



Review Article

## An update on pediatric surgical epilepsy: Part II

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Received : 03 November 19

Accepted : 22 November 19

Published : 27 December 19

DOI

10.25259/SNI\_418\_2019

Quick Response Code:



### ABSTRACT

**Background:** Recent advances may allow surgical options for pediatric patients with refractory epilepsy not previously deemed surgical candidates. This review outlines major technological developments in the field of pediatric surgical epilepsy.

**Methods:** The literature was comprehensively reviewed and summarized pertaining to stereotactic electroencephalography (sEEG), laser ablation, focused ultrasound (FUS), responsive neurostimulation (RNS), and deep brain stimulation (DBS) in pediatric epilepsy patients.

**Results:** sEEG allows improved seizure localization in patients with widespread, bilateral, or deep-seated epileptic foci. Laser ablation may be used for destruction of deep-seated epileptic foci close to eloquent structures; FUS has a similar potential application. RNS is a palliative option for patients with eloquent, multiple, or broad epileptogenic foci. DBS is another palliative approach in children unsuitable for respective surgery.

**Conclusion:** The landscape of pediatric epilepsy is changing due to improved diagnostic and treatment options for patients with refractory seizures. These interventions may improve seizure outcomes and decrease surgical morbidity, though further research is needed to define the appropriate role for each modality.

**Keywords:** Epilepsy surgery, Innovation, Minimally invasive, Pediatric, Technology

### INTRODUCTION

Pediatric epilepsy has a worldwide prevalence of 1%, and 20–30% are diagnosed with drug-resistant epilepsy (DRE) (persistent seizures despite treatment with two first-line antiepileptic medications).<sup>[2]</sup> Conventionally, surgery was considered a last resort, though it is now advocated to provide long-term seizure control (control rate of 50–70%).<sup>[19]</sup> Minimally invasive approaches include stereotactic electroencephalography (sEEG), laser ablation, focused ultrasound (FUS), and responsive neurostimulation (RNS), summarized in Table 1.

Recent developments allow surgical options for patients previously not deemed candidates, such as those with bilateral, deep, eloquent, or poorly localizing epileptogenic foci. The American Academy of Neurology now recommends early surgery for select patients with DRE. Nevertheless, there is still substantial delay between diagnosis and surgical referral.<sup>[15]</sup>

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## sEEG

Complete removal of the epileptogenic zone (EZ) is the most important factor associated with postsurgical seizure freedom. Accurate localization of the EZ is therefore critical, as is information obtained from semiology, EEG, structural magnetic resonance imaging (MRI), and other advanced testing.<sup>[15]</sup> Seizures localizable through scalp EEG or MRI are more amenable to surgical cure;<sup>[11,12,21]</sup> when noninvasive testing fails to localize epileptogenic focus, patients may require intracranial electrode recording.<sup>[15]</sup>

There are two main types of intracranial electrode monitoring: subdural strip/grid recordings, and stereotactically placed depth electrodes implanted through burr holes (sEEG). Robotic assistance has a 1–3 mm level of accuracy for placement of electrodes and allows safe trajectories with reduced operating time [Figure 1].<sup>[14]</sup> Once placed, electrodes may remain for 1–2 weeks.<sup>[17]</sup>

Patients with DRE may be considered for sEEG in the following situations: no structural lesion identified on MRI and

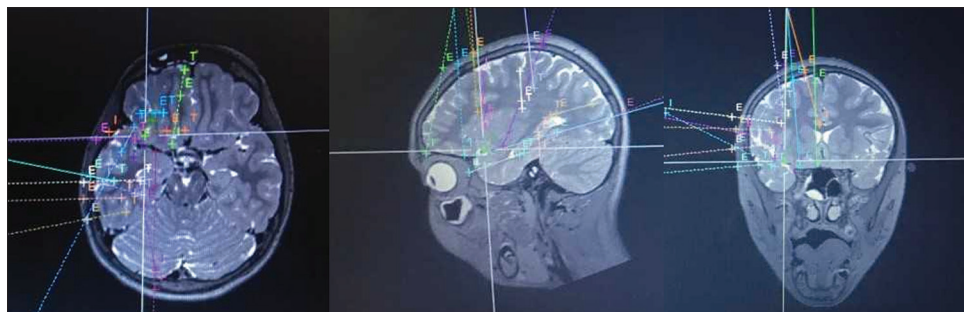
scalp EEG nonlocalizing, suspected multifocal/multilesional epilepsy, conflicting noninvasive data, suspected widespread seizure network, or EZ in close proximity to eloquent structures.<sup>[32]</sup> Targets of sEEG are determined by the EZ hypothesis, localization by scalp EEG, abnormalities on magnetoencephalography (MEG), interictal positron emission tomography, and ictal single-photon emission computed tomography.<sup>[6,19,24,31]</sup>

