Laser Ablation as Treatment Strategy for Medically Refractory Dominant Insular Epilepsy: Therapeutic and Functional Considerations

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Key Words

Laser ablation · Dominant hemisphere · Insula ·
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Abstract

Since its introduction to neurosurgery in 2008, laser ablative techniques have been largely confined to the management of unresectable tumors. Application of this technology for the management of focal epilepsy in the adult population has not been fully explored. Given that nearly 1,000,000 Americans live with medically refractory epilepsy and current surgical techniques only address a fraction of epileptic pathologies, additional therapeutic options are needed. We report the successful treatment of dominant insular epilepsy in a 53-year-old male with minimally invasive laser ablation complicated by mild verbal and memory deficits. We also report neuropsychological test data on this patient before surgery and at 8 months after the ablation procedure. This account represents the first reported successful patient outcome of laser ablation as an effective treatment option for medically refractory post-stroke epilepsy in an adult.

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Introduction

Since its introduction to neurosurgery in 2008, laser ablative techniques have been largely confined to the management of unresectable tumors. Recently, there have been two reports of the successful use of laser ablation of epileptogenic foci in children [1, 2]. There have been few reports of this technology's application to the management of focal epilepsy in the adult population. Given that nearly 1,000,000 Americans live with medically refractory epilepsy and current surgical techniques only address a subset of this population's epileptic pathologies, additional therapeutic options are needed. We report the successful treatment of dominant insular post-stroke epilepsy in a 53-year-old male. This demonstrates laser ablation as an effective treatment option for medically refractory adult post-stroke epilepsy.

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Fig. 1. Preoperative MRI (top), PET (middle) and SPECT (bottom) demonstrating left insular encephalomalacia and associated hypometabolism.

Case Report

History and Physical Examination

Our patient is a 53-year-old right-handed obese gentleman with a 10-year history of complex partial epilepsy. He and his wife described his seizures as episodes involving a metallic taste in his mouth followed by a sigh breath and a tendency to put objects in his mouth lasting 20–40 s. When he tried to speak during these events his speech was unintelligible. He typically maintained at least partial memory for these events. He had suffered a mild traumatic brain injury approximately 12 years previously, but there was no evidence that this contributed towards his epilepsy. There was no clinically evident identifiable source for or event causing his adult-onset epilepsy. He remained refractory despite three antiepileptic medications (carbamazepine, topiramate and lacosamide). He experienced multiple seizures weekly and had recently begun to develop a chronic, progressive encephalopathy over 3 months prior to presentation including forgetfulness and loss of some of his higher cognitive capabilities. He had no neurological deficits on physical examination.

Presurgical Neuropsychological Assessment

The patient underwent neuropsychological assessment approximately 7 months before the ablation procedure. At that time, the patient reported poor concentration, word retrieval problems and slowed processing speed. His wife believed he was depressed.

He reported that he completed 13 years of education, but repeated the third grade and struggled with reading. He previously worked as a chemical operator, but later became disabled.

His IQ was estimated to be within the low average range. He displayed a severe deficit in executive functions (characterized by deficient divided attention and perseveration) and a moderate deficit in language (reduced letter fluency, naming, and listening comprehension). Milder deficits were also noted in verbal anterograde memory and visual learning. Cognitive test results were consistent with left greater than right cerebral hemisphere dysfunction. Emotionally, he experienced severe levels of depression and anxiety and psychiatric follow-up was recommended (table 1).

Imaging

Magnetic resonance imaging (MRI) performed with seizure protocol revealed a loss of architecture in the left hippocampal head and body as well as increased fluid-attenuated inversion recovery (FLAIR) signal throughout the left hippocampus. MRI also revealed a region of encephalomalacia with gliosis at the junction of the left frontal and temporal opercula within the frontal insular region suggesting a previous subclinical ischemic insult (fig. 1). The insular abnormality was subcortical and spanned throughout the posterior short, anterior long, and posterior long insular gyri. This region of encephalomalacia was thought to be a potential source for his seizures.

