



Epilepsy Surgery in Children versus Adults

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Epilepsy is one of the most common chronic neurological disorder affecting 6–7 per 1000 worldwide. Nearly one-third of patients with newly diagnosed epilepsy continue to have recurrent seizures despite adequate trial of more than two anti-seizure drugs : drug-resistant epilepsy (DRE). Children with DRE often experience cognitive and psychosocial co-morbidities requiring more urgent and aggressive treatment than adults. Epilepsy surgery can result in seizure-freedom in approximately two-third of children with improvement in cognitive development and quality of life. Understanding fundamental differences in etiology, co-morbidity, and neural plasticity between children and adults is critical for appropriate selection of surgical candidates, appropriate presurgical evaluation and surgical approach, and improved overall outcome.

Key Words : Epilepsy · Surgery · Drug resistant epilepsy · Child.

INTRODUCTION

Nearly one-third of all patients with newly diagnosed epilepsy continue to have break-through seizure despite adequate trial of more than two anti-seizure drugs : drug-resistant epilepsy (DRE)^{26,33}. DRE is often accompanied by serious co-morbidities including cognitive delay, psychosocial impairment, and drug-related side effects^{19,20}.

Epilepsy surgery is considered to be the best treatment option if an epileptic focus is well defined and is removable without sacrificing eloquent function^{12,13,46}. While the basic principle remains the same regardless of age, epilepsy surgery in children requires understanding of unique neurobiological aspects of developing brain : age-dependent epilepsy syn-

drome; diverse etiology; effects of chronic epilepsy and anti-seizure drugs on brain development and plasticity.

AGE-DEPENDENT EPILEPSY SYNDROME

Epilepsy presents differently based on the age of patients. Focal pathology such as unilateral congenital stroke or hemimegalencephaly may present with infantile spasms in early infancy, while same etiology may present with a focal seizure in later life. This creates a challenge in terms of surgical decision as seizure semiology and electroencephalography (EEG) pattern may mimic generalized epilepsy despite apparent focal pathology. In addition, frequent epileptic seizures and epilep-

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tic spikes in children are associated with severe cognitive delay or regression out of proportion to the severity of epilepsy, termed as epileptic encephalopathy²⁰.

DIVERSE ETIOLOGY

Most of the adult onset epilepsy is due to acquired pathologies such as mesial temporal sclerosis (MTS), brain tumor, stroke, central nervous system infection, and immune mediated pathologies. In children, genetic and metabolic disorders as well as developmental malformation are much more common.

Presurgical evaluation in children with DRE requires thorough a clinical exam, laboratory, and imaging tests. It is important to rule out genetic/metabolic disorders such as B6 dependent epilepsy and glucose transporter deficiency. Genetic evaluation should be considered when DRE is accompanied by cognitive and neurological deficit without clearly identified structural pathology or when there is family history of epilepsy. While ion channel mutations such as sodium voltage-gated channel alpha subunit 1 or potassium sodium-activated channel subfamily T member 1 mutation can often mimic focal epilepsy, surgery is not beneficial except in the form of palliative surgery such as corpus callosotomy (CC). On the other hand, not all genetic etiology should be excluded from surgery; focal cortical dysplasia (FCD) due to germ line and somatic mutation in mammalian target of rapamycin (mTOR) pathway may be amenable to surgical intervention^{4,34,36}.

Recent advances in immunology have allowed the diagnosis of various autoimmune encephalitides presenting with DRE. Explosive seizure onset combined with mental status change should raise suspicion for an autoimmune encephalitis such as anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis⁴⁸. Early recognition and aggressive immune modulating therapy may be warranted.

BRAIN PLASTICITY

Epilepsy surgery is generally discouraged if epileptic focus overlaps eloquent cortices. Incomplete resection of epileptogenic zone because of the possible post-operative deficit may lead to surgical failure. In younger children (under age 6) or

cognitively delayed older children, functional mapping is not feasible, making the surgical treatment of DRE more challenging. However, children tend to have better and faster recovery than adults following surgery involving eloquent cortices because of brain plasticity¹⁰. In addition, congenital or early acquired pathology facilitate intra- or inter-hemispheric transfer of eloquent functions. These factors need to be considered in planning hemispherectomy for hemimegalencephaly or Rasmussen's encephalitis; and in determining resective margin in MRI negative DRE in children.

