Surgery for drug-resistant focal epilepsy

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Abstract

During the colloquium on drug-resistant epilepsy (DRE) at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore on August 16-18, 2013, a number of presentations were made on the surgically remediable lesion epilepsy syndromes, presurgical evaluation, surgical techniques, neuropathology of drug resistance focal epilepsy and surgical outcome. This pictorial essay with the illustrative case examples provides an overview of the various surgical techniques for the management of drug-resistant focal epilepsy.

Key Words

Drug-resistant epilepsy, epilepsy surgery, epilepsy, surgical techniques

Introduction

Epilepsy surgery is the resection or functional manipulation of part/region of the brain with the aim of alleviating seizures, improving the cognitive function and the quality of life.1 Resective surgery is based on pathological substrate identified as the cause of seizure and is associated with cure or control of focal seizures. If there is no pathological substrate present that is amenable for resection, disconnection or neurostimulation may reduce the frequency and severity of epilepsy.2 Lesion is a volume of altered cerebral tissue detected by neuroimaging techniques or during surgery. Focus is a volume of brain tissue that contains the epileptogenic area or the epileptogenic zone. The principle of epilepsy surgery is to identify and resect or disconnect a single identifiable epileptogenic focus and or lesion without inducing new neurological deficit.3 It has been reported that the success of epilepsy surgery depends on 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.4 New preoperative techniques offer the opportunity of improved presurgical planning and selection of cases more likely to be rendered seizure-free by current surgical techniques.

Surgery for Temporal Lobe Epilepsy

Mesial temporal lobe epilepsy (MTLE) with mesial temporal sclerosis (MTS) is the most common cause of drug-resistant epilepsy (DRE).5 Anterior temporal lobectomy (ATL) along with amygdalohippocampectomy is the most common epilepsy surgery procedure.6 In ATL, 4-5 cm of lateral temporal lobe neocortex, anterior two-thirds of the hippocampus and lateral two-thirds of the amygdala along with parahippocampal gyrus and uncus are resected depending upon the cerebral dominance, cortical vasculature and neuropsychological deficits. ATL for MTLE with MTS leads to improvement in seizure control, cognitive function, and quality of life.7 Suitable surgical candidates for ATL can be identified with standardized non-invasive protocols and the outcome will be cost-effective.8,9 For low-grade neoplasms like dysembryoplastic neuroepithelial tumors (DNET), ganglioglioma, vascular lesions like cavernoma, and arteriovenous malformation (AVM) and developmental lesions like focal cortical dysplasia (FCD) different resective surgical strategies are adopted based on the pre-surgical evaluation.10

Case 1

An 11-year-old girl presented with complex partial seizures since the age of 2 years. Her seizures frequency was 3-4 episodes per month despite taking multiple anticonvulsants. Clinical examination revealed no focal neurological deficit. Magnetic resonance imaging (MRI) of the brain showed [Figure 1, panel a] loss of volume of left hippocampus with
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signal changes and loss of internal architecture without any other associated lesions. Clinical events captured during the video electroencephalography (EEG) telemetry were characterized by adverse head turning to right with right upper limb dystonia. Ictal EEG showed build-up of theta activity with sharp waves in the left temporal region with phase reversal at T5 [Figure 1, panel b]. She underwent left temporal craniotomy, left ATL along with amygdalohippocampectomy. Histopathology revealed characteristic features of hippocampal sclerosis with loss of neurons in CA1, CA3 and CA4 subfields while CA1 was relatively preserved [Figure 1, panel c]. She remained seizure-free at 3-months follow-up.

Case 2
A 19-year-old lady presented with drug-resistant complex partial seizures since the age of 9 years. She also had memory impairment and poor scholastic performance. Clinical examination revealed no focal neurological deficit except for subnormal intelligence and recent memory impairment. MRI brain showed bilateral hippocampal atrophy with signal changes and loss of internal architecture [Figure 2, panel a and b]. Quantitative imaging with magnetic resonance (MR) Volumetry and T2 relaxometry revealed right more than left involvement. Scalp Video EEG study was inconclusive. She underwent invasive EEG monitoring with bitemporal subdural strip electrodes. Invasive monitoring clearly lateralized the seizure origin to the right temporal region [Figure 2, panel c]. She underwent right ATL and amygdalohippocampectomy. Histopathology confirmed hippocampal sclerosis. She had no seizure recurrence following surgery after 17-months of follow-up.

