Clinically Significant Visual Deficits after Laser Interstitial Thermal Therapy for Mesiotemporal Epilepsy

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Keywords

Brain atlas · Epilepsy surgery · Lesion · Magnetic resonance imaging · Stereotactic surgery

Abstract

Background: Laser interstitial thermal therapy (LITT) has recently gained popularity as a minimally invasive surgical option for the treatment of mesiotemporal epilepsy (mTLE). Similar to traditional open procedures for epilepsy, the most frequent neurological complications of LITT are visual deficits; however, a critical analysis of these injuries is lacking. **Objectives:** To evaluate the visual deficits that occur after LITT for mTLE and their etiology. **Method:** We surveyed five academic epilepsy centers that regularly perform LITT for cases of self-reported postoperative visual deficits. For these patients all pre-, intra- and postoperative MRIs were co-registered with an anatomic atlas derived from 7T MRI data. This was used to estimate thermal injury to early visual pathways and measure imaging variables relevant to the LITT procedure. Using logistic regression, we then compared 14 variables derived from demographics, mesiotemporal anatomy, and the surgical procedure for the patients with visual defi-

cits to a normal cohort comprised of the first 30 patients to undergo this procedure at a single institution. **Results:** Of 90 patients that underwent LITT for mTLE, 6 (6.7%) reported a postoperative visual deficit. These included 2 homonymous hemianopsias (HHs), 2 quadrantanopsias, and 2 cranial nerve (CN) IV palsies. These deficits localized to the posterior aspect of the ablation, corresponding to the hippocampal body and tail, and tended to have greater laser energy delivered in that region than the normal cohort. The patients with HH had insult localized to the lateral geniculate nucleus, which was associated with young age and low choroidal fissure CSF volume. Quadrantanopsia, likely from injury to the optic radiation in Meyer’s loop, was correlated with a lateral trajectory and excessive energy delivered at the tail end of the ablation. Patients with CN IV injury had extension of contrast to the tentorial edge associated with a mesial laser trajectory. **Conclusions:** LITT for epilepsy may be complicated by various classes of visual deficit, each with distinct etiology and clinical significance. It is our hope that by better understanding these injuries and their mechanisms we can eventually reduce their occurrence by identifying at-risk patients and trajectories and appropriately tailoring the ablation procedure.

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Introduction

Laser interstitial thermal therapy (LITT) is changing how we manage patients with mesiotemporal lobe epilepsy (mTLE) refractory to medical management [1–4]. With recent advances in MRI thermal imaging, LITT is now capable of producing discrete lesions with high precision. As a result, the technique has been quickly incorporated into epilepsy practices across the USA with a recent published case series suggesting similar or slightly lower seizure efficacy than the surgical gold standard, anterior temporal lobectomy (ATL); but with significantly less postsurgical discomfort, shorter hospital stays, and potentially fewer neurocognitive deficits from the sparing of perihippocampal temporal lobe tissues [1–5].

Thus far, LITT has proven to be a safe treatment for mTLE with no deaths reported. However, the procedure is not without risk. Similar to after ATL, visual deficits have been noted in every series published on the topic to date, and typically manifest as field cuts or diplopias [1, 3, 5, 6]. Proposed etiologies have included direct trauma or accidental thermal injury to early visual pathways, either from a lack of knowledge of preoperative visual system anatomy or from inadvertent spread of heat to these structures from the hippocampus [1, 3, 7]. Given the close proximity of the hippocampus to the brain's early visual circuitry, these deficits could potentially result from a variety of insults, but a thorough analysis of the subject has not been undertaken. It is essential that we gain a better understanding of the incidence and etiology of visual deficits after LITT for epilepsy in order to eventually minimize their occurrence.

Here, to better understand visual deficits after LITT we performed a survey for patients with these postoperative complications at five separate epilepsy centers. A deformable atlas was used to co-register patient images to an anatomic atlas derived from 7T MRI data in order to estimate injury to visual system structures not typically visible on standard pre- and postoperative MRI [8]. For normative data, this group of patients was compared to a cohort consisting of the first 30 patients who underwent the procedure at a single institution. In addition to better understanding the incidence and mechanism of visual deficits after LITT, our goal was to identify patient- or procedure-specific variables that one day could be used for identifying those at risk of developing these complications.

