Feasibility and Morbidity of Magnetic Resonance Imaging-Guided Stereotactic Laser Ablation of Deep Cerebral Cavernous Malformations: A Report of 4 Cases

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BACKGROUND: Magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (MRgLITT) has been used successfully to treat epileptogenic cortical cerebral cavernous malformations (CCM). It is unclear whether MRgLITT would be as feasible or safe for deep CCMs

OBJECTIVE: To describe our experience with MRgLITT for symptomatic deep CCMs

METHODS: Patients' records were reviewed retrospectively. MRgLITT was carried out using a commercially available system in an interventional MRI suite with efforts to protect adjacent brain structures. Immediate postoperative imaging was used to judge ablation adequacy. Delayed postoperative MRI was used to measure lesion volume changes during follow-up.

RESULTS: Four patients with CCM in the thalamus, putamen, midbrain, or subthalamus presented with persistent and disabling neurological symptoms. A total of 2 patients presented with disabling headaches and sensory disturbances and 2 with recurrent symptomatic hemorrhages, of which 1 had familial CCM. Patients were considered by vascular neurosurgeons to be poor candidates for open surgery or had refused it. Multiple trajectories were used in most cases. Adverse events included device malfunction with leakage of saline causing transient mass effect in one patient, and asymptomatic tract hemorrhage in another. One patient suffered an expected mild but persistent exacerbation of baseline deficits. All patients showed improvement from a previously aggressive clinical course with lesion volume decreased by 20% to 73% in follow-up.

CONCLUSION: MRgLITT is feasible in the treatment of symptomatic deep CCM but may carry a high risk of complications without the benefit of definitive resection. We recommend cautious patient selection, low laser power settings, and conservative temperature monitoring in surrounding brain parenchyma.

KEY WORDS: Cerebral cavernous malformation, Cavernous hemangioma, Familial cerebral cavernous malformation syndrome, Stereotactic laser ablation, Laser interstitial thermal therapy, Intracerebral hemorrhage, Intraoperative magnetic resonance imaging, Minimally invasive neurosurgery, Stereotactic and functional neurosurgery, Minimally invasive, Stereotactic and functional

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Cerebral cavernous malformations (CCMs) are interwoven collections of blood vessels lined by a thin endothelium without interposing brain tissue. These aberrant lesions may grow or hemorrhage, resulting in headache, seizures, and neurologic deficits.[1,2] CCMs occur with relative frequency in the population (incidence of 0.16%[3]) and are associated with 15.8% symptomatic hemorrhage risk over 5 yr.[4-8]

ABBREVIATIONS: CCM, cerebral cavernous malformation; **CRW,** Cosman-Roberts-Wells; **DVA,** developmental venous anomaly; **FCCM,** familial cerebral cavernous malformation; **MRgLITT,** MRI-guided laser interstitial thermal therapy

Magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (MRgLITT), also called stereotactic laser ablation, delivers

TABLE 1. Preoperative Patient Characteristics

Patient no.	Age (yr)	Sex	Duration of refractory symptoms	Symptoms attributed to CCM	Location	DVA detected	Lesion size (cm^3)	Prior surgical history
1	27	F	6 yr	Complex migraines (sudden disabling HAs associated with hemibody sensorimotor disturbance)	R posterior thalamus (pulvinar)	No	0.6	None
2	41	F	2 mo	Disabling HAs, periodic left hemibody sensory disturbance	R putamen	Yes	2.6	None
3	14	F	4 yr	Repeated symptomatic hemorrhage (3 over 4 yr) causing spastic hemiparesis and hemianopia	R thalamus, midbrain	No	4.2	FCCM, prior L frontal CCM resection
4	62	F	7 yr	Repeated symptomatic hemorrhage (3 over 7 yr), HAs, left hemibody sensorimotor disturbance	R posterior subtha-lamus	No	0.92	None

CCM, cerebral cavernous malformation; DVA, developmental venous anomaly; FCCM, familial cerebral cavernous malformations; HA, headache.

thermal energy (50°C-90°C) to target parenchyma while relying on near-real-time MR thermography to monitor surrounding structures.[9,10] MRgLITT is an alternative to open surgery for a range of neuropathologies.[10-17] Recent work demonstrated MRgLITT to be safe and effective for ablation of cortical epileptogenic CCMs,[18,19] but deep CCMs create distinct challenges. Specifically, CCMs presenting in the basal ganglia, thalamus, or brainstem are typically symptomatic from mass effect and brain injury rather than seizures and are surrounded by functionally sensitive structures to be protected. We describe clinical results, adverse events, and imaging associated with patients who underwent MRgLITT of deep CCMs in the thalamus, putamen, midbrain, and subthalamus.

METHODS

Patient Selection

Four sequential patients presenting with neurological symptoms were found to have brain lesions with typical MRI features of deep CCM. Each patient's symptoms proved persistent, disabling, and attributable to the location of presumed CCM.[8] All cases were reviewed by vascular neurosurgeons and referred for potential ablation. Lesion locations either made risk of microsurgery undesirable or the patient refused microsurgery. Patients were informed of risks. Our Institutional Review Board (IRB) approved this retrospective study and waived the need for patient consent for anonymized retrospective reporting. 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.