Table 1. Results of pre- and postoperative neuropsychological evaluations

Test	Preoperative t score	Postoperative t score
Wechsler Test of Adult Reading (standard score)	83	81
DKEFS		
Letter Fluency	23	20
Category Fluency	37	20
Category Switching-Total	20	23
Category Switching-Accuracy	23	27
MAE		
Token Test	45	<30
BDAE		
Complex Ideational Material	15	34
Boston Naming Test-II	34	30
Rey-Osterrieth Complex Figure		
Copy	37	51
Delayed Recall	43	52
Benton Judgment of Line Orientation	55	47
WASI		
Block design	41	43
Similarities	37	21
WMS-IV		
Logical Memory I	40	37
Logical Memory II	33	27
Visual Reproduction I	46	53
Visual Reproduction II	36	40
CVLT-II		
Total Trials 1-5	47	36
Short Delay-Free Recall	40	35
Short Delay-Cued Recall	40	30
Long Delay-Free Recall	50	35
Long Delay-Cued Recall	45	30
Recognition	45	55
False Positives	45	<20
WCST		
Cards Sorted	128	64
Categories Completed	3 (raw score)	3 (raw score)
Perseverative Errors	27	37
DKEFS		
Visual Scanning	43	43
Number Sequencing	57	30
Letter Sequencing	57	33
Number-Letter Switching	23	20
Motor Speed	50	20
Beck Depression Inventory-II	32 (severe)	28 (moderate)
State-Trait Anxiety Inventory		
State	47 (mild)	53 (moderate)
Trait	66 (severe)	50 (moderate)

DKEFS = Delis-Kaplan Executive Function Systems; MAE = Multilingual Aphasia Examination; BDAE = Boston Diagnostic Aphasia Examination; WASI = Wechsler Abbreviated Scale of Intelligence; WMS-IV = Wechsler Memory Test-Fourth Edition; CVLT-II = California Verbal Learning Test-Second Edition; WCST = Wisconsin Card Sorting Test.

Fig. 2. Skull X-rays showing invasive monitoring electrodes. Anterior-posterior (left) and lateral (right) images show subdural electrocorticography strips placed through a single middle cranial fossa burr hole and a single multicontact depth electrode placed with frameless stereotactic navigation through a frontal burr hole.

Fig. 3. Targeting lesion for laser-induced thermal therapy. The AXiiiS Mini-Frame is mounted to the skull (**a**) and intraoperative navigation probe aligned through the AXiiiS Mini-Frame (**b**); a burr hole is drilled for probe placement (**c**).

Color version available online

Fig. 4. Preablation intraoperative MRI confirming laser probe location within the left insular target location on coronal (left) and sagittal (right) T1-weighted images.

Further Evaluation, Invasive Monitoring and Decision Making

Video EEG revealed rare interictal right temporal sharp waves, left hemispheric slowing, and seven seizures with left hemispheric onset and evolution. Ictal single photon emission computed tomography (SPECT) identified a left frontoinsular focus. Positron emission tomography (PET) demonstrated hypometabolism in the left insula (fig. 1). Taken together, MRI, EEG and PET data suggested that the seizures were either originating from the left insula or left temporal lobe. The patient was discussed in a multidisciplinary epilepsy conference and was deemed to be a candidate for surgical intervention. The patient was offered invasive electrocorticography for seizure monitoring with plans for tailored management of the epilepsy focus. After a multidisciplinary conference, it was felt that a single four-contact insular depth electrode and several frontal, parietal and temporal strips would provide sufficient information to localize the seizures. Hence, multiple subdu-

ral subtemporal and frontotemporal strips and a left insular depth electrode were placed. The depth electrode trajectory was from a frontal burr hole and multiple subdural electrodes were placed via a single middle-cranial fossa burr hole (fig. 2).

Video invasive monitoring for 1 week revealed that the patient had complex partial seizures with left insular onset. This conclusion was based on recording (1) five typical clinical and electrographic seizures with left depth electrode onset and evolution followed by left frontal and temporal propagation, (2) frequent depth electrode epileptiform discharges, and (3) intermittent depth electrode slowing. Monitoring was notable for a predominance of intermittent theta and delta activity and frequent sharp waves throughout the depth electrodes. There were also sharp waves observed in a subdural electrode over the left posterior frontal region. Seizure semiology was characterized by behavioral arrest, staring with inattention, mild mouth movements or vocalization and au-

Fig. 5. Intraoperative thermometry and thermal dosage lines (TDL) for ablation of epilepsy focus. **a** Intraoperative thermometry and TDL are shown for the 45°C dose (left) and 52°C dose (right). The green area indicates the thermometry monitoring zone and the green line encompasses the target. The bold yellow line indicates the 2nd trajectory 45°C TDL and the light yellow line the 1st trajectory 45°C TDL. The bold blue line indicates the 2nd trajectory 52°C TDL and the light blue line the 1st trajectory 52°C TDL. Regions of color within the treatment zone represent thermometry recording illustrated within. Thermometry reference bar with °C is shown in the center. **b** Cumulative TDLs are shown relative to the target lesion (green) in axial, coronal and sagittal planes for 45°C TDL (yellow) and 52°C TDL (blue).

tomatisms. Electrographically, the seizures were stereotypical: initial periodic sharp waves in a depth electrode were followed by rhythmic theta or delta spike-wave complexes that were propagated into the left posterior-frontal and anterior-frontal subdural electrodes with sharply contoured theta activity. Later regions of the propagation included anterior-temporal regions. Seizures then evolved to rhythmic sharply contoured theta activity over broad distributions of intracranial electrodes. Following invasive monitoring, the seizures were therefore localized to the left insula.

