Open Resection versus Laser Interstitial Thermal Therapy for the Treatment of Pediatric Insular Epilepsy

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BACKGROUND: Various studies suggest that the insular cortex may play an underappreciated role in pediatric frontotemporal/parietal epilepsy. Here, we report on the postsurgical outcomes in 26 pediatric patients with confirmed insular involvement by depth electrode monitoring.

OBJECTIVE: To describe one of the largest series of pediatric patients with medically refractory epilepsy undergoing laser interstitial thermal therapy (LITT) or surgical resection of at least some portion of the insular cortex.

METHODS: Pediatric patients in whom invasive insular sampling confirmed insular involvement and who subsequently underwent a second stage surgery (LITT or open resection) were included. Complications and Engel Class outcomes at least 1 yr postsurgery were compiled as well as pathology results in the open surgical cases.

RESULTS: The average age in our cohort was 10.3 yr, 58% were male, and the average length of follow-up was 2.43 ± 0.20 (SEM) yr. A total of 14 patients underwent LITT, whereas 12 patients underwent open resection. Complications in patients undergoing either LITT or open resection were mostly minimal and generally transient. Forty-three percent of patients who underwent LITT were Engel Class I, compared to 50% of patients who underwent open insular resection.

CONCLUSION: Both surgical resection and LITT are valid management options in the treatment of medically refractory insular/opercular epilepsy in children. Although LITT may be a less invasive alternative to craniotomy, further studies are needed to determine its noninferiority in terms of complication rates and seizure freedom, especially in cases of cortical dysplasia that may involve extensive regions of the brain.

KEY WORDS: Pediatric epilepsy, Insular cortex, Surgical epilepsy

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Although pure-insular epilepsy is relatively rare, the incidence of "insular/opercular" epilepsy in children involving the insula and adjacent cortex (also called "insular-plus" or "temporal-plus" epilepsy) is likely underappreciated.[1-4] Previous studies have described insular seizures in patients presenting with primarily viscerosensitive or somatosensory complaints.[5] More recent studies describe a clinical sequence that can be used to identify insular lobe epileptic seizures, specifically being partial seizures, without impairment of consciousness associated with sensations of discomfort (laryngeal, thoracic, or abdominal), unilateral paresthesias, and/or dysphonic or dysarthric speech, followed by focal somatomotor manifestations.[4] These findings are likely related to its vast connectivity with surrounding structures, resulting in symptoms related to secondary sensory processing, language and motor control, and higher autonomic control. The location of the insula, however, has made it particularly difficult to identify seizures arising from this area on scalp electroencephalography (EEG), often being confused for frontal, temporal, or parietal lobe epilepsy.[6]

ABBREVIATIONS: EEG, electroencephalography; **icEEG,** intracranial electroencephalography; **LITT,** laser interstitial thermal therapy; **MRI,** magnetic resonance imaging; **MEG,** magnetoencephalography; **MRE,** medically refractory epilepsy; **SPECT,** single-photon emission computed tomography

Given its deep-seated location, conventional subdural grids cannot be used to accurately assess insular function; semiology, scalp EEG, or other noninvasive modalities are insufficient to pinpoint insular dysfunction. Insular depth electrode monitoring offers a relatively safe and accurate method of implicating the insula in seizure onset and offers information about insular involvement that is often not forthcoming with any of the noninvasive modalities (eg, semiology,[7,8] video EEG,[9] magnetic resonance imaging [MRI],[9] positron emission tomography,[10] ictal single-photon emission computed tomography [SPECT],[10] and magnetoencephalography [MEG]-MSI[11,12]). A prior report from our group details a technique for insertion of invasive insular depth electrodes utilizing a stereotactic, frame-guided posterior oblique trajectory in children with medically refractory epilepsy (MRE).[13] Although frame-based techniques are considered by many to be logistically demanding, time-consuming, and less accurate, we have provided data suggesting the feasibility of this approach, as costs for introducing robotic stereoelectroencephalography into a neurosurgical practice may be prohibitive.

Here, we report on the patient outcomes and surgical strategy (ie, either open surgical resection or laser interstitial thermal therapy [LITT]) in patients with confirmed insular involvement based on intracranial electroencephalography (icEEG) data. The high percentage of patients with insular involvement suggests that more liberal interrogation of the insular cortex should be considered in cases of pediatric MRE. Thus, careful identification of the epileptic zone involving the insula and adjacent operculum may spare patients from inappropriate surgery and improve their quality of life. Overall, we conclude that in children with MRE and depth electrode-confirmed insular involvement, both LITT and open surgical resection may be useful treatment options leading to favorable outcomes in a majority of patients.