INDICATION AND TIMING FOR PRESURGICAL EVALUATION

In adults, epilepsy surgery is considered when patient has recurrent disabling seizures despite adequate trial of anti-seizure drugs. Patients are typically referred to tertiary epilepsy center when seizures persist after trying several anti-seizure drugs over 2–3 years or longer. In children, the presentation of DRE is often rapidly progressive. Children can have very frequent seizures from the onset and often experience status epilepticus requiring intensive care unit (ICU) admission. In addition to seizures, children with DRE sometimes present with severe developmental regression. Therefore, children with DRE can require early and urgent referral to a tertiary epilepsy center.

PRESURGICAL EVALUATION

The goal of presurgical evaluation for DRE is four-fold : 1) to confirm the diagnosis of epilepsy; 2) to find the etiology of epilepsy; 3) to localize the seizure focus; and 4) to assess the risk of neurological deficits associated with removal of a potential seizure focus.

Confirmation of epilepsy and etiological work-up

Non-epileptic psychogenic seizures are not as common as in adults. However, other non-epileptic paroxysmal disorders unique to pediatric population needs to be considered, including cardiac arrhythmia, gastroesophageal reflux, paroxysmal movement disorder, tic disorder, breath-holding spells, and sleep disorders.

Etiological work-up

Once epilepsy is confirmed, the specific etiology of epilepsy needs to be investigated. Genetic and metabolic disorders present predominantly in early childhood. Some of these conditions can be treated with specific disease modifying treatments. For example, glucose transporter 1 deficiency or B6 dependent epilepsy can be treated with ketogenic diet or vitamin B6 respectively. In the case of an autoimmune or immune related epilepsy, immune modulating treatment should be initiated. Most importantly, only palliative surgical procedures such as corpus callosotomy should be offered to patients with genetic, metabolic, or autoimmune related epilepsies, as resective surgery is rarely effective for these types of epilepsy.

Localization of seizure focus

Presurgical evaluation in children should be customized depending on the age, developmental status, and reported seizure types, frequency, and duration. Most patients require long-term video-EEG monitoring and brain magnetic resonance imaging (MRI) with a special epilepsy protocol. When MRI and EEG do not provide adequate localizing information, fluorodeoxyglucose-positron emission tomography or single photon emission computerized tomography may be added to the evaluation. Magnetoencephalography (MEG) may reveal an irritative zone even if scalp EEG doesn't show any on account of a tangential source location.

Scalp EEG is often misleading in pediatric epilepsy. Focal or hemispheric pathology may present with generalized seizures and diffuse bilateral EEG onset^{17,51}. Furthermore, scalp EEG can falsely lateralize seizure onset to the healthy hemisphere in cases of congenital stroke or brain tumor⁵⁰. If a hemispherectomy is considered, the decision should include MRI findings in these cases regardless of discordant EEG findings.

MRI findings of FCD can be subtle before 2 years of age as the brain is not fully myelinated. FCD may only become evident on later MRIs when myelination is more complete. FCD type I is generally less circumscribed and less impressive than type 2. Additionally, the extent of FCD is often more diffuse than is appreciated by MRI, requiring invasive EEG monitoring (IEM) and sometimes multi-lobar resection³².

Neuropsychological evaluation

Pediatric DRE patients have a high incidence of neurodevelopmental and mental health disorders as a co-morbidities⁴⁹.