Table 1. Independent variables

Age (years)
Sex
Side of surgery
Presence of MTS
AHC volume (mm ³)
Choroidal fissure volume (mm ³)
Medial-lateral laser location
Superior-inferior laser location
Axial angle (°)
Sagittal angle (°)
Ablation volume (mm ³)
Ablation duration (s)
Total laser energy (J)
Laser energy in final two ablations (J)

These measures were calculated for all patients in order to assess features of patient demographics, preoperative anatomy, and of the LITT procedure associated with the occurrence of postoperative visual deficits. AHC, amygdalohippocampal complex; MTS, mesiotemporal sclerosis.

Materials and Methods

Patient Selection and Procedures

We conducted a survey of neurosurgeons performing LITT for mTLE at five academic epilepsy centers (Thomas Jefferson University, University of Miami, University of South Florida, Cook Children's Medical Center, and Vanderbilt University) to retrospectively identify visual complications following the procedure. At each institution patients underwent a standard epilepsy evaluation that included determination of language laterality, neuropsychological work-up, and high-resolution MRI before and 1–6 months after surgery. All cases were reviewed prior to surgery by a multidisciplinary committee at each institution. Surgical procedures were performed according to methods previously published by the authors of this study [3, 4, 9, 10]. Inclusion into the study required self-reporting of the visual deficit to the primary neurosurgeon by the patient. Only 2 patients received formal postoperative ophthalmologic evaluation (Patients 1 and 2). Inclusion of all patients into this study was approved by the Institutional Review Board of each patient's home institution.

For normative imaging data we used the first 30 patients at the University of Miami to undergo the procedure, which included one patient with a visual deficit (Patient 1). Epilepsy and neurocognitive outcomes for the majority of this cohort have been published previously [4].

Data gathered for each patient included demographic information, pre- and post-ablation MRI, intraoperative thermal damage estimate (TDE) maps, laser ablation settings (not available for Patient 5), and information from follow-up clinic visits. The preoperative MRI with laser trajectory overlaid is shown for each patient in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000504856).

Image Analyses

Because structures of the early visual system cannot be identified from standard 3T MRI, we used a deformable atlas to esti-

Table 2. Patient demographics and surgical outcomes

Patient	Sex	Age at surgery, years	Age of onset, years	Side	Visual deficit	MTS	Engel class	Follow-up, months
1	M	24	7	L	R HH	Yes	I	27
2	M	11	10	R	L HH	Yes	I	12
3	F	56	1	R	LS Quad	Yes	II	48
4	F	54	8	L	RS Quad	Yes	III	42
5	F	58	1	L	L TNP	No	I	21
6	F	51	39	R	R TNP	No	I	29
Cohort	M – 50% F – 50%	43±2	12±2	L – 53% R – 47%		Yes – 70% No – 30%	Class I – 63%	30±8

Patients 1 – 6 reported visual deficits. The cohort shows data averaged for 30 patients at the University of Miami; these cohort data are shown as mean ± SEM unless otherwise indicated. MTS, mesial temporal sclerosis; M, male; F, female; R, right; L, left; HH, homonymous hemianopsia; Quad, quadrantanopsia; TNP, trochlear nerve palsy.

mate locations of the optic tract, lateral geniculate nucleus (LGN), and optic radiations. All high-resolution MRIs obtained before, during, and after LITT were co-registered to a common reference atlas based on 7T MRI anatomic information using CranialSuite clinical software, developed by Vanderbilt University and Neurotargeting LLC (Nashville, TN, USA) [11]. Both global rigid (rotational and translational movements) and non-rigid (local deformations) registrations were used, with nonrigid deformations based off the adaptive bases algorithm [12]. Pre- and postoperative imaging used for this study consisted of T1 MP-RAGE sequences with 1-mm-thin cuts obtained prior to and 1–6 months after surgery, respectively. Intraoperative imaging consisted of contrasted T1 sequences collected after ablation. Visual structures were considered ablated if contrast extended into their borders as predicted by the anatomic atlas. These judgments were made difficult by the presence of numerous mesio-temporal structures that express contrast independent of coagulative injury (blood vessels, choroid plexus, pia, and arachnoid linings), thus the contralateral side was frequently used as an internal control.

