Laser interstitial thermal therapy: A first line treatment for seizures due to hypothalamic hamartoma?

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Summary

Successful treatment of hypothalamic hamartoma (HH) can result in the resolution of its sequelae including epilepsy and rage attacks. Risks and morbidity of open surgical management of this lesion have motivated the development of laser interstitial thermal therapy (LITT) as a less invasive treatment approach to the disease. Although overall morbidity and risk would appear to be lower, complications related to LITT therapy have been reported, and the longer-term follow-up that is now possible after initial experience helps address the question of whether LITT provides equivalent efficacy compared to other treatment options. We conducted a retrospective analysis of clinical outcomes in eight patients undergoing LITT for HH at our center using the Visualase/Medtronic device. Five patients had refractory epilepsy, one had rage attacks, and two had both. We also compared the published seizure-free outcomes over time and the complication rates for different interventional approaches to the treatment of epilepsy due to HH including open craniotomy, neuroendoscopic, radiosurgical, and radiofrequency approaches. With a mean follow-up of 19.1 months in our series of eight patients, six of seven epilepsy patients achieved seizure freedom, whereas the one patient with rage attacks only did not have improvement of his symptoms. A length of hospital stay of 2.6 days reflects low morbidity and rapid postoperative recuperation with LITT. Considering other reported series and case reports, the overall published seizure freedom rate of 21 of 25 patients is superior to published outcomes of HH cases treated by stereotactic radiosurgery (SRS), craniotomy, or neuroendoscopy, and comparable to radiofrequency ablation. The cumulative experience of our center with other published series supports relatively lower operative morbidity than more invasive approaches and efficacy that is as good or better than open craniotomy procedures and SRS. Although morbidity appears to be lower than other open approaches, complications related to LITT and their avoidance should be considered carefully.

KEY WORDS: **Hypothalamic hamartoma, Gelastic epilepsy, Laser interstitial thermal therapy, Stereotactic neurosurgery, Surgery for epilepsy.**

Hypothalamic hamartoma (HH) is a rare developmental malformation associated with gelastic and other types of seizures, neuropsychiatric symptoms including rage attacks, and precocious puberty.[1] The lesions occur as round or ovoid masses that may be sessile, where they are embedded within or attached to the hypothalamus along a large interface, or pedunculated, where they are attached to the hypothalamus via a stalk.[2,3] The sessile type tends to be associated with medically refractory epilepsy, whereas the pedunculated type tends to be associated with precocious puberty responsive to gonadotropin releasing hormone (GnRH) agonist treatment. The lesions consist of mature neurons, resembling those of the normal tuber cinereum, intermingled with glial cells and occasionally dysplastic neurons.[4] Myelinated and unmyelinated fibers connect the

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Key Points

- Laser interstitial thermal therapy (LITT) aimed toward curative ablation of hypothalamic hamartoma (HH) is emerging as a first-line treatment for seizures caused by HH
- LITT applied for treatment of seizures has resulted in favorable seizure-free outcomes (21/25) and low rate of complications as reported in the literature
- Long-term clinical follow-up of HH epilepsy patients treated with LITT will continue to define its role in the treatment of this pathology
- The role of LITT as a treatment for neuropsychiatric and neuroendocrine disturbances caused by HH is currently poorly defined and requires further experience

cellular components of the HH to hypothalamic nuclei.[5,6] Histochemical and electrophysiologic evidence shows clusters of spontaneously firing γ-aminobutyric acid (GABA) ergic neurons that drive the synchrony of pyramidal-like output neurons.[7,8]

Gelastic seizures secondary to HH are difficult to control with antiepileptic drugs alone, as are other HH-related seizure types, including focal, tonic, and atonic seizures.[2] The fact that better postoperative seizure control correlates with shorter preoperative duration of epilepsy,[9] highlights the importance and timeliness of surgical treatment in well-selected patients. Surgery is also indicated for severe behavioral problems, notably rage attacks that can occur with HH.[10] Given their paroxysmal nature, it has been suggested that rage attacks represent a type of seizure. However, the lack of localizable electroencephalographic correlates with seizures arising from HH makes this categorization difficult. Although central precocious puberty in HH is more responsive to medical treatment than epilepsy is, treatment failures may also occur. Surgical eradication of the lesion is therefore commonly offered for HH patients with refractory epilepsy and with endocrine treatment failure.[11,12]

