG activity, long term monitoring utilizing sphenoidal electrodes help to localize the spiking and ictal onset zones[49].

Several types of intracranial recording electrodes such as subdural strip and grid electrodes, epidural electrodes, intracerebral depth electrodes or combination of each are used[50,51]. Exclusive use of either intracerebral or subdural electrodes may occasionally result in erroneous localization because of insufficient sampling of the brain[52]. Patients with bilateral temporal interictal and ictal abnormalities often will require only bilateral depth electrode placement to the mesial temporal structures. However, temporal lobe epilepsy patients with normal MRI, if the SPECT and PET findings are equivocal, often need invasive monitoring with subdural and depth electrodes to localize the ictal onset zone[50].

Although scalp EEG in patients with suspected frontal lobe epilepsy may provide valuable information if carefully ascertained and interpreted, a majority of these patients will need invasive EEG data to define the ictal onset zone[53]. With the shift in surgical candidacy toward the younger age groups, invasive monitoring has regained its utility in pediatric patients with normal imaging studies and cortical dysplasia[54]. Invasive monitoring escalates the cost of epilepsy surgery, an important consideration in developing countries. Furthermore, the postsurgical seizure outcome in patients who require invasive monitoring for localization of seizure focus is less favorable when compared to those who could be selected based on noninvasive protocol[50].

Surgical treatment

Appropriate counseling of the patient and family about the diagnosis of epilepsy and its surgical treatment is the first step in the management. Questions concerning schooling, employment, driving, parenting children and the cost and consequences of medical and surgical management should be addressed. The assistance of medico-social worker in the counseling process is very valuable.

A significant proportion of patients with chronic epilepsy in developing countries are often treated with subtherapeutic dosages of multiple AEDs with resultant poor seizure control and AED toxicity[55]. Hence, when there is no clear evidence of benefit with polytherapy, the patient should be returned to optimal monotherapy at a dose that keeps the seizure frequency to a minimum without adverse side effects.

The surgical options available currently to treat patients with refractory epilepsy are cited in Table 4. The first surgery for refractory epilepsy in India[56] was undertaken in 1954. A sizeable number of patients with refractory epilepsy were operated at Christian Medical College, Vellore[57] and Institute of Neurology, Madras[58] in 1960s and 1970s. Over the last two decades there is a resurgence of interest in epilepsy surgery due to improvements in the presurgical localization of seizure focus with video-EEG telemetry, MRI and application of microsurgical techniques. Through the Comprehensive Epilepsy Program of the SCTIMST, Thiruvananthapuram, from March 1995 through June 2001, 350 patients underwent epilepsy surgery (Table 5). The All India Institute of Medical Sciences, New Delhi[59], Christian Medical College, Vellore[60], and the National Institute of Mental Health and Neurosciences, Bangalore, also have active epilepsy surgery programs.

Table 4. Types of surgical procedures for medically refractory epilepsy

Resective operations
Removal of an epileptic focus or discrete lesion
Focal corticectomy
Anterior temporal lobectomy
Gross removal of malfunctioning brain tissue
Hemispherectomy
Functional operations
Division of pathways of spread
Corpus callosotomy
Division of epileptogenic neuronal aggregate
Multiple subpial transections

Table 5. Epilepsy surgeries undertaken at SCTIMST from March 1995 through June 2001

Procedure	No
Anterior temporal lobectomy with amygdalohippocampectomy	330
Extratemporal resections	6
Corpus callosotomy	7
Hemispherectomy	7
Total	350

SCTIMST, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala.

Anterior temporal lobectomy with amygdalohippocampectomy

The most common surgical procedure performed to cure epilepsy is anterior temporal lobectomy along with amygdalohippocampectomy[6,7,35]. We perform anterior temporal lobectomy through a standard temporal craniotomy under general anesthesia[61]. The 'standard' anterior temporal lobectomy consists of resection of a 5 to 6 cm block of temporal neocortex along with superior temporal gyrus, and anterior two-thirds of the hippocampus and lateral two-thirds of the amygdala along with uncus and parahippocampal gurus[61]. In patients with well-defined epileptogenic zone restricted to the mesial temporal structures confirmed by intraoperative electrocorticography, selective amygdalohippocampectomy provides comparable results[62].