Stereotactic Surgical Procedure

Procedures occurred between 2014 and 2017 and adapted from methods previously described.[18,19] Ablations were performed under anesthesia with the Visualase Thermal Therapy System (3-mm diffusion tip, 1.65-mm-diameter cannula, Medtronic Inc, Dublin, Ireland). The device was placed stereotactically by Cosman-Roberts-Wells (CRW) frame (Integra Neurosciences Inc, Princeton, New Jersey) or by scalp-mounted direct MRI-guidance platform (ClearPoint Neuro Inc, Irvine, California).[10,20] In each case, we performed serial MRIs of the laser device placed superficial to the lesion and again after inserting into the lesion to assess deflection or hemorrhage. Laser energy (980 nm, 40%-60% of total available 15 W power) was delivered to generate focal tissue damage.[9] The Visualase workstation displayed real-time thermography and estimated tissue damage.

We strove to ablate the CCM but not surrounding hemosiderin-stained parenchyma. For this, we monitored voxels at the interface of lesion and parenchyma for thermal spread, and if conservative temperature limits of 50°C were reached, then ablation was paused. High temperature settings (90°C) were placed in voxels near the fiber tip. If thermometry signal within the CCM was absent, we relied upon temperature limits placed at the interface and maintained conservative laser power settings. Ablations were performed in 3-min cycles along the trajectory. Diffusion-weighed, fluid-attenuated inversion recovery, and contrast-enhanced T1-weighted MRIs were obtained following ablation. Multiple trajectories were used to shape ablation volumes. Patients were admitted to the intensive care unit or floor and discharged with dexamethasone taper.

Image Analysis

Volumes of lesions (including hemosiderin ring) and ablations (including enhancing borders) were outlined on sequential 1-mm resolution T2 and contrast-enhanced T1 sequences by a neuroradiologist using image processing software (Horos 3.3.6, Purview, Annapolis, Maryland).

RESULTS

Preoperative patient characteristics are described in Table 1. Operative results, imaging, adverse events, and follow-up are described in Table 2.

TABLE 2. Postoperative Results

Patient no.	Stereotactic method	Trajectories ablated	Average power (W)	Total power (J)	Ablation volume (cm^2)	Adverse events	Length of stay (d)	Follow-up (mo)	Resulting lesion size (cm^3) and relative volume reduction (%)	Clinical outcomes
1	First attempt: CRW headframe (deflection)2nd MRI guidance frame (completed)	2	7.0	5508	3.8	Perioperative mild parasthesia	2	7	0.3 (−50)	Fewer and less severe episodes
2	MRI guidance frame	1	8.9	3879	1.1	Device malfunction causing saline leakage into brain, incomplete ablation, transient upper extremity apraxia	3	15	0.7 (−73)	Less severe episodes
3	CRW headframe	3	5.8	11 634	8.2	Persistent exacerbation of hemiparesis, hemianopia	5	53	1.2 (−72)	No recurrent hemorrhages
4	MRI guidance frame	2	6.2	2230	1.0	Small asymptomatic tract hemorrhage	2	5	0.74 (−20)	No recurrent hemorrhages

Patient 1

A 27-yr-old right-handed female presented with 6-yr history of thunderclap headaches associated with transient weakness, left-sided clumsiness, falls, loss of consciousness, and 2 motor vehicle collisions. MRI demonstrated a 0.6-cm^3 CCM in the right pulvinar region of the thalamus (without developmental venous anomaly, DVA) (Figure 1A and 1B). The patient was evaluated by multiple neurologists over the 6-yr period and was diagnosed variably with "atypical seizures," "intracranial hemorrhage," and "complex status migrainosus." During observation, the lesion remained stable radiographically, but she suffered repeated incapacitating symptomatic episodes and medication intolerance. After much discussion with our neurologists, continued disabling events, and lack of alternatives, we offered ablation.

Motor pathways in the thalamus were visualized by tractography from primary motor cortex (Figure 1A-1C). An initial procedure attempt, performed awake with CRW frame (Integra Neurosciences Inc), was aborted because of deflection of the stereotactic cannula and patient intolerance. She then underwent successful ablation using direct MRI guidance under general anesthesia. The final trajectory passed through the superolateral temporal lobe. Despite accuracy of the trajectory superficial to the lesion, MRI demonstrated initial deflection of a blunt ceramic stylet (Figure 1D). We slightly altered the trajectory and successfully pierced the lesion with a pointed ceramic stylet followed by laser probe. Successive rounds of ablation were carried out at 3-mm depth adjustments within the lesion with protective monitoring of surrounding thalamus (Figure 1E and 1F). Immediate postablation imaging verified acute signal changes and adequate safety margins. The patient was admitted to the floor and discharged home postoperative day 2. Postop she reported paresthesias; however, this was mild and resolved at follow-up.

