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REVIEW ARTICLE

Pediatric Epilepsy Surgery: Indications and Evaluation

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Abstract

Epilepsy is a common neurological condition in children. It is usually amenable to drug therapy. However, nearly one-third of patients may be refractory to antiseizure drugs. Poor compliance and nonepileptic events should be ruled out as possible causes of drug-resistant epilepsy (DRE). After failing adequate trials of two appropriate antiseizure drugs, patients with focal DRE or poorly classifiable epilepsy or epileptic encephalopathy with focal electro-clinical features should be worked up for surgical candidacy. A randomized controlled trial provided a class I evidence for epilepsy surgery in pediatric DRE. Pre-surgical screening workup typically includes a high-resolution epilepsy protocol brain magnetic resonance imaging (MRI) and a high-quality in-patient video electroencephalography evaluation. Advanced investigations such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) may be required in selected cases especially when brain MRI is normal, and further evidence for anatomo-electro-clinical concordance is necessary to refine candidacy for surgery and surgical strategy. Some children may also need functional MRI to map eloquent regions of interest such as motor, sensory, and language functions to avoid unacceptable neurological deficits after surgery. Selected children may need invasive long-term electroencephalographic monitoring using stereotactically implanted intracranial depth electrodes or subdural grids. Surgical options include resective surgeries (lesionectomy, lobectomy, multilobar resections) and disconnective surgeries (corpus callosotomy, etc.) with the potential to obtain seizure freedom. Other surgical procedures, typically considered to be palliative are neuromodulation [deep brain stimulation (DBS), vagal nerve stimulation (VNS), and responsive neural stimulation (RNS)]. DBS and RNS are currently not approved in children. Pediatric DRE should be evaluated early considering the risk of epileptic encephalopathy and negative impact on cognition.

Keywords Epilepsy surgery · Drug-resistant epilepsy · Pre-surgical workup · Children

Introduction

Epilepsy surgery has significantly evolved over the last century, not only in terms of surgical approaches but also conceptually. The origin of epilepsy surgery dates back to the late nineteenth century when Sir Victor Horsley did epilepsy surgery for Jacksonian march [1]. The invention of electroencephalography (EEG) further improved the approach and management of epilepsy. However, the introduction of newer antiseizure drugs (ASDs) did not alter the proportion of drug-resistant epilepsy (DRE) [2]. Besides, with improving surgical techniques, perioperative anesthesia, intensive care, and experience, the perioperative morbidity and mortality of pediatric epilepsy surgery has significantly improved making it an acceptable treatment option early in the childhood DRE. Considering the prevalent acquired structural etiologies underlying DRE and relative scarcity of well-equipped epilepsy surgery centres in developing countries like India, a huge surgical treatment gap exists [3].

When to Consider and Refer Children for Epilepsy Surgery?

Although most patients with epilepsy respond to ASDs, nearly one-third remain drug-refractory [2, 4]. Also, epilepsy has a dynamic course, especially in young children with developing

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brains [5]. International League against Epilepsy (ILAE) defines drug-responsive epilepsy as epilepsy in which the patient has been seizure-free on ASD regimen, for at least three times the longest inter-seizure interval or 12 mo, whichever is longer [6]. Similarly, ILAE proposed a definition for DRE as "Failure of adequate trials of two tolerated and appropriately chosen and used ASD schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom where seizure freedom refers to freedom from all types of seizures for 12 mo or three times the pre-intervention inter-seizure interval, whichever is longer" [6]. Studies show that after the failure of two ASDs, chances of seizure remission with subsequent ASD trials is less than 10% while epilepsy surgery is effective in terms of seizure freedom in more than half of patients after temporal lobe resections and nearly 40% of patients following extratemporal resections [7–9]. A randomized controlled trial and a multicentric cohort study in children with DRE corroborated similar results with the attainment of seizure freedom in 7% and 31% of those in the medical treatment group and 77% and 60% in the surgical treatment group, respectively [10, 11]. Hence, all children with DRE should be evaluated for surgical amenability since epilepsy surgery is more effective than ASD therapy after the failure of two ASDs in those with surgically amenable epilepsy.

Why Consider Epilepsy Surgery?