The commonest pathology observed in over two-thirds of the resected temporal lobe is hippocampal neuronal loss with sclerosis (mesial temporal sclerosis)[20,63]. Low-grade neoplasms such as ganglioglioma (Figure 2) and dysembryoplastic neroepilthelial tumour, dysplastic lesions and vascular malformations comprise the rest[21,63]. The presence of large number of corpora amylacea bodies in the hippocampus is a helpful marker of mesial temporal sclerosis in cases where assessment of neuronal loss and gliosis is difficult due to technical problems such as tissue fragmentation and piecemeal surgical removal mesial temporal structures[20,64].

Extratemporal resections

Surgery for extratemporal epilepsies poses enormous challenge because the epileptogenic zone is difficult to define. Historically, Victor Horsely's[65] and Wilder Penfield's[66] first operations for epilepsy were for atrophic lesions involving the frontal lobe. However, in recent epilepsy surgery series, frontal resections account for only 10 to 20% of cases, whereas over 80% of epilepsy surgery involve the temporal lobe[6,67].

The seizure outcome following frontal resections generally is substantially worse than for temporal resections[68–70]. A number of reasons are often cited for this difference, including apparently more diffuse epileptogenesis in frontal lobe epilepsy, rapid seizure spread complicating electrophysiologic localization, and more frequent overlap with eloquent areas imposing limits on optimal resection of the epileptogenic zone[53,71]. The seizure outcomes after parietal[72] and occipital[73] resections are comparable to that of frontal resections. An MRI-detected lesion has been shown to be associated with a better post-operative seizure outcome[70,74]. Intracranial recording, intraoperative electrocorticography and functional mapping are often required in patients with no demonstrable MRI lesion. Surgical treatment of

patients with tuberous sclerosis and intractable epilepsy is most effective when a single tuber or epileptogenic area can be identified as the source of seizures and resected[75].

Hemispherectomy

In order to eliminate the late complications of anatomic hemispherectomy due to superficial cerebral hemosiderosis, variations of the procedure such as modified hemispherectomy, functional hemispherectomy, shunted hemispherectomy and hemidecortication are practiced for intractable epilepsy associated with major lesions involving one hemisphere, such as HHE syndrome, Sturge–Weber syndrome, Rasmussen's encephalitis and hemimegalencephaly[76]. In 75% of such patients, hemispherectomy may bring about complete cessation of seizures; in many AED eventually may be reduced or withdrawn[76]. Striking improvement in behavior and social functions occurs. Among the 8 hemisphrectomized SCTIMST patients, except one, all had a substantial seizure reduction, 5 among them are practically seizure-free.

Corpus callosotomy

Partial or complete section of the corpus callosum is utilized as a palliative surgical treatment for bihemispherical multifocal epilepsy resulting in frequent generalized seizures; particularly those forms associated with falling and risk of injury. Lennox–Gastaut syndrome with drop attacks is maximally benefited by callosotomy[77].

Multiple subpial transections

This operation is based on the concept that epileptic discharges propagate tangentially throughout the cortex whereas the impulses controlling voluntary movement propagate radially[78]. A series of vertical cuts are made to control the epilepsy and preserve the normal function. Multiple subpial transections alone seldom results in complete seizure control. Multiple subpial transections surrounding a lesionectomy may minimize the excised volume without compromising seizure control[79]. For lesions located in close proximity to eloquent areas such as motor and speech areas, multiple subpial transections is a safe option to reduce seizures without causing morbidity. Children with Landau–Kleffner syndrome may show substantial recovery of speech following multiple subpial transections[80].

Stereotactic procedures

Stereotactic lesionectomy, radio-frequency lesion, volumetric resection and radiosurgery have been reported with variable safety and effectiveness in controlling refractory seizures. A major advantage of the stereotactic technique is the capability of resecting deep-seated intracranial lesions involving functional or eloquent cortex with a low surgical morbidity[81]. A well-defined lesion can be resected stereotactically with much less morbidity than the conventional approach. In a series of 23 patients who underwent sterotactic lesionectomy for refractory partial seizures at the Mayo Clinic, Rochester, MN, USA, 74% had a significant seizure reduction and 56% were almost seizure free[82].