To compare patients who suffered a visual deficit after LITT to those who did not, 14 independent variables were quantified for all patients (shown in Table 1). Amygdalohippocampal complex volume was estimated using anatomic data from 7T MRIs deformed to the preoperative MRI, with borders manually adjusted by an expert (W.J.J.) as needed to conform to anatomic conventions defined by the European Alzheimer's Disease Consortium [13, 14]. The choroidal fissure was manually traced in 1-mm coronal cuts from the preoperative MRI. Ablation volume was traced from the immediate post-ablation MRI using the extent of contrast uptake to delineate boundaries. Laser position was measured from a coronal cut at the lateral mesencephalic sulcus. Superior-inferior position is the location of the laser relative to the cranial (value of 1) and caudal (value of 0) extents of the mesiotemporal lobe (including hippocampus, white matter, and perirhinal cortex), respectively. Medial-lateral position is the laser location relative to the medial (value of 0) and lateral (value of 1) walls of the hippocampus at the same coronal cut. The axial angle was measured from axial images as the angle of

the laser relative to the antero-posterior midline. The sagittal angle was measured from sagittal images as the laser angle relative to a line connecting the anterior and posterior commissures.

Statistical Analyses

All statistics were calculated using MATLAB (MathWorks, Natick, MA, USA). Means were compared using bootstrap analysis, with data resampled 1,000 times. Univariate logistic regression was used to compare the 14 independent variables for patients with a postoperative visual deficit to those without, with $p < 0.05$ used as the criterion for statistical significance.

Results

Of the 90 patients who underwent LITT for mTLE at five institutions, 6 (6.7%) reported a visual deficit after surgery (Table 2). These included 2 homonymous hemianopsias (HHs), 2 quadrantanopsias, and 2 cranial nerve (CN) IV palsies. When the 14 independent variables were compared for the 6 patients with visual deficits vs. the cohort, univariate logistic regression did not identify a significant difference between the groups, though a positive trend was observed for energy delivered in the final two ablations ($\chi^2_{33} = 2.0$, $p = 0.154$), corresponding to the location of the hippocampal body and tail.

Homonymous Hemianopsia

Patient 1 is a 24-year-old male with mesial temporal sclerosis (MTS) who developed a complete right HH following a left-sided ablation. In the months after surgery he regained the ability to see light and discriminate certain objects but not count fingers in the right superior quadrant, which has not shown improvement since. He

Fig. 1. Homonymous hemianopsia following LITT. Intraoperative post-ablation MRI for Patient 1 showing the left-sided lesion in coronal (a), axial (b), and sagittal (c) views. Below b and c are shown intraoperative TDE maps in the same imaging planes. Outlines of optic tract (dark blue), LGN (light blue), and optic radiation (green) were projected from the co-registered 7T atlas. The laser trajectory is shown by the pink line. Scale bar, 0.5 cm. d–f Same conventions but for Patient 2.

continues to have no vision in the right inferior quadrant. His post-ablation contrasted MRI is suggestive of thermal injury to the inferior thalamus, specifically to the LGN, on the deformable atlas (Fig. 1a–c). Irreversible thermal injury to the thalamus is shown by the sagittal TDE map, but this was not realized intraoperatively (Fig. 1c).

Patient 2 is an 11-year-old male with multifocal focal cortical dysplasia and MTS who acquired a left HH immediately after right-sided LITT. His visual deficit was complete and demonstrated no improvement 12 months after surgery upon ophthalmologic evaluation. His post-ablation contrasted MRI is also suggestive of injury to the LGN (Fig. 1d–f), with subtle extension of irreversible damage toward the thalamus on the sagittal TDE map (Fig. 1f).

