

MANAGING COMPLEX CASES

Cerebrovascular Disease | Spine Disease | Brain Tumor | Movement Disorders | Epilepsy

ON THE COVER:

Cerebral angiogram of a 19-year-old patient following placement of four overlapping Pipeline™ embolization devices for treatment of an *ACTA2* mutation-associated intracranial aneurysm with diffuse vascular involvement. See page 6.

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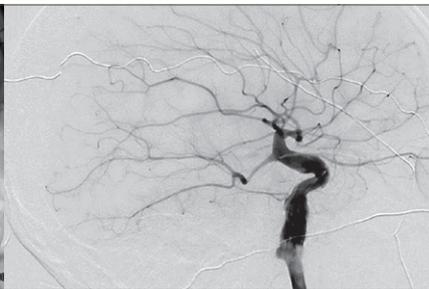
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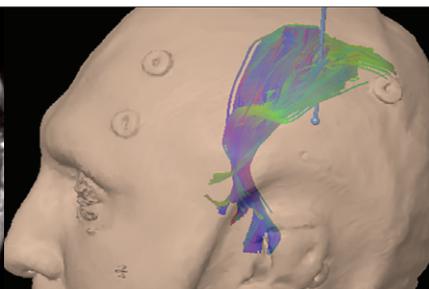
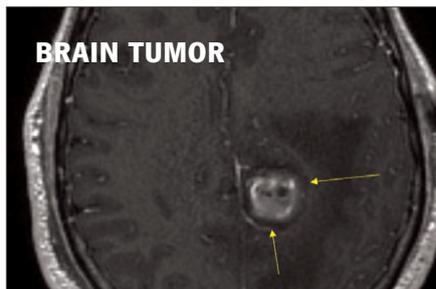


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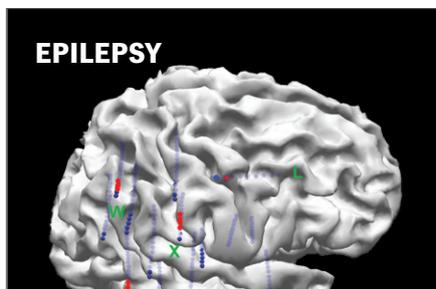
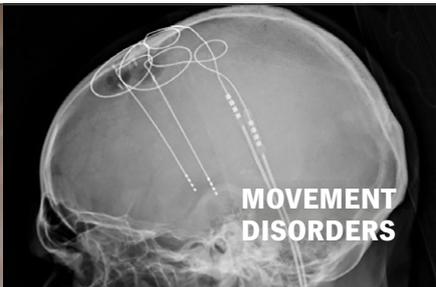


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COMPLEX CASES REMINDE US WHY WE DO WHAT WE DO



We decided to focus this Special Report on our true measure and common goal: To care for patients with the most complex neurological disorders.

What defines us? If you're an accomplished investigator, your peers around the country may know you primarily for research studies you've contributed to. If you're a great educator, the trainees you've mentored may think of you foremost as a teacher. While these are very important parts of our professional identity, they don't really reflect what's probably our most fundamental role — expert caregiver. Only our patients and their families, who trust us so much, are apt to see us exclusively from that most-important vantage point.

For this reason, we in Cleveland Clinic's Neurological Institute decided to focus this Special Report on what is our true measure and common goal: To care for patients with the most complex neurological disorders by harnessing our culture of innovation and our integrated, multidisciplinary approach to care delivery. We illustrate these strengths here across five case studies reported from diverse corners of our Neurological Institute.

Despite the broad range of cases profiled, they collectively illustrate what we believe is distinctive about the way we manage patients with highly challenging neurological conditions. Below are a few essential aspects of our approach.

A culture of innovation. Cleveland Clinic is one of the largest-volume centers in the world for epilepsy surgery and one of the busiest centers for everything from deep brain stimulation to brain tumor care. This allows our physicians and surgeons to amass deep experience in using — and often pioneering — the advanced technologies required to manage complex brain and spine diseases. Examples here range from an early (2011) use of laser interstitial thermal therapy to achieve a rare glioblastoma remission that's been going for 6.5 years and counting (page 16) to the combination of stereoelectroencephalography and cortico-cortical evoked potentials to localize the epileptogenic focus in a patient with multidrug-resistant epilepsy (page 24).