Surgery for Extra-Temporal Epilepsy

In contrast to temporal lobe surgery, extra-temporal epilepsy surgery demands complex pre-surgical evaluation and innovative surgical approaches.[11,12] Frontal lobe epilepsy surgery is the second most frequent type of epilepsy surgery, but the results are generally not as good as those after ATL.[13-15] Parietal and occipital seizures have been investigated relatively less. [16,17] The most prominent clinical manifestations are elementary sensory phenomena at the beginning of seizures in parietal epilepsy and elementary visual hallucinations in occipital epilepsy. Scalp EEG is frequently negative or maybe misleading and spread of epileptic discharges from the parietal and occipital lobes to frontal and temporal regions may obscure seizure origin. The main pathological substrates of uncontrolled parietal and occipital lobe epilepsies are low-grade tumors, developmental and gliotic abnormalities. Whereas resection of the tumors associated with chronic epilepsy produces nearly uniform seizure control, outcome after resection of developmental and gliotic abnormalities is less uniform.

Case 3
A 9-year-old boy presented with drug-resistant left focal motor seizures since the age of 1 year. Clinical examination revealed no focal neurological deficits. MRI of the brain showed focal area of cortical thickening with indistinct gray white junction involving the right post central sulcus and supramarginal gyrus [Figure 3a, panel a]. Task-based functional MRI (fMRI) revealed the motor cortex to be located more than 2 mm anterior to the lesion [Figure 3a, panel b]. The ictal video EEG showed build-up of rhythmic theta activity across the right central region with phase reversal

Figure 1 (Case 1): (Panel a) shows high resolution T2 coronal images perpendicular to the hippocampus that reveals loss of volume of left hippocampus associated with loss of internal architecture. (Panel b) shows ictal EEG buildup of theta activity with sharp waves in the left temporal region. (Panel c) shows loss of neurons in CA1, Ca3, and CA4 on Neu N stains suggestive of mesial temporal sclerosis (hippocampal sclerosis) (NeunxObj.10), EEG = Electroencephalography

Figure 2 (Case 2): FLAIR coronal (panel a) and T2W (panel b) images showing atrophy and hyperintensity of both hippocampi suggestive of bilateral mesial temporal sclerosis and EEG features in the (panel c) FLAIR = Fluid attenuated inversion recovery, EEG = Electroencephalography
at C4 consistent with the cortical lesion [Figure 3a, panel c].
Patient underwent right parietal craniotomy and lesionectomy under electrocorticographic guidance and cortical stimulation. There was persistent spike discharges from the motor cortex at the end of resection, however, it was not resected. He did not develop any focal neurological deficit following the surgery. Histopathology revealed widening of the cortical grey ribbon with complete dyslamination of cortical layers [Figure 3b, panel a]. Several large dysmorphic neurons with enlarged soma and marginalized Nissl substance was seen in addition to large Taylor type cells with glassy cytoplasm [Figure 3b, panel b] accumulating glial fibrillary acidic protein in cytoplasm [Figure 3b, c], features characteristic of Focal Cortical Dysplasia, type 2B [Figure 3b]. At 6-months follow-up, he reported significant improvement and has occasional seizures.

Case 4
A 13-year-old boy presented with drug-resistant complex partial seizures since the age of 8 years. At birth, he had poor cry with breathing difficulty requiring intensive care unit (ICU) management for 1 week. He had loss of vision in the right eye since birth. Clinical examination revealed no perception of light in the right eye with primary optic atrophy. He had no other focal neurological deficit. MRI of the brain showed left temporal and parietal atrophy [Figure 4, panel a and b]. Ictal video EEG showed frequent spike and wave activity from the left temporo-centro-occipital region with spread to the opposite hemisphere, suggestive of seizures arising from the left posterior quadrant. Positron emission tomography (PET) scan showed hypometabolism in the left parieto-occipital regions. He underwent craniotomy and left posterior quadrant disconnection. He developed acute postoperative seizures and right hemiparesis. Histopathology confirmed gliosis. His right hemiparesis improved over a period of 3-months, and he remained seizure-free at 22-months follow-up.