Detailed age-appropriate neuropsychological assessment should be performed in all patients if feasible before and after surgical intervention¹⁰. Comprehensive neuropsychological evaluation may be helpful to confirm localization of seizure onset in focal epilepsy, and can be used to assess the risk of cognitive morbidity associated with surgical treatment options. Advanced procedures such as functional MRI (fMRI) or intracarotid amobarbital testing may also be used to evaluate language and memory in selected older children. As such, the neuropsychology team should be actively involved in planning presurgical evaluation, determining and designing surgical procedures, and post-operative follow-up. Post-operative evaluations are important to identify the need for therapeutic interventions to address any changes that may occur after surgery. Cognitive delay or neurobehavioral disorder should not be used as justifications for deferring surgery. Successful surgery even in children with severe neurocognitive and/or behavior impairments (e.g., autism) can reduce caregiver burden and improve quality of life in the patient and caregivers. Post-operative changes in cognitive development and quality of life should be assessed as separate outcome measures in epilepsy surgery.

Counseling on benefit and risk for epilepsy surgery

The most common reason for underutilization of pediatric epilepsy surgery in developed countries is parents' fear of new neurological deficit following surgery. Unlike adults, young children or cognitively delayed young adolescents may not be eligible for non-invasive functional mapping tools such as fMRI or MEG. When a seizure focus is localized to the left hemisphere regardless of handedness, a clinician needs to discuss not only the risk of language deficits from surgery but also recovery potential due to brain plasticity. It is well accepted that language function can be transferred within or outside an epileptic hemisphere especially when the pathology is congenital or acquired shortly after birth⁶. This concept of brain plasticity in the developing brain applies to the epilepsy surgery itself, making a compelling argument for early surgery.

Another important aspect of preoperative counseling with the family is to set the expectation for benefits from surgery. While seizure outcome can be roughly estimated based on prognostic variables, eventual functional outcome could be quite difficult to predict even with seizure-freedom. If a primary pathology is responsible for both epilepsy and cognitive

impairment, simply removing a seizure focus may not reverse progressive cognitive decline²⁰.

Finally, the family should be informed of the risk of uncontrolled seizures in children, including sudden unexpected death in epilepsy (SUDEP). The definition of SUDEP is “the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death”. The risk of SUDEP in pediatric epilepsy is estimated to be 0.90–2.22 per 1000 patient years similar to adults according to a recent study²⁸. Early age of onset, high seizure frequency, mental delay, multiple anti-seizure drugs, and structural abnormalities are associated with a higher risk of SUDEP¹.

IEM

A patient may be amenable to one step surgery without IEM when an well circumscribed lesion is corresponding to the clinical semiology and scalp EEG and its removal is not expected to create a functional deficit.

IEM is considered for the following reasons. 1) Inconclusive preoperative data (e.g., normal or nonspecific MRI scan or multiple lesions) : IEM continues to play a significant role in this patient subgroup, especially when functional imaging data are inconclusive. Removal of the entire region of seizure onset zone identified on IEM is generally required to achieve seizure freedom²³. IEM also helps clarify uncertainties of seizure origin and propagation in children with ill-defined cortical dysplasia or multiple lesions such as tuberous sclerosis⁷. 2) Divergent preoperative data : when divergence occurs in the context of large or deep-seated lesions, a combination of subdural and strategically placed depth electrodes is recommended²⁴. And 3) proximity of eloquent cortex : subdural EEG is preferred methods of cortical stimulation mapping over stereo-EEG (SEEG) while this preference may change with more experience in SEEG⁵. Electrocorticography (ECoG)-based functional mapping has been studied to help cortical mapping in children.

Choice of IEM between subdural EEG and SEEG should be strictly based on a hypothesized epileptogenic zone and patient characteristics. Subdural EEG generally has a higher

complication rate than SEEG but may be able to provide more accurate cortical mapping results especially when suspecting neocortical epilepsy³⁸.

SEEG is suited better for deep seated foci (insular, cingulate, orbitofrontal, inferior occipital), multiple lesions (tuberous sclerosis complex), and suspected diffuse epileptogenic network³⁷. The use of SEEG has increased dramatically in the U.S. since the wide adoption of robot assisted frameless stereotaxic system¹⁵.

Combination of subdural EEG and depth EEG may be useful in small number of patients where cortical mapping is critical but cannot ignore possible involvement of deep gray matter or poorly accessible cortical regions³⁹.

