Management of Refractory Childhood Epilepsy and Epilepsy Surgery

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32.1 Introduction

Drug-resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules, whether as monotherapy or in combination to achieve sustained seizure freedom. It is also referred interchangeably as medically refractory, medically intractable, or pharmacoresistant epilepsy. This definition was put forth by the International League Against Epilepsy (ILAE) in 2010 intended as a consensus. This definition is useful for most clinicians and to facilitate clinical research. It is recommended that all drug-resistant epileptic (DRE) patients be evaluated in a tertiary neurology center, where available, for expert care and also surgical considerations [1].

The basis for two medications as a standard for drug-resistant epilepsy is supported by the Kwan and Brodie adult study and has been confirmed in other groups [2]. The first AED has about a 50% chance of controlling epilepsy. The second medication has approximately an additional 10% chance of controlling epilepsy. A third medication may only have a 1–3% chance of controlling epilepsy. Thus, about 30–40% of children with epilepsy may be refractory to medication.

The definition of drug-resistant epilepsy seems straightforward, but given the diversity of epilepsy, it may not be so clear. First the medication must be appropriately chosen for the type of epilepsy. A patient with a generalized epilepsy but given a focal medication and continues to have seizures does not fail that medication

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because it was not an appropriate choice for their epilepsy type. Second, discontinuation of a medication due to an adverse effect (e.g., medication allergy) does not apply.

Third, the dose of the mediation must be adequate. The adequate dose may be difficult to determine for multiple reasons. Some drugs do not have a standard dose range or drug level. The level also may be confounded by the metabolism of the drug in a particular patient or having multiple drugs in one patient. Often a drug may be stopped prior to an adequate dose trial due to unsatisfactory seizure control, adverse effects, psychosocial reasons (i.e., planning a pregnancy), financial reasons, patient preference, or other reasons. If a drug is stopped prior to an adequate dose, its usefulness may be uninformative as a trial of medication and thus may not be counted as part of a treatment failure in medication.

Fourth relates to the definition of seizure freedom. Seizure-free should refer to freedom from all seizures including auras. Seizures that may be caused by provoking factors (illness, sleep deprivation for example) should still be counted as inadequate seizure control, but poor treatment compliance should not be considered inadequate. The time period to determining seizure freedom is also not clear. One suggestion is the "rule of threes." Seizure free after three times is the longest seizure-free interval prior to the last intervention that can be regarded as a success, with a minimum of 12 months of seizure freedom. For those with only one seizure or seizures less than once a year, this rule is not helpful [3].

From a practical perspective, certain seizures may have varying impacts on a person, and the treating clinician must use their own judgment in treating the patient. The classification for each patient may change in the course of the treatment to become more drug responsive or drug resistant.

There are a few additional considerations influencing the urgency of tertiary care referral [4]. Those with focal epilepsy, whether they are structural, metabolic, or unknown in etiology, are less likely to be controlled on the first AED than those with generalized genetic epilepsy syndromes (43% vs. 58%) [3]. Those that have better prognosis tend to be easily controlled on the first or second AED on modest to moderate doses without intolerable side effects. Those with harder to control epilepsies also tend to have more intolerable side effects (17% vs. 8%). Those that have to have a second drug due to lack of efficacy (11% seizure free) achieved seizure freedom less than those that had a second drug due to adverse effect (41%) or idiosyncratic drug reaction (55%). Those that also have more seizures prior to first treatment also tend to have more refractory epilepsies [2]. Other predictive factors for refractory epilepsy are onset less than 1 year of age, infantile spasms, and diffuse slowing and focal spike-and-wave activity on EEG [5].

Identification of children at risk for refractory epilepsy is important as early, appropriate, and aggressive therapy is thought more likely to achieve seizure control and to optimize outcomes. Chronic uncontrolled focal seizures for some patients may be associated with regional and diffuse tissue loss and metabolic abnormalities [6–8]. Uncontrolled epilepsy is thought to affect/alter distributed brain networks (akin to "kindling" in animal models) that make subsequent medical or surgical treatment less effective [8, 9].

Consider referring all patients less than 2 years of age to a tertiary care center. Many of these children may have an identifiable epilepsy syndrome such as Dravet syndrome, KCNQ2 encephalopathy, SCN8A, Glut-1 transporter deficiency, mitochondrial cytopathies, and children with tuberous sclerosis where early treatment (or contraindicated medications) specific to the disorder may have a profound outcome on seizure control, developmental outcome, and medical safety. Early diagnosis is important due to the possibility of improving cognitive outcome with earlier control of seizures via specific treatments or surgery [5, 10–12].

