Review Article

Surgery for pediatric drug resistant epilepsy: a narrative review of its history, surgical implications, and treatment strategies

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Background and Objective: Drug-resistant epilepsy (DRE), also known as medically refractory epilepsy, is a disorder of high prevalence and negatively impacts a patients quality of life, neurodevelopment, and life expectancy. Pediatric epilepsy surgery has been conducted since the late 1800s, and randomized controlled trials have demonstrated the marked effectiveness of surgery on seizure reduction and the potential for cure. Despite the strong evidence for pediatric epilepsy surgery, there is also strong evidence describing its underutilization. The objective of this narrative review is to describe the history, strength, and limitations in the evidence of surgery for pediatric drug resistant epilepsy.

Methods: This narrative review was conducted utilizing standard search engines to include the relevant articles on the topic of surgery for drug resistant epilepsy in children, with main keywords including surgery in pediatric epilepsy and drug-refractory epilepsy.

Key Content and Findings: The first components describe the historical perspective of pediatric epilepsy surgery and the evidence that highlight the strengths and limitations of epilepsy surgery. We then highlight the importance of presurgical referral and evaluation, followed by a section detailing the surgical options for children with DRE. Lastly, we provide a perspective on the future of pediatric epilepsy surgery.

Conclusions: Evidence supports the role for surgery in pediatric medically refractory epilepsy in seizure frequency reduction, improved curative rates, and improvements in neurodevelopment and quality of life.

Keywords: Drug-resistant epilepsy; epilepsy surgery; temporal lobectomy; pediatric neurosurgery

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Introduction

Drug-resistant epilepsy (DRE) is defined by the International League Against Epilepsy (ILAE) as the failed response of epilepsy to two adequately dosed anti-epileptic agents (1). Of the 50 million people with epilepsy worldwide, one-third are inadequately controlled with medications (2). Among all children, 5% experienced a seizure by age 20 and recent studies show up to 470,000 children in America are diagnosed with epilepsy (3-5). Pediatric DRE is more complex when compared to adults with DRE, and may be secondary to an interplay of diverse etiologies, such as focal cortical dysplasia, variability in seizure semiology and electroencephalography (EEG) (3). Children also have remarkable capabilities of neuroplasticity that isn't seen in adults (6). Thus, early identification and remedy of DRE may reduce the possibilities of undertreated epilepsy's longstanding consequences. DRE is found to diminish cognitive function, education, and employment, and increase a child's risk of death when compared to the general population (3,7-10).

Patients who fail 2 or more first line agents are less likely to respond to further combinations and may greatly benefit from surgical evaluation and management (2,11,12). The goal of surgery is to eliminate or mitigate seizure activity,

Table 1 The search strategy summary

Items	Specification
Date of search	March 1st, 2022
Databases and other sources searched	PubMed, EBSCO, Cochrane Database
Search terms used	"drug resistant epilepsy", medically refractory epilepsy", "neurosurgery", "seizure", "epilepsy", "treatment failure", "pediatrics"
Timeframe	1887–2022
Inclusion and exclusion criteria	Historical review, Observational and Experimental trials were included
Selection process	Study selection was conducted by independent authors

EBSCO, Elton B. Stephens Company.

preserve neurological function, reduce or eliminate the need for medications, and to improve the patient's quality of life (13,14). Authors describe that early epilepsy surgery provides improved seizure outcomes (15). In 2008, over 70% of surgical cases were readily apparent operative epilepsy cases (16). Yet despite these findings, and other strong evidence that supports the utility of surgery in medically refractory epilepsy, the number of patients referred for surgery and who undergo epilepsy surgery are less than expected (17,18). Traditional, open surgical resection and disconnection surgery aim to achieve seizure freedom, reducing the need for medications and improving the patient's quality of life. However, there have been a number of less invasive surgical options with remarkable benefit that focus on seizure reduction and potentially cure, such as laser interstitial thermal therapy (LITT), responsive neurostimulation (RNS) or vagal nerve stimulation (VNS). Continued advancements in artificial technology, neuroimaging, and stereotaxis are enhancing surgical options while achieving meaningful outcomes for pediatric patients with DRE (19).

In this narrative review, we aim to describe the existent literature behind pediatric surgery for medically refractory epilepsy, including resection, disconnection, and stimulation options. We also aim to describe the surgical considerations that pediatricians, neurologists, and neurosurgeons can utilize in their practices. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-200/rc).

Objectives

(I) To define the current management of drug-resistant pediatric epilepsy;
(II) To describe the indications for a surgical role in pediatric DRE;
(III) To highlight potential barriers to pediatric epilepsy surgery.