SURGICAL PROCEDURES

Surgical procedures for pediatric epilepsy can be broadly categorized as curative vs. palliative procedures. Curative procedures include lesionectomy, corticectomy, lobectomy, and hemispherectomy. Palliative procedures include implantation of vagus nerve stimulators, deep brain stimulators, responsive neurostimulators, and corpus callosotomy.

Lesionectomy

Removal of a pathologic lesion can be performed with or without IEM depending on the location and pathology of the lesion. For example, when scalp EEG and clinical semiology are concordant with a benign appearing tumor such as ganglioglioma or dysembryoplastic neuroepithelial tumor in non-dominant hemisphere, complete resection of tumor may be recommended as the first step⁴².

IEM : goal, complication and its prevention and surveillance

Most pediatric patients require IEM to identify seizure onset zone(s), improve seizure outcome, and to limit neurological deficit following surgery. During IEM, the patient is closely monitored in an ICU setting with 24 hour a day, 7 days a week EEG technician surveillance and frequent neurological assessments. Complications of IEM such as cerebral edema, intracranial hemorrhage, and ischemic stroke may present with non-specific deterioration of mental status, which may not be easily detected without close monitoring. In addition, a pa-

tient may develop atypical seizures different from habitual seizures during IEM because of subdural or SEEG related complications.

Hemispherectomy

Hemispherectomy is indicated if an epileptic pathology is diffusely distributed in one hemisphere and seizure-freedom is unlikely without complete disconnection of the hemisphere. Common etiologies for hemispheric epilepsy include hemimegalencephaly, diffuse hemispheric FCD, congenital large vessel stroke, Sturge-Weber syndrome, and Rasmussen's encephalitis.

Hemispherectomy in children could be challenging for a few reasons. 1) While majority of hemispheric epilepsy patients have pre-existing neurological impairment including hemiparesis and language delay, patients with preserved language and motor function may require a long period of rehabilitation following the surgery. When hemispherectomy is performed in younger patients, the rate and extent of recovery is greater than when surgery is performed in older children. 2) Despite MRI evidence of hemispheric pathology, EEG and seizure semiology can be misleading with either generalized onset or falsely lateralizing to a healthy hemisphere. For example, diffuse hemispheric FCD or hemimegalencephaly may present with infantile spasms not lateralized either by EEG or clinical semiology. While hemispherectomy of the diseased hemisphere most often leads to seizure-freedom, the possibility of bilateral seizure onset due to a somatic mutation or mosaicism needs to be clearly explained to parents before surgery. And 3) surgical failure following hemispherectomy is not uncommon and may be related to either incomplete disconnection or independent epilepsy onset from the healthy hemisphere⁹. The most common areas of incomplete disconnection include basal forebrain anterior to hypothalamus, insular cortex, and corpus callosum. Intra-operative MRI with diffusion tensor imaging tractography and insular ECoG may be beneficial in ensuring that a technically adequate disconnection has been accomplished^{29,30}. Genetic evaluation of pathologic tissue may suggest the possibility of bihemispheric pathology³⁶. Reoperation is considered only after careful reevaluation demonstrating incomplete disconnection and after seizure onset from the healthy hemisphere has been ruled out³.

MRI-guided laser interstitial thermal therapy (MRgLITT)

MRgLITT ablates an epileptogenic zone using laser generated thermal energy delivered by a stereotactically placed laser probe. The extent of thermal injury is monitored using near-real-time MR thermography. MRgLITT can be used as a single step procedure without IEM in selected lesional cases such as MTS and cavernous hemangioma. In more complex cases, confirmation of epileptogenic zone using SEEG may improve seizure outcome. MRgLITT can be especially useful in ablating deep seated seizure focus such as MTS, hypothalamic hamartoma, insular foci, cingular foci, and periventricular heterotopic nodule²⁷.