At 7 mo, she reported fewer headaches that were no longer disabling and overall high satisfaction. MRI showed the lesion shrank from 0.6 to 0.3 cm^3 (Figure 1B compared to Figure 1G). Ultimately, the procedure achieved positive clinical and imaging results.

Patient 2

A 41-yr-old right-handed female with a history of chronic headaches presented with a 2-mo history of headache exacerbation associated with new left hemibody dysaesthesia. MRI revealed a putative 2.6-cm^3 CCM in the right putamen abutting the internal capsule (Figure 2A and 2B) and a superolateral DVA. A vascular neurosurgeon counseled that the lesion was not favorable for open resection, and after 6 wk of further conservative medical management she elected to undergo MRgLITT with the goal to reduce symptoms.

Using direct MRI guidance, we planned a trajectory through the right frontal lobe that avoided the DVA. The device was advanced into the CCM without evidence of hemorrhage (Figure 2C). After ablation at the top of the lesion at 60% power (mean 8.9 W), interval imaging revealed fluid with mass effect (T2 intensity similar to cerebrospinal fluid) surrounding the superior and lateral aspects of the lesion and tracking up along the cannula (Figure 2D). The ablation was terminated, and after removal, device inspection revealed malfunction with sterile saline irrigant leakage from the tip. Repeat imaging revealed decompression of fluid mass, further indicating saline rather than blood (Figure 2E). A new enhancing area was consistent with partial ablation of the intended target, but further ablation was aborted. The patient was extubated and admitted to the intensive care unit (ICU), where serial imaging remained stable. The patient had transient left hemiparesis which improved rapidly until she was discharged to home postop day 3 with mild apraxia.

Two weeks postoperatively, the patient reported continued headaches but improving apraxia. At 6 mo, the patient had improved with respect to apraxia and headaches, exam was full strength, and MRI showed the lesion shrank from 2.6 to 0.7 cm^3 (Figure 1A compared to Figure 2F). At 15 mo, she reported resolution of apraxia and further headache improvement. Ultimately, ablation provided significant headache improvement but was complicated by device malfunction, incomplete ablation, and transient apraxia.

Patient 3

Patient 3 was a 14-yr-old female with a history of familial cerebral cavernous malformation (FCCM) syndrome and prior craniotomies. She presented with recurrent symptomatic hemorrhagic expansion of a 4.2-cm^3 CCM of the right thalamo-mesencephalic junction with mass effect upon her lateral geniculate nucleus and basal ganglia (Figure 3A). No DVA was evident. A cluster of 3 hemorrhagic events over 4 yr had resulted in hospitalization and rehabilitation, chronic left spastic hemiparesis, and a right visual field defect. Because of mass effect and aggressive history, definitive open surgical resection via posterior temporal approach was recommended (by 3 separate providers), which she refused in favor of MRgLITT to reduce the risk of another bleed.

Using a CRW frame, 3 stereotactic trajectories from a right lateral temporal approach were planned (Figure 3B), each targeting a different portion of the lesion. Each insertion was verified as to accuracy with ablations at 3-mm depth adjustments along each trajectory without evidence of acute hemorrhage (Figure 3C). We marked nearby pixels that pause ablation if temperature thresholds are reached outside the planned region (Figure 3D). Particular attention was directed toward protecting the thalamus (superiorly) and midbrain (medially). The patient was admitted to the floor. Hemiparesis and visual deficits worsened similar to her prior hemorrhages (recrudescence), and she discharged to acute rehabilitation after 5 d.

At 53 mo, she exhibited improved left spastic hemiparesis but is now back to running independently. Upper extremity gross function improved, but fine motor function of the hand remained impaired. Visual field defects subjectively improved. MRI performed at 12 mo showed that the lesion shrank from

