Epilepsy Surgery

Monitoring and Novel Surgical Techniques

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KEYWORDS

• Drug-resistant epilepsy • Stereo-electroencephalography
• Minimally invasive surgery • Laser interstitial thermal therapy

KEY POINTS

- Patients with drug-resistant epilepsy should be referred to epilepsy surgery centers as soon as possible.
- The epilepsy presurgical evaluation may include multiple testing modalities, including neurophysiology, imaging, and functional studies.
- Stereo-electroencephalography (SEEG) is often preferred over subdural electrodes due to decreased morbidity and the ability to sample multiple anatomic regions including depth of sulci and deep brain structures.
- There is increasing evidence for the efficacy and safety of minimally invasive surgical treatments for epilepsy, including laser ablation, thermo-SEEG, gamma knife, and endoscopic surgery.

INTRODUCTION

Drug-resistant epilepsy, defined as the persistence of seizures despite 2 appropriately trialed medications, occurs in approximately one-third of epilepsy cases.[1] Given the potential for morbidity and mortality over a lifetime, it is important to consider additional therapeutic options. It is recommended that patients with drug-resistant epilepsy be evaluated at an epilepsy surgery center, particularly patients with surgically amenable brain lesions.[2,3] Despite this, epilepsy surgery represents an underutilized treatment, often with significant delays between seizure onset and surgical intervention.[4] Traditional surgical techniques include potentially curative approaches such as craniotomy with lobectomy, lesionectomy, anatomic or functional hemispherectomies, and resections further tailored with invasive monitoring techniques. Traditional

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palliative surgical approaches include craniotomy with corpus callosotomy and vagus nerve stimulator implantation. These traditional approaches, although efficacious, are subject to significant corridor-related morbidity, namely the morbidity associated with craniotomy, opening of the dura, and accessing the intended tissue.

Advances in technology use a minimally invasive approach both in defining the epileptogenic zone and proceeding with surgical treatment. These techniques reduce corridor-related morbidity and are often more attractive to potential surgical candidates who otherwise decline to proceed with surgical evaluation due to the perceived risks of a large operation. The approaches described in this article in conjunction with a thorough epilepsy center evaluation may help to reduce this treatment gap.[5,6]

PRESURGICAL EVALUATION

The presurgical evaluation, often referred to as “Phase I,” is central to determining the underlying etiology of the patient’s epilepsy, localization of seizure-onset zones, and most appropriate surgical approach. Features of the history, including handedness, risk factors for epilepsy, age of seizure onset, presence or absence of infantile spasms, and clinical semiology, provide important details about whether the patient’s epilepsy represents a focal, multifocal, or generalized process. Curative or palliative goals (such as reducing total seizure burden or targeting a specific debilitating seizure type) should be discussed with the patient or relevant caregivers to establish realistic expectations before embarking on a thorough and potentially expensive evaluation. Neuroimaging and electroencephalogram (EEG) monitoring are considered mandatory in the presurgical evaluation but additional ancillary testing may be necessary on an individualized basis.[7]

MRI of the brain is critical for identification of structural etiologies and may provide prognostic information. Epilepsy with mesial temporal sclerosis, for example, is associated with increased high risk of drug resistance but higher chances of surgical success.[8,9] In the absence of abnormalities on initial imaging, high-resolution MRI with thin slices is recommended, as well as 3T imaging if available, to increase the likelihood of detecting subtle focal cortical dysplasias (FCDs).[9] Infants, who are in the process of myelination, may require serial MRI to identify FCDs.

The neurophysiology portion of the evaluation is paramount to localizing seizure onset. Interictal and ictal abnormalities on continuous EEG-video may identify regions of cortical irritability and probable seizure onset while precisely documenting semiologic features that may not have previously been observed or reported by the patient or family. Notably, however, when arising from deep structures within the frontal lobes, parietal lobes, or near locations involved in prior brain surgery, the ictal onset may be nonexistent, diffuse/bilateral, or merely lateralized to a hemisphere on scalp EEG.

In the absence of concordant clinical, imaging, and neurophysiologic data, additional diagnostic testing may provide additional insight into the seizure-onset zone. Subtraction interictal-ictal single-photon emission computed tomography (SISCOM or Ictal-SPECT) may be performed during continuous EEG-video. Focal seizures are associated with increased blood flow at the site of seizure onset such that a radiotracer injected at seizure onset will accumulate in the region of cerebral hyperperfusion, thereby visualizing the seizure onset.[10] Subtle differences in radiotracer uptake can be enhanced by subtraction of a scan taken in the interictal state. Brain electrical source analysis can be used to analyze EEG interictal and ictal waveforms and model their 3-dimensional localization. Magnetoencephalography (MEG) can be performed to visualize tangentially oriented sources in the interhemispheric region or along sulci, which are typically poorly visualized on surface EEG.

Functional studies are used in conjunction with neurophysiologic studies to clarify eloquent regions and clarify risks of functional deficits with surgery. Fluorodeoxyglucose-positron emission tomography (FDG-PET) identifies areas of hypometabolism that regionalize brain dysfunction, although often greater in volume than the actual epileptogenic zone.[11] Task-based and resting state functional MRI are used to localize language and motor regions. MEG also can be used to map sensory and motor areas in pediatric patients and language areas in adults.[12,13] Transcranial magnetic stimulation is useful to identify eloquent motor regions.[14] In selected cases in which language or memory is unable to be noninvasively identified, a Wada test may assist with hemispheric localization of language and memory functions. Last, but arguably most important, a comprehensive neuropsychology evaluation provides insight into current focal cognitive deficits, the risk for further deficits with surgery, and comorbidities, such as autism, attention-deficit/hyperactivity disorder, and mood disorders, which may impact surgical decision making for the patient and family.[15]

Following completion of these studies, results are discussed in a multidisciplinary epilepsy surgery conference to develop an individualized treatment plan. Some surgical options may be recommended based on the noninvasive data alone. If the data implicate several regions potentially amenable to surgery or if the surgical solution is unclear, invasive monitoring is often recommended to further localize seizure onset and guide a surgical plan.