Controlling seizures is a goal itself, but refractory epilepsy also has other negative outcomes such as cognitive deterioration, psychosocial dysfunction, and sudden unexpected death. High seizure numbers, prolonged seizures, and episodes of status epilepticus may lead to cognitive decline. Inadequate seizure control can produce disturbed psychosocial integration, poor academic achievement, diminished self-esteem, dependent behavior, and restricted lifestyle leading to a poor quality of life. Those with intractable epilepsy also have higher rates of sudden unexplained death in epilepsy [13].

Once it is determined that a patient has refractory epilepsy, they should be referred to a tertiary care center skilled in the care of epilepsy where the next course of treatment should be considered including candidacy for epilepsy surgery. While epilepsy surgery for a lesion with concordant studies (see below) is preferred, surgery is not always an option for a patient with refractory epilepsy for various reasons including multifocal lesions, lack of resources, and location of the focus in eloquent cortex. There have been many new medications in the last 25 years in addition to growing use of dietary therapy (see below). Some medications work through novel mechanisms of action, and some exhibit better side effect profiles or fewer drug interactions. There can be more medications to try in combination to achieve different combinations of mechanisms of action. Additionally, for non-lesional cases, it is crucial to reexamine the diagnosis, results of appropriate epilepsy-specific brain imaging protocols, genetic testing, patient's compliance with medication, and possibility of negative lifestyle factors such as alcohol or drug abuse. In skilled hands a fair proportion of patients will achieve improved seizure control [14].

Since the 1990s, more than 15 new medications have been introduced for the treatment of epilepsy. These include oxcarbazepine, vigabatrin, zonisamide, lamotrigine, felbamate, gabapentin, topiramate, fosphenytoin, tiagabine, and levetiracetam. Since the 2000s stiripentol, pregabalin, rufinamide, lacosamide, eslicarbazepine, ezogabine, clobazam, and perampanel have appeared. This list is not all-inclusive and the availability of these medications varies by country. Antiepileptic drugs are discussed in more detail in Chap. 30.

32.2 Dietary Therapies

Dietary therapy is not a novel treatment; it was first developed in the 1920s. With the advent of antiepileptic medications, dietary therapy went out of vogue. However there has been renewed interest in diets such as the ketogenic diet (KD) [15]. The KD

is a high-fat, low-carbohydrate, and low-protein diet that is administered traditionally in a 4:1 ratio, 4 grams of fat to 1 gram of carbohydrate and protein. This is usually referred to as the "classic" ketogenic diet.

There are several potential mechanisms of action of the ketogenic diet and the KD likely works through multiple mechanisms. Ketone bodies may have anti-seizure effects themselves. There may be changes to neurotransmitter and ion channels that increase levels of GABA and decrease glutamate. There may be mitochondrial changes with an increase in ATP levels and decrease in reactive oxygen species. Glycolytic restriction is thought to have anti-seizure properties. Polyunsaturated fatty acids may also be neuroprotective properties [16].

The ketogenic diet demonstrated efficacy in a class 2 randomized controlled trial; up to 38% of children have greater than 50% seizure reduction compared to 7% of control groups [17]. Lower ratios such as 3:1 may provide better tolerance but run the risk of lower efficacy. However, one study showed that when patients were switched from a 4:1 to 3:1 ratio, the seizure-free outcomes were maintained [18]. There are also diets which are easier to tolerate and administer, such as the modified Atkins diet and the low glycemic index diets which suggest efficacy in small uncontrolled studies [19, 20].

In the 1970s medium-chain triglycerides (MCT) were used as an alternative fat source. MCT produces more ketones per kilocalorie of energy than long-chain triglycerides (LCT) and is absorbed more efficiently, meaning less total fat is needed, allowing more carbohydrates and protein, classically 60% of the diet. There is also a modified MCT diet using a mix of MCT and LCT for better tolerability. Similar efficacy was seen in the MCT diet and the classic ketogenic diet with similar side effect profile, mainly gastrointestinal in nature. Ketone levels were higher in the classic KD group, but efficacy for seizure control was not significantly different up to 12 months [21].

The ketogenic diet can be used for any type of epilepsy but is first-line treatment for glucose transporter protein 1 (GLUT-1) deficiency and pyruvate dehydrogenase deficiency and may be particularly helpful for generalized seizures, myoclonic epilepsy (including Döose syndrome), infantile spasms, severe myoclonic epilepsy of infancy (Dravet syndrome), tuberous sclerosis complex, and Rett syndrome.