Besides seizure control, epilepsy surgery has been associated with improved trajectory of cognitive development (depending on the type of resection and region removed), psychiatric and social functioning, a better quality of life, and reduced mortality in patients with DRE [10, 12–17]. DRE is often associated with cognitive and psychosocial dysfunction in children. Stabilization or improvement of these issues is seen in a significant proportion of children following epilepsy surgery (especially in those with epileptic encephalopathy due to focal brain lesion) [13, 14, 16, 18]. This might be attributed to better seizure control, prevention of progression to epileptic encephalopathy, reduction or stoppage of ASD, and neuroplasticity. A recent meta-analysis in children also concluded a significant improvement in the quality of life compared to preoperative state [weighted mean difference (WMD): 16.7 points] and matched medically treated controls [WMD:12.4 points] [16]. Also, seizure freedom is associated with a reduction in the risk of epilepsy-related mortality and sudden unexplained death [17]. Besides, epilepsy surgery is a relatively safe procedure and major complications are rare when surgery is done at centers with experience in pediatric epilepsy surgery [19]. Therefore, epilepsy surgery is effective in children and offers durable benefits beyond seizure remission. No age should be considered bar for early and timely epilepsy surgery.

How to Select Children for Epilepsy Surgery?

Many children require simple noninvasive tests to assess surgical candidacy. For example, in cases with a well-defined brain magnetic resonance imaging (MRI) lesion in a noneloquent brain region that is concordant with the seizure semiology and video electroencephalography (VEEG) data, lesionectomy can be done without further testing with a good outcome. In other cases, further testing is likely needed. There is a common misperception that a history of status epilepticus, generalized seizures, epileptic encephalopathy such as infantile spasms, Lennox–Gastaut syndrome (LGS) are contraindications to epilepsy surgery. Although pre-surgical evaluation of children with epileptic encephalopathy is demanding, presence of epileptic encephalopathy does not rule out surgical candidacy, and these children should not be excluded from presurgical evaluation [20]. Children with DRE commonly have associated comorbidities such as cognitive delay or regression, behavioral, and psychiatric conditions and these tend to worsen with higher seizure burden and longer duration of epilepsy. Although epilepsy surgery in children poses additional challenges, such as young age, low weight, frequent need for large brain resections, physiological immaturity, and difficult functional mapping in young children (< 6 y), the recovery following surgery tends to be better in children than that in adults due to neuroplasticity [21–23]. Table 1 illustrates the selection criteria for candidature for epilepsy surgery.

General Principles and Hypothesis Underlying DRE

The concepts of epilepsy surgery have been extrapolated from adults to children, however with modifications, incorporating neuroplasticity in children. The pathophysiology underlying epilepsy surgery can be explained under two basic concepts:

1. *Localization hypothesis and zone concept*: This aims at the identification of "epileptogenic zone (EZ)" i.e., the region of

Table 1 Selection criteria for candidature for epilepsy surgery

- Established diagnosis of epilepsy
- Drug refractoriness
- Debilitating seizures
- Recurrent status epilepticus
- Localizable epileptogenic region with a brain MRI lesion and/or when without an MRI lesion supported by concordant evidence from VEEG and functional imaging
- Informed and motivated parents
- Any progressive underlying cause/neurodegenerative disease ruled out (except Rasmussen's encephalitis)
- High likelihood of improvement in quality of life with seizure control

MRI Magnetic resonance imaging; *VEEG* Video electroencephalography

brain capable of generating seizures, which when completely resected leads to seizure freedom [24]. This assumes that in patients with DRE, there is a central lesion, with an ictal-onset zone (where the seizure originates; detected by the ictal EEG) and irritative zone (involved in generating inter-ictal epileptiform discharges; detected by inter-ictal EEG) (Fig. 1) [24]. Symptomatogenic zone is the area that produces clinical symptoms of ictus, but whose removal may not result in seizure freedom while functional deficit zone refers to hypometabolic area on functional imaging and it is usually larger than the EZ. Epileptogenic lesion refers to an anatomical abnormality visible on imaging, which can produce seizures and should be ideally removed during epilepsy surgery. Hence, the zone of surgical resection should include EZ but not necessarily entire EZ to elude resection of the critical cortex. However, EZ is often undefined since the available investigations only provide an approximate estimate.

2. *Network hypothesis*: The concept of EZ fails to explain localization in DRE with complex epileptogenesis (35%) [25]. Gradually, the identification of epilepsy as a network disorder led to the evolution of the network hypothesis [26]. This hypothesis assumes that the neurons in the brain are not randomly connected and the epileptogenic networks evolve dynamically and tend to recruit newer neurons over a while. The upfront networks may be easily defined by a good quality MRI (epilepsy protocol) and a VEEG. But the more complex networks require advanced investigations such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), and invasive evaluation using stereotactically implanted depth EEG electrodes (SEEG), and in some instances subdural electrodes.