METHODS

Cohort Description

Our study was approved by our institution's review board (CR16041). ICD and CPT codes were used to identify patients undergoing intracranial stereotactic depth electrodes placement. Patient consent was not required for this study. All procedures (insular depth electrode placement, LITT, and open resection) were performed by a single surgeon (Mark R. Lee), which may represent a potential bias in this study. We then identified the cases in which insular involvement was confirmed using insular depth electrodes, which unanimously prompted surgical intervention by either open resection or LITT.[13] Only patients with sufficient follow-up (>1 yr) were included in this series. The focus of the current report is to analyze the cohort of patients in whom icEEG confirmed insular involvement. Insular involvement was defined as one of the following: 1) electroencephalographic seizure onset occurring simultaneously with epileptiform activity of any insular depth electrode, or 2) in the case that seizure onset immediately proceeded (<0.5 s) triggering of an insular depth discharge, these data suggested either direct insular involvement or ultra-rapid spread involving the insula. Surgical placement of insular depth electrodes was performed as previously described.[13] We then analyzed postoperative seizure outcomes as well as surgical complications after LITT or open resection. Variables analyzed included demographic information, underlying pathology, imaging modalities implicating the insula, other areas of brain involved in the epileptogenic zone (eg, frontal, temporal, or parietal operculum), type of operation performed (open resection vs LITT), immediate and delayed postop complications, and long-term (>1 yr) Engel Class outcomes. Of a cohort of 49 patients with MRE, 32 patients displayed some involvement of the insula, with the vast majority (88%) displaying involvement of adjacent cortices, with the frontal cortex being the most common (56%).[13] Of the 32 patients identified with insular depth electrode-confirmed insular involvement, we report on 26 of those patients undergoing open insular resection or LITT with sufficient follow-up (>1 yr) here.

RESULTS

We identified 26 patients in whom insular depth electrode placement implicated the insula in epileptogenesis underwent either LITT or open resection of some portion of the insula with or without adjacent cortices (Tables 1 and 2). The average age in our cohort was 10.3 yr, and 58% were male. The average length of follow-up for all patients was 2.43 ± 0.20 (SEM) yr. Patients who underwent open resection tended to be younger than patients undergoing LITT (12.4 vs 7.8 yr; $P = .006$). The 26 patients here represent a complicated cohort, as 12 patients underwent prior operations for epilepsy and had to be reoperated on for persistent or recurrent seizures. Three patients had prior resection of the insula and a portion of the frontal lobe, whereas 1 patient underwent resection of residual insula left from a prior operation. Three patients had prior LITT of the insula, but seizures persisted, leading to additional operative intervention. Of note, 4 patients had prior corpus callosotomy, with 2 of those 4 patients also undergoing resection of a portion of the frontal lobe. Eighteen out of 26 patients (69%) had confirmed lesions on MRI, but only 5 of those patients' MRI had findings in the insula. Fourteen out of 26 patients (54%) had suspected insular involvement based on SPECT imaging, whereas 12 patients (46%) had MEG imaging characteristics implicating insular involvement.

Of the 14 patients who were treated with LITT, 7 patients had suspected cortical dysplasia (biopsy was previously not routinely performed), 6 patients had biopsy-proven cortical dysplasia, 1 patient had tuberous sclerosis, and 1 patient had no evidence of cortical dysplasia, but showed presence of mild and diffuse gliosis. Nine patients (60%) had lesion-positive preoperative MRIs. Eight patients had no postoperative complications, 4 patients had postoperative hemiparesis, 1 patient had a mild facial droop, and 1 patient experienced dysphagia; however, all postoperative complications were resolved at 3 mo postoperation. A total of 43% of patients undergoing LITT of the insula had an Engel Class outcome of I at least 1 yr after surgery, and 71% of

TABLE 1. Characteristics of Patients who Underwent LITT for Treatment of Insular Epilepsy