Methods

This narrative review was conducted utilizing PubMed, EBSCO and Cochrane database search engines to include the relevant articles on the topic of DRE. Keywords included "drug-resistant epilepsy", "medically refractory epilepsy", "neurosurgery", "seizure", "epilepsy", "treatment failure", and "pediatrics" (*Table 1*). This was not a systematic review; therefore, no formal framework was utilized for the review of abstracts, and manuscripts and for choosing full texts for the inclusion in this manuscript. We utilized references from highly cited articles published on medically refractory epilepsy, including manuscripts detailing observational trials, experimental trials, and systematic reviews.

Discussion

History of surgery for pediatric epilepsy

Surgery for pediatric epilepsy dates to the late 19th century when neurosurgeons such as Victory Horsley, William Macewen, and Fedor Krause established the potential role of surgery. Dr. Victor Horsley in 1886 performed a craniotomy for a 22-year-old male with seizures. He utilized the conceptual framework from Jackson and Ferrier on cerebral localization of seizure discharges. This was when Dr. Macewen reported epilepsy-related surgery within the pediatric population in 1879 (20,21). In 1893, Fedor Krause described the first use of electrical stimulation during surgery and expanded epilepsy surgery to include

cases of non-lesional epilepsy (20). Dr. Wilder Penfield in the 1920s utilized the work of prominent neurologists using EEG to plan surgery based on electrocorticography. Dr. Penfield describes cortical functional mapping with intraoperative stimulation throughout the cerebral cortex in a 14-year-old boy. Soon after, Penfield and the Montreal Neurological Institute in the 1930s were the first to utilize invasive electrodes for long-term EEG monitoring, which paved the future way for the technique we term stereoelectroencephalography (SEEG) later described by by Talairach (22). Jean Talairach and Leksell developed frame-based techniques that allow for more accessible and faster implantation of depth electrodes. Intraoperative electrocorticography with subdural grids was reported by Penfield in the 1950s (23). The efficacy and utility of the SEEG technique by a North America group in Cleveland, Ohio has reintroduced and expanded its use.

In 1938, McKenzie performed the first hemispherectomy for epilepsy in a child with infantile hemiplegia (24). Where van Wagenen utilized the corpus callosotomy for a patient with epilepsy and a callosum infiltrating tumor (25). Krynauw in 1950 performed anatomic hemispherectomy in 12 children and reported complications such as significant blood loss, coagulopathy, aseptic meningitis, hydrocephalus, and death. Around that time, Frederic and Erna Gibbs in the United States attempted to define temporal lobectomy surgery (26). In 1949, Penfield described the standard temporal lobectomy technique, and the understanding of temporal lobe epilepsy was further advanced by Murray Falconer in London by defining mesial temporal sclerosis (MTS) as the most common histopathological entity in temporal lobe epilepsy. Falconer's advocacy for pediatric epilepsy surgery and his published case series highlighted the benefit of surgery in children. These results paved the way for others including Dr. Rasmussen and Dr. Sidney Goldring who describe larger case series with good outcomes (27). In 1974, Theodore Rasmussen developed the functional hemispherectomy, where a large resection and an extended temporal lobectomy achieved an epilepsy cure. Various techniques have been described with an endoscopically-assisted hemispherectomy approach being most recently described (28). Later on in 1982, Wieser described the selective amygdalohippocampectomy approach for mesial temporal epilepsy (29). In 1998, the ILAE formulated a set of guidelines and recommendations for epilepsy in children and defined DRE (30).

The utilization of imaging techniques in the 1990s further expanded surgery for epilepsy, but it was not until the 21st century that the first publication of a randomized controlled trial described the benefit of surgery in DRE in adults. In 2001, Wiebe *et al.* demonstrated seizure freedom at 1 year in 58% of patients compared to 8% in the medical arm in patients with temporal lobe epilepsy who underwent temporal lobectomy (31). Just over 10 years later, Engel and his group published results from the Early Randomized Surgical Epilepsy Trial which highlighted 73% of patients were seizure-free two years after surgery compared to the medical arm for patients with temporal lobe epilepsy (32). Before this study, the same group in 1996 described the outcomes of the surgical procedures in their single-center experience with rates of seizure freedom being as high as 67% (33). As these trials included only adults, evidence for surgery for children with temporal and extratemporal epilepsy was lacking. The first randomized controlled trial for pediatric epilepsy surgery was conducted by Dwivedi and group in Southeast Asia (34). They included children and adolescents who met ILAE criteria for DRE, with focal or secondary generalized seizures. They showed that 77% of patients in the surgical arm were seizure-free at 1 year compared to 7% in the medical arm. Most commonly performed was temporal lobe resection, but extratemporal resection, hemispherectomy, corpus callosotomy, and disconnection or resection of hypothalamic hamartoma were also performed. Those with temporal lobectomy or hypothalamic hamartoma all became seizure-free. Patients with extratemporal resection and hemispherectomy had 92% and 87% seizure freedom, respectively. Adverse effects, such as include monoparesis, hemiparesis, and hypotonia, were seen in 33% of patients in the surgical arm, with most showing meaningful improvement over their 12-month follow-up. This study in addition to those performed in the adult population pronounced the efficacy of surgery as a formidable treatment modality for intractable epilepsy.