Palliative surgery

When an epilepsy onset zone can be identified and safely resected, an epilepsy cure can be achieved. Unfortunately, many DRE patients are not candidates for curative surgery. For those individuals, palliative surgery may be an option. To palliate is to relieve or lessen without curing. Palliative epilepsy surgical procedures are designed to reduce but not eliminate a patient's seizure burden. Any of the curative surgical procedures can be performed as a palliative procedure if patients and family agree with the idea that subsequent reduction of seizure frequency and severity may improve the quality of life. For example, lobectomy or hemispherectomy may be offered in patients with multifocal or bihemispheric epilepsy who have daily seizures despite multiple anti-seizure drugs with a clearly stated goal of improving seizure control, not seizure-freedom. The following procedures were designed to be inherently palliative regardless of epileptic syndrome : 1) corpus callosotomy (CC), 2) multiple subpial transection (MST), 3) vagus nerve stimulator (VNS), 4) deep brain stimulator (DBS), and 5) responsive neurostimulation (RNS).

CC is most effective for drop attacks – tonic/atonic/generalized tonic-clonic seizures leading to falls^{2,41,47}. In addition, CC may lateralize seizure focus in otherwise generalized, unlocalizing epilepsy^{8,21}. Patients with super-refractory status epilepticus have been treated with CC¹⁸. Complete CC is more effective than anterior 2/3 CC with no substantial differences in complication except transient disconnection syndrome^{16,22}. While acute disconnection syndrome was more common in complete CC group, none of the patients reported permanent disconnection syndrome.

MST is a surgical procedure for a seizure focus overlapping eloquent cortical regions such as language and primary sensory, motor cortices. MST has been reported to have modest effect in seizure reduction (70% of patients with >50% reduction and 33% seizure-free) with few long-term deficits (6.4%) in adults⁴⁰. In children with Landau-Kleffner syndrome, MST did not provide any additional benefit over medically treated group¹¹.

VNS was originally approved as an adjunctive treatment for partial seizures in adults with DRE. However, the indication has been extended to under age 4 since 2017. VNS has modest seizure reduction : 40–60% of patient reporting >50% seizure reduction⁴⁴. VNS is reported to reduce the incidence of status epilepticus⁴⁴. VNS is less effective than CC for drop attacks, but may have synergistic effect in combination⁴³.

DBS is an open-loop neural stimulation system targeting thalamic nuclei or hippocampus. Current approval of DBS in the U.S. is only for focal epilepsy in adults targeting anterior thalamic nucleus. However, off-label use of centromedian thalamic nucleus stimulation is reported to be effective against generalized convulsive seizures or drop attacks³⁵.

RNS is distinct from VNS and DBS because electrical stimulation is only delivered when electrographic seizure is detected by implanted subdural or depth electrodes (close loop stimulation). RNS is currently approved for adult DRE patients with 1–2 identified seizure foci not amenable to resective surgery due to expected functional deficit or bilateral independent seizure foci. RNS in patients with bilateral independent seizure foci provides an added benefit of chronic intracranial EEG monitoring on anti-seizure drugs which could lead to a better lateralization and subsequent resective surgery. In adults, median seizure reduction was 51–70% depending on the location of seizure focus²⁵. There are only a few case series in pediatric DRE, but the seizure outcome seem to be equivalent to adults^{31,45}.

CONCLUSION

DRE in children is an enormous challenge for patients, families, and communities. Optimal treatment of pediatric epilepsy requires understanding of the unique neurobiology of pediatric epilepsy : diverse etiology, age-dependent epilepsy syndrome, and brain plasticity. Selecting a treatment option

should be tailored to the patient's specific epilepsy etiology, co-morbidity, developmental status, and risk tolerance. The decision and choice of surgical intervention in pediatric DRE requires consensus of multidisciplinary epilepsy team including epileptologists, neurosurgeons, and neuropsychologists. The patients and their family should be fully informed of benefits and risks of surgery as well uncontrolled epilepsy. Adoption of minimally invasive surgery procedures such as robot assisted SEEG and MRgITT may increase the utilization of epilepsy surgery in children.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

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