INVASIVE MONITORING BY STEREO-ELECTROENCEPHALOGRAPHY

Bancaud and Talarach used subdural and depth electrodes as early as 1959 to study the onset and early propagation of seizures. Stereo-EEG (SEEG) as a localizing tool in the setting of inconclusive noninvasive data became established in the Montreal Neurologic Institution in 1972. The minimally invasive nature of this monitoring method is attractive to families and has the benefit of decreased tissue distortion and the ability to localize deeper seizure onsets. SEEG electrodes can be placed through small twist drill holes using a conventional stereotactic frame, frameless stereotactic apparatus, or more recently, robotic assistance (**Fig. 1**). In our experience at Texas Children's Hospital, SEEG electrodes may be successfully placed in children as young as 12 months, although limited skull thickness challenges the security of bolts and SEEG electrodes. Precise electrode placement is crucial for neurophysiologic sampling, as well as to avoid injury to vascular structures. The most common complication associated with SEEG is intracranial hemorrhage, with a reported risk of 0.075% to 0.45% per electrode.[16] Depending on the number of SEEG electrodes placed, the risk of hemorrhage may be comparable to the 4% risk reported for monitoring with subdural grids.[17] The risk of infection, however, is only 1% for SEEG compared with 3% for grids.[16,17]

Having well-defined hypotheses to guide placement of SEEG electrodes is important. Strategies for electrode placement are dependent on the presence or absence of lesions and the proposed epileptic network based on clinical seizure semiology and electrographic evolution on surface EEG.[18] SEEG monitoring is helpful in cases of bitemporal epilepsy or distinguishing between frontal or temporal epilepsy, especially in nonlesional cases.[19] A common case may include confirming mesial temporal sclerosis as the source of seizure onset in the presence of discordant history of diagnostic features (often referred to as "temporal-plus" scenarios).[18,20] To explore this, mesial temporal structures in addition to lateral temporal and extratemporal (anterior cingulate, orbitofrontal, and insular) regions may be sampled. More recently, SEEG

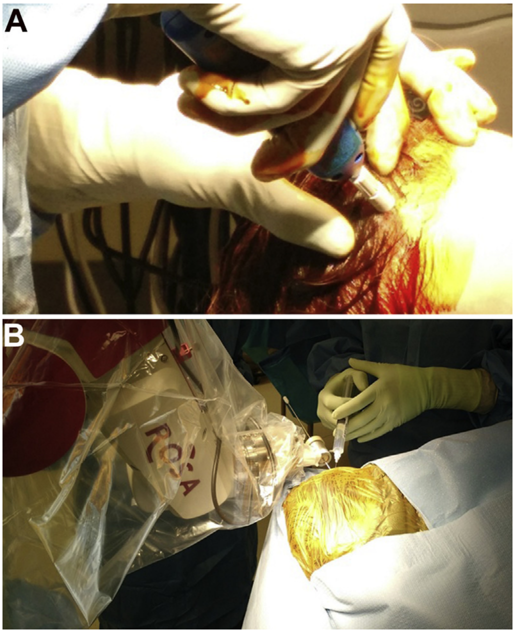

Fig. 1. Placement of SEEG electrodes. (*A*) A small twist drill can be used to generate craniostomies of ~3-mm diameter lining up with the planned electrode trajectory. (*B*) Frameless stereotaxy in combination with robotic assistance (eg, ROSA system shown) allows for more rapid in placement of depth electrodes.

has been used to identify the most epileptogenic region in cases of multifocal, disparate lesions.[21] At our institution, we aim to target the entire network of the seizure in our coverage to include anatomic regions implicated in both the onset and propagation of the seizure. Wide coverage is favored and possible through the minimally invasive nature of the recording electrodes.

SEEG implantation can also be used as part of a staged surgical process to narrow down to a more focused hypothesis that may require further invasive exploration or mapping before surgical treatment.[18] In our center, for complex cases, SEEG is sometimes seen as an “extension” of the noninvasive presurgical workup to regionalize the seizure-onset zone. If extensive coverage is needed due to complex epileptic networks or multiple targeted seizure types, limitations in amplifier size may occur. In these cases, recording from every other contact of the SEEG electrode in areas deemed less likely to be implicated in the ictal onset may be a useful strategy. As coverage is limited with SEEG, recording scalp EEG simultaneously may be beneficial to help distinguish nonepileptic events that may be similar to their ictal semiology (eg, behavioral inattentiveness or nocturnal arousals).

Case Example

A 3-year-old boy with refractory epilepsy due to tuberous sclerosis complex (TSC) had daily seizures of 2 semiologies: focal hypermotor and gelastic seizures. This genetic condition caused the development of cortical tubers in multiple brain regions (**Fig. 2**A, B). Discordant results during the Phase I presurgical evaluation guided placement of 14 SEEG electrodes in regions of both the right and left hemispheres (**Fig. 2**C).