Pre-surgical referral and evaluation

The ILAE suggests that all children with DRE be evaluated at a comprehensive epilepsy center and offered a consultation for surgery (6,35). Providers must consider all aspects of the child's epilepsy, including the etiology, semiology, and patient-specific disparities to streamline the child's care. First, it is important to consider if there is subtherapeutic dosing of the antiepileptic medications, inaccurate seizure diagnosis, and non-compliance with AEDs (35,36). It should be considered that children may grow out of their epilepsy, while others such as children

Table 2 Pediatric surgical considerations

Seizure semiology	Auras are uncommon, seizures may remit; complex montage on EEG
Pre-surgical testing	Advanced neuroimaging and neuropsychological testing may be challenging and confounded
Etiology	Most common seizure etiology are focal cortical dysplasia or brain tumor
Stereotaxy and frame-based navigation	Leksell head holder is not optimal for children <3 years of age
Blood loss	Children have less overall blood volume than adults with (70 cc/kg)
Stimulative technique	Evidence for DBS and RNS is limited at this time, but growing
Access	There are 256 epilepsy centers in the United States, but disparities exist for low-income households
Neuroplasticity	Children far more capable to achieve neuroplasticity compared to adults
Referral (45)	DRE diagnosed on average 6 months following epilepsy, and 10–17 months thereafter

EEG, electroencephalography; DBS, deep brain stimulation; RNS, responsive neurostimulation; cc, cubic centimeter; DRE, drug-resistant epilepsy.

with lesional epilepsy, West Syndrome, or Lennox-Gastaut syndrome may benefit from earlier surgical referral (2). All patients are unique with variable genetic, environmental, pharmacodynamics, unique imaging characteristics, and should be treated on a case-by-case basis.

Despite the prevalence of DRE, a great majority of patients are not referred for surgery. The lack of surgical referral may reflect a misunderstanding of the surgery in comparison to the risks of persistent DRE (35,37,38). Knowledge and attitude toward surgery for referring providers may be contributing factors (35). Roberts intended to identify neurologist attitudes toward epilepsy surgery (39). Amongst the Canadian population, roughly 60% did not believe seizure freedom was a reason for referral and nearly half believed the failure of two antiepileptic agents defined DRE. Those that were refractory to medications for over one year warranted a surgical referral. Studies report the average time to surgery for children is over 5 years. This may be attributed to concerned parents regarding surgery, lack of knowledge of surgical options, undiagnosed epilepsy, and lack of information on surgery after an epilepsy diagnosis (40). A study in adult patients demonstrated their concern for the loss of independence, paralysis, and brain death (41). More than half of patients reported that they would not undergo surgery unless there was a 100% success rate. This may be a shared belief held by children's caregivers. Another barrier to surgical referral and performance is access and availability of multidisciplinary care of epilepsy before and after surgery. Englot *et al.* and the ILAE encourages the need for referral of medically refractory pediatric patients to comprehensive epilepsy centers, assuming that all comprehensive epilepsy centers, have multidisciplinary care, including neuropsychological and neurodevelopmental testing (6,42). Evidence strongly supports the pre-surgical neuropsychological testing to determine the degree of behavioral, executive, and cognitive function because surgery may impact these functions (43). This evaluation may be difficult and subject to confounding variables when performed in children. In surgery for hypothalamic hamartoma, neuropsychological and developmental testing of memory, vision and endocrine function should be considered given the location adjacent to the chiasm and hypothalamus (6).