sEEG is a minimally invasive approach for seizure localization that provides significant advantages over subdural electrodes such as sampling of extended regions, interrogation of deep structures not accessible to subdural electrodes,<sup>[6]</sup> bilateral sampling in cases of rapid generalization, and staged electrode placement. Several studies show the efficacy of sEEG in children for localizing the EZ and guiding surgical resection.<sup>[5,26,35]</sup> Nevertheless, subdural electrodes still provide robust diagnostic capabilities for superficial foci or when extensive cortical mapping is required.<sup>[26]</sup>

**Table 1:** Minimally invasive options for drug-resistant epilepsy

| Modality | Uses  | Strengths/weaknesses   |
|----------|---|--|
| sEEG     | EZ localization if no structural lesion on MRI and nonlocalizing scalp EEG, suspected multifocal or multilesional epilepsy, conflicting noninvasive data, suspected widespread seizure network, or EZ in close proximity to eloquent structures | Characterization of wide epileptic network, extended or bilateral sampling, minimally invasive, interrogation of deep structures<br>Less robust for superficial foci or cortical mapping |
| LITT     | Thermal ablation of EZ for mesial temporal sclerosis, hypothalamic hamartoma, or deep periventricular lesions   | Minimally invasive, real-time monitoring to avoid surrounding tissue damage<br>Possible lower seizure-free rate, long-term data lacking  |
| FUS      | Tissue ablation of intracranial lesions, possible application to epilepsy-associated benign tumors and other deep-seated epileptogenic lesions  | Noninvasive, real-time monitoring to avoid surrounding tissue damage<br>Clinical trials in early stages  |
| RNS      | Closed loop neurostimulatory device in patients with eloquent, multiple, or broad epileptogenic foci  | Palliative reduction in seizure rate<br>Off-label for pediatric patients, limitations in growing skull, inability to get MRI with device   |
| DBS      | Open loop neurostimulation of centromedian nucleus of the thalamus or anterior thalamic nucleus in patients unsuitable for resective surgery  | Palliative reduction in seizure rate<br>Limited studies in pediatric patient   |

sEEG: Stereotactic electroencephalography, EZ: Epileptogenic zone, LITT: Laser interstitial thermal ablation, FUS: Focused ultrasounds, RNS: Responsive neurostimulation, DBS: Deep brain stimulation. MRI: Magnetic resonance imaging



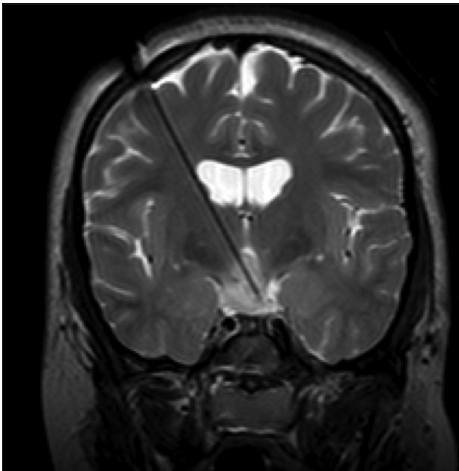
**Figure 1:** Axial, sagittal, and coronal views of a T2-weighted magnetic resonance imaging scan depicting depth electrode planning trajectories for stereotactic electroencephalography, Phase 2 epilepsy monitoring.