A well-integrated, multidisciplinary approach to care. At a time when *multidisciplinary* has become a buzzword, Cleveland Clinic's institute-based and patient-centered structure has truly brought the concept to bear in practice. We have disrupted the typical organization of neurological care delivery by bringing together medical and surgical experts in a single organizational entity under a single leadership to focus on the problems of

Because brain and spine diseases so often have insidious effects on cognition, mood and function, our patients are particularly in need of personalized, empathetic caregiving.

patients, whether they have Parkinson disease, spine problems or cerebrovascular disorders. The result is a model of care that treats multidisciplinary collaboration as a given, not an afterthought. Examples include the hybrid surgical-endovascular approach seamlessly deployed for a patient with an intracranial aneurysm (page 6) as well as the multidisciplinary patient management conferences that guided care for the patients with spinal deformity (page 12), glioblastoma (page 16), Parkinson disease (page 20) and epilepsy (page 24).

Seeing patients as we'd view a family member. Because brain and spine diseases so often have insidious effects on cognition, mood and daily function, our patients are particularly in need of personalized and empathetic caregiving. Nowhere is this better exemplified than in the case study on page 20 recounting how our movement disorders team patiently managed and counseled a young patient with early-onset Parkinson disease over the course of six years, 20-plus office visits, multiple drug trials and extended-family visits until he was emotionally and psychologically ready to try deep brain stimulation, which has since served him very well.

Commitment to long-term follow-up. Each of the case studies here demonstrates expertise and excellence in acute care. But many of our most complex patients come from outside Northeast Ohio. Thanks to distance health technology, such as two-way video-enabled virtual visits using Cleveland Clinic's Express Care® Online app, we increasingly help manage these

patients remotely in their home communities after they leave Cleveland following their acute care. We welcome the opportunity to work with patients' referring providers to supplement their local care to whatever extent desired.

These are a few of the key cultural values underlying the successful management of patients with complex cases outlined in the pages that follow. We welcome your inquiries and opportunities for collaboration on similarly challenging patients.



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CEREBROVASCULAR DISEASE

Combined Surgical-Endovascular Treatment of an Intracranial Aneurysm in a Patient with *ACTA2* Mutation

Direct surgical carotid cutdown overcomes multiple access obstacles.

By Gabor Toth, MD, and Mark Bain, MD, MS

Flow diverter therapy with the Pipeline™ embolization device (PED) has been shown to be a successful treatment for large and giant intracranial aneurysms. A stable proximal support system is required to allow successful delivery of the device. With tortuous proximal vascular anatomy such as a complex aortic arch, delivery of this device can be difficult — and sometimes not possible. Proximal vascular instrumentation, vascular fragility and previous dissections are reasons to consider alternative vascular access to intracranial lesions.

We present a patient with *ACTA2* mutation and diffuse vascular involvement, including bilateral fusiform internal carotid artery (ICA) aneurysms, recurrent aortic dissections and extensive aortic instrumentation. A large right intracranial ICA aneurysm in this

patient was treated with endovascular PEDs, requiring vascular access through open surgical carotid exposure.

Case Presentation

A 19-year-old man with *ACTA2* mutation presented with a right intracranial ICA fusiform aneurysm. His past medical history included recurrent aortic dissections involving the arch and thoracoabdominal aorta, previously treated with arch replacement and grafts to the innominate and left common carotid artery, left common carotid to left subclavian bypass, and bilateral iliac and thoracoabdominal aortic stents (Figure 1). In 2013, he had a right hemispheric ischemic stroke with complete recovery after administration of intravenous tissue plasminogen activator.