Conditions such as cortical dysplasia, tuberous sclerosis complex, polymicrogyria, hypothalamic hamartoma, hemispheric syndromes, Sturge-Weber syndrome, and Rasmussen syndrome are appropriate diagnoses for early surgical referral (6). Education on these potentially surgical indications and the risks and benefits of surgery are critically important to addressing early need for pediatric epilepsy surgery (44) (*Table 2*). Factors that have been described to impact surgical referral include age at diagnosis, the presence of developmental delay, psychiatric comorbidities, availability of a comprehensive epilepsy center and appropriate neurological imaging (36). Once access to appropriate epilepsy testing is available to the child, continuous EEG with scalp electrodes is recommended. Seizure foci localization and identification on EEG and radiographic imaging portend better results from surgery (30). If localization is indeterminate, high-

resolution imaging, with 3T or voxel-based magnetic resonance imaging, or even positive emission tomography, single-photon positive emission tomography, and magnetoencephalography are potential options to be considered for identifying regions associated with seizure events (46). In patients with challenging pathologies, such as multifocal epilepsy with multiple tubers, ictal SPECT and/or invasive SEEG may be helpful modalities to delineate epileptogenic zones or indicate the need for multiple staged operations (6). Transcranial magnetic stimulation is an option for the functional mapping of key eloquent regions before surgery to create a safer pathway in surgical resection. It has also been described to have efficacy in the treatment of cortical epilepsy not amenable to resection (47,48). Additionally, cortical stimulation during acute and chronic recording affords for localization of eloquent cortex in patients older than two years of age (6). Cognitive analysis demonstrates worse function with earlier epilepsy onset (10). Pre-surgical evaluation makes these patients challenging given the developing white matter tracts and increased likelihood of multifocal epilepsy, as is seen in cryptogenic or catastrophic epilepsies, congenital migration disorders, such as polymicrogyria, or perinatal stroke epileptogenic zones. These patients are most likely to undergo hemispherectomy or multilobar resection with intraoperative corticography (16,49).

Socioeconomic disparities in surgery for pediatric epilepsy are not to be ignored. There are disparities in the referral to epilepsy centers, which may be the result of referrals directed to low-volume centers (35). Patients with a lower income status are more likely to have epilepsy than those that are not (50). Lower socioeconomic status may not only prolong the time to surgery, but it may reduce the odds of having surgery when indicated (17,51). Those with higher household incomes are more likely to have surgery, which may be consistent with the greater hospital cost required for those with pediatric surgery compared to patients without surgery. There are over 120,000 children hospitalized with epilepsy alone, compared to 2,000 who obtain pediatric surgery per year (17). Children that have epilepsy are considered to require more healthcare resources when compared to children without epilepsy (50). In the long run, if seizure freedom is achieved with surgery, healthcare utilization will decrease over time.

Surgical approaches

The first cases of pediatric epilepsy surgery set the precedent for treating a life-altering, debilitating condition, but the expansion of pediatric neurosurgery in epilepsy has been further increased over the last two decades as evidence of a proven success. If there is a focus of epileptogenic activity, there are three forms of surgery that may be discussed with the patient and the caregiver, resective, disconnective or stimulative surgery.

Invasive surgical encephalography may also be utilized in non-lesional and lesional epilepsy to characterize seizure foci and cortical spread. The placement of depth electrodes for seizure foci localization dates to the mid-1900s, however the advent of frame-based and frameless stereotaxy, including robotic-assisted technology has strengthened the utilization of this methodology in surgical epilepsy, as it has decreased operative time, increased the speed, and accuracy of depth electrode placement (52-54). Invasive monitoring typically requires a two-stage operation with placement, removal of depth electrodes, and subsequent surgical resection if the seizure origin is identified. Invasive monitoring helps identify the source of the seizures in cases where scalp EEG may show multifocal or bilateral ictal discharges, discordance between epileptiform activity and the ictal zone, and the EEG and imaging. Most often, it cannot be performed until three years of age when the calvarium is sufficiently thick (>2 mm) (53). Although, the risks of multi-stage depth electrode surgery may include CSF fistula, meningitis, wound infections, scar formation, neurological deficit, edema, and withdrawal from antiepileptic medications, they are low and the technique is considered safe and well-tolerated in patients. As an alternative, Bansal *et al.* described the prospective study of single stage surgical resection with intraoperative electrocorticography (ECOG) for children with a variety of underlying pathologies (55). In their cohort, they observed rates of 80% seizure freedom (Engel class I). They described no major neurological complications and 3% of subjects had minor or temporary complications. The surgery entails performing a craniotomy with intraoperative ECOG, followed by surgical resection of the focus of interictal attenuation and/or spikes. Patients may have a preceding pathology visualized on preoperative imaging, such as focal cortical dysplasia or an intracranial tumor, in which direct surgical resection is indicated. In some instances, resection with ECOG can be performed as a second stage after invasive monitoring localizes an epileptogenic zone. Throughout surgery, the utility of anti-epileptic agents must be kept at a minimum in order to make interictal recording feasible. As compared to SEEG alone where the incisions are much smaller, with more

invasive surgical approaches there are higher risks of wound complications, infection, stroke and permanent neurological deficits, including memory loss (49). The risks and benefits must be weighed by the referring surgeon and discussed with the child's parents. Another indication for open surgical, single staged resection may be in the case of highly localized focal cortical dysplasia with preoperative identification as was described by Macdonald, in which functional status was preserved without complication seen (56).