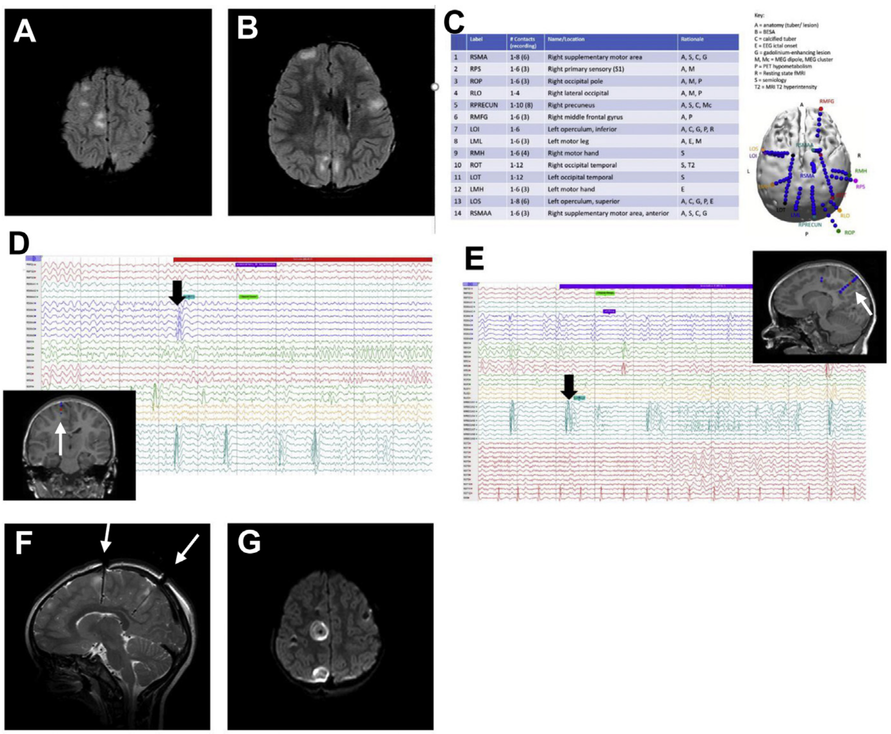

Fig. 2. Case example of SEEG characterization of seizures in TSC. (*A*, *B*) MRI brain, axial T2 fluid-attenuated inversion recovery images show multifocal tubers, including a prominent tuber in the right central midline region (*A*) and multiple tubers in the bilateral mesial occipital, right frontal, and left frontal regions (*B*). (*C*) SEEG electrode list and 3-dimensional brain reconstruction. (*D*) SEEG onset (*black arrow*) in RSMA2-4 with focal hypermotor seizures, corresponding to a cortical tuber in the right midline region, near the supplementary motor region (indicated in red on MRI brain coronal T1 image). (*E*) SEEG onset (*black arrow*) in RPRECUN2-6 with gelastic seizures. This corresponded to a cortical tuber in the right precuneus region (indicated in red on MRI Brain sagittal T1 image). (*F*) Intraoperative MRI brain sagittal T2 image shows trajectories through 2 implicated tubers. (*G*) MRI brain axial diffusion weighted image following laser ablation of 2 tubers.

Electrocorticography (ECoG) revealed that the habitual seizure types arose from distinct tubers (Figs. 2D, E) and the patient underwent MRI-guided stereotactic laser ablation of both seizure foci using 2 trajectories (Fig 2F, G). The patient remained seizure-free at 2-year follow-up (Engel 1A outcome).

Role of high-frequency oscillations in stereo-electroencephalography

There is emerging evidence that high-frequency oscillations (HFOs) may be useful as markers of the epileptogenic zone. HFOs can be subdivided into ripples and fast ripples. Definitions vary between studies, generally 80 to 200 or 80 to 250 Hz activity for ripples and 200 to 500 or 250 to 500 Hz activity for fast ripples. HFO identification requires a high sampling rate (≥2000 Hz) and good signal-to-noise ratio. Visual analysis is time-consuming, so automated detection is commonly used, frequently focusing on non–rapid eye movement sleep when HFOs are more abundant.[22]

HFOs detected by macroelectrodes have been described independent and coincident of interictal epileptiform discharges, occurring more frequently in seizure-onset zones in adults (**Fig. 3**).[23] Ictally, studies of small patient cohorts have shown localized brief or prolonged runs of HFOs near the time of seizure onset in regions that correspond to the ECoG seizure-onset zone in both adults and children.[24,25] Some studies suggest that removal of HFO-generating regions is associated with better surgical outcomes.[25,26] Although these data are intriguing, HFOs also can be seen physiologically, for example, over the motor cortex during finger movements,[27] and physiologic HFOs are morphologically similar to HFOs occurring in seizure-onset regions. Given this, a 2014 Cochrane review found that there is insufficient evidence for the use of HFOs to guide epilepsy surgery decision making at this time, and larger, randomized studies are needed.[28]

Functional mapping with stereo-electroencephalography

The goal of epilepsy surgery is to remove the epileptogenic zone with minimal induced deficits. Although brain regions can be presumed functional based on our understanding of normal brain anatomy, patients can exhibit significant variability, especially in the context of insults at a young age. Electrical stimulation mapping using implanted electrodes can be performed at the bedside or intraoperatively to determine if the epileptogenic region overlaps with eloquent cortex involved in movement, sensation, language, vision, or higher-order brain functions. This mapping technique can induce positive signs (eg, arm movement) or negative signs (eg, interruption of speech) and is dependent on rapid assessment of functional changes while stimulation is applied. For most functions, patient cooperation is also required. Importantly, the absence of clinical signs does not exclude all functions in the stimulated tissue but may reflect functions not acutely tested, functions with broad or bilateral representation, or inadequate stimulation. ECoG is simultaneously monitored for stimulus-induced afterdischarges or seizures.

Technically, using SEEG electrodes for mapping has significant differences from subdural electrodes.[29] SEEG contacts within an electrode are spaced 5 mm apart so bipolar stimulation affects only a focal region in direct proximity to the contacts. Stimulation is, however, efficient, as there is greater surface area in contact with the brain and less dissipation from cerebrospinal fluid. Because of these differences, the maximum stimulation parameters that can be safely used for SEEG electrode mapping are reduced compared with subdural electrodes.

A novel technique for functional mapping involves quantification of high gamma frequency (70–150 Hz) activity evoked during functional tasks such as limb movement, auditory perception, picture naming, and question-answer trials.[30,31] Case studies have shown evoked gamma activity localized to functional regions predicted anatomically or proven by electrical stimulation mapping with good specificity. The region of gamma activity may, however, be broader than indicated by stimulation mapping. This technique has several potential benefits over stimulation mapping in that multiple brain regions can be assessed simultaneously without risk for induced seizures and it may allow for language mapping in patients of a younger age or with delayed processing speed. Further development of paradigms are, however, necessary to validate this approach and increase its sensitivity.