Vagus nerve stimulation

Left vagus nerve stimulation is an emerging new treatment for medically refractory partial onset seizures in adults[83] and children[84], who are not optimal candidates for intracranial surgery. For patients with non-lesional non-mesiotempopral epilepsy without lateralizing evidence, and symptomatic and cryptogenic generalized epilepsy unresponsive to AED treatment, VNS might be an alternative[85,86]. The effectiveness of vagus nerve stimulation is comparable to new AEDs; about half of the patients achieve 50% seizure reduction, however, seizure freedom is rare[83,84]. In 1997, vagus nerve stimulation was approved in the United States as an adjunctive treatment for medically refractory partial-onset seizures in adults and adolescence. The cost may be a prohibitive factor in developing countries.

Complications of epilepsy surgery

The recent developments in microsurgical and computer-assisted techniques have provided the neurosurgeon with the possibility of tracking visually any region of the brain with a low morbidity. In a recently reported series of 429 consecutive patients operated in the University of Bonn epilepsy surgery program, the total rate of neurological complication was 5.4%, with 3.0% causing transient morbidity and 2.3% causing permanent morbidity; no mortality occurred[87]. Specific complications with anterior temporal lobectomy include: homonymous superior quadrantanopsia due to involvement of either optic tract or radiation, and language deficits and manipulation hemiplegia due to vascular injury or spasm involving the sylvian vessels, anterior choroidal artery branches supplying the cerebral peduncle or the perforators supplying the internal capsule. Frontal lobe resections may cause personality changes. Gerstmann syndrome may occur as a complication if the dominant inferior parietal lobule is resected. Total hemispherectomy may cause delayed superficial cerebral hemosiderosis. Callosotomy may result in the syndrome of mutism, apraxia of the non-dominant leg, and incontinence, which is often transient.

In the SCTIMST series of 350 patients, one died few hours following an uneventful surgery, the cause of which remained obscure. Two patients developed disabling hemiplegia due to injury to the anterior choroidal artery. Four patients underwent repeat surgery. In two of them, the indication for re-surgery was persistence of seizures and inadequate resection of the epileptogenic focus. Two patients developed asymptomatic cysts at the temporal lobectomy site about one year after temporal lobectomy, which necessitated re-craniotomy and cyst decompression. The rest of the complications were transient.

Outcome assessment

Treatment outcome in epilepsy is too often a vague, ill-defined subjective measure[88]. Epileptologists till recently took a myopic view of evaluating outcome in terms of diminished seizure frequency alone. In patients with refractory epilepsy, extreme variation in seizure frequency are common and different seizure patterns occur even in the same patient. Furthermore, the psychosocial, educational and occupational consequences of epilepsy and its treatment and overall involvement of the quality of life of the patient are rarely considered when reporting the outcome of epilepsy surgery.

Seizure outcome measurement

The present method of classifying postoperative seizure outcome introduces the disadvantage of subjective judgement. The postoperative seizure frequency is expressed as a percentage of pre-operative state, ignoring other variables such as seizure severity, time of occurrence, and peri-ictal phenomenon that greatly influence the resultant disability.

Engel's classification. The four-part classification recommended at the First Palm Desert Conference is in widespread use today[89] (Table 6). This classification has the following problems: (1) patients with residual auras (which may be disabling) are considered to have an excellent class I outcome; (2) class I patients off AED are not distinguished from those who are on AED; and (3) lack of a quantitative definition of 'worthwhile improvement' that differentiates between class III and class IV patients.

Seizure scoring system. In order to partly overcome the above problems and to introduce more objectivity in assessment, Engel *et al.*[90] recently recommended a focused postoperative Seizure Scoring System (Table 7). This 12-part scale takes into account the full range of seizure frequencies and increasing severity of seizure occurrence. The scale can be applied prior to surgery and again at varying intervals postoperatively. The postoperative seizure outcome can be defined in terms of the number of steps the patient has moved up or down the scale. A recent study effectively evaluated seizure outcome utilizing the Seizure Scoring System[91]. The scoring system can also be used in following the natural history or the treatment outcome of nonsurgical patients.

The Seizure Scoring System has its own limitations. Scores 3 and 4 are qualified by the requirements that seizures be nondisabling which introduces subjective interpretations, thus potentially influencing the way outcome is scored. Efforts should be made to further improve the method of assessing epilepsy outcome by introducing important factor of seizure intensity or severity.