Age (yr)	Gender	Pathology	Prior surgery	Surgery	Lesional MRI	Other imaging implicating the insula	Complications	Engel Class	Follow-up (yr)
3.7	M	BP-CD	Complete corpus callosotomy and L frontal lobectomy	L stereotactic ablation	Y	SPECT	R-sided hemiparesis, resolved by 3-mo postop	III	2.20
6.2	M	CDS	Stereotactic ablation of L superior insula	Stereotactic ablation with repeat ablation of L superior insular cortex w/o depth placement	Y	MEG/SPECT	Mild R paresis, resolved by 3-mo postop	I	3.20
7.0	M	BP-CD	R insular resection	LITT of residual R insula	Y	SPECT	None	I	2.60
8.0	F	CDS	LITT of L anterior insula	LITT of L anterior insula and ablation of residual tissue	Y	SPECT	None	II	1.35
12.0	F	CDS	None	Stereotactic ablation of L insula	N	MEG/SPECT	R-sided hemiparesis, resolved by 3-mo postop	I	1.40
12.5	F	BP-CD	L frontal and insular resection	L insular LITT	Y	MEG	R-sided hemiparesis, resolved by 3-mo postop	I	3.10
13.4	M	BP-CD	Corpus callosotomy, L frontotemporal grids, and L frontal resection	Craniotomy for placement of 5 depth electrodes and stereotactic ablation of L insula	Y	MEG	None	II	2.70
13.7	F	TS	None	Stereotactic ablation of R frontal lesion and R superior insula	Y	MEG/SPECT	None	II	1.20
15.0	M	CDS	R insula stereotactic ablation	Repeat R insula stereotactic ablation	N	MEG	None	III	1.05
15.8	M	CDS	Corpus callosotomy and VNS placement	Stereotactic ablation of L insula	N	MEG	R-sided weakness and facial droop, resolved by 3 mo postop	IV	1.29
16.0	M	CDS	None	Stereotactic ablation of R anterior insula and orbitofrontal cortex	N	MEG	None	I	1.60
16.2	F	BP-CD	Ablation of L opercular and parietal depth regions	L postcentral cortex resection, followed by LITT of L superior insula and repeat ablation of L opercular and parietal depth regions	N	MEG	None	III	1.02
16.4	M	CDS	None	Stereotactic ablation of R insula	Y	MEG/SPECT	None	II	2.51
17.3	M	BP-CD	L posterior frontal lobe resection	LITT of L superior insula	N	MEG/SPECT	Dysphagia, resolved by 3-mo postop	I	1.58

Abbreviations: BP-CD, biopsy-proven cortical dysplasia; CDS, cortical dysplasia suspected; F, female; L, left; LITT, laser interstitial thermal therapy; M, male; MEG, magnetoencephalography; MRI, magnetic resonance imaging; N, no; postop, postoperation; R, right; SPECT, single-photon emission computerized tomography; TS, tuberous sclerosis; VNS, vagus nerve stimulation; w/o, without; Y, yes.

TABLE 2. Characteristics of Patients who Underwent Open Resection for Treatment of Insular Epilepsy

Age (yr)	Gender	Pathology	Prior surgery	Surgery	Lesional MRI	Imaging implicating the insula	Complications	Engel Class	Follow-up (yr)
3.9	M	BP-CD	None	L frontotemporal and insular resection	Y	None	Focal paresis and apraxia, resolved by 3-mo postop	III	1.03
4.4	M	BP-CD	None	L frontal and insula resection	Y	None	None	I	4.32
5.3	F	BP-CD	None	R frontotemporal and insular resection	Y	SPECT	None	I	3.35
5.7	F	BP-CD	Prior corpus callosotomy	R hemispherectomy	Y	SPECT	L-sided hemiparesis, resolved by 4-mo postop	II	2.82
7.1	M	BP-CD	None	Craniotomy for subdural grids and depth placement followed by R hemispherectomy	Y	None	L-sided hemiparesis, resolved by 3-mo postop	I	1.56
7.9	F	TS	None	R frontotemporal and insular resection with corpus callosotomy	Y	SPECT	L-sided hemiparesis, resolved with 1-wk postop	III	3.85
8.0	F	BP-CD	None	R frontal and anterior insular resection	Y	SPECT	Mild facial droop, resolved before discharge	I	1.59
8.5	M	BP-CD	L frontal lobectomy and grid insertion	L frontal lobectomy and anterior insular resection	Y	MEG	Meningitis	II	3.73
8.5	M	CDS	None	R frontal lobectomy and insular resection	N	None	Hydrocephalus requiring shunt and L hemiparesis	III	3.30
9.4	F	CDS	None	R hemispherectomy with insula resection	Y	SPECT	None	II	4.07
10.1	M	BP-CD	None	L temporal lobectomy and insular resection	N	None	None	I	3.20
15.3	F	TS	None	R frontotemporal and insular resection	Y	SPECT	L-sided hemiparesis	I	3.57