Other epilepsy syndromes that it may particularly benefit are certain mitochondrial disorders (but may be contraindicated in others, see below), glycogenosis type V, Lafora body disease, and subacute sclerosing panencephalitis (SSPE). As more patients are identified with epilepsy syndromes associated with specific genetic mutations, this list may expand or become more refined.

A low-glucose diet may be harmful in some metabolic syndromes. Contraindications are carnitine deficiency (primary); carnitine palmitoyltransferase (CPT) I or II deficiency; carnitine translocase deficiency; beta-oxidation defects such as medium-chain acyl dehydrogenase deficiency (MCAD), long-chain dehydrogenase deficiency (LCAD), and short-chain dehydrogenase deficiency (SCAD); long-chain 3-hydroxyacyl-CoA deficiency; medium-chain 3-hydroxyacyl-CoA deficiency; pyruvate carboxylase deficiency; and porphyria.

Relative contraindications are inability to maintain adequate nutrition, surgically resectable seizure focus, and caregiver noncompliance.

A 3-month trial period for efficacy is usually performed. If the diet is felt to be effective, it may be continued for 2 years before deciding to taper off the diet or to continue the treatment. Adverse effects include metabolic abnormalities including acidosis, hypocalcemia, hypomagnesemia, and hyperuricemia. Gastrointestinal symptoms including constipation, vomiting, diarrhea, and abdominal pain can occur in 12–50% of the patients. Hypercholesterolemia is reported in 14–59% of children on the KD. Renal calculi can occur. Growth must be monitored to ensure adequate caloric intake. Cardiac abnormalities have been reported including cardiomyopathy and prolonged QT. Pancreatitis has also been reported. Children require monitoring of serum chemistries (electrolytes, renal, hepatic function) in addition to calcium, magnesium, phosphate, zinc, selenium, fasting lipid profile, triglycerides, cholesterol, beta-hydroxybutyrate, and urine analysis, urine calcium and creatinine, and acylcarnitine profile after 1 month on the diet. Children may require supplementation with calcium, carnitine, bicarbonate, and vitamin D.

The dietary therapies should be administered under the guidance of a dietician and a neurologist familiar with the diet therapy. It is beyond the scope of this chapter to describe the implementation of the ketogenic diet or other dietary therapies in detail. A useful website for reference and to get in contact with a dietary therapy center is the website of The Charlie Foundation (https://www.charliefoundation.org).

32.3 Epilepsy Surgery

Epilepsy surgery is not new. Its theoretical basis was established by the time Hughling Jackson implicated the cerebral cortex in the pathogenesis of seizures in 1873. Six years later, Macewen performed epilepsy surgery by way of a tumor resection for a patient with intractable seizures in 1879. Wilder Penfield performed his first temporal lobectomy for posttraumatic seizures by 1928. With advancements in surgical technology and better understanding of the pathogenesis of epilepsy, epilepsy surgery has significantly evolved from these early beginnings to a well-established, safe, and effective therapy. In this section, we will review the present indications for epilepsy surgery, the evidence basis for epilepsy surgery, and future advancements in epilepsy surgery in children, in other words, when it is indicated, how it is pursued, and evidence for its efficacy.

32.4 When Is Epilepsy Surgery Indicated?

The American Academy of Neurology, the American Association of Neurological Surgeons, the American Epilepsy Society, and the International League Against Epilepsy [4, 22] recommend that patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs, should be considered for referral to an epilepsy surgery center skilled in pediatric epilepsy surgery for consideration for epilepsy surgery.

Continuing to add medications after two adequate medications failed, the child has a less than 7% chance of being effective. Although surgery is known to be effective particularly in refractory focal epilepsy, epilepsy surgery evaluations continue to be underutilized [23, 24].

The general principle of resective epilepsy surgery is that it should ideally be for seizures arising from a single epileptogenic focus and not in "eloquent" cortex and can therefore be resected without causing an unacceptable neurological deficit.

32.5 How?

32.5.1 Preoperative Evaluation

Epilepsy surgery is best carried out in a multidisciplinary context consisting the epilepsy neurologist, neurosurgeon, neuropsychologist, and neuroradiologist all with pediatric skills. This is a critical aspect of epilepsy surgery and cannot be overemphasized. Preoperative evaluation will start with detailed history and physical examination documenting seizure onset and evolution over time, seizure semiology features, AEDs used and compliance, and family history of genetic syndromes.