Seizure severity scales. A seizure severity scale was introduced by Baker *et al.*[92,93] and has been modified by O'Donaghue *et al.*[94]. Because certain measures are more important than others in assessing some types of epilepsy surgery, scales or classification systems appropriate to specific clinical conditions or treatments may be more appropriate. For example, a classification that emphasizes measures of seizure severity than the measure

Table 6. Classification of postoperative seizure outcome (modified Engel classification)

Class I: free of disabling seizures[a]
- A. Completely seizure-free since surgery
- B. Nondisabling simple partial seizures only since surgery
- C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
- D. Generalized convulsion with antiepileptic drug withdrawal only.

Class II: rare disabling seizures
- A. Initially free of disabling seizures but has rare seizures now. ('almost seizure free')
- B. Rare disabling seizures since surgery
- C. More than rare disabling seizures after surgery, but rare seizures for at least 2 years
- D. Nocturnal seizures only

Class III: worthwhile improvement[b]
- A. Worthwhile seizure reduction
- B. Prolonged seizure-free intervals amounting to greater than half the follow-up period but not less than 2 years.

Class IV: no worthwhile improvement[b]
- A. No significant seizure reduction
- B. No appreciable change
- C. Seizures worse

[a] Excludes early postoperative seizures (first few weeks).
[b] Determination of 'worthwhile improvement' requires quantitative analysis of additional data, such as percentage of seizure reduction, cognitive function and quality of life.

of seizure frequency may be preferred for evaluating the outcome of palliative surgical procedures such as corpus callosotomy.

Temporal trends in postoperative seizure outcome

It is now a well-established fact that a prolonged longitudinal follow-up is essential for accurate assessment of seizure outcome, since initially seizure-free patients may relapse, and some patients with early postoperative seizure may become seizure-free subsequently (running-down phenomenon)[95,96]. Hence it is not surprising that unconventional outcome studies based upon the average of results arising from different follow-up periods have provided variable results. A transverse analysis where all patients achieve the same prolonged follow-up period (which is difficult, if not impossible to achieve), or a actuarial analysis which takes into account both the temporal variability of seizure recurrence and variable follow-up would be required to provide reliable seizure outcome results.

Only very few studies are yet available in the literature which have utilized actuarial analysis of seizure outcome. Elwes *et al.*[97] measured the temporal pattern of seizure remission and stability of seizure outcome among 102 patients who underwent anterior temporal lobectomy for medically refractory epilepsy. The probability of achieving one-year remission was 57% by one year, 70% by two years and 77% by 7 years. The probability of remaining seizure free once the patient was in one year and two years remission was 90% and 94%, respectively. So *et al.*[91] showed that patients who have remained seizure-free during the first year of postoperative follow-up have over 80% chance of achieving long-term seizure freedom.

Table 7. Seizure frequency scoring system

Seizure frequency	Score
Seizure-free, off antiepileptic drug	0
Seizure-free, need for antiepileptic drug unknown	1
Seizure-free, requires antiepileptic drugs to remain so	2
Nondisabling simple partial seizures	3
Nondisabling noctural seizures only	4
1–3 per year	5
4–11 per year	6
1–3 per month	7
1–6 per week	8
1–3 per day	9
4–10 per day	10
> 10 per day but not status epilepticus	11
Status epilepticus without barbiturate coma	12

Table 8. Predictors of seizure outcome following epilepsy surgery

Favourable outcome
Presurgical factors
MRI detected lesion
IEDs concordant with the MRI lesion
Ictal discharges concordant with the MRI lesion
Postsurgical factors
Absence of IEDs in scalp EEG
Complete seizure freedom during first year
Having nondisabling seizures during first year in non seizure-free patients
Unfavourable outcome
Presurgical factors
Normal MRI
Bilateral IEDs
Rapid interhemisperical spread of ictal EEG activity
Postsurgical factors
Absence of detectable lesion in pathology
Recurrence of disabling seizures during the first year

IEDs, interictal epileptiform discharges; EEG, electroencephalogram; MRI, magnetic resonance imaging.