Lesional Epilepsy Surgery
Lesionectomy for epilepsy is a surgical procedure that is directed at the structural lesion, believed to be the etiology of the seizure disorder.[11,12] In the case of isolated structural lesions, such as dysembryoplastic neuro-epithelial tumors, low-grade astrocytomas, or focal vascular abnormalities, total macroscopic and radiologic evidence of lesion excision is associated with excellent seizure-free outcome. The surgical approach will often depend on the preoperative and intraoperative identification of the particular structural substrate. The operative strategy may include a. Lesionectomy, i.e. complete lesion excision, as determined by MRI, without attempting to resect the epileptogenic zone, b. Extended lesionectomy, i.e. resection of the lesion with margins, c. Resection of the lesion and the epileptogenic zone, and d. Resection of the epileptogenic zone without resecting the lesion.

The extent of the resection may be determined by different criteria:
1. Intraoperative visualization of the tissue,
2. Lesion margins determined by MRI signal abnormalities,
3. Histologic margins based on intraoperative frozen section evaluation of the tissue,
4. Electrocorticographic margins based on intraoperative electrocorticography (ECoG), and
5. Intraoperative MRI or ultrasound evaluation or a combination of these techniques.
Case 5
A 23-year-old lady presented with complex partial seizures with secondary generalization of 2-years duration. Clinical examination revealed no focal neurological deficits. MRI of the brain showed a mixed intensity lesion in the right hippocampus with volume loss involving the right temporal lobe [Figure 5a, panel a and b]. In the video EEG telemetry, the clinical and its counterpart interictal and ictal EEG was suggestive of seizures arising from right anterior temporal region, consistent with the right hippocampal lesion [Figure 5a, panel c]. She underwent craniotomy and ATL, amygdalohippocampectomy including the lesion under electrocorticography guidance.

Histopathology revealed a neoplasm with large ganglion cells with large cell body, vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm clustered in a fibrillary glial stroma characteristic of ganglioglioma [Figure 5a]. The glial component was labelled intensely with GFAP while ganglion cells revealed aberrant cytoplasmic synaptophysin immunoreactivity [Figure 5b]. She remained seizure-free at 26-months follow-up.

Case 6
A 24-year-old man presented with drug-resistant complex partial seizures with secondary generalization since the age of 16 years. Clinical examination revealed no focal neurological deficits. MRI brain showed a discrete non-enhancing cortical lesion in the left inferior temporal gyrus with scalloping of the overlying skull bone [Figure 6, panel a and b]. Video
EEG telemetry was suggestive of seizure origin from the left temporal region [Figure 6, panel c]. He underwent left temporal craniotomy and lesionectomy. Histopathology confirmed dysembryoblastic neuroepithelial tumor. He remained seizure-free at 10-months follow-up.

**Case 7**

A 9-year-old boy presented with drug-resistant complex partial seizures of right temporal origin for 18-months duration with a frequency of 4-5 episodes per day. Clinical examination revealed no focal neurological deficit. MRI of the brain showed a well-defined predominantly hemorrhagic lesion with a "popcorn" appearance suggestive of cavernoma in the right hippocampus and parahippocampal gyrus [Figure 7a, panel a and b]. Ictal EEG showed build-up of theta activity with sharp waves in the right temporal region with phase reversal at T4. He underwent right amygdalohippocampectomy with excision of the lesion. Histopathology revealed a cavernoma in the hippocampus with numerous thin, dilated venous channels embedded in a fibrous matrix [Figure 7b]. The surrounding parenchyma revealed gliosis and hemosiderin deposits. He remained seizure-free at 3-months follow-up.

**Pediatric Epilepsy Surgery**

Even in the pediatric patients, diagnosis of drug resistant epilepsy should be made much earlier, particularly if children present with epileptic encephalopathy, infantile spasms, catastrophic onset of epilepsy, and frequent and disabling seizures.[19] Children with specific epilepsy syndromes such as Sturge-Weber syndrome, hemispheric syndromes, Rasmussen’s encephalitis and hypothalamic hamartoma should be referred for pre-surgical evaluation without delay and if found suitable, surgery should be offered earlier.[20] In children presenting with drug-resistant and disabling seizures without delineation of an epileptogenic zone or Lennox-Gestaut syndrome, functional procedures such as corpus callosotomy can be performed especially to control the drop attacks.