Detection of key cortical areas in epilepsy surgery is critical to avoid morbidity and mortality (34). The use of intraoperative electrocorticography allows for cortical mapping and localized resection, with sparing of normal grey and white matter especially in regions of eloquent cortex. Advances in preoperative and intraoperative neurophysiology and neuroimaging are constantly developing, making surgery safer and faster (57). The use of robotic stereotactic depth electrodes has increased the rapidity of surgery and enhanced localization of epilepsy zones in non-lesional epilepsy (53). Younger children may have multifocal pathology in the presence of solitary lesions making this type of ancillary testing necessary (36). Cases in which multiple lesions, such as in tuberous sclerosis, are found and where focal cortical dysplasia difficult to discern but is suspected, the role of advanced imaging and comprehensive electrophysiology assessment to determine epileptogenic focus may be challenging for the surgeon (58). The utilization of high-frequency oscillations may be a biomarker for identifying epileptogenic zones (59). Magnetoencephalography may be an imaging modality for correlating localizations with seizure localization (60). The broadened utility of 7T MRI may identify small areas of neocortical dysplasia that would otherwise not be seen with less powerful magnets (61). BOLD functional MRI and diffusion tensor MRI with tractography allow for advanced mapping when eloquent cortex and/or white matter tracts may be involved in epileptogenic focus or prospective surgery (62). Additional utilization of MRI in the intraoperative setting may assist in complete total resection rates, especially with tumor, dysplastic lesions or electrocorticography is difficult to ascertain (63).

Resective or ablative surgery

The goal of resective or ablative surgery is to identify a surgical target and safely remove or provide thermal energy to the focus, to provide epilepsy freedom. We describe the following techniques included in this category.

Temporal lobectomy

The support for surgery for epilepsy stems from surgery for mesial temporal epilepsy originally described by Penfield and by the randomized controlled trials that have then followed (23). In a worldwide review of epilepsy reported in 2008, frontal and temporal lobe resections accounted for up to 40.7% of resective surgery with 23% of surgery reported as an anteromesial temporal resection (16). The resection of pediatric brain tumors, such as dysembryoplastic neuroepithelial tumors and gangliogliomas are the predominant reason for performing temporal lobectomy in children, followed by cortical dysplasia and MTS (16). The success of surgery for epilepsy was first described for adults with seizure freedom rates as high as 78% to 100%, but as previously mentioned Dwivedi later described the efficacy in children (32,64). Despite the rates described, an overall decline in temporal resection has been reported, with the rates of less invasive surgical options increasing (18,65).

Spencer describes the traditional anterior temporal lobectomy for resection of temporal epilepsy (66). The surgeon here targets the lateral middle and inferior temporal gyri, approximately 3.5 to 4 cm from the anterior temporal tip on the language dominant side and up to 6 cm on the non-dominant side to the region of the vein of Labbe. Key neurovascular structures at risk include the optic radiations, uncinate fasciculus, and inferior longitudinal fasciculus, but the surgeon's understanding of these neuroanatomical relationships can mitigate the risk to these white matter tracts. Injury to the lenticulostriate branches and the anterior choroidal artery can yield unilateral hemiparesis. The surgeon must be aware of the approaches to the insula, via the transsylvian or transopercular (right-sided) approaches, and be mindful of the crossing white matter tracts such as the arcuate fasciculus, extreme capsule, and external capsule (inferior aspect of insula). Minor and major complications of surgery have been reported as up to 8%. Deficits could include a decline in verbal memory, aphasia if extensive resection is performed on the dominant hemisphere, and neurological injury secondary to vascular injury to the deep brain stem perforators on the medial side.

In 2000, Foldvary described seizure outcomes in their cohort of adolescents and adults after temporal lobectomy for temporal lobe epilepsy (67). Over the follow-up of 14 years, 65% achieved Engel class I. As described earlier, Wiebe *et al.* described a randomized controlled trial of surgery for temporal lobe epilepsy, describing seizure freedom and quality of life benefit (31). In 2003, Sinclair *et al.* described their pediatric cohort of 5-year follow-

up with 78% seizure freedom and 12% with a significant reduction in seizures (68). York *et al.* highlighted a 20-year surgical cohort of 150 patients with complex partial seizures and typical or atypical temporal sclerosis, or a temporal lobe tumor that underwent anterior temporal lobectomy. They demonstrated classic MTS had the best outcomes, with atypical mesial sclerosis demonstrating less benefit (43).