Abbreviations: BP-CD, biopsy-proven cortical dysplasia; CDS, cortical dysplasia suspected; F, female; L, left; M, male; MEG, magnetoencephalography; MRI, magnetic resonance imaging; N, no; postop, postoperation; R, right; SPECT, single-photon emission computerized tomography; TS, tuberous sclerosis; Y, yes.

patients had an Engel Class outcome of I or II at least 1 yr after surgery.

Of the 12 patients who underwent open surgical resection, 8 patients had histology consistent with cortical dysplasia, 2 patients had suspected cortical dysplasia (the histopathology report was not definitive), and 2 patients had tuberous sclerosis (Table 2). Two patients had undergone prior intracranial operations, including 1 corpus callosotomy and 1 frontal lobectomy. Ten out of 12 patients (83%) had lesions visible on MRI. Five patients (42%) had no imaging implicating the insula. Five patients experienced postoperative hemiparesis, 1 patient experienced apraxia and weakness, and 1 patient experienced facial droop; however, these deficits were resolved within 4 mo of surgery. In addition, 1 patient developed meningitis and 1 patient developed hydrocephalus requiring permanent cerebrospinal fluid diversion. Four patients did not experience any complications of any kind. A total of 50% of patients undergoing open resection of the insula had an Engel Class outcome of I at least 1 yr after surgery, and 75% of patients had an Engel Class outcome of I or II at least 1 yr after surgery.

DISCUSSION

Key Results

Our study and others demonstrate that both LITT and open resection are feasible and effective treatment options for MRE insular/opercular epilepsy.[3,4,14] Additional case series describing pediatric patients with MRE insular/opercular epilepsy have reported seizure freedom rates ranging from 56%[15] to 69%,[3] albeit in cohorts of 16 and 13 patients, respectively, and only included patients undergoing open resection. Additional smaller series have reported similar seizure freedom rates as well.[14,16-21] Importantly, the vast majority of these patients had never undergone epilepsy surgery before. However, the intricate connections and functional neuroanatomy of the insula cortex often cause misinformation during the presurgical evaluation, leading to another anatomical site being identified as the region of seizure onset. This accounts for 46% of the patients included in this series undergoing a prior operation. However, the rate of seizure freedom in our cohort agrees with prior reports of patients undergoing open resection for MRE insular epilepsy.[3,14] Additional studies of an equivalent number of patients with MRE insular epilepsy undergoing LITT also demonstrates similar levels of seizure freedom compared to our cohort.[22] Although LITT has been used to treat MRE insular epilepsy in adults,[23] these results indicate that LITT can be used for both MRE insular epilepsy and potentially additional types of pediatric epilepsy.

Interpretation and Generalizability

Factors prompting insular open resection vs targeted insular LITT for epilepsy are not standardized and have not been systematically studied.[2-4,22,24-26] Decisions on surgical approach take a number of variables into account, including anatomical location of foci, volume of epileptic zone, underlying cause of epilepsy, number of prior operations, and surgeon preference, among other considerations. All of these factors played a role in the decision-making process in the series presented here, with most consideration given to the epileptic zone volume and location. However, a number of patients required open resection because of incomplete resection of the epileptic zone from prior operations. Additional studies should be aimed at standardizing the decision to pursue open resection vs LITT once more data becomes available.

We did not observe any differences in patient outcomes with LITT or open resection of the right or left insular cortex. Although used at this center more than most, LITT in its present form is a relatively new technique; therefore, it remains unclear if outcomes may improve as user experience grows in the distribution and amount of ablation required. The number of patients included herein did not allow for comparison of partial vs more diffuse ablations or for anterior vs posterior insular ablations. Although both open resection and LITT have been used successfully,[3,15,27] the level of insular involvement identified by both depth electrodes (and other means), number of prior operations, and both surgical and ablation strategies are highly variable. Thus, although open resection and LITT show similar rates of seizure freedom in our cohort in patients with similar clinical presentation and history, each case presented unique considerations. Additional studies are needed to determine the ideal patient selection, efficacy, and long-term outcomes of LITT vs open resection for MRE insular epilepsy.