**Hemispherectomy and Hemispherotomy**

Hemispherectomy or hemispherotomy is performed successfully to treat medically intractable hemispheric epilepsy in adolescents and older children, providing remarkable results in terms of seizure outcome and quality of life.[21,22] Three different surgical techniques are performed according to the specific etiology and extension of anatomic abnormalities:

1. Anatomic hemispherectomy, consisting of removal of the frontal, parietal, and occipital lobes with the preservation of the basal ganglia, thalamus, and insular cortex;
2. Functional hemispherectomy, consisting of
   a. Temporal lobectomy extending to the trigone, including the amygdala and hippocampus,
   b. Central cortex excision, exposing the body of the lateral ventricle,
   c. Subpial aspiration of the cingulate gyrus and corpus callosum disconnection from within the ventricle,
   d. Frontal lobe disconnection by following the course of the pericallosal and anterior cerebral artery to the basal frontal region, and
   e. Posteriorly, the subpial disconnection follows the corpus callosum, meeting the mesial parieto-occipital disconnection from the temporal lobectomy;
3. Modified functional hemispherotomy, consisting of a technique similar to that of the anatomic hemispherectomy but with the preservation of the disconnected frontal lobe or occipital lobe or both, depending on the location of the epileptogenic zone, anatomic abnormality, and etiology.

**Case 8**

A 5-year-old girl presented with drug-resistant left focal motor seizures since the age of 2 years. Clinical examination revealed grade 3/5 power in the left upper limb and 4/5 power in the lower limb. MRI of the brain showed atrophy involving the right hemisphere with focal areas of hyperintensity [Figure 8, panel a]. Ictal EEG changes were found with almost continuous right fronto-central and occasional right temporal medium amplitude
sharp waves [Figure 8, panel b]. She underwent right functional hemispherotomy. Histopathology from the surgical specimen revealed characteristic features of Rasmussen’s encephalitis with microglial nodules with aggregates of cytotoxic T cell around vessels and reactive astrocytosis [Figure 8, panel c]. She remained seizure-free at 4-months follow-up.

Case 9
A 31-year-old lady presented with left focal motor seizures since the age of 3 years. She was a second born twin, delivered by caesarean section with difficult extraction. She had perinatal hypoxic brain injury and was found to have left hemiparesis from early childhood. Clinical examination revealed grade 4/5 power in the left upper and lower limbs with hemiparetic gait. MRI of the brain showed large hemispheric gliosis involving the entire right middle cerebral artery territory [Figure 9, panel a, b, c]. Ictal video EEG showed bilateral symmetrical spike and wave discharges. There was amplitude suppression on the right side with secondary bilateral synchrony. She underwent right-modified functional hemispherotomy. Histopathology confirmed gliosis. At 6-months follow-up, she had recurrence of seizures and was advised reevaluation.

Surgery for Non-Lesional Focal Epilepsy
Non-lesional focal epilepsy surgery usually requires extensive invasive presurgical evaluation, which differs from patient to patient according to the non-invasive findings. The objective of pre operative investigations in this context is to identify and demarcate the epileptogenic zone as accurately as possible. Non invasive modalities like VEEG, PET, SPECT and MEG will be able to provide localization in some cases. Further, invasive EEG with grid-, strip-, and depth- electrodes, often in combination, will be necessary, to delineate the epileptogenic seizure onset zone.

Corpus Callosotomy
Corpus callosotomy is a palliative surgical procedure, which eliminates the interhemispheric spread of epileptic activity.

Outcome studies suggested that anterior corpus callosotomy resulted in a 25-30% seizure-free rate, whereas with a complete callosotomy, 80% were seizure-free at 12 months, decreasing to 60% after 3 years. The reduction in seizure relief with time appears to be more pronounced with regard to generalized tonic-clonic seizures and relatively stable with regard to drop attacks. Complications are few, with no disconnection syndrome reported with the procedure carried out before 10 years of age. Current recommendations are that the procedure should be directed at the seizure type rather than the seizure syndrome. [23, 24] A resectable lesion should be fully excluded with full presurgical evaluation and workup. An MRI brain after surgery would be recommended to document the degree of completion. However, it must be recognized that responder identification still remains difficult.

Multiple Subpial Transections
Multiple subpial transections are intended particularly to be used in those cases where the epileptogenic lesion lies in “unresectable” cortex, i.e. those cerebral regions sub serving speech, memory, and primary motor and sensory function [25]. The procedure is based on experimental evidence indicating:
1. That epileptogenic discharge requires substantial side-to-side or horizontal interaction of cortical neurons and
2. That the major functional properties of cortical tissue depend on the vertical fiber connections of the columnar units.