Stimulation-induced seizures

Although spontaneously recorded seizures are ideal for the localization of the ictal onset zone, some centers perform cortical stimulation to activate epileptic networks and elicit seizures. Electrically induced seizures that recapitulate the electrographic

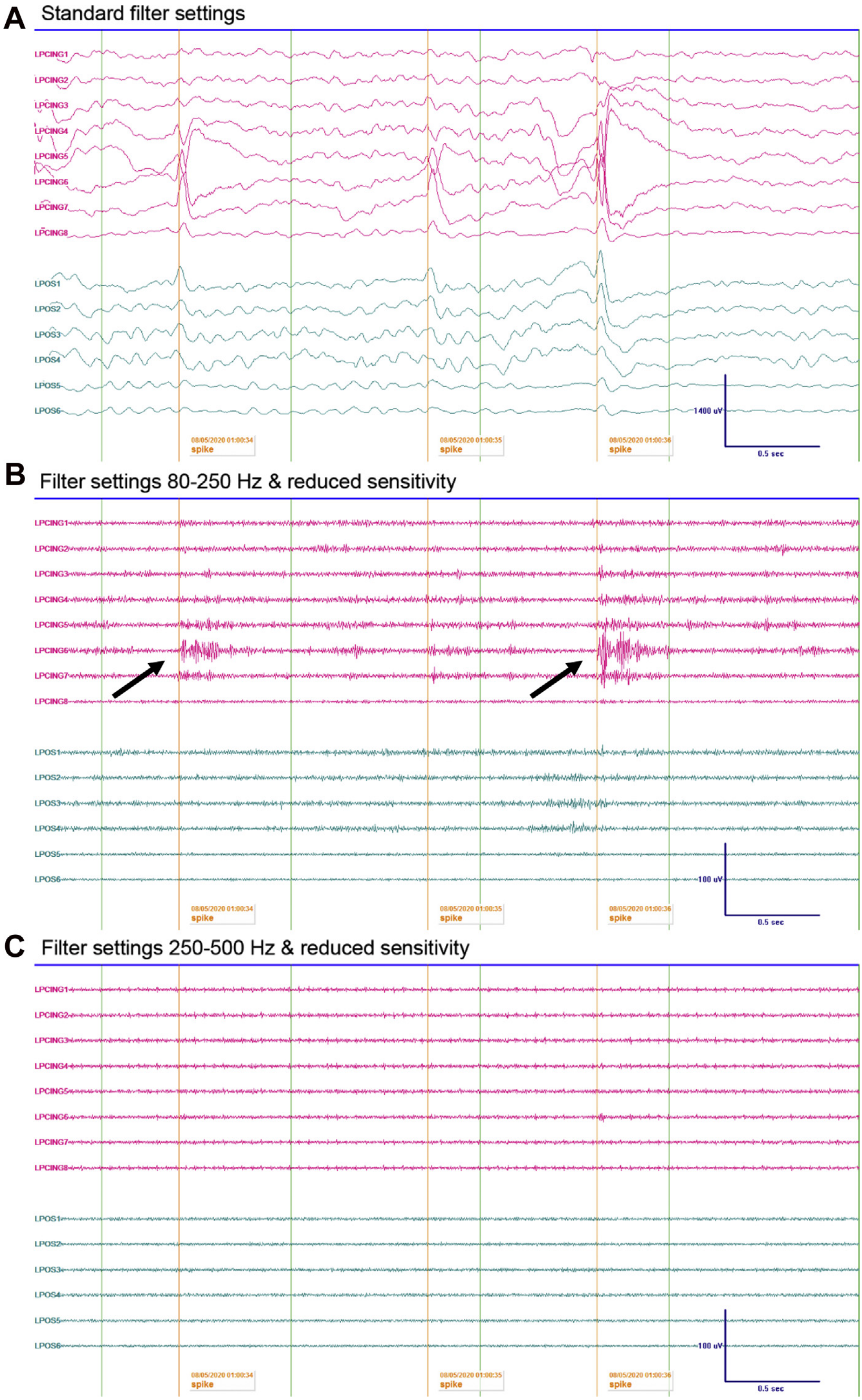

Fig. 3. HFOs. (*A*) Four-second ECoG sample showing 3 spikes maximal at LPCING6-LPCING7 (*pink*) with a field that extends to LPOS1-LPOS2 (*green*). (*B*) Filter settings of 80 to 250 Hz reveals ripples maximal at LPCING6 (*arrow*) coincident with spikes. No ripples are seen at LPOS1-LPOS2. (*C*) Filter settings of 250 to 500 Hz reveals no fast ripples.

spread and semiology of the patient's habitual spontaneous seizures can support a hypothesized ictal onset zone (Fig. 4).[32] Induction of nonhabitual seizure semiologies is not beneficial, as stimulation can induce seizures in the absence of underlying irritability. Limited studies from Europe report a 75% to 100% concordance between spontaneous and analogous stimulation-induced seizures with greater concordance seen in mesial temporal lobe epilepsy than lateral temporal or frontal lobe epilepsy.