Pre-Surgical Evaluation

Children with DRE should be evaluated at a comprehensive epilepsy center by a multidisciplinary team of pediatric neurologists/neurologists/epileptologist, neuroradiologists, neurosurgeons, and neuropsychologists. The goal of epilepsy surgery is seizure freedom and a better quality of life. The presurgical evaluation consists of establishing surgical candidacy by confirming focal-onset epilepsy, and defining epileptogenic zone by anatomo-clinical-electrographic-concordance and its relationship to eloquent function mapping when necessary [24, 27]. Evaluation begins with a thorough history and physical examination. The importance of a comprehensive evaluation of ictal semiology and frequency cannot be understated. The ultimate goal of the pre-surgical evaluation is to establish a region of the brain that is sufficient and necessary to obtain seizure freedom by studying the concordance of data obtained from the anatomo-clinical (history, physical examination, event video, MRI brain, nuclear imaging); electrographic (scalp VEEG, MEG, invasive EEG in selected cases); and functional (assessment of pre-existing deficits, neuropsychologic testing, functional MRI, brain mapping by direct cortical stimulation) testing.

Noninvasive Localization of EZ

1. *Clinical localization based on seizure semiology*: Seizure semiology corresponds to the symptomatogenic zone. However, it can provide ancillary information about EZ or the ictal-onset zone. The ictal symptoms may be produced by the spread of epileptiform activity from secondary areas despite the origin from the ictal-onset zone. Hence, the reliability of clinical localization is not that good. Specific auras and ictal semiology have different localizing and lateralizing value [28]. However, seizure semiologies in young children are elementary as compared to adolescents and adults [29]. Common seizure semiology in infants and young children with DRE are often nonlocalizing, nonlateralizing, and bland and include epileptic spasms, myoclonic seizures, hypomotor seizures, etc. [30]. Few lateralizing signs which may be useful in children and infants include focal clonic, focal tonic, predominantly unilateral spasms, and ictal nystagmus [29]. Also, the difficulties in getting an accurate seizure account in children cannot be understated. Hence, a poor repertoire of semiology and difficulties in eliciting an accurate history of seizure from parents and nonverbal children limits the clinical localization in infants and young children [29].
2. *Inter-ictal and ictal EEG:* Inter-ictal EEG (for irritative zone) and ictal video EEG (with at least 3 habitual seizures; for ictal-onset zone) are typically necessary to help in localization. However, in infants and young children, focal findings may be masked by generalized epileptiform abnormalities [31]. Structural etiology (including focal structural abnormalities) constitutes a significant proportion of those with LGS and West syndrome [32, 33]. The age-dependant tendency of secondary synchronization and evolution of epileptic encephalopathy results in specific epilepsy syndrome, thereby concealing the focal EEG abnormalities in some patients [32].
3. *High-resolution brain MRI:* High-resolution brain MRI (3 Tesla) with epilepsy protocol is needed to identify any focal lesion such as focal cortical dysplasia, mesial temporal sclerosis, etc. The ILAE Neuroimaging Task Force recommends the use of the Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol with high-resolution 3D T_1 gradient echo sequences, 3D fluid-attenuated inversion recovery (FLAIR) sequences, and 2D sub millimetric T2 sequences [34]. It is critical to obtain MRI appropriate for child's age due to significant age-based differences. Between the ages of 9 mo and 18 mo with