Increased clinical awareness of HH has led to specialized referral patterns and the formation of robust interdisciplinary teams capable of approaching the condition with an increasingly varied armamentarium of treatment options. In the hands of experienced surgeons, craniotomy with subtemporal, subfrontal, and transcallosal approaches have frequently resulted in excellent seizure control and marked improvement in behavioral and neuropsychiatric symptoms.[13] However, risks of injury to limbic structures and central endocrine function, in addition to extended hospitalization for craniotomy, have inspired innovations in surgical technique aiming to achieve cure while reducing neurologic morbidity of open surgery.[14,15] Representing one such advancement, the transventricular neuroendoscopic approach for HH that lies within the third ventricle, is an effective alternative to open craniotomy with a transcallosal approach, with comparable efficacy and significantly shorter postoperative recovery time (mean 4.1 days vs. 7.7 days).[16–21] Stereotactic radiosurgery (SRS) is also an effective treatment option in patients with small HHs displaced from radiosensitive structures, which have a stable symptomatic picture affording them time (up to 18 months) for the effects of radiosurgery to occur.[22–24] Stereotactic radiofrequency thermocoagulation (SRT) has also been reported with favorable clinical outcomes.[25,26]

Most recently, laser interstitial thermal therapy (LITT) has provided a compelling alternative treatment, providing immediate efficacy, sharp-margin ablation, minimal damage to adjacent structures and decreased lengths of hospital stay and perioperative costs.[27–31] Wilfong and Curry (2013) reported 86% seizure freedom in 14 HH patients treated with LITT with mean follow-up of 9 months.[32,33] Herein we provide complementary evidence for the safety and efficacy of LITT in our series of eight patients with a mean follow-up of 19.1 months, including five patients with >1-year follow-up.

Methods

Patient selection

Between 2012 and 2016, eight patients with HH and medically refractory symptoms were treated with LITT. Patient demographics are listed in Table 1. A total of nine catheter/laser fiber assemblies were placed in the eight patients. Candidacy for LITT was based on anatomic configuration of the HH, with consideration of maximal diameter (<2 cm), laterality (two left, left right, one bilateral), and whether patients had undergone prior surgery (2/6 patients), and with smaller size, unilaterality and having prior surgery being favorable for LITT. Although some patients or patient advocates specifically requested LITT, refusing any other open surgical option, cases were discussed by a multidisciplinary team of epilepsy specialists and deemed appropriate for LITT treatment.

LITT device

The Medtronic/Visualase software uses the Arrhenius model that integrates temperature over time to calculate an estimated damage zone that updates every 10 s. Depending on the targeted tissue and surrounding structures, which can dissipate heat differentially such as cerebrospinal fluid (CSF) and blood vessels, up to a 2–4 cm circumferential, spherical ablation can be achieved. A contour may be achieved by either withdrawing the fiber or by using multiple devices. The intensity of the laser energy as well as the duration of treatment is manually controlled by the surgeon during this procedure. Although it is possible to deliver up to 15 W, ≤8 W is delivered for >90 s to any part of the HH, and near the plane of attachment, no ≤5 W is delivered for no ≤30 s. This is due to risk of injury to the contiguous

Table 1. Patient demographics

Patient	Age at treatment	Age at seizure onset	Lesion size	Delalande & Fohlen classification	Type of seizure	Pre-op seizure frequency	Neuropsychiatric comorbidities
1	40	6	8 ×9 × 9 mm	I	Complex partial	1–2 per week	MR, autism, rage attacks
2	25	7	4 × 4 × 4 mm	II	Complex partial	4 per day	None
3	3.5	0	14 × 13 × 14 mm	III	Gelastic	5–10 per day	Rage attacks
4	17	1	9.5 × 9.5 × 9 mm	II	N/A	None	Rage attacks
5	24.5	23	16 × 13 × 12 mm	I	Focal and GTC	1 per day	None
6	3	2	9.7 × 8 × 8.6 mm	II	Gelastic	2–6 per day	None
7	25	0	15 × 10 × 10 mm	III	Gelastic and GTC	1–2 per day	None
8	15	2	9 × 16 × 14 mm	II	Focal and GTC	4–5 per day	MR, Lennox-Gastaut

Patient	Prior treatment	Outcome	Length of hospital stay (days)	Last follow-up (months)
1	None	Engel I, improvement in rage attacks	2	30
2	Transcallosal interforniceal at age 13	Engel I	2	30
3	None	Engel I, improvement in rage attacks	3	27
4	Endoscopic at age 8	No improvement in rage attacks	2	25
5	None	Engel I	3	22
6	None	Engel I	4	13
7	SRS	Seizure-free, short-term memory loss	3	5
8	None	75% sz reduction	2	7