Video EEG monitoring with scalp EEG is indicated to document interictal epileptiform discharges and ictal discharges and characterize seizure semiology. The EEG should confirm diagnosis and capture the patient's typical seizures. Reliability of localization is higher for foci in the convexity compared to basal, mesial temporal, or interhemispheric foci, which are more prone to false localization and even false lateralization. While the video EEG ictal recording may not always provide localizing information, they may help with confirming seizure semiology and identifying multiple seizure types and also non-epileptic events.

Newer methods of EEG analysis may provide additional localizing information in cases of extratemporal lobe epilepsy, e.g., EEG dipole analysis and 3D EEG source imaging. Magnetoencephalography (MEG) is more sensitive to tangential sources such as basal or interhemispheric regions. 3D EEG is more sensitive to radially oriented sources. MEG is also able to define smaller foci (4–8 cm^2) compared to EEG (10–15 cm^2).

Structural neuroimaging MRI with specified high-resolution epilepsy protocol MRI, preferably with 3 Tesla and reviewed by a physician skilled in pediatric MRI is mandatory (14, ILAE guidelines) as the identification of epileptogenic substrate on MR imaging has implications for postsurgical outcome. Examples of epileptogenic substrates that may be identified on neuroimaging include focal cortical dysplasia, mesial temporal sclerosis, vascular anomalies (stroke, AVM, hemangioma), inflammatory/infectious lesions (cysticercosis), or tumors (Fig. 32.1). In general a focal cortical lesion is a reliable marker of the epileptogenic region (ER), but the lesion may be smaller or larger than the ER. Multiple lesions may also not mean that there is multifocal onset of seizures, i.e., in tuberous sclerosis or (subependymal) nodular heterotopia. Atrophy and encephalomalacia are less reliable for identifying seizure origin.

There is a window between 4 months and 2 years of age when a lesion, especially focal cortical dysplasia, can be masked, and thus not appreciated, due to increasing but incomplete myelination. Repeating imaging after two years of age is recommended in this setting should seizures persist.

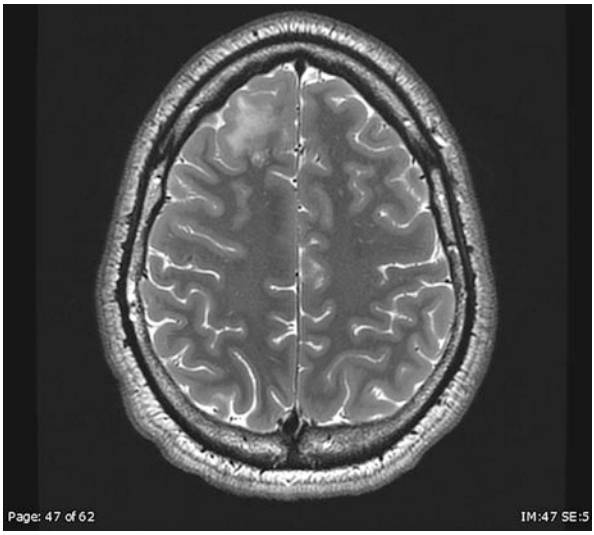


Fig. 32.1 Axial T2W brain MRI scan showing right frontal T2 hyperintensity and blurring of gray-white matter interface indicative of a focal cortical dysplasia. Image credit: Chima Oluigbo, MD

MRI sequences recommended for ages 2 years and older are an anatomic, thin-slice 3D T1-weighted gradient-recalled echo, axial and coronal T2-weighted sequence, fluid-attenuated inversion recovery sequence (FLAIR) axial and coronal, and high-resolution oblique coronal T2-weighed imaging of the hippocampus (fast or turbo spin echo-weighted sequence). Image thickness should be 3 mm with thinner slices of 2 mm T2-weighted for subtle FCD and with 1 mm slice thickness for 3D T1 sequences. For those less than 1 year of age, MRI sequences recommended are high resolution thin (2 mm or less) T2-weighted in three planes: 3D T1-weighted, FLAIR axial (or CUBE), and oblique coronal high-resolution T2-weighted perpendicular to the hippocampus [22, 25].

Metabolic imaging in the form of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) may provide further information. FDG-PET measures regional glucose metabolic rates. It is performed in interictal period and measures relative glucose utilization in suspected epileptogenic regions compared with the contralateral areas. They are prone to effects of seizure propagation and thus more useful for lateralization. Ictal SPECT, on the other hand, shows ictal hyperperfusion in the epileptogenic zone. Subtraction ictal SPECT scans coregistered with MR images can increase diagnostic yield. SPECT (and MEG) may sometimes be misleading due to propagation effects.