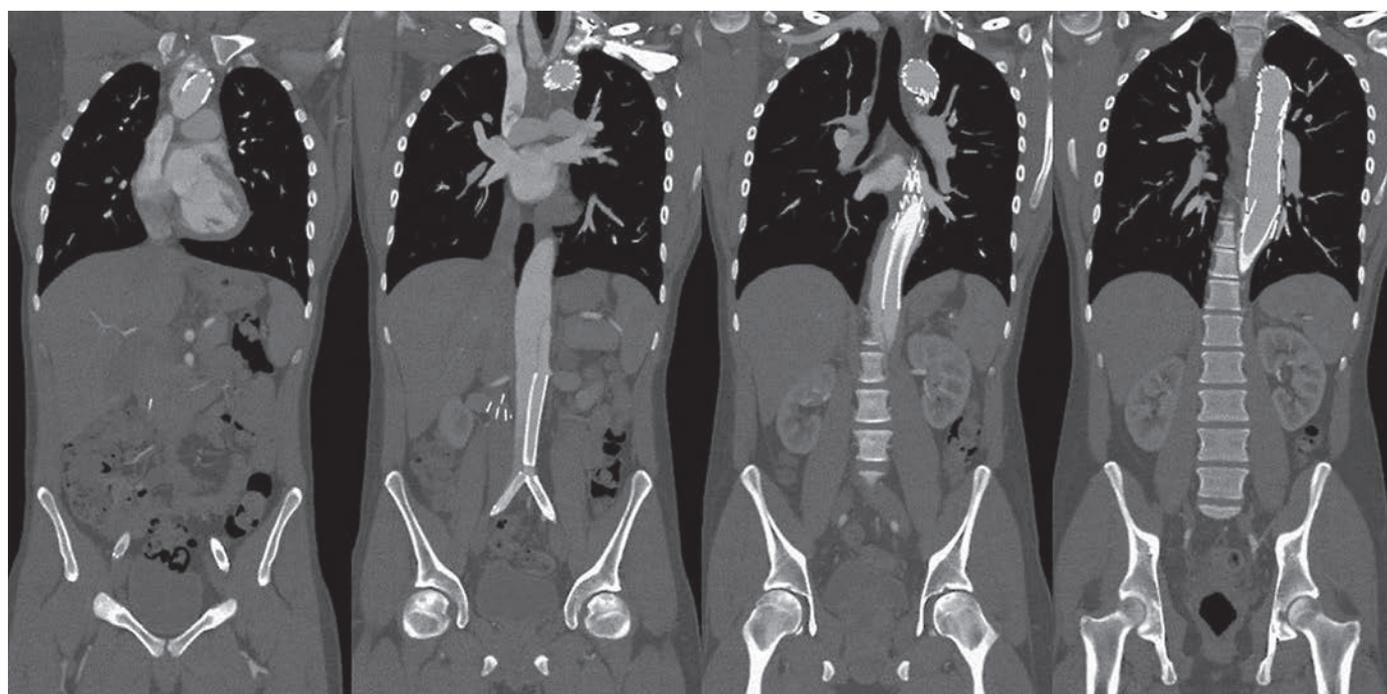


FIGURE 1. Coronal CT angiogram demonstrating prior instrumentation in the aortic arch, thoracic and abdominal aorta, and bilateral iliac arteries.



FIGURE 2. Pre-intervention cerebral angiograms demonstrating a right internal carotid irregular fusiform aneurysm, with dysplastic appearance of the cavernous and supraclinoid internal carotid artery. Note the characteristic “straight” appearance of the middle and anterior cerebral artery distributions seen with *ACTA2* mutations.



FIGURE 3. Four overlapping Pipeline embolization devices (PEDs) were placed, extending from the distal cervical internal carotid artery to the proximal cavernous segment. (A) Native fluoroscopic image demonstrating the PEDs in place. (B) Angiogram demonstrating preferential flow through the lumen of the PED with reduced flow into the fusiform aneurysm. (C) Image demonstrating delayed contrast opacification of the aneurysm with the PEDs in place.