The patient was offered Monteris laser ablation of his left frontal insular seizure focus. Minimally invasive ablation under general anesthesia was ultimately favored over other surgical options for several reasons. First, the target was in a difficult-to-access subcortical location which would require a large awake surgery and resection of a broad region of insular cortex and subcortical tissue. The patient had several anesthesia-related contraindications for awake surgery such as excessive patient anxiety, obesity, and obesity-related upper airway management concerns [3–5].

Ablative Procedure

The patient was brought back to the operating room approximately 1 week following electrode placement for invasive monitoring. He was placed supine with his head fixed in an MRI-compatible Mayfield cranial fixation device (Integra Life Sciences, Plainsboro, N.J., USA). All monitoring electrodes were removed and a preoperative MRI was obtained for targeting purposes. Following completion of this MRI, operative planning with the Monteris NeuroBlate System commenced (Monteris Medical, Plymouth, Minn., USA). Two insular targets were selected, one located in the anterior

and one in the posterior portion of the insula. A 2-cm linear incision was made in the patient's frontal scalp to allow for burr hole placement. A 2.2-mm central cannula was used to allow the passage of the laser probe. The Monteris AXiiiS Stereotactic Mini-Frame was affixed to the skull (fig. 3a) and the Stealth Navigus probe (Medtronic Inc., Minneapolis, Minn., USA) was inserted into the AXiiiS Mini-Frame (fig. 3b). The trajectory and depth for the Monteris probe were defined by the Monteris VizApp software. Both ablation trajectories were selected via the single-access burr hole (fig. 3c). The probe was inserted via trajectories from the apex of the skull, and the ablation of the posterior portion of the defined seizure focus was delivered following confirmation of probe placement (fig. 4). The rotational component of the affixed AXiiiS Mini-Frame was mobilized anteriorly via the Navigus probe and the Monteris laser probe was inserted to the preselected depth target. Intraoperative thermal dosage lines and thermometry data confirmed that successful laser ablation of the anterior portion of the insular encephalomalacia was completed (fig. 5). Intraoperative temperatures to achieve apoptosis and necrosis were 45 and 52°C, respectively [6]. The treatment target measured 5.8 cm³. Eighty-seven percent and 81% of the target reached 45 and 52°C, respectively.

Postoperative Course

The patient was monitored in the Neurosurgical Intensive Care Unit overnight following the ablative procedure. Postprocedurally, seizures abated immediately. The patient was mildly emotionally labile and had new mild speech and memory difficulties requiring cognitive rehabilitation. He was discharged 4 days later without event. On short-interval follow-up, the patient displayed

Fig. 6. Radiographic effects of laser interstitial thermal ablation of left insular epilepsy focus. Axial T1-weighted, FLAIR and T1-weighted with gadolinium MRI images are shown preoperatively (**a**), 1 day postoperatively (**b**) and 5 months postoperatively (**c**).

mild and easily manageable verbal and memory symptoms. He had no cranial neuropathies, motor deficits or sensory deficits. He ambulated well with a normal gait. His speech was fluent but intermittently hypophonic. He occasionally repeated himself and made rare paraphasic errors. Impairment in verbal memory improved steadily over time. Transient anxiety and mood alterations returned to baseline levels after approximately 6–8 weeks. The patient has been seizure-free since the time of surgery 23 months ago.

Postoperative Imaging Changes

Postoperative MRI sequences were obtained 1 day and 5 months postoperatively. Compared with a preoperative MRI, the 1-day postoperative MRI shows a hyperintensity in the insular target on T1-weighted images. This corresponds to artifact on susceptibility-weighted imaging sequences and represents coagulation blood products. This region corresponds to high intensity on T2-weighted MRI, surrounded by perilesional edema. T1-weighted images with gadolinium contrast show some new enhancement suggesting breakdown of the blood-brain barrier (fig. 6). Although postoperative enhancement can be seen, MRI sequences 5 months

postoperatively may show persistent enhancement due to blood-brain barrier disruption, which may enhance delivery of antiepileptic medications.