Imaging is important as identification and resection of a clear focal MRI abnormality will result in seizure freedom in 75–85% of children; 40–60% of children will achieve seizure freedom when MRI is normal but PET, SPECT, or 3D source localization are focal (review of MRI following functional imaging may identify a previously unappreciated relevant abnormality). For children who are truly image negative, seizure freedom will occur in fewer than 10%.

Functional imaging in the form of functional MRI scan may be indicated to identify eloquent cortex. It is a form of blood oxygenation level dependent (BOLD) imaging that is based on the observation that increased neuronal activity is associated with an increase in cerebral blood flow and therefore an increase in

oxyhemoglobin/deoxyhemoglobin ratio. It is used for mapping language, memory, and sensorimotor location for presurgical planning. Its main role is in lateralizing language function where it has supplanted Wada testing (intracarotid sodium amobarbital), having greater than 90% concordance with Wada testing.

Neuropsychology and neurodevelopmental testing is a requirement for patients being assessed for epilepsy surgery. This provides a preoperative baseline for later comparison to quantify surgical impact and outcome. It characterizes cognitive strengths and deficits more clearly and may provide risk of postoperative deficits and help plan for rehabilitation. It may also aid in localization of the seizure focus.

32.5.2 Invasive Intracranial Monitoring for Localization of Epileptic Focus

In certain situations, the foregoing investigations are unable to provide definitive identification of the epileptic focus, or there is a concern that eloquent cortex lies within or close to the epileptogenic zone. In such a situation, chronic invasive intracranial monitoring is indicated. Thus, this is indicated in non-lesional localization-related epilepsy or in lesional epilepsy where clinical, neuropsychological, EEG, or imaging data are not concordant. It is done by way of placement in intracranial subdural grids or strips or depth electrodes in direct contact with the brain in order to obtain better spatial resolution and definition of the region of seizure onset (Fig. 32.2). In addition to identification of ictal onset, the intracranial electrodes may be used for brain mapping by way of cortical stimulation to identify eloquent cortex. For grids placed over the region of the central sulcus, electrophysiological phase reversal may be used for mapping the motor cortex.

In North America, most chronic invasive intracranial monitoring has typically been done with subdural grids and strips, and parenchymal "depth" electrodes were typically used for recording from hippocampus or specific deep foci. There has recently been a trend toward the more widespread use of stereoencephalography (sEEG), which has been popular for decades in Europe. sEEG allows for placement of multiple depth electrodes through minimal access 2.5 mm twist drill holes in the skull, thus obviating the need for the large craniotomies that is required for subdural strips while enabling