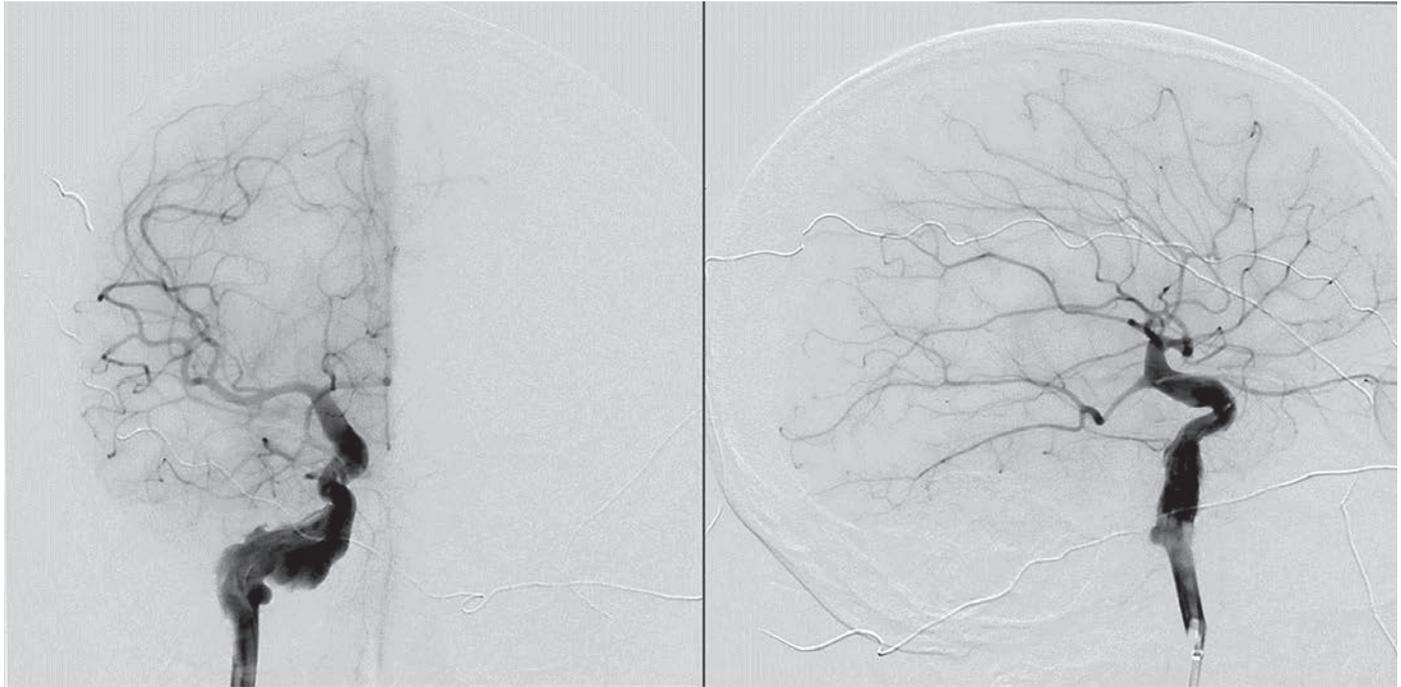


FIGURE 4. Final cerebral angiogram demonstrating adequate placement of the Pipeline embolization devices extending from the distal cervical internal carotid artery to the proximal cavernous segment.

Evaluation

Workup demonstrated large bilateral fusiform petrous-cavernous ICA aneurysms (one of them shown in Figure 2), the right larger than the left. He developed worsening headaches and significant aneurysm growth over one year of follow-up, with erosion of the bone at the skull base and protrusion of the aneurysm sac to the mesial temporal lobe.

Due to the risk of subarachnoid hemorrhage despite the proximal location, the decision was made to treat the right ICA aneurysm first with flow diversion. Given the patient's *ACTA2* mutation, recurrent dissections and extensive aortic instrumentation resulting in an extreme angle of the right common carotid artery off the aortic arch, a transfemoral vascular approach was considered exceptionally difficult and high-risk. The decision was made to access the aneurysm surgically through the cervical carotid.

Treatment and Outcome

Aspirin 325 mg/d and clopidogrel 75 mg/d were started 10 days prior to the procedure, with adequate platelet suppression on platelet aggregometry testing. With the patient under

general anesthesia, the neck was prepped and draped in a sterile fashion. Following surgical exposure of the right carotid bifurcation, an incision was made in the proximal ICA, a 6-French Shuttle® guide sheath was introduced and the carotid incision was sutured around the Shuttle. Heparin was administered.