Examination of the independent variables reveals that both HH patients were relatively young and had small choroidal fissures, but Patient 1 had a relatively superior trajectory with average laser energy delivered and Patient 2 had an inferior trajectory with a large energy dose delivered (see online suppl. Fig. S2). When these 2 HH pa-

tients are collectively compared to the University of Miami cohort, univariate logistic regression reveals younger age as the only difference between the groups ($\chi^2_{29} = 9.9$, $p = 0.002$). The 2 HH patients trend toward male sex ($\chi^2_{29} = 2.5$, $p = 0.113$), smaller choroidal fissure volume ($\chi^2_{29} = 2.4$, $p = 0.124$), and greater laser energy delivered ($\chi^2_{29} = 2.2$, $p = 0.14$) when compared to the cohort, but the differences in these variables are not statistically significant.

Quadrantanopsia

Patient 3 is a 56-year-old female with MTS who underwent right-sided LITT. Upon awaking from surgery, she reported blurry vision and was found to have a left superior quadrantanopsia. She noted slow improvement in her vision in the months after surgery and currently has no disability from the injury but continues to have a noticeable deficit upon examination. Co-registration of her post-ablation MRI with the deformable atlas reveals extension of contrast into the right optic radiation, lateral to the LGN (Fig. 2a–c). Such a finding is not apparent for

Fig. 2. Quadrantanopsia following LITT. Intraoperative post-ablation MRI for Patient 3 showing the right-sided lesion in coronal (a), axial (b), and sagittal (c) views. Below b is the axial intraoperative TDE map; a sagittal TDE map was not used. Outlines of optic tract (dark blue), LGN (light blue), and optic radiation (green) were estimated using the deformable atlas. The laser trajectory is shown by the pink line. Scale bar, 0.5 cm. d–f Same conventions but for Patient 4, with axial and sagittal TDE maps shown below e and f, respectively.

any of the other patients in this study. Her intraoperative TDE map is suggestive of a lateral ablation (Fig. 2b).

Patient 4 is a 54-year-old female who noted altered vision after left-sided LITT and upon examination and was diagnosed with a right superior quadrantanopsia. This deficit was detectable by visual field examination on post-operative day 1, but no longer by her 2-week follow-up visit. Co-registration of her post-ablation MRI with the deformable atlas does not show insult to the early visual pathways; however, the predicted location of the left optic radiation is relatively close (within 4 mm) to the ablation (Fig. 2d–f). Her TDE map also shows a relatively lateral ablation (Fig. 2e).

Visual inspection of these patients' trajectories and ablations suggests an excessively lateral laser trajectory may have contributed to their quadrantanopsias. Logistic regression demonstrates that these 2 patients had more lateral trajectories than observed for the cohort ($\chi^2_{29} = 14.8$, $p = 0.0001$), and a trend toward larger ablation volume that does not achieve statistical significance ($\chi^2_{29} = 2.7$, $p = 0.098$) (online suppl. Fig. S3).

CN IV Palsy

Patient 5 is a 54-year-old woman who reported double vision immediately after left-sided LITT and was found to have positive head tilt test suggestive of left CN IV palsy. Her symptoms improved over the weeks after surgery and eventually returned to her preoperative baseline, with no current disability to daily activities. Her postoperative MRI shows contrast extending to the edge of the tentorium (Fig. 3a–c), a finding also evident on the intraoperative axial TDE map (Fig. 3b). Extension of contrast to the tentorium is also observed in 12 of 30 patients in the cohort. Generally, this finding was not as severe for those cohort patients as it was for Patient 5; however, 2 or 3 of the cohort patients show contrast abutting the tentorium for nearly 1 cm of its anteroposterior extent but did not report postoperative visual disturbances.

Patient 6 is a 51-year-old woman who developed an ipsilateral CN IV palsy after right-sided LITT. Her visual deficit was completely resolved by the time of her 1-month postoperative visit. Post-ablation MRI demonstrates a mesial trajectory, also with contrast extending to the ten-

Fig. 3. Cranial nerve IV palsy following LITT. Intraoperative post-ablation MRI for Patient 5 showing the left-sided ablation in coronal (**a**), axial (**b**), and sagittal (**c**) views. Below **b** is the axial intraoperative TDE map; a sagittal TDE map was not used. Outlines of optic tract (dark blue), LGN (light blue), and optic radiation (green) were estimated from the deformable atlas. The laser trajectory is shown by the pink line. Scale bar, 0.5 cm. **d–f** Same conventions but for Patient 6.

torial edge, though to a lesser degree than for Patient 5 (Fig. 3d–f).