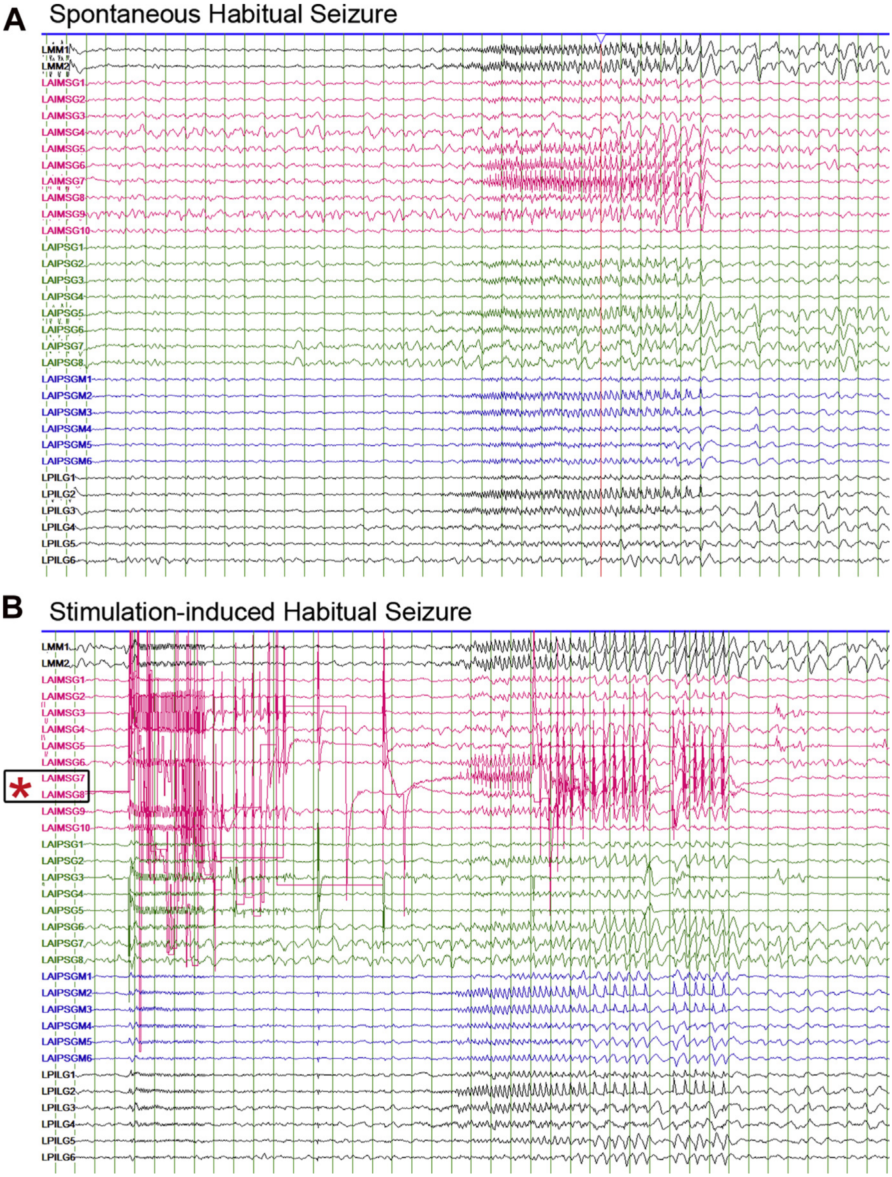

Fig. 4. Stimulation-induced seizures. (*A*) ECoG pattern of patient's habitual seizure; (*B*) 2 mA bipolar stimulation at contacts LAIMSG7-LAIMSG8 (indicated by *box*) induces the patient's habitual seizure semiology and a similar ECoG pattern.

NOVEL SURGICAL INTERVENTIONS

MRI-Guided Laser Interstitial Thermal Therapy

Since Food and Drug Administration (FDA) approval of 2 MRI-guided laser interstitial thermotherapy (LITT) systems, Medtronic Visualase in 2007 and Monteris NeuroBlate in 2009, this minimally invasive technique has been used to treat solid tumors and focal epilepsies.[33,34] These systems involve drilling a small hole, placing a stereotactic bolt, and inserting a saline or CO_2-cooled catheter into the tissue of interest. Because stability of the catheter is dependent on cranial fixation, individuals with thin bone or open cranial vaults, like infants, may require a surgical frame with multiple fixation points. Electrode trajectories used for SEEG monitoring can be used for laser ablation following electrode removal. A fiberoptic with laser tip is inserted to introduce infrared laser energy resulting in increased tissue temperature over time. Using real-time MRI thermographic monitoring, very localized coagulative necrosis can be induced with a small area of surrounding edema (**Fig. 5**). The laser fiber can be moved along the trajectory to produce linear ablation tracts up to 3 cm in diameter. Multiple tracts can be ablated in 1 session and LITT can be performed repetitively if needed. In the Visualase system, protective safety limits to be programmed by the user, shutting off the laser automatically when nearby critical structures show temperature elevation of 50°C (default temperature). One major limitation of LITT is that flowing cerebral spinal fluid or blood, ventricles, and prior resection cavities can lead to heat dissipation, making regions in direct proximity more difficult to ablate. Pathologic tissue samples can be obtained at the time of catheter implantation but may be of insufficient size if a pathologic diagnosis is needed. Postoperative recovery from LITT is generally rapid, usually with discharge the following day.

Use of MRI-guided LITT for the treatment of epilepsy was first described in 5 pediatric patients with lesional epilepsies with all patient becoming seizure-free at last follow-up (2–13 months).[35] Since then, many small case series reporting the use of LITT for pediatric epilepsy have been published. LITT may be preferred to open resection for tissues that are difficult to access surgically (eg, deep brain sites), individuals with multiple anatomically separate seizure-onset zones, and individuals likely to have recurrent epilepsy surgery. LITT also induces less anatomic distortion than open resection. Larger studies are, however, needed to compare the effectiveness and safety of LITT relative to open resection.

Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common focal epilepsy and is commonly drug resistant. Anterior temporal lobectomies and selective amygdalohippocampectomies have a high rate of seizure freedom (55%–70%) but are often associated with neurocognitive impairments. Several case series have been published using LITT for mesial and neocortical TLE in pediatric and adult patients. In a meta-analysis, only 5 cases of LITT for neocortical TLE with MRI abnormalities were described.[34] All were seizure-free but follow-up was limited (9.0–12.7 months). For mesial TLE, a multicenter trial of 234 patients reported 58% seizure freedom at 1 to 2 years following LITT.[36] The presence of radiographic hippocampal sclerosis did not affect outcomes, but patients with focal to bilateral tonic-clonic seizures were less likely to become seizure-free. A 15% complication rate was reported, which is comparable to resective approaches. The overall seizure freedom rates reported for LITT in TLE are slightly lower than the gold-standard open anterior temporal lobectomy. LITT can, however, be repeated if there are residual mesial structures or followed by an open resection if needed.