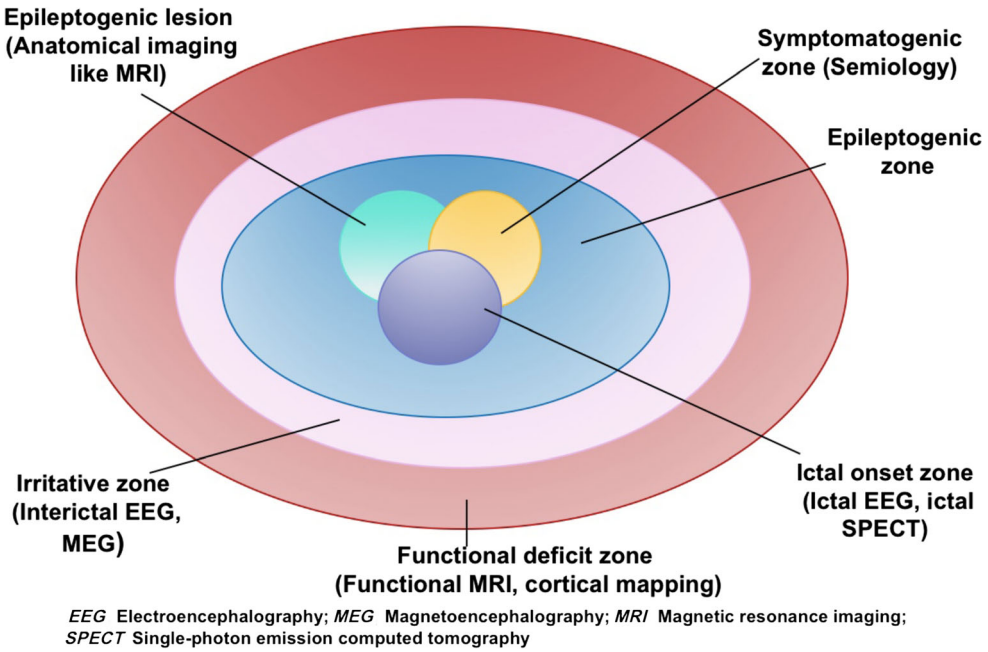

Fig. 1 Different zones along with yielding investigations (mentioned in brackets) according to the localization hypothesis

changing pattern of myelination, lesions may disappear or become less obvious, to re-emerge later with adult MRI characteristics [35].

4. *Other imaging modalities:* SPECT and PET are useful in cases when concordance between video EEG and a non-lesional brain MRI requires further confidence in the localization of EZ. Concordance between SPECT and PET is useful. An inter-ictal PET scan may reveal a focal region of hypometabolism which helps in EZ localization [36]. Similarly, ictal SPECT may also be useful in EZ localization by identifying an area of hyperperfusion corresponding with the focal ictal onset and early ictal spread. Using the subtraction ictal SPECT co-registered to MRI (SISCOM) technique, ictal SPECT image can be subtracted from inter-ictal SPECT image and superimposed onto MRI resulting in better delineation [36]. However, ictal SPECT poses challenges in children since extratemporal epilepsy (with brief and rapidly propagating seizures) is common. It should be considered in selected children when PET imaging is discordant with MRI or in patients with epilepsy surgery failure [36].
5. *MEG:* This helps in locating the 3-dimensional (3D) source of inter-ictal discharges. MEG detects the brain activity produced by recording magnetic fields due to the electrical currents generated by neurons. It is an advanced investigation with high spatiotemporal resolution. In comparison to EEG source imaging which is sensitive to vertical dipoles, MEG is sensitive to tangential dipoles [37]. Inter-ictal MEG may help in the localization of epileptiform activity which corresponds to the irritative zone [37]. MEG localization is especially useful in patients with previous neurosurgery or other skull defects or failed surgery [37, 38].

Invasive Localization of EZ

1. *Long-term invasive EEG evaluation:* Selected children may require intracranial EEG for better delineation of EZ and ictal-onset zone and/or mapping of eloquent brain function. Intracranial electrodes may be inserted through craniotomies (for strip and grid subdural electrodes) or via robotic-assisted navigation for precise placement of depth electrode without craniotomy. Recently, stereotactic EEG (SEEG) is becoming popular as it is minimally invasive and provides 3-D orientation of the epileptogenic focus [39]. Since the electrode coverage is limited, both these require a prior hypothesis for possible EZ location that should be confirmed or improved with the data acquired during the invasive EEG evaluation.
2. *Intra-operative electrocorticography (ECoG):* This technique involves placing an electrode grid or depth electrode directly on the brain's surface for performing EEG recordings in the operation room at the time of planned surgery and can be done before and after resection. This may be useful especially for focal cortical dysplasias in children with repetitive and frequent inter-ictal epileptiform discharges [40].

Noninvasive Localization of Eloquent Cortex

Eloquent or critical cortex is the cortical area, which if removed, results in paralysis or loss of linguistic ability or sensory processing such as vision. Either functional MRI (fMRI) or MEG may help in lateralization of language function and motor mapping. However, there are very few studies on fMRI