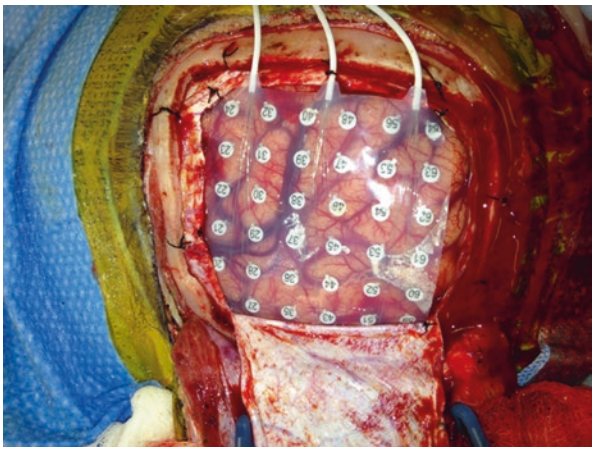
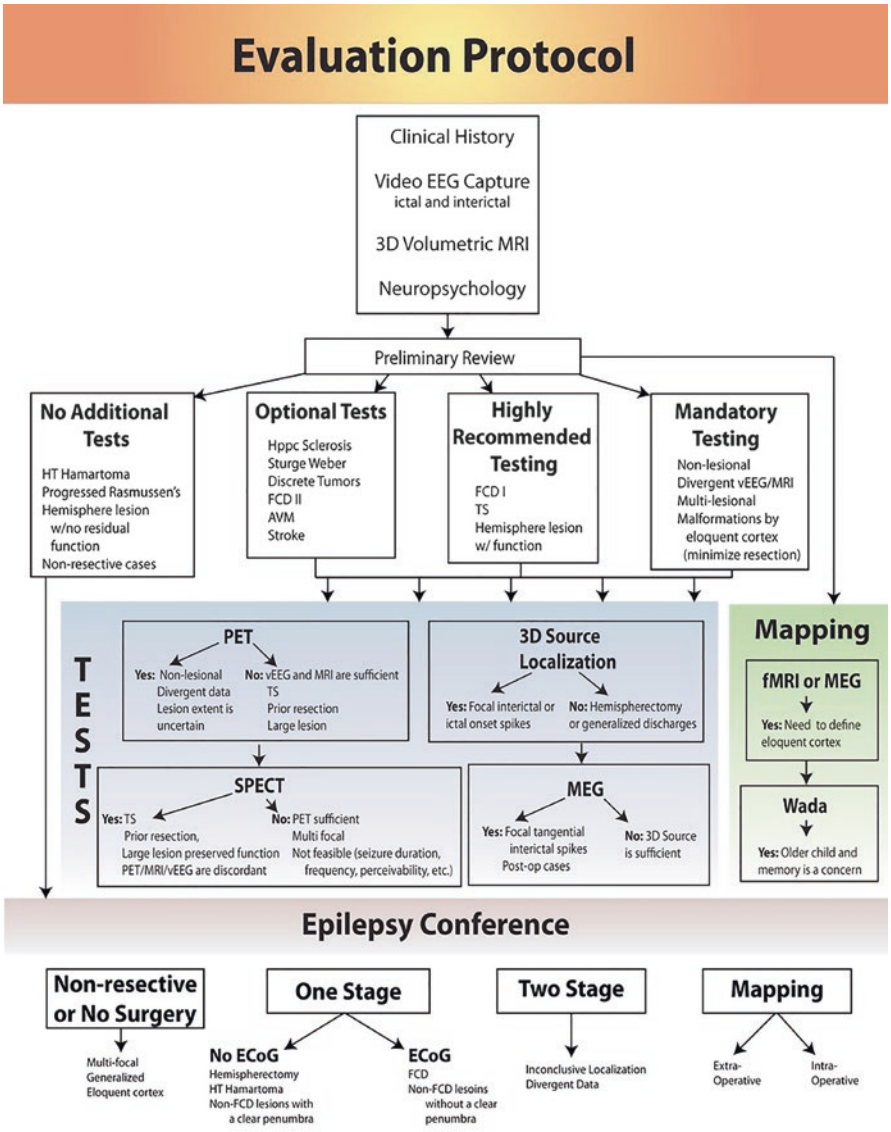


Fig. 32.2 Intraoperative image showing subdural grid in place in the right parietal brain region. Image credit: Chima Oluigbo

electroencephalographic interrogation of deep cortical and subcortical structures. Three-dimensional interrogation of the epilepsy networks and pathways may then be undertaken [26].

Electrocorticography (ECoG) requires prior definition of the origin of seizures and may be influenced by anesthesia and generally provides interictal data. It may be helpful to define the ER extent beyond the anatomical boundaries of a lesion. With focal cortical dysplasia, ECoG may reveal continuous discharges, which are a reliable marker for the epileptogenic region and alleviate the need for extraoperative monitoring.



Proposed ILAE flow diagram for evaluation for children with refractory epilepsy being considered for epilepsy surgery. Source: (14) Jayakar, P, Gaillard, WD, Tripathi M, et al. Diagnostic test utilization in evaluation for respective epilepsy surgery in children. Epilepsia, 55 (4):507–518, 2014

32.5.3 Types of Surgical Procedures for Epilepsy

Epilepsy surgery can be divided into resective epilepsy surgery and disconnective or palliative epilepsy surgery. Resective epilepsy surgery is directed at the surgical extirpation of an identified epileptogenic substrate (identified on the basis of either imaging or electroencephalographic evidence or a combination of both). Disconnective surgery aims to disconnect the pathways of seizure propagation from an identified epileptogenic focus. The reason for resorting to disconnection instead of extirpation of the epileptogenic focus may be because it located in eloquent cortex or it involves a large cortical area. The different types of surgical procedures for epilepsy are listed below. The technical details of these surgeries are not covered as they are beyond the scope of this chapter.

Resective Surgery
- Lesionectomy.
- Selective amygdalohippocampectomy.
- Corticectomy.
- Lobectomy (e.g., temporal lobectomy).
- Multilobar resection.
- Anatomic hemispherectomy.

Disconnective/Palliative Surgery
- Functional hemispherectomy.
- Corpus callosotomy.
- Multiple subpial transections.
- Vagus nerve stimulator.