Examination of these patients' imaging and operative data suggests that an overly mesial trajectory through the hippocampal body and excessive ablation energy delivered at that location could have caused inadvertent thermal injury to CN IV. Univariate logistic regression shows a relationship for the occurrence of this deficit with absence of MTS ($\chi^2_{29} = 4.4$, $p = 0.036$), as well as nonsignificant trends with larger ablation volume ($\chi^2_{29} = 2.8$, $p = 0.093$) and a mesial laser trajectory ($\chi^2_{29} = 1.23$, $p = 0.267$) (online suppl. Fig. S4).

Discussion

Despite visual deficits being the most frequent neurological complication of mesiotemporal LITT, this is the first case series devoted to the subject [1, 3, 5, 6, 15]. We identified three types of visual deficit, each associated with distinct mechanisms of injury to the early visual ap-

paratus. While it is difficult to draw conclusions from this small retrospective study, the results do suggest an association between findings on the preoperative MRI and the occurrence of these various visual deficits. It is our hope that these data may one day be used for identifying LITT epilepsy patients at risk for visual deficit and modifying the laser trajectory accordingly.

Perhaps it is not unexpected that, similar to ATL, visual deficits are the most common neurologic complications following LITT. The amygdalohippocampal complex is within millimeters of the subcortical visual system along its entire anteroposterior extent. However, differences do exist between the visual insults complicating ATL versus those complicating LITT. ATL has been suggested to cause clinically significant visual deficits in 4–52% of patients and, according to some studies, subclinical deficits in the remainder. These injuries are predominantly contralateral superior quadrantanopsias or smaller superior field cuts, caused by damage to Meyer's loop as it courses through the temporal lobe [16, 17]. However, overt visual complications, such as HH or cranial neuropathy, are not common

after ATL. Following LITT, not only did we find similar field cuts, likely also from injury to the optic radiation, but insults to LGN and CN IV were also acquired. Interestingly, our overall rate of visual deficits at 6.7% is lower than what has been reported for LITT to date, with initial series documenting rates of visual deficits at 10–20 % [1, 3, 5, 6, 15]. While this discrepancy, in part, is likely a result of under-reporting in our study, it could also be an early manifestation of improvements in the safety with which LITT for mTLE is delivered.

The first published visual deficit after LITT for mTLE was caused solely by traumatic injury, specifically by a mispositioned laser that directly pierced the LGN and was identified and removed prior to ablation [1]. But the cases presented here differ in that all were caused by conductive spread of heat from the target to the visual structures. For the most part, these subjects' lasers were entirely within the amygdala and hippocampus, in what would have typically been labeled a good trajectory.

The difficulty in predicting LITT treatment-related effects lies in the variability in brain anatomy observed between patients. Septations, blood vessels, and CSF spaces show great diversity and have been proposed to have large impacts on tissue thermoablative properties [1, 7, 18, 19]. We believe that CSF volume in the choroidal fissure, which separates the LGN from the hippocampal body and shows great variability between patients, may have been a factor in the HH cases and could account for the occurrence of these injuries among the youngest patients in the study. It is also likely that certain patients have anatomy that predisposes their trochlear nerve to thermal injury during LITT. For example, if the hippocampus is more curved, a surgeon may tend to use a more medial trajectory to increase chances of ablating the most mesial extents of the amygdalohippocampal complex, putting CN IV at risk, especially if laser power is not reduced. In addition, we also speculate that variations in tentorial trochlear nerve anatomy could influence the susceptibility of this nerve to thermal injury. Cadaveric studies have shown that when the cisternal component of the nerve comes into contact with the medial tentorial edge, as early as the posterior border of the cerebral peduncle, it entrenches to varying degrees in a groove along the inferior border of the tentorium, before entering its dural canal en route to the cavernous sinus [20, 21]. This segment, adjacent to the hippocampal body, is the most variable portion of the trochlear nerve. Also, in some patients this portion of the nerve is surrounded by a small cistern, whereas in other patients it is tightly adherent to the dura [21]. It is presumable that these variations in local troch-

lear nerve anatomy could have large implications for its susceptibility to thermal injury.