Figure 1.
MRI-guided laser ablation. *Left:* Thermometry map. *Right:* Inferred ablation area.
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hypothalamus, mammillary bodies, and mammillothalamic tract. The Arrhenius calculation may be used to estimate the size of the lesion at 10 s intervals.[34] This calculation derives a temperature at a given site on magnetic resonance imaging (MRI), which may be manually chosen by the surgeon. By placing one set of safety markers at the target and another set at vulnerable structures, the delivery of LITT may be controlled by software in a closed-loop fashion to maintain a 50–90°C temperature at the target and to shut off when temperature rises over 43°C at adjacent tissue that is intended to be protected (Fig. 1, center and bottom rows). As another safety precaution, the surgeon may manually stop the treatment at any time if there is concern.

Surgical technique

The Visualase system was used for all patients in this series. Details of the device have been presented elsewhere, and our operative technique has been discussed previously.[28] Notable considerations for HH include the use of a 3 mm diffusing tip to the fiberoptic cable, as opposed to the 10 mm tip that is used for mesial temporal lobe epilepsy (MTLE). Our technique involves placement of the fiber/catheter assembly in the operating suite under general anesthesia followed by transport to the MRI suite, where the treatment is delivered under thermometric guidance.

One or two trajectories were designed to align maximally along the long axis of the HH, avoiding critical neural and vascular structures and, when possible, CSF spaces. The dura was punctured with either a 14-gauge alignment rod (two devices), a 20-gauge obturator (five devices), or a 22-gauge spinal needle (two devices). Temperature boundaries (typically 45°C over areas to be spared and 90°C at the lesion center) were programmed to limit hyperthermia. The ablation was performed and monitored with thermometry for the length of time and number of retractions deemed appropriate by the surgeon as seen in Figure 1. After completion of ablation, a T_2-FLAIR (fluid-attenuated inversion recovery) and T_1-weighted MRI with contrast were performed to visualize the final lesioned area.

Comparison of treatments for hypothalamic hamartoma

A literature search was undertaken in PubMed for the established treatments for epilepsy-associated hypothalamic hamartoma. Search terms were "hypothalamic hamartoma," "stereotactic radiosurgery," "LITT," "radiofrequency ablation," "thermocoagulation," "craniotomy," and "endoscopy." The treatments considered are transcallosal/orbitozygomatic craniotomy, neuroendoscopic resection or disconnection, stereotactic radiosurgery, radiofrequency thermocoagulation, and LITT. Selected published results of Engel-classification seizure control characteristics and long-term complications were considered.

Results

Demographics

Preoperative patient demographics are listed in Table 1. All lesions were sessile in relation to the hypothalamus and third ventricle. Delalande and Fohlen's classification of sessile HH was used to describe the lesional characteristics; two patients' lesions had type I morphology, four had type II, and two had type III.[33] One patient underwent LITT, followed 2 weeks later with SRS, to treat a noncontiguous residual lesion that had been treated with open craniotomy 10 years prior.

Stereotactic targeting

Nine trajectories were used in eight patients. The target of the catheter was chosen at a point 3–6 mm within the lesion at the midpoint of the plane of attachment. The decision to use one or two devices was made on the basis of the size of the lesion and plane of attachment. The entry point was chosen at a point 1–2 cm posterior to the coronal sulcus, and to minimize brain shift, the trajectory was designed to avoid the ventricles. Special consideration was made toward the locations of the optic tract, mammillary bodies, basilar artery, and fornix. Of these, the optic tract and basilar arteries were deemed to be of least concern, as the CSF within the suprasellar and interpeduncular cisterns act as heat sinks. The position of the mammillary bodies and the mammillothalamic tract was most concerning if the HH had a more posterior position. In all cases within this series, the mammillary bodies appeared to be posterior to the plane of attachment of the HH. All devices were placed within 1 mm of the intended target as confirmed by MRI and compared to preoperative planning.

LITT treatment

A test dose was applied at 2–3 W under thermometry guidance to confirm the locus of treatment. Treatments were delivered at 3–7 W for 30–240 s while monitoring temperature via calculated thermometry on coronal and sagittal planes. High safety markers to automatically shut off treatment at 90°C were placed in the region of the diffusing tip. Low safety markers to shut off treatment when thermometry calculations indicated temperatures >45°C were placed at the point of attachment of the hypothalamus, mammillary body, and optic tract that was closest to the diffuser tip. At the conclusion of the treatment, a T_2-FLAIR and T_1 postcontrast sequence was obtained to estimate the region of treatment (Fig. 1 middle and lower panels). Technical details of LITT treatment for individual cases are described in Table 2.