Selective amygdalohippocampectomy

The goal of selective amygdalohippocampectomy surgery is to spare the lateral temporal cortex, traversing the white matter while removing the epileptogenic amygdala and hippocampus (69). Niemeyer in 1958 described this selective approach as he described sparing the temporal cortex through a transventricular approach (70). Wieser described patients with seizures localized to the amygdala or hippocampus who underwent amygdalohippocampectomy. Twenty-two patients were free of seizures, and compared to patients with temporal lobectomies, preservation and improvement of certain cognitive features were seen (29). There are several surgical approaches including the trans-middle temporal gyrus, transsylvian, and subtemporal approaches (69). Today, the operation is less commonly performed, given the advent of novel epilepsy surgical approaches, such as MRIgLITT therapy (71).

Extratemporal epilepsy

In children, extratemporal lobe epilepsy has been identified as more common than mesial temporal lobe epilepsy (16). The principle of mitigating damage to surrounding neocortical regions is imperative (72). Relapse is more likely to be found in neocortical resective surgery compared to mesial temporal surgical resection (72). Conditions including cortical dysplasia, prior stroke, arteriovenous malformation, and Rasmussen encephalitis are likely etiologies for this epilepsy condition (73). Focal cortical dysplasia the most common etiology of pediatric epilepsy is predominantly seen in multilobar epilepsy. It is more commonly observed in the frontal lobe than in the temporal lobe (16,74). Tuberous sclerosis, gliosis, Sturge-Weber and a history of stroke are more commonly seen extratemporally compared to brain tumors (16). Patients who have extratemporal brain tumors do better with electrocorticography-guided resective surgery, in comparison to cortical dysplastic lesions (55,75). Surgical resection may be aided by both intraoperative neuronavigation and mapping, particularly in patients who are younger with less identifiable lesions on preoperative imaging. Patients with a longer duration of presurgical extratemporal epilepsy have less improvement in cognition after extratemporal resection compared to those who are younger who may have greater benefit (37).

In a recent review of epilepsy surgery in low and middle income countries, there has been an increase in extratemporal lobe epilepsy surgery. In the United States between 2012 and 2019, there has been an expanded use of extratemporal lobe surgery. In comparison to temporal lobe surgery, it is performed twice as often, but still lags far behind the growth rate seen in other less invasive treatment options (18).

Magnetic resonance guided laser interstitial thermal therapy (MRIgLITT)

MRIgLITT is a developing methodology that provides thermal ablation targeted at epileptogenic foci (76). A small craniotomy allows for interval stereotactic placement of a laser applicator with subsequent magnetic resonance imaging assuring placement and subsequent planning and application of thermal damage. Classically, an open pterional craniotomy was performed for patients with hypothalamic hamartoma, but the evidence for laser interstitial thermal therapy (LITT) is as an extremely effective option for the gelastic seizures caused by this pathology (77). As a feasible option in MTS management, LITT has proven efficacy of up to 78% seizure reduction in patients, with greater success if the amygdala, head of the hippocampus, and the parahippocampal gyrus are also targeted (78). Englot in 2016 described mesial temporal lobe epilepsy ablation, but the provider must be mindful of heat application to avoid visual disturbances secondary to thermal spread to the lateral geniculate nucleus (14). Studies across multiple centers in the US describe this as a safe, reliable alternative to conventional selective amygdalohippocampectomy (71,79,80). Most patients achieved seizure freedom. Roughly 15% of patients had complications, including visual field deficits and psychiatric affective disorders. Lewis described a cohort of pediatric patients with lesional epilepsy of various etiologies in which 7 of 17 patients achieved seizure freedom after LITT (76). Smaller cohorts demonstrate safety and efficacy such as in cortical tuber and low grade glioma pediatric patients, all of which may be epileptogenic in children (81). McCracken and group achieved seizure freedom in 4 of 5 patients with cavernous malformations, with the additional patient requiring surgical resection to achieve Engel class I. Multi-staged surgeries utilizing laser ablation were also performed for some subjects in order to provide seizure freedom (82).

In a case series of two patients with periventricular nodular heterotopia who underwent LITT, both achieved seizure freedom (83).