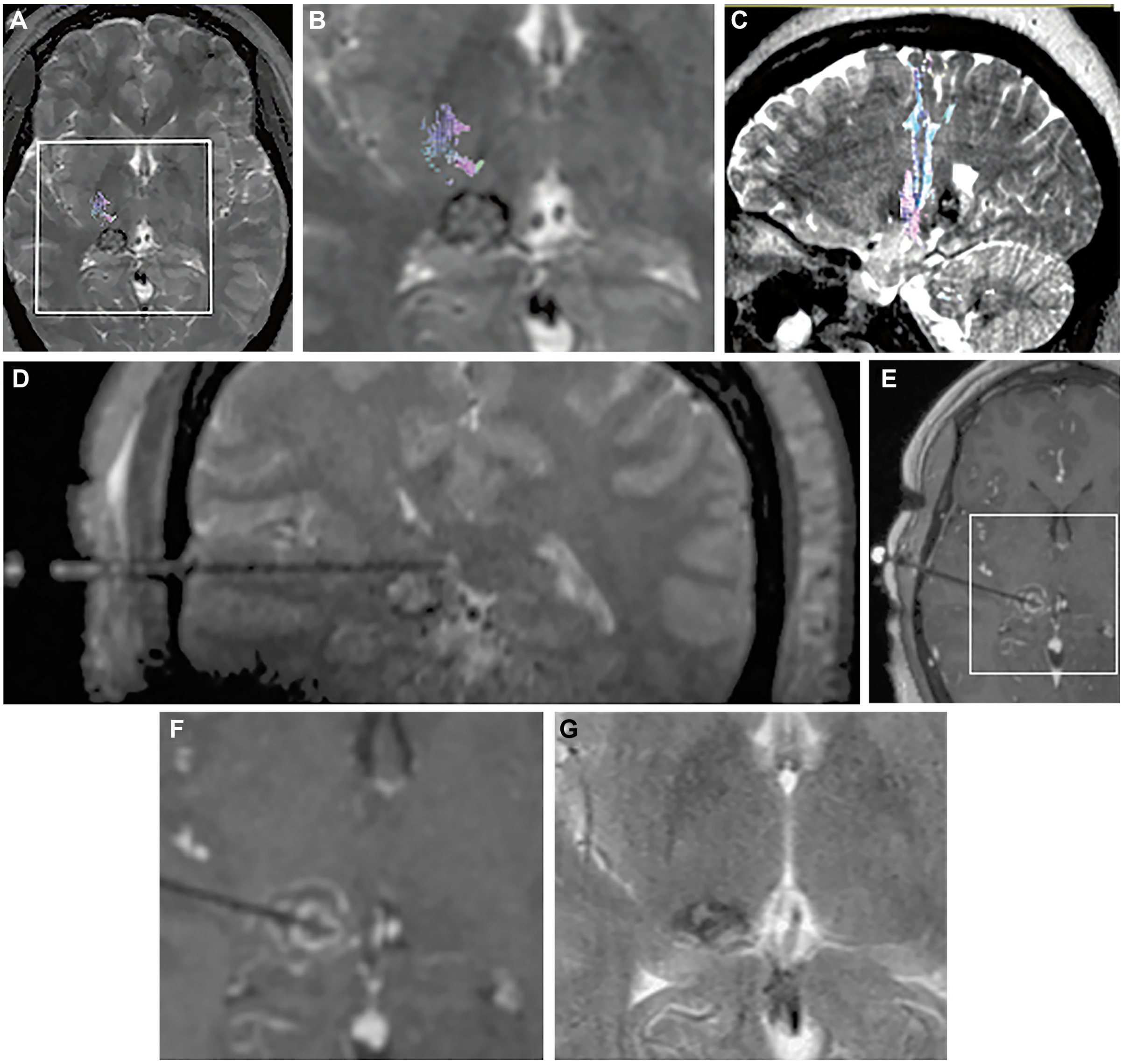

FIGURE 1. *Ablation of CCM of right pulvinar in patient 1.* **A**, *Preoperative axial T2-weighted image of mixed-intensity lesion with overlaid postprocessed motor tractography (colored) derived from diffusion tensor imaging (DTI), which was seeded from the location of blood-oxygen-level-dependent (functional) MRI during left hand movement. The content of the white box is magnified in* **B** *to emphasize posterior location of lesion relative to primary motor pathways.* **C**, *Preoperative sagittal T2-weighted image with tractography again showing position of lesion relative to motor pathways (colored).* **D**, *Intraoperative paracoronal T2-weighted image showing initial superior deflection of laser probe (linear low intensity) placed by Cosman-Roberts-Wells (CRW) headframe (Integra Neurosciences Inc).* **E**, *Intraoperative gadolinium-contrasted axial T1-weighted image showing correct placement of probe into the lesion using an MRI-guidance platform following initial ablation. This image demonstrates postablation contrast enhancement reflecting early post-LITT changes and is magnified in* **F**, *which corresponds to the analogous axial section and magnification* **A** *and* **B**. *Tissue changes take time to observe and can be seen in* **G**, *a follow-up axial T2-weighted image at 14 mo at same magnification as* **B** *and* **F** *demonstrating evidence of partial involution.*