## LASER ABLATION

After the seizure focus has been appropriately localized, there are multiple surgical options, including open surgical resection and minimally invasive stereotactic techniques such as radiofrequency thermo-coagulation and stereotactic radiosurgery. However, radiofrequency thermo-coagulation does not allow real-time monitoring of tissue destruction and is less effective than open microsurgical resection.<sup>[10]</sup> Stereotactic radiosurgery has a delayed treatment effect (last seizure on average 11–19.7 months after treatment) and may result in complications such as radionecrosis (20% of patients).<sup>[8,28,33]</sup> MRI-guided laser interstitial thermal therapy (LITT) thermally ablates the epileptogenic focus while minimizing local tissue damage.<sup>[3]</sup> There is an approximate 23% complication rate following MR-guided LITT.<sup>[17]</sup>

MR-guided LITT is used to treat mesial temporal sclerosis, hypothalamic hamartoma, and deep periventricular lesions.<sup>[32]</sup> Approximately 50% of these patients are seizure-free at 1 year follow-up.<sup>[3,18,24,38]</sup> Although temporal lobectomy results in a higher rate of seizure freedom (60–80%), sparing the lateral temporal lobe structures may correlate with better neuropsychological outcomes, such as reduced naming and verbal/working memory deficits.<sup>[3,18,24,38]</sup> Therefore, some support laser ablation as first-line therapy for dominant mesial temporal lobe epilepsy.<sup>[3]</sup>

In pediatrics, hypothalamic hamartoma is the most frequently reported indication for LITT, allowing disconnection of these deep-seated lesions while avoiding damage to surrounding structures [Figure 2].<sup>[17]</sup> There is a 73% rate of seizure freedom following LITT for these lesions.<sup>[7,17]</sup> MR-guided LITT is



**Figure 2:** Intraoperative T2-weighted coronal magnetic resonance imaging of a child undergoing laser ablation for intractable gelastic epilepsy resulting from hypothalamic hamartoma. The laser cannula is in place with the tip terminating in the hamartoma, allowing focused delivery of heat that can be monitored in real-time using magnetic resonance thermography.

best suited for lesions difficult to access with open surgery and presumably results in improved cognitive function and reduced complications.<sup>[17]</sup>

## FUS

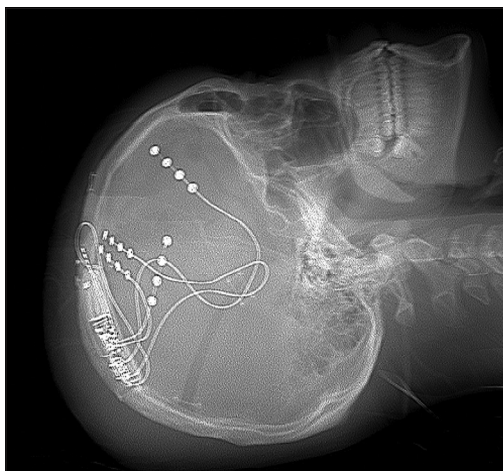
FUS is another minimally invasive modality used to create targeted tissue ablation by delivering high-intensity ultrasound waves through external transducer elements which cause irreversible coagulation. FUS creates a 2–6 mm diameter intracranial lesion with 1 mm precision. Tissue ablation can be monitored in real-time using MR thermography. FUS avoids the need for skin incision or burr holes and carries a reduced complication rate compared to open microsurgery or LITT.<sup>[1]</sup>

The current primary application of FUS is for treating essential tremor, Parkinson's disease, and neuropathic pain, and more recently, deep brain tumors.<sup>[1,9,27]</sup> DRE is a potential application of FUS in patients with lesional epilepsy (hypothalamic hamartoma, deep-seated cortical dysplasia, or low-grade tumors).<sup>[23]</sup> While one mechanism of action of FUS is thermal tissue destruction, lower temperatures may alter neural activity without causing cell death.<sup>[4,37]</sup> FUS is a minimally invasive, targeted treatment that may potentially be used in the future to treat benign tumors and other deep-seated epileptogenic lesions with reduced morbidity.