Disconnection

The main principle of disconnection surgery is to provide disconnection between hemispheric epilepsy. An example of this approach is hemispherectomy. It involves complete resection of one hemisphere. For patients with infantile spasms, Rasmussen encephalitis, hemimegalencephaly, hemispheric cortical dysplasia, Sturge-Weber syndrome with vascular calcifications, perinatal cerebral infarction, hemispherectomy can be considered. First described by Walter Dandy for glioma. In 1938, McKenzie utilized it first for hemispherectomy for seizures in infantile hemiplegia. While in 1950, Krynauw performed the anatomic hemispherectomy on 12 children. Risks include significant blood loss, coagulopathy, aseptic meningitis, hydrocephalus, and death, but a great benefit for disconnection was seen. In 1974, Theodore Rasmussen developed the functional hemispherectomy, with a large resection and extended temporal lobectomy (27,28). Various techniques have been described since including the hemispherotomy technique described by Delalande, the endoscopically assisted hemispherectomy technique and endoscopic transventricular approach used for hypothalamic hamartoma being most recently described which aim to reduce the amount of brain tissue removed (84,85). A multicenter analysis described the evolution of the Hemispherectomy Outcome Prediction Scale evaluating outcomes of over 1,200 patients (86). With utilization of this score, dysplastic etiologies or patients with infantile spasms do worse after hemispherectomy and the use of preoperative MRI was a significant component in determining indication for surgery.

Seizure freedom occurs in up to 85% of patients, with acquired or progressive conditions, unilateral seizure targets on EEG being predictive of success (87). Risks of this surgical option must be considered. As the advent of functional hemispherectomy mitigated risks of hydrocephalus and hemosiderosis, the incidence of post hemispherectomy hydrocephalus remains up to 30% (88). Evidence does support the cauterization of the choroid plexus in these cases to reduce the risk of hydrocephalus. In a review of 208 children who had undergone surgery, hemispherectomy was associated with defined complications that included surgical blood loss, and the need for transfusion (89). Cognitive improvement is reported in patients undergoing functional hemispherectomy. In a study of 23 children, older than 6 years of age followed for at least 2 years, intelligence was significantly increased following hemispherectomy (90).

Corpus callosotomy

Corpus callosotomy can be indicated for generalized or multifocal tonic, atonic or myoclonic seizures or Lennox Gastaut syndrome. Anterior partial and complete callosotomy resection are options. The feared complication in this surgery is disconnection syndrome which is more evident in complete callosum resection. This surgery allows for the exposure of the interhemispheric fissure with the corpus callosum, thus careful attention must be made to the distal segments of the anterior cerebral arteries, venous sinuses, deep cerebral veins, motor cortex, and cingulum (neuropsychiatric injury). Recent progress in less invasive surgical approaches including LITT and endoscopic techniques for corpus callostomy may be forthcoming options for pediatric patients without needed exposure of those critical neurovascular structures (91). Surgical freedom does not typically exceed 20%, but seizure improvement rates have been recorded in up to 40% of patients (92,93).

Stimulation

Stimulation techniques provide safe, reliable, reversible, potentially localized seizure management, with slightly less potential for seizure freedom (13).

Vagus nerve stimulation (VNS)

VNS is an extracranial treatment for partial medically refractory seizures that involves interval electrode placement wrapped around the vagus nerve within the carotid sheath with connection to a programmable generator located in the upper chest. In 1995, the first randomized controlled trial described the efficacy of VNS with improvement in seizure control in 31% of patients (94). A cohort of >400 patients soon later described seizure reduction in 43% of patients at three-year follow-up (95). Again the utilization of this technique required further exploration in the pediatric epilepsy population. The first randomized controlled trial performed in pediatrics demonstrated that VNS has a reasonable benefit of >50% seizure reduction, and also provides a moderately safe profile for patients (96). In a review and meta-analysis including 101 pertinent articles

on VNS application in pediatric epilepsy, 56.4% of patients achieved a 50% reduction in seizures with 11% achieving seizure freedom. They described children who were older and who were on fewer AED before VNS placement did overall better (97). Of note, the leads may begin to fail overtime, the seizures may remain refractory and patients may be unable to be weaned off their antiepileptic medications. Other risks associated with the device include vascular injury from surgical placement, hoarseness, dysphonia, and bradycardia (95).