Postoperative outcome

All patients were extubated on the same day as the procedure. Patients were monitored in an intensive care unit (ICU) setting for 24 h, with urine output and serum sodium monitored every 6 h. No patient developed diabetes insipidus as defined by hypotonic polyuria. Patients were given 4 mg dexamethasone every 6 h postoperatively for 1 day, which was tapered over 1 week. The eight patients stayed in the hospital on average 2.6 days total.

Seizure and behavioral outcomes were collected for eight patients based on chart review and telephone interview, with an average posttreatment follow-up period of 19.1 months (range 3–30 months). Postoperative outcomes are listed in Table 1. For all patients with epilepsy, improved seizure control was observed, and all are seizure-free except one patient, who has 75% reduction in seizure frequency. All five patients with 1-year follow-up and all four with 2-year follow-up were seizure-free. Two of three patients with

Table 2. Technical details of LITT treatment

Patient	# of ablations	Position of safety markers	Maximum watts delivered	Time of LITT application at maximal dose (seconds)
1	2	Hypothalamus, optic tract	7	90
2	4	Hypothalamus, optic tract	7	240
3	4	Hypothalamus, optic tract, mesial temporal lobe	7	225
4	1	Hypothalamus, optic tract	4	90
5	4	Hypothalamus, optic tract	7	218
6	1	Hypothalamus, optic tract	4	90
7	2	Hypothalamus, optic tract	7	90
8	2	Hypothalamus, optic tract	5	110

behavioral disturbance had resolution of behavioral symptoms.

Complications and suboptimal outcomes

One procedure was complicated with an epidural hematoma. It is likely that this occurred as a result of inadequate dural puncture and dissection of the dura from the periosteum during placement of the alignment rod. The epidural hematoma was seen on the scout MRI (patient 5 in Fig. 2, middle row), but the mass effect was local and the size of the hematoma could be monitored during the 10-min treatment, it was possible to complete the ablation. The patient was then returned to the operating room prior to extubation where a craniotomy was performed to evacuate the hematoma. The patient was discharged from the hospital on the third postoperative day without neurologic deficit.

In another patient, there was a failure of the software to generate accurate damage estimates using the Arrhenius equation that became apparent only after treatment had been initiated. In this case, the device was stopped manually stopped based on dosimetry, such that up to 30 s of 5 W was delivered to the point of attachment of the hamartoma to the hypothalamus. Nonetheless, MRI imaging confirmed the lesion to include and be restricted to the targeted area.

Metaanalysis of the literature

Published series of seizure-control outcomes and complications in patients who underwent craniotomy, neuroendoscopic, SRS, SRT,or LITT, or a combination are shown in Table 3. This shows 21 (84%) of 25 patients to be seizure-free after an average of 19.1 months of follow-up using LITT, with permanent complications observed in two cases (8%): epidural hematoma in the patient described in the current study, and a patient with severe anterograde amnesia resulting from ablation-related bilateral mammillary body damage in the context of prior right temporal lobectomy. In the recently published series by Kameyama of 100 consecutive hypothalamic hamartoma patients undergoing SRT, a 71% seizure-freedom rate was observed, with permanent complications observed in only two patients (2%) with permanent pituitary dysfunction in patients who had both undergone more extensive, multiple SRT interventions for bilateral lesional attachments. Kameyama reports the occurrence of transient post-SRT supplemental motor area syndrome peculiar to the SRT modality, attributed to transient inactivation of the network between the thalamus and hypothalamus during the course of the procedure, and which resolves. Published series of HH treated with SRS demonstrate a 46.2% (24/52) seizure-freedom rate with no permanent neurologic deficits. Laiseca notes a case of radiation-related edema several months after the SRS treatment that required hospitalization for depressed consciousness, but which resolved completely.[45] Large published series of surgical approaches to HH at high-volume centers reported by Rosenfeld,[46,47] Rekate,[11,49] and Andrew[48] achieved 48.6% (52/107) seizure-freedom rates, with a 9–15% rate of permanent complications including memory loss and hemiparesis, endocrine dysfunction, and perioperative death.[34–37]

Discussion

Laser interstitial thermal therapy (LITT) is gaining popularity at many epilepsy surgery centers as a minimally invasive alternative to open craniotomy approaches to resection of seizure foci.[38] Some of the potential benefits of LITT over craniotomy include decreased surgical morbidity, fewer complications, and shorter length of stay.