## RNS

RNS adapts therapeutic stimulation in response to a continuous feedback loop. Depth or strip electrodes within the ictal onset zone continuously monitor electrocorticography activity; the device uses a programmed algorithm to detect incipient seizures. Once an abnormal activity is detected, the device supplies responsive therapeutic electrical stimulation designed to reduce or abort the seizures.<sup>[4,20,36]</sup> This may be used as a palliative approach for patients with eloquent, multiple, or broad epileptogenic foci.<sup>[23]</sup> Intracranial monitoring may be performed before RNS implantation to guide electrode placement.<sup>[23]</sup>

NeuroPace RNS (Neuropace, Mountain View, CA) is the first and only FDA-approved RNS device available to patients aged 18 years or older.<sup>[34]</sup> Most studies have focused on adult patients with mesial temporal (particularly bilateral mesial temporal) seizure onset or neocortical seizure onset in the eloquent cortex (such as language or sensorimotor). Studies have demonstrated long-term seizure reduction in almost two-thirds of patients, but few patients showed complete seizure freedom.<sup>[16,29]</sup> However, there were improvements in quality of life, though those undergoing temporal lobectomy may have had better results.<sup>[29]</sup> RNS is primarily advocated as a palliative option in patients who have no further treatment options. Patients with bitemporal epilepsy or those with



**Figure 3:** Lateral skull radiograph of a 16-year-old male after NeuroPace device implantation. Subdural electrode strips are connected to the device, which is seated in the patient's skull.

epileptogenic foci in eloquent areas of the brain may have the most benefit from this procedure.<sup>[30,36]</sup>

RNS has been used off-label in pediatric patients with DRE in those with no surgical resection options (bilateral or eloquent epileptogenic foci).<sup>[22,34]</sup> Limited studies show promise for its use in children; shortcomings include performing a craniectomy for device implantation in a growing skull, and as well as the inability to obtain future MRI studies. Karsy *et al.* speculated that NeuroPace would be useful as an ambulatory Eastern Cooperative Oncology Group modality for pediatric patients who might not tolerate intracranial monitoring as well as adults.<sup>[19]</sup>

An example of RNS placement is demonstrated in Figure 3, which depicts a 16-year old male with refractory complex partial seizures consisting of staring and pacing without responsiveness. Despite using three first-line antiepileptic medications, seizures occurred 3 times daily. MRI demonstrated no abnormality, and long-term scalp EEG demonstrated interictal discharges of the left frontal region with occasional bifrontal and right frontal discharges. MEG demonstrated spikes in the left inferior frontal and superior frontal gyri. Positron-emission tomography demonstrated decreased metabolic activity throughout the left frontal lobe, and a possible second metabolic focus in the left temporal lobe. The patient underwent Phase 2 monitoring with placement of subdural electrodes; events were captured with onset from multiple regions spanning a large area of the left frontal lobe involving eloquent speech and motor cortices. The patient underwent NeuroPace placement with strip electrodes on the left frontal motor and opercular regions. Electroconvulsive therapy noted seizure activity arising from all areas, and RNS therapy initiated. The patient has been seizure-free at 1-year follow-up and is being weaned off his antiepileptic medications.

## DEEP BRAIN STIMULATION (DBS)

DBS is an open-loop neuromodulatory program that involves the delivery of electrical stimulation to deep brain structures through implanted electrodes connected to a pulse generator. The safety profile is similar to DBS for movement disorders.<sup>[25]</sup> The landmark SANTE multicenter randomized trial enrolled adults with refractory epilepsy who underwent bilateral stimulation of the anterior nuclei of the thalamus; this reduced seizure frequency for up to 2 years.<sup>[13]</sup> Other noncontrolled studies have explored targets such as the hippocampus, centromedian nucleus of the thalamus, cerebellum, and nucleus accumbens.<sup>[25]</sup> There are, however, few pediatric studies. A recent systematic review of 40 pediatric DBS patients with DRE showed a reduction in seizures, but only small percentage was seizure free.<sup>[39]</sup> The centromedian nucleus of the thalamus and anterior thalamic nucleus were the most common targets. In the future, DBS may be considered as a palliative measure in children with DRE.

## CONCLUSION

Advances in diagnostic capabilities and minimally invasive treatments, including stereotaxy, surgical robotics, laser ablation, and neurostimulation may improve seizure outcomes while minimizing surgical morbidity.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Gadgil N, Muir M, Lopresti MA, Lam S. An update on pediatric surgical epilepsy: Part II. *Surg Neurol Int* 2019;10:258.