Responsive neurostimulation (RNS)

RNS system is an implanted, closed loop system approved for patients with partial onset DRE and unresectable foci. As the system provides a connection to a series of contact leads that are either depth or surface electrodes they provide constant electrocorticography. As particular patterns of EEG activity are detected, various stimulation patterns can be programmed in response to create seizure control (98). The stimulator detects patient specific electrocorticography and delivers a stimulation in response to a programmed pattern. The first randomized controlled trial demonstrated the efficacy of RNS published in 2017 in adults (99). Multicenter, large prospective cohort studies reiterate the efficacy of RNS in adults (100-102). Although no randomized controlled trial has been published in the pediatric population, several cohort analysis has described the efficacy and safety profile of RNS (103). Nagahama *et al.* describe the utilization of this technique in children >3 years old (103). About half (N=17) of their cohort was less than 18 years old, with 41% of patients achieving ≥50% seizure reduction. Three complications were seen, including infection and lead damage, but none were seen in children. Another study of 8 pediatric patients with either bilateral or eloquent epileptogenic focus were retrospectively analyzed after RNS and all achieved >50% seizure reduction at median follow-up of 16 and a half months (45). The safety profile of RNS includes infection, partial or complete removal of the system, with a theoretical risk of intracranial hemorrhage, stroke, or death, although in one cohort of 27 patients none of these latter complications were seen (104).

Deep brain stimulation (DBS)

DBS is another established modality for refractory epilepsy (105). The SANTE trial in 2015 included patients with refractory partial epilepsy of various kinds and demonstrated 56% seizure reduction with some achieving complete seizure freedom. They did witness postoperative depression and memory disturbances (106). Five-year outcome analysis demonstrated 69% seizure reduction rates, but a third of the patients had adverse effects related to the device. These included implant site pain, abnormal sensations at the stimulator implant site, infection, or lead malpositioning. Almost a third of patients also experienced a depression-related event (107). At 7 years follow-up, 75% of patients had seizure frequency reduction, with focal and tonic-clonic seizures having the greatest impact. In 2012, Lee *et al.* reported anterior nucleus of thalamus DBS has shown 40% mean seizure reduction with a 70% reduction after 7 years following surgery (108,109). Cognitive improvement has also been studied and identified in other observational analyses for patients with bilateral anterior thalamic surgery. The centromedian nucleus of the thalamus is another potential target in severe and refractory partial seizures but is not well studied in pediatrics. A very recently published single-center analysis described 91% mean seizure reduction in 14 patients who underwent centromedian nucleus targeted DBS (110). Yan performed a systematic analysis of DBS in pediatric epilepsy with 85% achieving seizure reduction, and 12.5% of 40 pediatric patients having seizure freedom after DBS (105).

Weighing the risks and benefits of surgery

Although there are risks and doubts associated with surgery, there is undoubted positive benefit seen in pediatric epilepsy (111,112). As described, seizure frequency reduction and cure are possible for patients with medically refractory epilepsy, yet in a recent evaluation of surgical trends among Epilepsy Centers in America, an overall decline was seen in overall surgical procedures performed for pediatric epilepsy (18). They describe an increase in LITT, RNS and invasive intracranial monitoring, and a decrease in resective surgery and vagus nerve stimulator insertions. Another analysis demonstrates similar trends (17,65). A criticism of surgery and concern for referrals are the potential risks of surgery. In Dwivedi's analysis, 33% of patients had serious adverse effects, including paralysis of one or more limbs most commonly hemiparesis seen in patients undergoing hemispherectomy. Alternatively, the benefits were demonstrated. When compared to the medical therapy arm, 93% of patients in the medical arm continued to have seizures. They also saw significant improvement in the quality of life and behavioral indices, that were not seen in the medical arm. In a nationwide analysis spanning 8 years for patients who underwent temporal lobectomy or

amygdalohippocampectomy, older age and male patients had a greater risk of having a major complication. Mortality was seen in 1.4% of patients while 6.5% of patients had major complications (113). Rydenhag *et al.* demonstrated major complications in 3.1% of patients, with minor complications of 8.9% (114).

The risk of surgery must be weighed against the risk of non-surgical management. Evidence risk of sudden onset death in epilepsy patients is higher than the risk of serious complications that could occur because of surgery (115). Epilepsy surgery has been found to reduce mortality in patients with epilepsy (8). Mikati *et al.* had also demonstrated significant benefit in quality-of-life indicators in children who underwent surgery compared to those who did not (116). Cognitive and developmental benefits are seen in patients who undergo surgery earlier in life and earlier in the existence of epilepsy. Benefits include quality of life improvement, employment benefit, cognitive outcomes, and reduction in antiepileptic medications (8,117-119). Quality of life indicators were deemed higher in patients who underwent early surgical therapy compared to those that did not (32).

Conclusions

Pediatric epilepsy surgery must be considered early in the course of DRE by all practitioners caring for children with this illness. From its birth in the 19th century until current times with the advent of emerging technologies, including neuronavigation, functional mapping and the advent of minimally invasive surgical techniques, surgery for pediatric epilepsy can continue to make profound impacts on the lives of children with DRE while reducing complication rates. Providers should be mindful of the common misconceptions and disparities in surgical workup and referral, in order to provide the most comprehensive and inclusive care to these patients.

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