Determinants of postoperative seizure outcome

The identification of factors predictive of postsurgical seizure outcome is important in the selection and the counseling of epilepsy surgery candidates. Since the pattern of seizure control can vary over time, conventional methods of outcome analysis provide unreliable data on outcome itself, and therefore the predictors of outcome as well. Actuarial statistics can rectify this problem since it calculates the cumulative percentage of patients who have ever been in remission, based on the number of patients at risk.

Only very few studies have evaluated prognostic variables utilizing actuarial statistics. Berkovic *et al.*[36] studied 135 consecutive anterior temporal lobectomy patients. Among them, 80% of patients with neoplastic lesions, 62% of those with hippocampal sclerosis, and 36% of those with no lesion on MRI achieved an eventual seizure free state of 2 years or more. Radhakrishnan *et al.*[35] utilized univariate and stepwise logistic regression analysis to identify presurgical and postsurgical factors that are predictive of outcome among 175 consecutive anterior temporal lobectomy patients. Presurgical identification of unilateral hippocampal atrophy and interictal epileptiform discharges concordant with the MRI lesion, and absence of seizure recurrence during the first year after surgery predicted an excellent long-term seizure outcome. Absence of a detectable lesion in the MRI and in the pathology of the resected specimen have been shown to be a negative predictor for a favorable post-operative seizure control in both temporal and frontal epilepsies[6,35,70]. The presurgical and postsurgical factors that are helpful in predicting the outcome following epilepsy surgery are listed in Table 8.

The attributes of ideal surgical candidates for anterior temporal lobectomy with amygdalohippocampectomy are antecedent history of early childhood febrile seizures and development of unilateral mesial temporal lobe epilepsy in adolescence with typical seizure semiology (characterized by epigastric aura, behavioural arrest, and oro-alimentary and limb automatisms), unilateral mesial temporal sclerosis on MRI, and unitemporal interictal and ictal EEG findings concordant with the side of the MRI lesion[35,36,98,99] (Table 9). Nearly 90% of patients with unilateral mesial temporal lobe epilepsy achieve excellent seizure outcome following anterior temporal lobectomy with amygdalohippocampectomy[35,49].

However, the absence of good prognostic factors does not invariably suggest an unfavourable postoperative outcome. Chung *et al.*[100] demonstrated that outcome is still good in those with bitemporal epileptiform discharges if there is over 90% lateralization of the discharges to the side of seizure onset. Jack *et al.*[101] showed that even in the absence of lateralized hippocampal atrophy, the probability of favourable seizure outcome was still 54%. Therefore, even among patients with unfavourable prognostic factors, intensive attempts should be made to identify subgroups of patients who are likely to achieve relatively better postoperative seizure outcome.

Temporal trends in the epilepsy surgery outcome around the world. Analysis of the pooled data from epilepsy centers around the world (Table 10) reveals that outcome for seizure control has improved in recent years in patients with temporal lobe resections, while it has remained almost unchanged in patients with extratemporal resections[89,90]. While over 70% of the patients become seizure-free after temporal lobe surgery in recent years, this outcome can be expected in only less than 50% of those with extratemporal resections. The exact type of temporal lobe resections (standard versus selective amygdalohippocampectomy) did not influence the seizure outcome. The better seizure outcome in recent years appear to be related to the advent of techniques like digital EEG-video monitoring and MRI which has improved the selection of ideal surgical candidates[102].

Wiebe *et al.*[103] recently compared the seizure outcome of 40 patients with temporal lobe epilepsy randomly assigned to surgery with 40 patients on treatment with AED. At one year, the cumulative proportion of patients who were free of consciousness impairing seizures was 58% in the surgical group and 8% in the medical group ($P < 0.001$). This first randomized, controlled trial conclusively established that, in refractory temporal lobe epilepsy patients, surgery is superior to prolonged medical therapy.

Among the 68 SCTIMST patients who have completed 2 years of post- anterior temporal lobectomy follow-up, 68% were completely seizure free, and 78% had an excellent seizure outcome (no disabling postoerative seizures)[61]. Out of the patients who had disabling seizures following anterior temporal lobectomy, a majority had a reduction in seizure frequency. Thus, only 6% of patients exhibited lack of improvement or worsening in seizure frequency. Our results, therefore, are similar to those reported from other major epilepsy surgery centers around the world. It may be worth emphasizing that we utilized a non-invasive presurgical evaluation protocol to decide the candidacy for anterior temporal lobectomy[61].