Table 2 Epilepsy surgery techniques

1. Resective surgeries (mostly curative)
   - i) *Lesionectomy:* Removal of the lesion such as focal cortical dysplasia
   - ii) *Sublobar tailored resection and lobectomy:* Removing a part of cerebral lobe e.g., temporal lobe, frontal lobe, etc. or whole lobe (lobectomy)
     - a) Anterior temporal lobectomy with amygdalo-hippocampectomy (ATLAH)
     - b) Selective amygdalohippocampecotmy (SAH)
     - c) Extratemporal resections
   - iii) *Multilobar resections:* Removal of parts or all of two or more cerebral lobes
   - iv) *Hemispherectomy:* Anatomic (removal of hemisphere) and functional (removal of small part with disconnection)
   - v) *Lesioning by ablation*
     - a. Ultrasound guided ablation
     - b. Laser interstitial thermal therapy (LITT)
     - c. *Gamma* knife radiosurgery
2. Disconnective surgeries
   - i) *Corpus callosotomy*: Splitting of corpus callosum
   - ii) *Multiple sub-pial transections*: Transections in the cortex underneath pia mater to disrupt the neural connections
   - iii) *Multilobar disconnections*: Disconnection of fibers connecting different lobes
3. Neuromodulation
   - i) Vagal nerve stimulation (VNS)
   - ii) Responsive neural stimulation (RNS) — not approved in children
   - iii) Deep brain stimulation (anterior thalamus) — not approved in children

in pre-surgical evaluation of children [36]. Also, the use of fMRI in children is difficult considering movement artifacts and poor cooperation for specified tasks due to young age and developmental delay [24, 36].

Invasive Localization of Eloquent Cortex

Wada test used to be done for lateralization of language but it is currently sparingly used due to the availability of fMRI. Also, it cannot be used in young children due to a lack of cooperation. The standard investigation for functional localization is electrocortical stimulation mapping. This is done by cortical stimulation with gradually increasing stimulus intensity and duration. It can be used either intraoperatively or in an extraoperative setting (via stereotactic depth or subdural electrodes). Invasive methods are also difficult in children because of the associated patient discomfort and the need for patient cooperation [24, 41].

Surgical Options

Surgical options can be broadly classified as curative (with an aim to attain seizure freedom) and palliative (with an aim to achieve a significant reduction in seizure burden). Further, the surgeries may be classified as:

1. *Resective surgeries*: These are usually curative and are resorted to when a focus or network has been identified such as lesionectomy, resection for focal cortical dysplasia, temporal lobectomy for mesial temporal sclerosis, etc. (Table 2).
2. *Hemispherectomy:* In patients with hemispheric DRE, hemispherectomy (functional or anatomic) may be useful. Indications include Rasmussen encephalitis, Sturge–Weber syndrome, hemimegalencephaly, or extensive unilateral hemispheric damage. Anatomic hemispherectomy comprises of the resection of gray matter of cerebrum sparing the subcortical structures. Functional hemispherectomy (or hemispherotomy) encompasses temporal lobectomy, disconnection of the frontal and parieto-occipital white matter, corpus callosotomy, and a large central resection [42]. Also, hemispherectomy may be a practical option in young children as compared to adults, considering less morbidity due to neuroplasticity.
3. *Disconnection surgeries:* They are usually palliative surgeries such as corpus callosotomy in children with multiple drop attacks (especially tonic seizures in LGS) [43].
4. *Neuromodulation:* Neuromodulation should be considered only when any resective curative option has been ruled out by a comprehensive pre-surgical evaluation.

This includes several options (Table 2). Most experience in children is with vagal nerve stimulation in DRE and it is also reported to reduce the frequency and severity of drop attacks in LGS [43].

Evaluation of Epilepsy Surgery Outcome

Two classification systems are used for postoperative seizure outcomes after epilepsy surgery. These include Engel classification and ILAE classification [44]. Engel classification includes four categories: class I (optimal; free from disabling seizures), class II (acceptable; rare disabling seizures), category III (worthwhile improvement), and category IV (least desirable; no worthwhile improvement) while ILAE classification with six categories gives a better measure of seizure outcome. Considering the ambiguity in delineating EZ, category IV outcomes are not rare. In children, outcomes after resective surgeries are similar to adults and are better for well-circumscribed lesions as compared with malformations of cortical development [9, 11, 22]. Overall, seizure-free outcome at 2 y after surgery is seen in around 75% of children who underwent hemispherectomy, 67% of children with lobar or focal resections, and 55% of children with mutilobar resections [45].

Conclusion

Epilepsy surgery is a safe and effective treatment option for children with DRE. With growing research and experience, the number of possible candidates for epilepsy surgery has increased and the peri-operative morbidity and mortality of pediatric epilepsy surgery has also significantly improved making it safe and effective even in infants. Establishing anatomo-electrographic-clinical concordance remains the cornerstone of pre-surgical evaluation. Pre-surgical evaluation for epilepsy should be considered early and timely in all children who fail to respond to medical treatment.

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Compliance with Ethical Standards

Conflict of Interest None

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