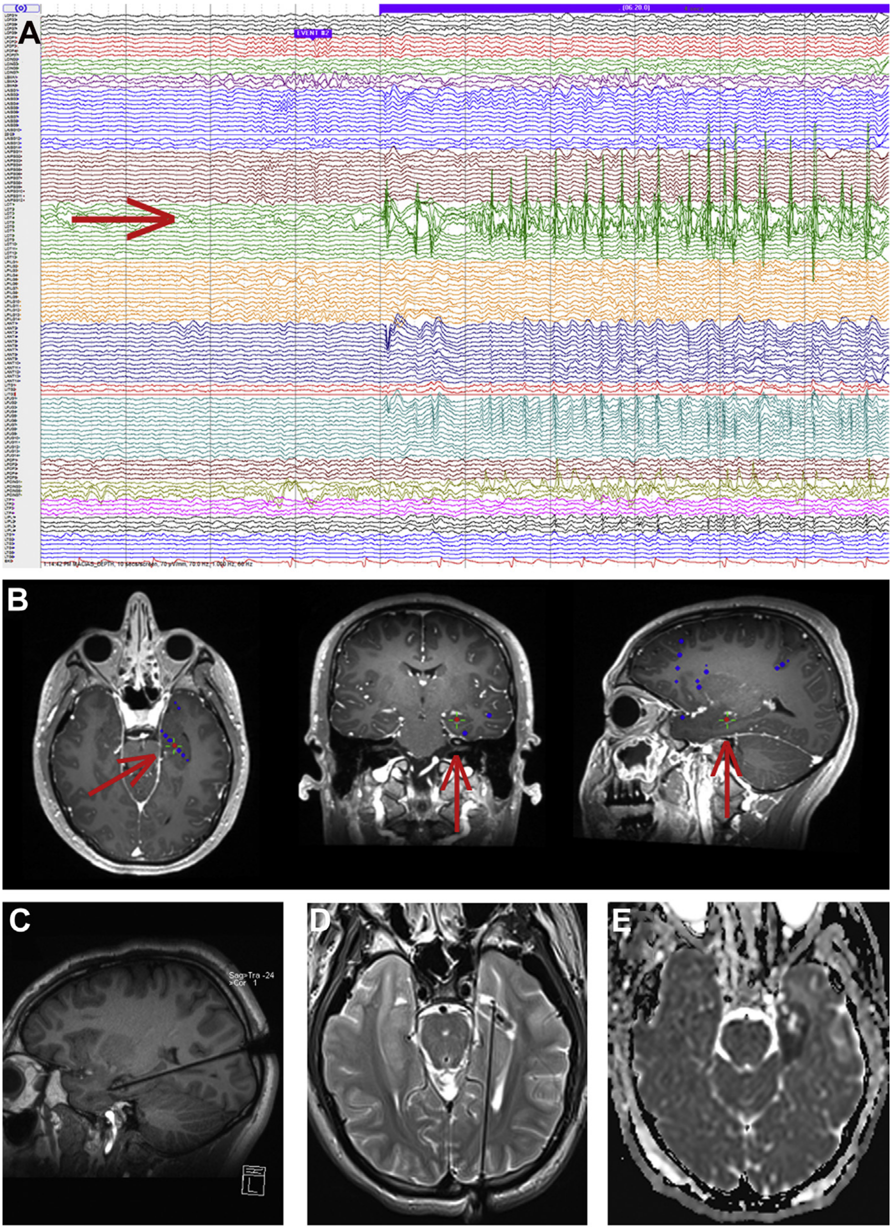

Fig. 5. Case example of SEEG seizure localization followed by laser interstitial thermal therapy. (*A*) SEEG in a patient with multiple FCDs showing habitual seizure onset arising from LOT3-5 (*arrow*). (*B*) Overlay of implanted electrodes on MRI brain T1 images shows localization of electrographic onset in left mesial temporal lobe focal cortical dysplasia (*arrow*). (*C*, *D*) MRI brain sagittal (*C*) and axial (*D*) images show positioning of laser applicator with tip in probable seizure-onset zone. (*E*) MRI brain axial apparent diffusion coefficient image obtained during the ablation shows region of thermal damage.

Dominant and nondominant temporal lobe resections are associated with neurocognitive impairments. Better naming, verbal fluency, and object recognition following LITT amygdalohippocampotomy has been reported compared with anterior temporal lobectomy.[37] Studies have shown variable impairments in memory function,[33,38] and further studies investigating memory function are needed.

Focal cortical dysplasias

FCDs are malformations of brain developmental frequently with epileptogenic potential. FCDs can be overt or indistinguishable from normal tissue on MRI. Several case reports documenting the use of LITT for the treatment of FCDs have been published, the largest by Lewis and colleagues.[39] In their case series,[39] 12 patients had drug-resistant epilepsy and presumed FCDs treated with LITT following video-EEG seizure characterization; 3 of the 12 were later determined to have biopsy-proven tumors. Of the remaining 9, 6 patients had a reduction in seizures with 2 seizure-free at 11 to 35-month follow-up. There was a complication in 1 patient with catheter misplacement resulting in hemorrhage and hydrocephalus. The seizure outcome for LITT treatment of FCDs performed by Lewis and colleagues[39] is inferior to the 60% seizure freedom after open resection,[40] likely due to incomplete ablation of the seizure-onset zone. More complete resection may be achieved by either repeat SEEG monitoring or intraoperative ECoG of the surgical boundaries, followed by further LITT or open resection.[41]

Tuberous sclerosis complex

TSC is a genetic disease that causes tumors in the brain and other organs. Cortical tubers often lead to seizures, developmental delay, and intellectual disability. Use of LITT for treatment of epilepsy in patients with TSC was first described in 2012 and has since been reported in several small series with nearly all patients experiencing a meaningful reduction in seizures.[35,39,42–45] A few patients were also reported to have developmental and neuropsychological improvements.[44,45] No complications occurred. Although results are encouraging, these studies are limited by small patient numbers, differences in seizure-onset zone identification (surface EEG or SEEG), and overall short duration of follow-up. Use of LITT in TSC warrants further investigation, as these individuals are likely to develop new seizure networks over time and may require recurrent epilepsy surgery.