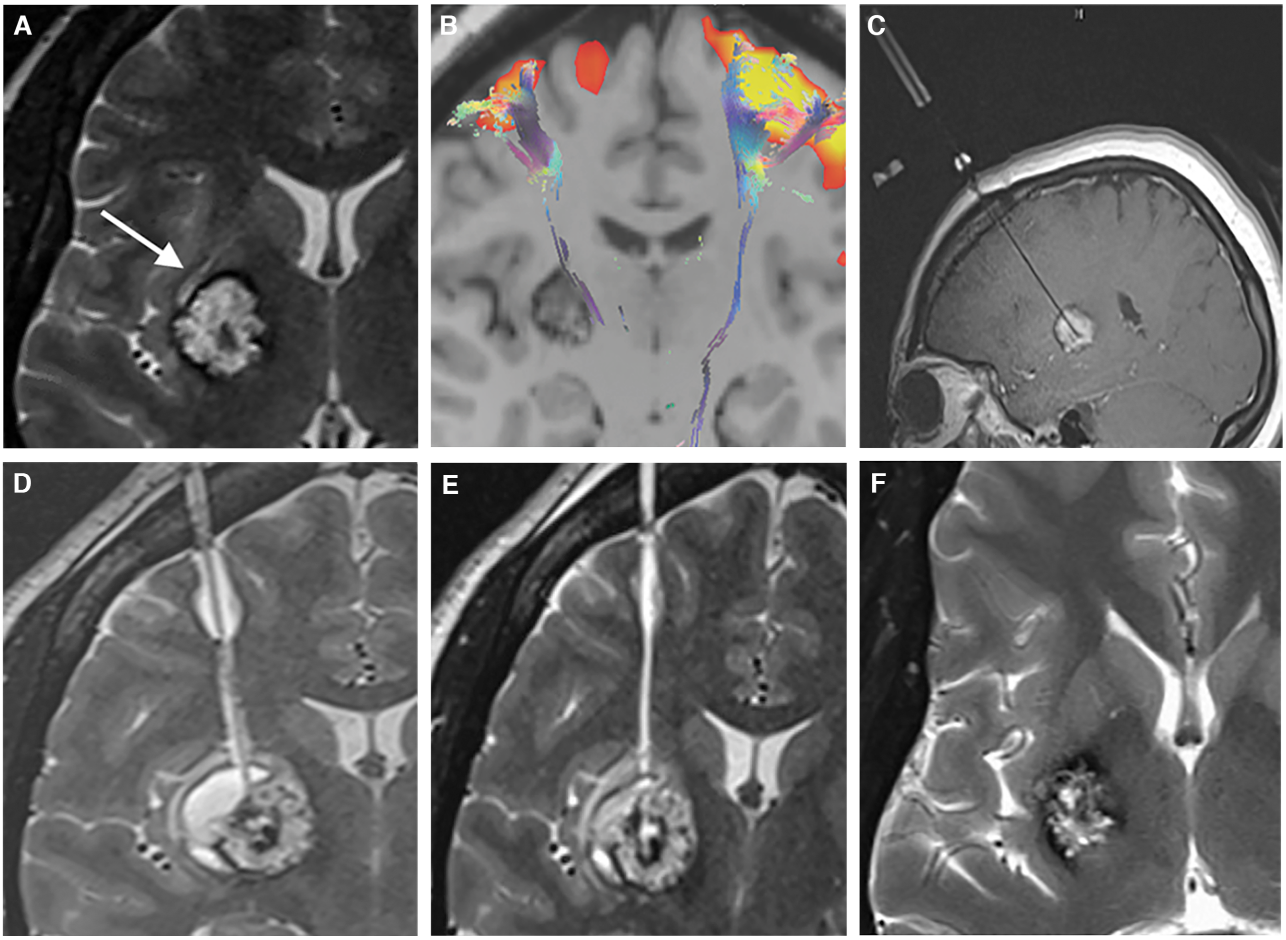

FIGURE 2. *Ablation of CCM of right putamen in patient 2.* **A**, *Preoperative axial T2-weighted image showing the mixed-intensity lesion prior to ablation with arrow indicating location of developmental venous anomaly (DVA).* **B**, *Coronal T1-weighted image with processed motor tractography showing lesion mass effect upon fibers of the internal capsule.* **C**, *Intraoperative sagittal T1-weighted image showing cannula placement into the lesion.* **D**, *Intraoperative paracoronal T2-weighted image showing interval collection of fluid with same intensity as cerebrospinal fluid (saline) overlying the lesion and tracking up the cannula. Central hypointensity in the lesion itself reflects early post-LITT changes. Device inspection confirmed malfunction with saline leak.* **E**, *After cannula removal, the fluid decompressed along the tract and deeper within the lesion.* **F**, *Follow-up at 6 mo axial T2-weighted image showing partial involution of the lesion.*

4.2 to 1.2 cm^3 (Figure 3A compared to Figure 3E), which has remained stable through 33-mo follow-up imaging (see Figure 3F-3H). She suffered no further hemorrhages or new deficits and expressed high satisfaction. Ultimately, ablation appears to have halted further bleeding events with a dramatic reduction in the lesion despite mild recrudescent deficits.

Patient 4

Patient 4 was a 62-yr-old female with a history of 3 symptomatic hemorrhages over 7 yr causing left hemiparesis, diplopia, and memory impairments associated with a 0.92-cm^3 CCM in the right subthalamus without DVA (Figure 4A and 4B). Open resection was considered high risk. After prolonged conservative management that saw repeated bleeding events, she elected to undergo MRgLITT to reduce the risk of further bleeds.