Postoperative employment status

Many studies have shown that people who had never worked before undergoing epilepsy surgery were unlikely to work even after seizures were successfully controlled[26,104]. Vickrey *et al.*[105] showed that 202 operated patients had no advantage in employment com-

Table 9. Ideal candidates for anterior temporal lobectomy with amygdalohippocamectomy

Prolonged febrile seizures during childhood
Normal neurological examination and IQ
Stereotyped semiology of the complex partial seizures
Unilateral temporal spikes in scalp EEG
MRI showing hippocampal atrophy/sclerosis or a temporal lobe lesion
Video-EEG: site of seizure origin same as scalp EEG and MRI abnormalities

EEG, electroencephalogram; IQ, intelligence quotient; MRI, magnetic resonance imaging.

Table 10. Pooled data from around the world on postsurgical seizure outcome

	n	Seizure free	Improved	Unchanged
Standard Anterior Temporal Resections (ATL), 1987 (ref. 89)	2336	55.5	27.7	16.8
Standard ATL 1993 (ref. 90)	3579	67.9	24	8.1
Selective Amygdalo-hippocampectomy	413	68.8	22.3	9.0
Extratemporal resections, 1987 (ref. 89)	825	43.2	27.8	29.1
Extratemporal resections, 1993 (ref. 90)	805	45.1	35.2	19.8

pared with 46 nonoperated refractory epilepsy patients. By contrast, Sperling *et al.*[106] recently observed in a group of 86 epilepsy surgery patients, unemployment decreased from 25 to 11% and underemployment diminished as well. Reeves *et al.*[27] analysed the factors associated with work outcome among 134 patients who underwent temporal lobectomy for refractory epilepsy at the Mayo Clinic, Rochester, MN, USA. After surgery, significantly more patients were independent in activities of daily living, including driving. Income from work also increased. Work outcome was favourably influenced by presurgical work experience, successful postsurgical seizure control and ability to obtain further education after surgery. Since a majority of the population in the developing world may have no permanent employment, it becomes more difficult to objectively evaluate and compare the employment status before and after epilepsy surgery.

Quality of life outcome

Health-related quality of life (HRQOL) describes an overall state of health that includes domains of physical, social, psychological, vocational and economic well-being. Only recently have epileptologists appreciated the importance of quality of life measurements[107]. The Washington Psychosocial Seizure Inventory (WPSI), developed by Dodrill *et al.*[108] has been extensively used for assessing epilepsy-related quality of life. To increase the number of domains of HRQOL assessed, other measures like Epilepsy Surgery Inventory (ESI 55) and Quality of Life in Epilepsy Inventories (QOLIE-10, QOLIE-39, QOLIE-89) are in use in many centers today[109–111]. Patients who are completely seizure free (including aura free) after surgery usually achieve an excellent quality of life[111].

The SCTIMST comprehensive epilepsy surgery outcome protocol utilizes the seizure score along with psychological, psychiatric, educational and occupational outcome measures to define the postoperative outcome of individual patients and compares with the preoperative status[112].

Economics of epilepsy surgery

The mean direct recurring cost of a patient with refractory temporal lobe epilepsy continued on medical treatment is about Indian Rupees (Rs) 6000 per year[113]. A major part of the recurring direct costs of epilepsy is the cost of AEDs. The out of the pocket payment for temporal lobe epilepsy surgery (including presurgical evaluation) in SCTIMST is about Rs 50,000, but is likely to be double this amount in a nongovernmental medical organization. Although this amount is substantial, there is a 70% chance that the patient will be seizure-free after anterior temporal lobectomy with amygdalohippocampectomy and a 30% chance that the patient will be completely off the AED treatment within two years after surgery[61].

Even with new AEDs, complete freedom from seizures for one year is not more than 10% for patients with refractory temporal lobe epilepsy[4,23,24]. A seizure-free person could be better employed, has less psychosocial problems and more often achieve an improved quality of life[27,111]. Therefore, surgical treatment of medically refractory temporal lobe epilepsy is a better cost-effective option than continued medical treatment[113,114].

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ACKNOWLEDGEMENTS. We wish to thank our colleagues in the R. Madhavan Nayar Center for Comprehensive Epilepsy Care for their contributions.