Hypothalamic hamartoma

Hypothalamic hamartomas (HHs) are congenital malformations associated with gelastic seizures that occur in isolation or syndromically. Due to their location in the center of the brain, resection by traditional surgical approaches can be associated with corridor-related morbidity.[46,47] A case series of 14 patients treated with LITT reported 86% seizure freedom at a mean of 9 months' follow-up and a good safety profile with only 1 patient experiencing an asymptomatic subdural hemorrhage.[48] Our program at Texas Children's Hospital has performed surgery on 125 patients. Subsequent studies have similarly reported good efficacy and rare complications, such as memory deficit and worsening diabetes insipidus.[49,50]

Corpus callosotomy

Traditionally, corpus callosotomies for palliation of drug-resistant epilepsy have been performed by open craniotomies. In 2016, LITT of the splenium was used to complete an anterior callosotomy in an adult patient with persistent generalized seizures, resulting in a >50% reduction in seizures at 4-month follow-up.[51] Since then, LITT has been reported in pediatric and adult patients for anterior two-thirds callosotomies and completions with seizure outcomes similar to open craniotomies.[52–55] Rare complications were reported, including hemorrhage, asymptomatic thalamic ablation, and disconnection syndrome.[52,54]

Stereo-Electroencephalogram–Guided Radiofrequency Thermocoagulation

SEEG-guided radiofrequency thermocoagulation (also known as thermo-SEEG) uses the SEEG electrodes initially used for seizure characterization to lesion the seizure-onset zones.[56] The French Clinical Neurophysiology Society and French chapter of the International League Against Epilepsy have established guidelines for thermo-SEEG, recommending its consideration when conventional surgery is not feasible and for deep heterotopias or HHs.[57] Thermo-SEEG is performed intraoperatively during wakefulness without anesthesia to allow for clinical monitoring. A radiofrequency (RF) generator is connected to an SEEG electrode and RF current is delivered between 2 contacts in the seizure-onset zone. This creates an electric field and an oscillatory ionic current density field that causes frictional heating. Initially, a short direct stimulation is applied before to test for eloquent cortex. If nonfunctional, a more prolonged ablative stimulation of ∼50 V is applied to heat the tissue to 78 to 82°C. Higher voltage is associated with larger lesions up to 5 to 7 mm in diameter. Unlike LITT, temperature is not monitored, but coagulation of tissue proteins is associated with a sudden change in resistance such that further current does not produce a larger lesion. Multiple lesions can be induced in a single session. Recovery is rapid, typically with discharge the next day. Patients may experience transient improvement or worsening of seizures before stabilizing. Thermo-SEEG can be performed repetitively in the same patient or followed by other surgical approaches if needed.

A meta-analysis of 296 patients showed significant variability in seizure outcomes, possibly due to technical differences across centers. Overall, 23% were seizure-free and 58% with ≥50% reduction in seizures at 1 year.[56] Notably, patients with periventricular nodular heterotopias had a favorable responder rate, while TLE had inferior outcomes compared with open resection. Thermo-SEEG had a very low unanticipated complication rate due to the functional mapping before thermocoagulation. Only 1 patient in the series had an unanticipated deficit (thumb hypoesthesia).

Gamma Knife Radiosurgery

Gamma knife (GK) is a noninvasive technique that targets convergent small gamma rays on the epileptogenic zone with each beam inducing minimal radiation to surrounding tissues along each track. Although the procedure itself can be completed within a day, the radiation-induced neuromodulation and necrosis can take months to years. In adults, GK for mesial TLE has resulted in significant reduction in seizures after 2 years that is comparable to traditional surgical approaches.[58] There are also limited data for GK treatment of cavernous malformations as well as palliative corpus callosotomies. GK targeted to the anterior or posterior corpus callosum in children and adults leads to significant improvement in drop attacks and/or generalized tonic-clonic seizures in a median of 3 months.

In a prospective trial of GK for the treatment of HH, 69% of 57 patients had significant improvement in seizures with 40% being completely seizure-free after more than 3 years of follow-up[59]; 58% of patients did require a second treatment to achieve these outcomes. Outcome is dependent on lesion size and anatomic localization, with best outcomes seen with small hamartomas within the hypothalamus and third ventricle.[60] Reduction in aggressive behavior was also reported. Giant HHs and those above the floor of the third ventricle may require staged intervention with disconnection of the lower portion followed by GK of the upper part. No permanent neurologic complications were reported. A major disadvantage to this approach, however, is that lasting clinical improvement can take up to 2 to 3 years and is often preceded by periods of fluctuating seizure improvement and exacerbation.

One concern for radiosurgery, especially in the pediatric population, is radiation-induced damage that contributes to tumorigenesis. There is no definite causal relationship seen between radiosurgery and new tumors, and the risk of tumor development following radiosurgery is reportedly far lower than the risk of dying from brain surgery.[60]

Magnetic Resonance–Guided Focused Ultrasound

Originally FDA approved for the treatment of uterine fibroids and pain secondary to bone metastases, MR-guided focused ultrasonography (MRgFUS) is being investigated for the treatment of focal epilepsies.[61,62] This technique uses high-frequency waves to induce a focal increase in tissue temperature. Mild increases in temperature can modulate neuronal activity, whereas high temperatures of $\sim 55^{\circ}$C lead to irreversible cell death. Real-time MRI is used for beam guidance and thermometry for monitoring of the ablation as treatment occurs, thereby minimizing off-target damage.

Although MRgFUS does not require surgical implantation of a laser catheter as in LITT, there are potential complications to this noninvasive technique. Hair underlying the ultrasound transducer must be shaved, as energy absorption by the skin can result in pain and burns. Absorption by the skull can lead to heat damage to the dura and nearby brain parenchyma if cooling is insufficient. In addition, the skull can cause wave distortion and attenuation that impairs targeting and achievement of ablative temperatures. This can be somewhat mitigated by use of specialized ultrasound transducers. High-intensity ultrasound also can affect blood vessels, resulting in bleeding.[63] Additional studies are needed to investigate the feasibility and safety of this technique for the treatment of epilepsy.