Given that experience with LITT has grown in the treatment for epilepsy, it is logical that this approach has been applied to HH. The largest published series (Wilfong and Curry[33]) of 10 HH patients treated with LITT

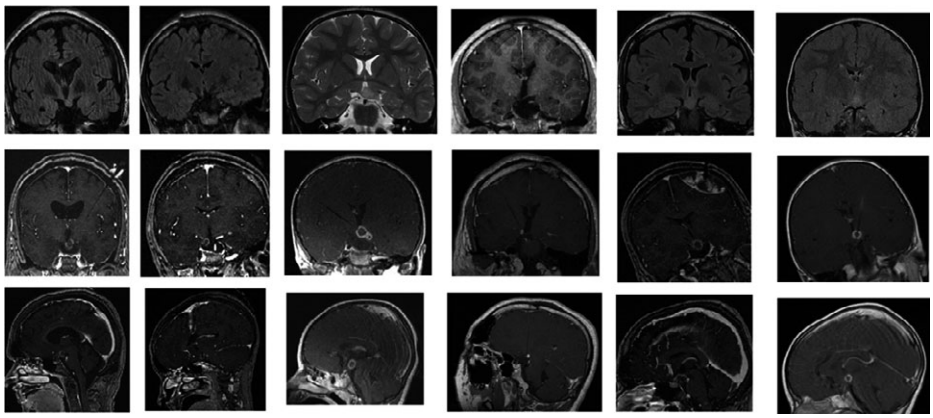

Figure 2.
Top row: Preoperative coronal MRIs demonstrating the HH. *Middle and bottom rows:* Postoperative coronal and sagittal MRIs demonstrating the treatment lesions in eight patients.
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Table 3. Review of published LITT treatments

Study	Treatment	Avg. follow-up (months)	Outcome
Wilfong (2013)[33]	LITT	15.9	12/14 seizure-free
Zubkov (2015)[39]	LITT	8	0/1 seizure-free
Brandmeir (2016)[38]	LITT		1/1 seizure-free
Ralston (2016)[40]	LITT	6	2/2 seizure-free
Current study	LITT	19.1	6/7 seizure-free
		Total	21/25 (84%) seizure-free
Wang (2009)[25]	SRT	12	1/1 seizure-free
Kameyama (2016)[26]	SRT	Median 36 months	71/100 seizure-free
		Total	72/101 (71.3%) seizure-free
Selch (2005)[41]	SRS	13.7	2/3 seizure-free
Regis (2006)[42]	SRS	All >36 months	10/27 seizure-free
Mathieu (2010)[43]	SRS	27.3	4/9 seizure-free
Abla (2010)[24]	SRS	43	6/10 seizure-free
Susheela (2013)[44]	SRS	12	1/1 seizure-free
Laiseca (2016)[45]	SRS	16	1/1 seizure-free
		Total	24/52 (46.2%) seizure-free
Rosenfeld (2004)[46,47]	Transcallosal craniotomy	All >12 months	15/29 seizure-free
Andrew (2008)[48]	Transcallosal craniotomy	All >24 months	1/5 seizure-free
Abla (2011)[49]	COZ	37	4/10 seizure-free
Wait (2011)[11]	Transcallosal craniotomy	20.3	14/26 seizure-free
Wait (2011)[11]	Endoscopic surgery	21	18/37 seizure-free
		Total	52/107 (48.6%) seizure-free

demonstrated seizure freedom in 12 of 14 cases at an average 9-month follow-up, and reported no clinically relevant complications. In our series, six of seven patients who underwent LITT to treat epilepsy are seizure-free at average 17.7 months of follow-up. The one patient who underwent LITT to treat rage attacks only, did not have posttreatment improvement, whereas behavioral problems did improve in two of the patients with epilepsy. No patient developed diabetes insipidus or sensorimotor neurologic deficit from the LITT procedure. Although we do not have detailed neuropsychological follow-up in the higher functioning patients, for those with >6 months of follow-up, all patients or patient caretakers subjectively noted improvement in overall functioning. As with any cranial procedure, there is a risk of postoperative hemorrhage, and the present series calls attention to a technical nuance of the procedure. That is, successful dural puncture must be ensured after trephination before attempting to pass a device to the target. Our experience also highlights the potential of software failure in the calculation of the Arrhenius equation and cautions against overreliance on the calculated heat maps and setting of safety markers. Furthermore, and as opposed to the case for MTLE, HHs are not surrounded by CSF spaces to act as heat sinks, leaving the contiguous hypothalamus near the zone of attachment vulnerable to thermal injury. For this reason, we emphasize consideration of dosimetry in terms of integrated energy delivered, and recommend that no more than 30 s of 5 W energy be delivered within 3 mm of the attachment. As such, further refinement of the technology to provide a more contoured treatment and more accurately perform thermometric calculation would represent a meaningful advance.