32.6 Does It Work? (Evidence for the Efficacy of Epilepsy Surgery)

Studies on the efficacy of epilepsy surgery are one of the few studies with level 1 evidence basis in the neurosurgical literature. In 2001, Wiebe et al. published their work on their result on a randomized, controlled trial of surgery for adult temporal lobe epilepsy [27]. In this study, 80 patients were randomized: 40 to surgery and 40 to continued AED therapy. The primary outcome of the study was freedom from seizures, and secondary outcomes were impact on the frequency and severity of seizures, quality of life (QOL), and death. At 1 year, 58% in surgical group versus 8% in medical group ($p < 0.001$) were free from seizures. One patient in the medical group died from Sudden Unexpected Death in Epilepsy (SUDEP); in the surgical group four had memory decline, one had a stroke, and one an infection. This study helped in making epilepsy surgery an established part of the epilepsy treatment armamentarium.

It should be noted that the results of epilepsy surgery are better with temporal lobe epilepsy and lesional epilepsy compared to extratemporal lobe epilepsy and non-lesional epilepsy. For example, seizure freedom rates for lesional temporal lobe epilepsy at 5 years are 69% compared to 45% for non-lesional temporal lobe

epilepsy [28] in adult studies. More recent experience in children with current image techniques suggests that complete resection of a clear abnormality is more important than location of the lesion [29, 30].

32.6.1 Evidence for Timing of Epilepsy Surgery

Even following the establishment of the efficacy of epilepsy surgery, some lack of clarity remains with regard to how much time must elapse or how many AEDs must be found to be inadequate, before surgery is recommended. Thus, the US National Institutes of Health sponsored a large prospective study, the Early Randomized Surgical Epilepsy Trial (ERSET). ERSET was designed to compare anterior temporal lobectomy against 2 additional years of aggressive AED management. Thirty-eight adult patients were randomized to treatment: 23 patients to only continued AED while 15 patients were randomized to anterior temporal lobectomy and AED. Seventy-three percent of the surgical patients became seizure free compared to none (0%) of the medical patients ($p < 0.001$). The surgical patients also had a superior quality of life (QOL) compared to the medical group ($p = 0.01$) [31].

32.6.2 Disconnective and Palliative Surgeries

Corpus callosotomy is particularly helpful in Lennox-Gastaut syndrome (LGS). It was first described in 1940 and used to treat drop seizures (atonic and tonic seizures). The theory behind the corpus callosotomy is to prevent generalized spread of seizures. Newer techniques with microsurgery including radiosurgery ("gamma knife") have reduced adverse effects which included hemispheric edema, mesial hemispheric infarcts, and deaths. The callosotomy may be partial (usually anterior) or complete. It has been associated with improved patient and family quality of life [32].

Another palliative option for children is the vagus nerve stimulator (VNS), which has shown to reduce seizures by 50% in 40% of the patients studied. VNS is a palliative surgery that is extracranial and may be considered in children who are not candidates for respective (curative) surgery. Side effects are relatively minimal with voice alteration, increased drooling, coughing, and dyspnea. VNS has similar reduction rates of seizures compared to corpus callosotomy except for atonic seizures where corpus callosotomy is superior, 54% vs. 80% in reducing atonic seizures >50% [32].

32.7 Emerging Surgical Strategies

32.7.1 Stereotactic MRI-Guided Laser Ablation of Epileptogenic Foci

This novel technique involves the minimally invasive deployment of small profile laser probe using imaging-based stereotactic techniques. Following confirmation of the accurate placement of the probe in the target, laser thermal energy is then

delivered to ablate the identified epileptogenic lesion guided by real time MRI thermography (Fig. 32.3). The real-time MRI thermography images and associated software, which can predict the volume of tissue ablation, allow for precise ablation with real-time control. The system also allows for delineation of temperature limits, which protects adjacent critical structures from the laser energy. This technique is rapidly being established in the management of hypothalamic hamartomas, periventricular nodular heterotopias, tuberous sclerosis, and deep cortical dysplasias [33–36].