Endoscopic Surgery

Another alternative to traditional open resective surgeries makes use of endoscopes. Endoscopes can be introduced through significantly smaller craniotomies and may thereby be associated with reduced intraoperative blood loss and more rapid recovery. Endoscopic approaches are, however, challenging in that tissue visualization and the ability to control bleeding are limited relative to open surgery.

Corpus callosotomy

Endoscopic corpus callosotomies can be performed through a 2 to 3 cm diameter frontal or parietooccipital craniotomy, significantly smaller than the 8 cm $\times$ 4 cm incision for the open approach.[64,65] The placement of the craniotomy and length of the endoscopic tools allows the corpus callosum to be reached without brain retraction, one cause of potential complications. Although reported series have limited patient numbers, no complications were reported and the investigators elude to similar seizure outcomes as open procedures. Endoscopic callosotomies can be combined with disconnection of the anterior, posterior, and habenular commissures with improved seizure outcomes, 71.4% with a $\geq$50% reduction in seizures compared with 53% with callosotomy alone in 1 series of 57 patients.[66] Inclusion of the commissures was not associated with an increase in complications with both treatment groups including infrequent cases of hematoma, hygroma, and hydrocephalus.

Functional hemispherotomy

Expanding on corpus callosotomy disconnections, endoscopic functional hemispherotomies can be performed though craniotomies as small as 4 cm $\times$ 2 to 3 cm.[67–69]

Disconnection can be confirmed by intraoperative MRI or postoperative tractography. A case series of 59 patients compared open hemispherotomy with robotic-assisted endoscopic hemispherotomy.[70] Both techniques resulted in similar reductions in seizures at 1 year, but the endoscopic approach was associated with significantly less intraoperative blood loss and modestly shorter hospital stays. Some complications were seen in both treatment groups, the most common being postoperative fever without evidence of infection.

Hypothalamic hamartoma

Trans-ventricular endoscopic disconnection of HHs was first described in 2003.[71] Using a stereotactic robot or neuronavigation system to guide placement, 2 burr-hole incisions are made, one for the endoscope entry to the lateral ventricle and one with a trajectory targeted to the interface between the hamartoma and third ventricle wall.[72] Disconnection is then performed under direct visualization using either a laser probe or ultrasonic aspirator. In a cohort of 112 pediatric patients treated endoscopically, 57% of patients were seizure-free at more than 2-year follow-up with best outcomes seen for small hamartomas located intraventricularly.[73] Notably, 51% of patients required 2 to 4 surgical procedures to achieve these outcomes, with 15 patients having open surgeries to either disconnect or resect residual tissue. An endoscopic complication rate of 7.9% was reported, including cases of memory deficit, motor deficit, meningitis, and transient diabetes insipidus. This rate is acknowledged by the study investigators to be slightly higher than other minimally invasive or noninvasive approaches to address HHs.

Neurostimulation

Neurostimulation for the treatment of epilepsy involves implantation of a battery-operated device that provides nerve or brain stimulation in a programmed or triggered manner. A discussion of these devices can be found in Ali and colleagues' article, "Neuromodulation in Pediatric Epilepsy," in this issue.

DISCUSSION

Epilepsy is the most common chronic neurologic condition in childhood[74] and is associated with increased risk for injury,[75] academic underachievement,[76] social stress,[77] and sudden death. For those with drug-resistant epilepsy, early referral to an epilepsy center is important for consideration of surgical options as well as dietary therapies. This is especially true for patients with lesional epilepsy who are unlikely to undergo spontaneous remission of their seizures over time. In a randomized controlled trial, pediatric patients with drug-resistant epilepsy who underwent epilepsy surgery had a better chance of seizure freedom and better behavior and quality-of-life scores than those who just continued medical therapy.[78] Surgery at a young age also allows for remodeling of functional brain networks, such as relocalization of language following hemispherectomy.[79] Caregivers of pediatric epilepsy surgery patients often wish that epilepsy surgery had happened sooner.[80,81]

Advances in EEG analysis, imaging, and genetic testing allow us to better understand each patient's underlying etiology and seizure types. Working as a multidisciplinary team, neurologists, neurosurgeons, and neuropsychologists can design a treatment plan for each individual. With the development of SEEG monitoring and minimally invasive treatments, patients with multiple seizure types or disparate seizure-onset zones are no longer poor surgical candidates. At our institution, lack of fully concordant presurgical data does not preclude SEEG characterization if reasonable hypotheses can guide the implantation. Early epilepsy surgery and reduction of seizure burden may help maximize developmental potential even in conditions like TSC in which new epileptic networks may develop over time. Reduction of seizure medications following surgery also may have neurocognitive benefits. Given this, successful epilepsy surgery should be measured not only by the percentage of seizure reduction or duration of seizure freedom, but also neuropsychologic and quality-of-life measures. Reduced risk of injury and sudden unexpected death in epilepsy patients are benefits not to be overlooked.

As epilepsy monitoring and surgical intervention become less invasive with lower associated morbidity, our threshold for using these techniques for the treatment of epilepsy will likely decrease. Curing epilepsy remains a goal, but seizure palliation and iterative minimally invasive interventions are becoming increasingly common. In the future, epilepsy surgery indications may expand to include surgical treatment of subtle clinical or subclinical seizures, lesional epilepsies after failure of the first antiepileptic drug, or even well-controlled epilepsy on multiple medications.

CLINICS CARE POINTS

- Consider epilepsy surgery in patients with medically refractory epilepsy
- SEEG serves as a minimally invasive diagnostic tool allowing for the sampling of multiple, bilateral regions to confirm seizure onset
- Epilepsy surgical techniques are increasingly minimally invasive and may increase the number of potential surgical candidates
- Curative and palliative epilepsy surgery goals are equally important in specific clinical scenarios
- Improved developmental outcome measures are needed to guide long-term benefits for palliative epilepsy surgery in children

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