We used a right frontal approach. Upon advancement into the target, imaging showed a 1.3-mm deviation and evidence of new trace blood along the tract within the subcaudate region appearing separate from the CCM (Figure 4C). After serial images over 20 min confirmed stability, the laser cannula was removed, and the device was successfully replaced via slight trajectory adjustment, and the anteromedial aspect was ablated (Figure 4D). A second trajectory was placed targeting the posterolateral aspect of the lesion and postablation imaging confirmed signal changes (Figure 4E). The patient was extubated with no new neurological deficits or complaints. She was admitted to ICU for monitoring and discharged home postoperative day 2.

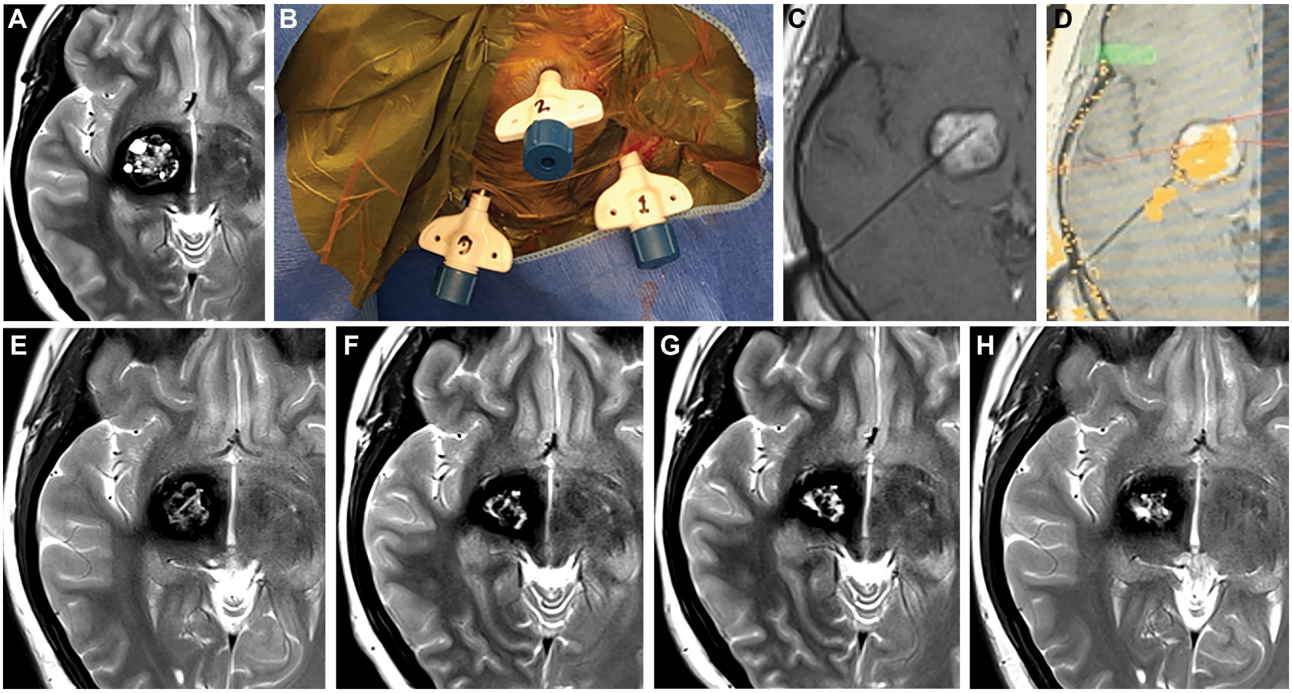

FIGURE 3. *Ablation of CCM of right midbrain/thalamus in patient 3.* **A**, *Preoperative axial T2-weighted image shows the mixed-intensity lesion prior to ablation.* **B**, *Intraoperative photograph of Visualase (Medtronic Inc) stereotactic bolts (placed by CRW headframe) placed for 3 planned trajectories.* **C**, *Intraoperative para-axial T1-weighted image showing cannula placement within lesion.* **D**, *Intraoperative screenshot from Visualase workstation showing para-axial T1-weighted monitoring plane with processed thermal damage estimates (orange pixels) derived from gradient echo-weighted MR thermography. Follow-up axial T2-weighted image at* **E** *6 mo and* **F** *1 yr showing partial involution that then remained stable at* **G** *2 yr and* **H** *3 yr.*

At 5-mo follow-up, she was at her preoperative neurological baseline with no further events. MRI showed that the lesion shrank from 0.92 to 0.74 cm^3 (Figure 4A and 4B compared to 4F). She was lost to subsequent follow-up. Ultimately, despite a small asymptomatic tract hemorrhage, ablation saw no further events during follow-up and imaging confirmed lesion reduction.

DISCUSSION

Deep CCMs present a vexing problem in neurosurgery. Although elegant surgical approaches to various locations along the neuroaxis feature frequently in neurosurgery journals, the morbidity and mortality rates can be high.[8] We report a small series illustrating MRgLITT to ablate deep CCMs in the thalamus, putamen, midbrain, and subthalamus. All patients presented with disabling headaches or recurrent symptomatic hemorrhages. All were denied or refused open surgery. Study limitations include a single-center retrospective case-series design with a small heterogeneous sample size, inherent selection bias, reliance upon subjective reports (eg, headaches), and limited follow-up.