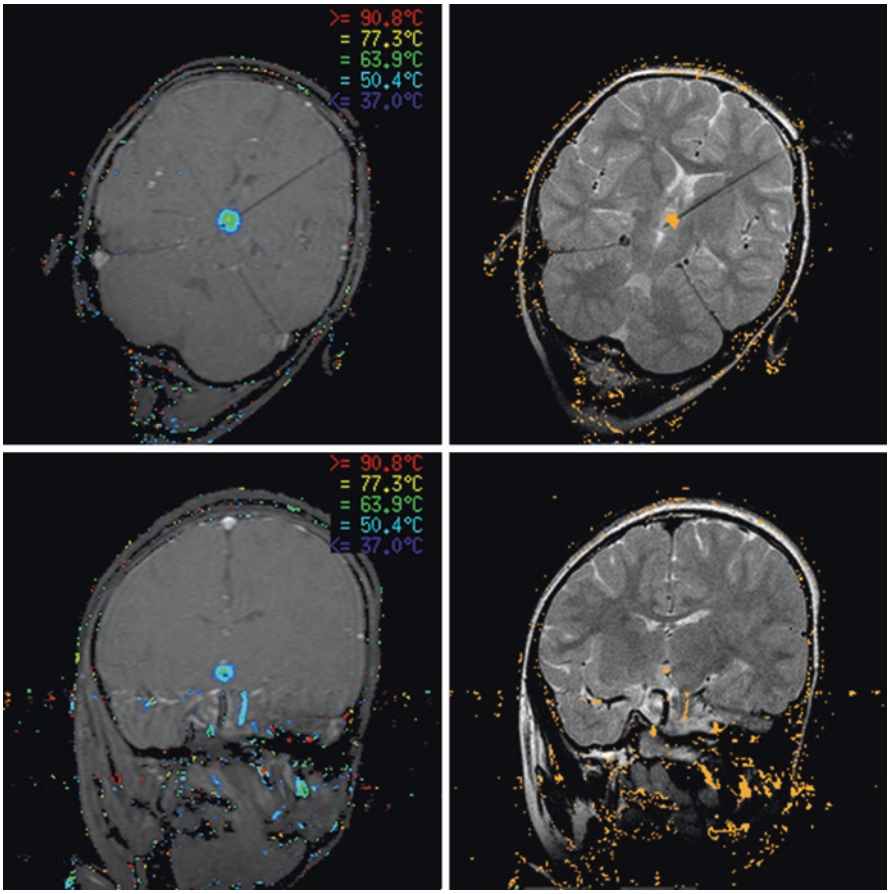


Fig. 32.3 Intraprocedural MRI thermographic and lesion estimate images during MRI-guided laser ablation of a hypothalamic hamartoma. A laser catheter has been placed using stereotactic technique with its tip within the hypothalamic hamartoma. Image credit: Chima Oluigbo

32.7.2 Electrical Neuromodulatory Procedures: Deep Brain Stimulation, Responsive Neurostimulation

Electrical neuromodulation, as a form of epilepsy surgery, is deployed when an identified epileptic focus is very widespread or overlaps eloquent critical parts of the brain such as the sensorimotor cortex. Present neuromodulation therapies for epilepsy include vagus nerve stimulation (VNS) [32]; deep brain stimulation (DBS) of deep brain nuclei including the anterior nucleus (AN) of the thalamus, centromedian (CM) thalamus, STN, and hippocampus; and most recently closed-loop responsive neurostimulation.

The rationale for deep brain stimulation of the thalamic structures is evidence that thalamocortical connections are involved in the development and spread of various types of seizures. The SANTE trial evaluated the efficacy of bilateral DBS of the anterior nucleus for adults with refractory epilepsy in the SANTE trial [37]. This was a prospective, multicenter, double-blind, randomized trial of 110 patients in which a 50% responder rate was achieved in 54% of patients, and approximately one-quarter of patients receiving stimulation were seizure-free. On the basis of this trial, deep brain stimulation (DBS) of the anterior nucleus of the thalamus has been approved for the treatment of refractory epilepsy in Europe and Canada.

Responsive neurostimulation is a progression of cortical or deep brain stimulation. It entails a closed electrical loop design, which allows for delivery of electrical stimulation to an epileptogenic focus following detection of a seizure by a sensor attached to this system. In November 2013, the US Food and Drug Administration granted premarket approval for the NeuroPace RNS System, used to treat medically intractable partial epilepsy. This is the first closed-loop stimulation brain implant in clinical use in the world [38, 39].

32.8 Conclusions

Early recognition and appropriate treatment of epilepsy in children are essential to optimize seizure control and developmental outcomes. Whenever possible, referral should be made early to teams skilled in treating infantile and childhood epilepsy. Any child in whom two medications have failed to control seizures or infants less than 2 years of age should be referred to specialized centers to confirm diagnosis, etiology, tailor therapy, and when appropriate to pursue surgical options. Complaisance in treatment is deleterious to long-term outcomes. In selected patients epilepsy surgery has an excellent likelihood of achieving seizure control. There is mounting evidence that early surgery during infancy before the onset of encephalopathy optimizes long-term developmental outcomes with little risk of untoward outcomes [12, 40]. For children undergoing epilepsy surgery, there is little risk of harming cognitive domains and growing evidence of long-term cognitive and behavioral benefits [41, 42].

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