There have been several surgical approaches characterized in the literature aimed at disconnection and/or resection of HH. These approaches have been associated with morbidities related to hypothalamic dysfunction.[14] Furthermore, the craniotomies utilized are among some of the more invasive skull-base approaches, carrying significant morbidities aside from hypothalamic dysfunction such as forniceal damage.[14] In our experience, the application of LITT for HH has avoided most of these complications with good results. At least as an initial approach, LITT may represent a favorable treatment strategy for HH. Although we acknowledge that no lesion exceeded 2 cm on any axis within our series, approaches aimed at disconnection, analogous to the SRT approach, may provide a possible means to treat larger HHs. We have not yet encountered a situation in which an open, resective approach was needed after a failure of LITT for HH. It would seem logical though, that if a resective approach was required after LITT, it could be performed in much the same manner as in a patient who had never been surgically treated, as the minimally invasive approach would result in minimal scarring and distortion of anatomy. Treatment failures resulting from previous open surgery may potentially benefit greatly from LITT in terms of symptomatic control as well as complication avoidance. Conversely, adjuvant treatment with SRS may be considered in some patients where the LITT treatment does not result in complete obliteration of the lesion. Due to the presence of a small contralateral remnant, one patient

underwent additional treatment with Gamma Knife 2 weeks after the LITT procedure. However, given her immediate seizure-free outcome, it is likely that the LITT provided adequate treatment to her most disabling seizures. In our series, LITT has been well tolerated, and resulted in minimal serious complications, short hospitalization, and excellent seizure control.

Although LITT has the potential to supplant more invasive procedures such as craniotomy and neuroendoscopy by demonstrating comparable seizure cure rates and avoiding craniotomy-associated complications, its efficacy and complication profile must also be considered in comparison with other stereotactic, minimally invasive procedures such as stereotactic radiosurgery (SRS) and stereotactic radiofrequency thermocoagulation (SRT).

A major advantage of SRS in treating intracranial advantage is its avoidance of intraoperative complications. However, it achieves rates of cure in HH cases that appear to be lower than in LITT, and symptomatic postoperative radiation-related edema is a known risk.[39] Furthermore, the 12-to 18-month latency to therapeutic effect would carry consequences relevant to children, potentially limiting the developmental future. It can nevertheless be an effective tool used in conjunction with LITT and other modalities to approach HH pathology. Further study should be undertaken to examine the use of LITT in failed SRS, and vice versa, the use of SRS in failed LITT.

Stereotactic radiofrequency thermocoagulation is also an established modality for the treatment of HH and has a complication profile like that of LITT due to the technical similarities. In the published series of SRT cases, both seizure control and complication rates are comparable to that of LITT. However, LITT carries theoretical advantages of sharp ablation margins, much larger ablation volumes achievable with one catheter compared with SRT, and real-time imaging feedback. These factors and clinical results potentially support the use of LITT over SRT as the initial consideration when stereotactically targeted lesioning treatment is indicated for HH. While the present series presents longer follow-up with maintained seizure-free outcome, greater numbers of patient outcomes with long-term follow-up must be achieved to more definitively elucidate the indications for LITT versus SRT. Ultimately, the major factor in choosing one of these modalities may simply be availability. In the United States, there are two different companies providing equipment for LITT treatment, whereas availability outside the United States remains limited. On the other hand, SRT may be accomplished using basic stereotactic techniques for placement and electrical current generators.

The present results add to the ongoing collection of patient experiences at multiple HH referral centers and provide encouraging results for establishing LITT as a primary consideration for treatment planning when available. Important tasks remain to determine long-term Engel outcomes as longer-term clinical follow-up becomes available and more patients undergo LITT. Technical refinements, better methods to calculate thermometry, and increased HH clinician familiarity with the LITT paradigm will also contribute to the evolution of LITT as a powerful tool in the treatment of this challenging pathology.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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