Some results were encouraging: all subjects achieved some relief of their preoperative symptoms, and all lesions exhibited some involution (20%-73%). Indeed, the patient with FCCM who had suffered multiple preoperative hemorrhages suffered no further events over 4 yr of postoperative follow-up. Our overall enthusiasm is tempered, however, by potential adverse events. Further experience and longer follow-up are needed to judge safety and effectiveness of MRgLITT relative to microsurgery.[21]

Complications

Consistent with prior experience of MRgLITT for epileptogenic CCM,[18] there were no clinically significant intracranial hemorrhages, despite some lesions in this series having had a natural history of bleeding. The most serious complication was device malfunction with leakage of saline into the brain (case 2). In 2 patients, neurological deficits were transient (case 2, putamen) or worsened from baseline (case 3, thalamus/midbrain). Although open resection was technically possible in both cases, it is highly unlikely that any surgical approach to these lesions would have completely avoided similar collateral injury. Notably, in cases 1 (thalamus) and 4 (subthalamus), in which open resection would be ill advised, both patients did well with ablation. Careful patient

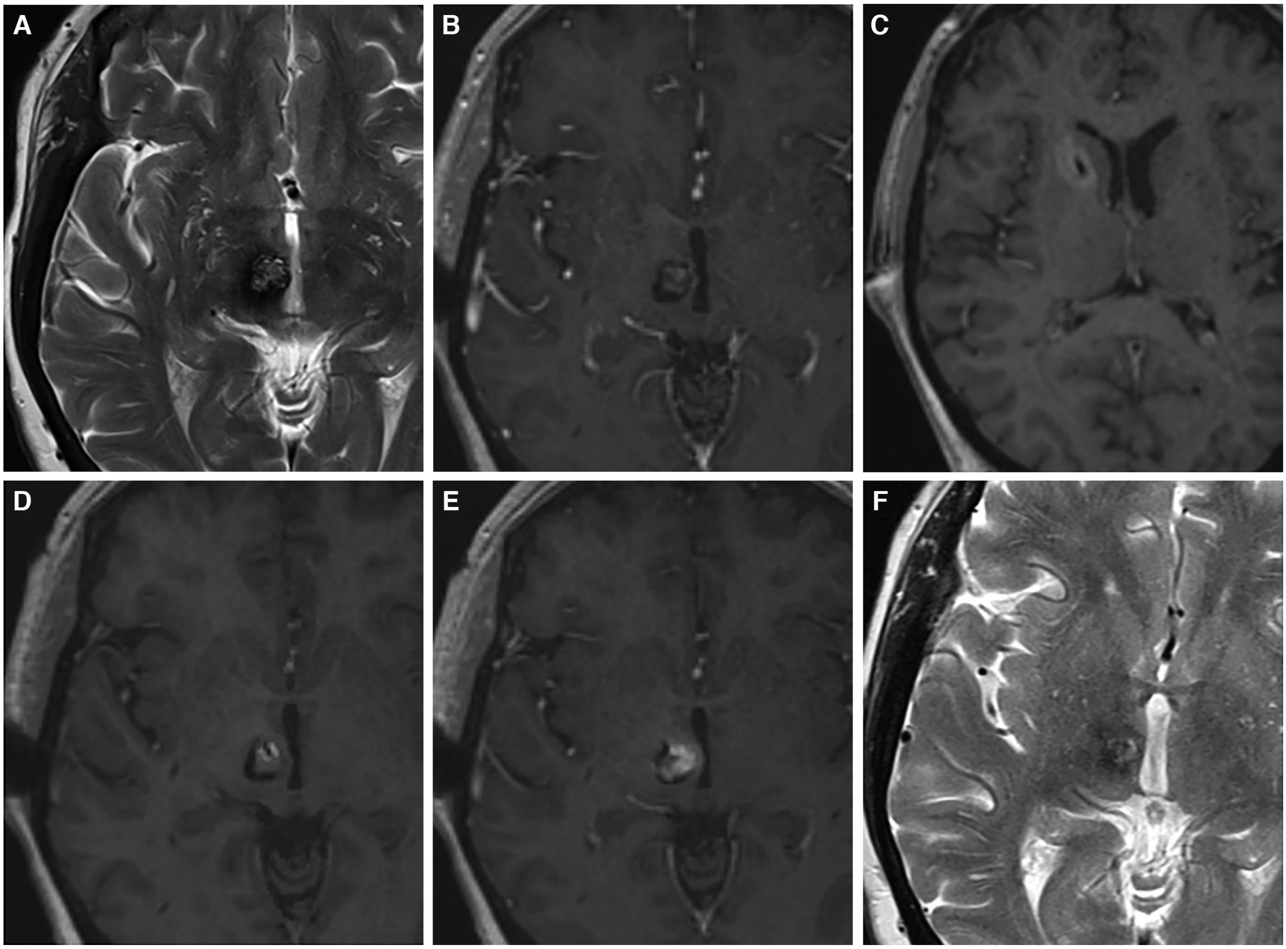

FIGURE 4. *Ablation of CCM of posterior right subthalamus in patient 4.* **A**, *Preoperative axial T2-weighted image showing the mixed-intensity lesion prior to ablation.* **B**, *Intraoperative gadolinium-enhanced T1-weighted image showing lesion pre-ablation.* **C**, *Intraoperative contrast-enhanced T1 showing a small subcaudate tract hemorrhage (high intensity) around the cannula (low intensity).* **D**, *Intraoperative axial T1-weighted image immediately following first medial ablation (high intensity) around the cannula (low intensity).* **E**, *Intraoperative axial T1-weighted image showing lesion immediately following a second more lateral ablation. Note the difference in cannula position within the lesion and increased medial contrast enhancement.* **F**, *Follow-up axial T2-weighted image at 4.5 mo showing partial involution.*

selection is undoubtedly critical when considering MRgLITT for deep CCMs

Targeting Ablation

Precise shaping of ablation volumes may be important for minimizing collateral injury. Our series illustrates how trajectory planning may be used intraoperatively to remediate deflection or further tailor total ablation volume. As the MRI frame (ClearPoint) allows stereotactic actions to be guided in real time, we prefer it when anticipating a single entry site for one or more closely related trajectories. By contrast, we prefer a traditional stereotactic arc (CRW) (Integra Neurosciences Inc) for workflow efficiency in which multiple distinct entries (case 3) would have been sterically hindered with ClearPoint (Figure 3B).

Ablation was guided by efforts to minimize parenchymal injury. This approach is distinct from targeting of hemosiderin-laden cortex that causes seizures in cortical CCMs[18] The safety margins of MRgLITT depend upon reliable thermometry, yet blood products associated with CCM have unpredictable heating (light is internally reflected by the lesion capsule and absorbed by blood products to generate heat) and can also interfere with Gradient Recalled Echo-weighted thermometry. Indeed, the adverse event of device tip melting (case 2) is likely due to high laser energy (Table 2) in the absence of adequate thermal feedback. We