Interestingly, it appears that posterior aspects of the ablation, at the hippocampal body and tail, are most closely tied to visual deficits. This is likely because this is typically the portion of the LITT trajectory where the laser comes into closest proximity to the early visual pathways and cranial nerves, a result of the curvilinear shape of the hippocampus and the occipital trajectory used. In addition, the hippocampal body and tail have smaller coronal cross-sections than the amygdala and hippocampal head, potentially making small deviations from the intended target costlier. We believe that too superior of a laser trajectory at the hippocampal body may predispose to LGN injury, too lateral or posterior of a trajectory to optic radiation damage, and a mesial trajectory to CN IV injury. But it is not only laser position and local anatomy that matter. The visual deficit patients as a group tended to receive larger thermal doses at the hippocampal body/tail than the normal cohort. It is possible that risk to the visual system could have been mitigated by using lower laser power at the tail end of the ablation, though it is unclear what impact this would have had on achieving seizure freedom. Moving forward, we believe that morphometric comparison of the hippocampal body and tail to these surrounding visual structures is warranted for the preoperative planning of safe and effective LITT trajectories.

Significant limitations of this study make it difficult to draw conclusions applicable to the general medication-resistant mTLE population. First, not only do we present just 6 cases, but these cases are further subdivided into 3 groups. Thus, conclusions drawn from this data are quite preliminary. Second, this study was not prospective. Instead, cases were accrued retrospectively among institutions with established academic contacts. Larger prospective clinical trials are currently underway. Third, the normal cohort was entirely from only one of the participating institutions. Given the lack of consensus on what the ideal ablation is, it is likely that various approaches are used among surgeons, thus false-positive differences between visual deficit patients at other institutions and the cohort are likely to have occurred. Furthermore, the visual deficit group contained one pediatric patient, but the University of Miami cohort did not. While this certainly affects our results, we still believe lessons learned from the case and its comparison to the cohort are applicable to adult LITT for mTLE. Fourth, only 2 patients received formal ophthalmologic evaluation. Finally, a deformable atlas was used to deduce injury to structures of the subcortical visual system. While much work has been done using this

software for deep brain stimulation, it is still in its relative infancy for epilepsy applications. In its current form, we cannot take its parcellation of anatomy to be ground truth, particularly for nonvisible structures, such as the LGN or optic radiation, for which it would be ideal to validate representations from the atlas to the current standard of tractography. Regardless, the deformable atlas does at least give us a general idea of the location of these structures and their proximity to the ablation.

Conclusions

Because most neurosurgical postoperative complications are caused by mechanical, ischemic, or toxic injury, the thermoablative nature of LITT puts most surgeons out of their comfort zone, likely hindering adoption of this novel technique [1, 3, 4, 22]. In this study, the identification of anatomic lesions associated with the various visual deficits, the majority of which were visible on intraoperative TDE maps, is encouraging by suggesting the injuries could have been prevented if mechanisms for detecting such ablation patterns and deactivating the laser were present. We believe that in the near term these results could be used to protect critical visual structures by guiding the placement of low-temperature safety markers. Also, it is our opinion that incorporation of preoperative diffusion-based and functional MRI data into our predictive models is the most reasonable way to tailor each ablation to the individual patient. Tractography has already been successfully used to predict visual outcomes from ATL [23]. It is likely that as we continue to accrue and normalize multiparametric MRI data surrounding LITT and its treatment of epilepsy then we will improve our ability to balance seizure outcome with risk of visual complications.

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Statement of Ethics

This study protocol was approved by the Institutional Review Board on human research of each institution. All patients or their guardians signed informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.J.J. worked with partnering institutions on aggregating cases, performed image analyses, and contributed to all aspects of manuscript preparation. C.W. aided in case collection and was instrumental in the preparation of the manuscript. E.N. helped with case collection and proofing of the manuscript. I.C. performed statistical analysis and was involved in manuscript preparation. P.-F.D. aided in image analyses and manuscript proofing. D.J.D., A.D.S., and F.L.V. performed surgical procedures and were involved in manuscript proofing. J.R.J. organized the study, performed surgical procedures, and aided in manuscript proofing.

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