The technique requires severing of tangential intracortical fibers while preserving the vertical fiber connections of both incoming and outgoing nerve pathways and of the penetrating blood vessels that also have a vertical orientation. MST may be considered when seizures originate from within eloquent cortex and more specifically in the Landau-Kleffner syndrome (epileptic aphasia) performed over the Wernicke area and deep into the Sylvain fissure. Specifically MST, alone with regard to seizure origin, appears to lead to an approximate 30% improvement in seizures, increasing to 60% when it is performed in conjunction with resection. Overall, MST should be considered where seizure onset is demonstrated to be within eloquent cortex, either alone or preferably in combination with resection. It remains the
surgical procedure of choice in the Landau–Kleffner syndrome, although no doubt exists that specialist evaluation is required in a center used to evaluating such patients, in view of the detailed neurophysiology required. Its role in multifocal epilepsy with autistic regression is yet to be proven.

### Stereotactic Techniques

Frame-based stereotactic techniques have been extensively used in India for both temporal lobe epilepsy and generalized seizures. However, since the introduction of image guidance and neuronavigation, these techniques are being used currently for the electrode implantation of both depth and subdural electrodes, as well as to localize lesions and facilitate anatomical resections.

### Radiosurgery

Radiosurgery for management of DRE has been introduced in the past two decades. [26] Radiosurgery is being proposed in cases of refractory seizure wherein the epileptogenic focus can be well defined radiologically and is smaller in volume. The classical conditions that are being considered are MTS, hypothalamic hamartoma and arteriovenous malformations. The long-term outcome and neurobiological consequences are yet to be delineated.

### Neurostimulation

Electrical stimulation to treat seizures in patients who are not suitable for resective surgery is a novel idea. Electrical stimulation is reversible. If it does not work, it can be discontinued and the electrodes can be removed. Neuronal tissue need not be destroyed or resected, except for the tissue directly along the tract of the stimulating electrodes. Stimulation can occur within seconds, enabling patients to turn the stimulator on at the beginning of a seizure. Despite these theoretical advantages, electrical stimulation is still far from being an established and effective therapeutic technique. There are indications that neurostimulation improves seizure control in a group of patients previously not suitable for resective surgery and this methodology has enormous potential. [27] Questions regarding the best target sites, best candidates for stimulation as well as the efficacy and safety of the stimulation have not yet been answered.

### Vagal nerve stimulation

Though the exact mechanism by which the vagal nerve stimulation controls seizure is still unknown, it was felt that continual stimulation of the vagus nerve by an implantable electrical device might result in widespread bilateral activation or deactivation of the brain circuits thought to be involved with epileptic seizures. The efficacy of the vagal nerve stimulation is based on two randomized control trials that reported a modest response of reduced frequency of seizures by 50% or more in 30-40% of patients. This technique is currently being proposed in select cases of non-localized DRE, where resective surgery is not the option. In comparison with the corpus callosotomy, VNS is expensive, but reversible procedure.

### Case 10

An 18-year-old college student presented with DRE since the age of 8 years. Seizure semiology was varied with right sensory seizures, right focal motor seizures, drop attacks, and occasional generalized tonic-clonic seizures. Clinical examination revealed no focal neurological deficits. MRI of the brain showed no significant abnormality with only left hippocampal atrophy on volumetry without signal changes or loss of internal architecture. Video EEG performed twice, in 2006 and 2007 showed right temporal discharges with secondary generalization and in 2012 showed left fronto-central focus. PET study showed hypometabolism in the bilateral temporal and high parietal regions. Single-photon emission computed tomography (SPECT) study performed in 2006 showed left temporal focus and 2007 did not reveal any focus. Invasive monitoring performed at another institution showed bilateral extratemporal foci. She underwent implantation of left vagal nerve stimulator. At 1-year follow-up, she had partial reduction in the frequency of seizures.

### Deep Brain Stimulation in Epilepsy

The idea of stimulating deeper areas of brain stereotactically to modulate the seizure activity is fascinating and has led to a number of studies. The rich experience obtained in Parkinson’s disease management has added to these attempts. Most of the studies that have attempted to identify the targets for seizure control consist of small number of patients. Stimulation of the centro-medial nucleus and the anterior nucleus of the thalamus, sub thalamic nucleus, and amygdalohippocampal complex has been performed with partial seizure control. [28] It is ample clear that the idea of identifying targets for deep brain stimulation in epilepsy is at its infancy. However, it is distinctly possible that these techniques will result in expansion of the list of conditions that will come under the surgical realm for treatment in the future.

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