recommend a conservative approach with attention to temperature safety markers at lesion margins (Figure 3D) and use of relatively lower power settings and brief ablations. Subsequent signal changes, such as darkening hypointensity on T2-weighted images (Figure 2D) and subtle increases in contrast enhancement on T1-weighted images (Figure 1E and 1F), confirm ablation but are inherently retrospective. We avoid ablating lesions with recent hemorrhage because blood products contribute to ambiguous lesion borders, and there may be a greater risk of rebleeding. Further investigation of such technical limitations is needed.

Patient Selection

Although the MRgLITT device has been approved by the US Food and Drug Administration, this novel indication and use has not been specifically endorsed. This technique is best conducted in centers with multidisciplinary adjudication of indications and outcomes and, preferably, with IRB oversight. Indications are best be aligned with evidence-based guidelines for management of CCMs,[8] likely excluding cases without disabling symptoms. It remains debatable whether risks of intervention were justified in cases with headache symptoms and no demonstrated bleeding or lesion growth (cases 1 and 2). Evaluating outcomes can be difficult, as illustrated in case 3, in which suspected bleeding was later interpreted as a procedure-related saline leak. Hence, there is a need for proactive definitions and third-party assessment of adverse events. Efficacy could not be ascertained, given the small number of cases, postprocedural symptomatic setbacks, and limited follow-up. Finally, because of our conservative targeting in deep brain areas, the lesion was not eliminated and the natural history of residual CCM is uncertain. From the literature on stereotactic radiation for cavernous malformations, there is some suggestion that reduced volume is associated with reduced hemorrhage rate, something that deserves further investigation using LITT.[22,23]

The current literature of LITT for CCMs is still nascent. Some CCMs show a malignant natural history of clustered bleeding events. Such patients may only benefit long term if the lesion is completely removed.[21] Lesions that have demonstrated growth and rebleeding may have additional risk of bleeding or recurrence postablation. Specific anatomic characteristics are likely important when judging risks of stereotaxis, and DVAs associated with CCMs carry higher bleeding risk. Target temperatures for LITT (50°C-90°C) are likely too low for direct hemostasis of active bleeding. Indeed, macrovasculature is probably relatively impervious to LITT because of heat sinking.[19] Thus, open microsurgery must still be considered in patients with high-risk lesions or history of bleeding.

CONCLUSION

MRgLITT appears feasible for deep CCMs Early clinical and imaging results are encouraging, but adverse events may be common without complete lesion obliteration. Larger, longer-term, controlled studies with standardized indications and outcomes are required to define risks and rewards of MRgLITT relative to open surgery and further optimize minimally invasive approaches.

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Disclosures

Drs Willie and Gross serve as consultants and have research contracts with Medtronic Inc related to the use of Visualase for ablation in brain and receive compensation for these services. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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