Although LITT is an attractive option for insular ablation given the insula's deep-seated anatomy, it is limited in its ability to cause ablation only along a single vector plane. However, in children with cortical dysplasia (the majority of our cohort and other studies of focal MRE), prior studies have shown that incomplete removal of the focal cortical dysplasia is associated with seizure recurrence.[28,29] Thus, these patients may be more likely to benefit from open resection. Additional studies have reported on positive seizure outcomes after LITT, including in patients with insular epilepsy.[22,30] Thus, although positive outcomes were still achieved in patients presented here and elsewhere, it is worth considering whether or not the extent of the epileptic zone, in addition to anatomical location and other operative considerations, should be one of the most important pieces of information to consider when deciding between LITT vs open resection. More extensive case series need to be aggregated and analyzed to better understand the advantages of LITT vs open resection.

Epilepsy surgery is relatively safe, with few studies citing severe adverse events. Overall, the risk of death due to epilepsy surgery is less than 1% and very rare. Rates of surgical site infection are similarly low,[31] and very few complications are seen even in very young patients.[32] The vast majority of patients who experienced complications were mild and manageable. The most common complication was mild weakness, which was resolved in all patients within 4 mo of intervention. In our series, there were zero instances of surgical site infection, although 1 patient developed meningitis, which was resolved with appropriate antibiotic treatment. Furthermore, 4 additional patients (age 19-20 yr) not included in this pediatric series had undergone open resection for insular epilepsy with no postoperative complications and each achieved seizure freedom with a 1.93-yr average length of follow-up, providing additional evidence supporting the feasibility of insular resection. Our data trend towards a positive safety profile, although larger studies are needed to confirm the safety and efficacy of this approach.

However, the patients included in our study who experienced mild complications, such as transient hemiparesis or weakness, completely resolved within 4 mo, albeit at similar rates in patients treated with either LITT or open resection. Thus, although the risks associated with craniotomy are still present, other risks such as weakness, hemiparesis, dysphagia, and aphasia resulting in prolonged hospital stays, increased costs, and rehabilitation services should still be strongly considered even when considering the less invasive LITT approach. In adults, over half of patients undergoing insular resection for epilepsy report transient hemiparesis because of occlusion of a M_2 perforator branch,[33] whereas pediatric patients undergoing insular resection have a 20% risk of developing permanent hemiparesis.[17] This was,

however, not the experience in our cohort, in which risk of hemiparesis was exceedingly low. Therefore, careful consideration of the approach aimed at seizure amelioration should also take into account other potential complications. In addition, we observed similar complication rates in patients undergoing right- vs left-sided surgery and LITT despite variable and complex anatomy overlying the insular cortex.[34] Although the complication rates reported here are similar to prior reports, additional studies will be needed to determine which patients may be the best candidates for LITT.

Limitations

Our study is not without limitations. First, we are limited by retrospective review and data collection on a small number of patients. Thus, we were only able to report descriptive information rather than delineate predictors of operative success with LITT vs open resection. In addition, we are limited by a heterogeneous patient population with variable demographic and clinical features, as well as a wide range of prior interventions from patients with no prior operation to patients with prior extensive resections of various cortices. Thus, although we report one of the largest series to date of patients with insular epilepsy undergoing operative intervention, we recognize that broad conclusions cannot be drawn without additional studies. Although a variety of outcomes and complications were followed closely, including pre- and postoperative neuropsychiatric testing in most of our patients, testing was not performed in a standardized format such that long-term cognitive outcomes can be discerned from this study.

CONCLUSION

Operative intervention via open surgical resection or LITT are feasible options for treatment of children with MRE insular/opercular epilepsy. We report the largest series of pediatric patients undergoing operative intervention of confirmed insular or insular-plus epilepsy. Future studies should be aimed at determining the optimal course of surgical treatment: open resection vs LITT as well as age- and pathology-specific indications for treatment. These data suggest that LITT and open insular resection are both safe and feasible treatment options for insular epilepsy in children, but additional studies are needed to confirm safety and efficacy of these procedures on a broader scale.

Disclosures

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