Postoperative Neuropsychological Assessment

The patient underwent repeat neuropsychological assessment approximately 8 months after the ablation. He and his wife reported declines in both his short-term memory and processing speed since surgery. He reported that he felt more depressed transiently following surgery, but that his mood had improved in recent months. Declines in the patient's cognition were predetermined to be significant if he scored at least one standard deviation lower postoperatively than he scored during his preoperative assessment. Therefore, compared to his preoperative neuropsychological assessment, the patient displayed declines on numerous verbal measures including category fluency, listening comprehension, verbal anterograde memory and verbal abstraction (table 1). Stable performance was noted on measures assessing spatial abilities, visual memory, and executive functions. His mood remained depressed and anxious but not as severely as before surgery.

Discussion

Approximately 1 million Americans are living with medically refractory epilepsy [7]. Up to 300,000 of these individuals could benefit from surgical intervention for the management of their epilepsy with clinical improvements enjoyed in a variety of realms including seizure freedom [8], improved return to work/school rates [9, 10], overall improved quality of life [10–13], improved life expectancy [9], among others. While surgery for epilepsy is well tolerated overall, the prospect of open craniotomy discourages both patient referrals and patient willingness to consider surgery [14–16]. Additionally, some patients with discrete, well-defined seizure foci may not be candidates for resection due to anatomical location of their lesion, as is the case in our patient.

Laser ablative technology is a relatively new treatment modality for deep tumors that would otherwise not be amenable to surgical resection. The technology capitalizes on the readily available stereotactic navigation that can be used to localize deep tumors for biopsy. Building on this navigation technology, laser ablation goes one step further and delivers thermal energy under real-time MRI guidance to a surgical target for therapeutic purposes. It was originally conceived of as a treatment for otherwise inoperable tumors. The laser's ablative effect is believed to be multifactorial including local tissue damage from thermal energy, protein denaturation, and potentially a breakdown of the blood-brain barrier to enhance therapeutic effects of postoperatively delivered chemotherapeutic agents [6, 17–22]. Although speculative, it is intriguing that there was persistent enhancement in the treatment zone of this case, suggesting that the blood-brain barrier may be permanently disrupted. This could in part facilitate higher dosage concentration of systemic antiepileptic drugs to an epileptogenic region.

Laser ablation has been employed to treat a variety of targets including tumors and radiation necrosis as well as hippocampal sclerosis and other epilepsy targets [6, 17–32]. Initial reports suggest a potential role for laser therapy in the treatment of epilepsy. Curry et al. [27] performed laser ablation of 5 patients with a variety of epilepsy targets and all patients remained seizure-free as of 2- to 13-month follow-up. Mesial temporal lobe laser ablation in 13 patients by Willie et al. [32] led to seizure freedom in 7 patients and worthwhile improvement in 3 patients. Ablation of an insular seizure focus in this report led to seizure freedom at 23-month follow-up. In addition to showing clinical effectiveness in several stud-

ies, laser ablation of intracranial targets carries several advantages to overcome limitations of open surgery. First, deeply located seizure foci or seizure foci located within eloquent cortex would be amenable to laser ablative technologies preferentially over surgical resection. Second, the minimally invasive nature of the procedure may address concerns on the part of patients or referring physicians who would be otherwise hesitant to accept surgery as a viable treatment option. Finally, laser ablation may reduce hospital and intensive care unit durations and reduce costs [28]. Despite its promise as a viable therapeutic, laser ablation also carries risks of complications. Willie et al. [32] reported a homonymous hemianopia, emergency room visit and an asymptomatic subdural hematoma. Others have reported complications similar to those observed with traditional craniotomies including neurological deficits, hyponatremia, infection, deep vein thrombosis and death [28]. This patient showed decline on several verbal measures at the time of the postoperative neuropsychological assessment approximately 8 months after surgery, however, which is consistent with cognitive changes observed in individuals with dominant hemisphere epilepsy who undergo more traditional resective surgery [33–35]. Therefore, caution must be emphasized for any surgery in the dominant insula. It is recommended that patients are counseled about the possible cognitive declines they might experience even when using laser ablative techniques.

Conclusions

Laser ablation therapy offers a minimally invasive option for select epilepsy patients. Additional studies are warranted to better understand the mechanism of action of both the neurocognitive and antiepileptic effects of this treatment option.

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Disclosure Statement

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