A working angle for PED deployment was obtained. Under fluoroscopic guidance, an intermediate catheter was navigated over a standard microcatheter and microwire to the distal cervical ICA. The microcatheter was then positioned distal to the aneurysm. Four overlapping PEDs were deployed successfully in a telescopic fashion from distal to proximal (Figure 3). Angiography demonstrated adequate wall apposition of the PEDs at the distal and proximal landing zones (Figure 4), with reduced flow to the aneurysm and partial contrast stasis. The catheters were removed, the carotid was sutured and the neck incision was closed, leaving a drain in place for 24 hours. The patient went home three days later without complications.

Discussion — and an Interesting Family Footnote

ACTA2 is a gene encoding alpha-2 actin, a major component of vascular smooth muscle. *ACTA2* mutation is associated with early-age thoracic aortic aneurysms and dissections.¹ Some patients have manifestations of diffuse smooth muscle involvement and cerebrovascular abnormalities, including Moyamoya disease and fusiform and saccular intracranial aneurysms.^{2,3}

Our patient with *ACTA2* mutation had bilateral ICA fusiform aneurysms. Given the worsening headaches, aneurysm growth and concern for intradural extension, the decision was made to treat with flow diversion. In light of the patient's previous aortic dissections involving the arch and descending thoracoabdominal aorta, as well as his extensive prior vascular procedures, transfemoral access with a large guide sheath was concerning for potential vascular complications, including new dissections or injury of the previously dissected and replaced thoracoabdominal vessels. Furthermore, his extensive aortic instrumentation made percutaneous femoral access and catheter navigation through the aorta nearly impossible. Surgical exposure of the carotid artery at the neck with access through a carotid cutdown was performed, followed by endovascular delivery and deployment of the PEDs without complications.

Notably, the patient's twin brother carried the same genetic mutation and developed aneurysms in the identical location. Our combined surgical-endovascular approach was successfully used to treat the brother's aneurysm as well.

A previous study reported alternative access for a variety of neurointerventional procedures in 21 patients.⁴ Surgical cutdown was performed in 12 patients (eight in the carotid and four in the vertebral artery) and percutaneous puncture in nine (five in the carotid and four in the brachial artery), with no access-related complications. These authors included patients between 50 and 82 years of age in whom the intracranial vasculature could not be accessed via the transfemoral route, mainly due to tortuosity in the aorta and supra-aortic vessels.⁴ The transradial approach is an alternative access route for PED delivery in elderly patients who have a tortuous aortic arch.⁵

Conclusion

Managing intracranial vascular lesions in patients with significant proximal large-vessel tortuosity, aortic arch disease or instrumentation, and genetic conditions is highly complex, due to vessel fragility and the risk of complications. Alternative access for an intracranial procedure should be considered in these patients. As demonstrated in the case of this young patient with *ACTA2* mutation, cervical carotid surgical cutdown can provide optimal access, allowing a safe and efficient approach to endovascular flow diverter treatment of a large dysplastic aneurysm.

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One Among Many Hybrid Treatment Strategies

The hybrid surgical-endovascular approach used in this case study is an outgrowth of the integrated nature of Cleveland Clinic's Cerebrovascular Center, which brings stroke and neurocritical care neurologists, interventional neurologists and neuroradiologists, and vascular neurosurgeons under a single organizational structure for close day-to-day collaboration. This structure fosters interdisciplinary interaction and empowers the management team to always consider complex cases from a multitude of subspecialty perspectives.

The result is a proliferation of multimodal approaches to a number of additional challenging case types. Other examples of the Cerebrovascular Center's hybrid capabilities include:

- Targeted cerebral bypass for large intracranial aneurysms requiring a trap technique. Angiography techniques allow surgeons to use contrast to identify clipped vessels that require a targeted bypass so that the aneurysm can be treated without compromising blood supply to normal brain.
- Hybrid treatment of a large carotid thrombus in the cervical carotid with an intracranial middle cerebral artery occlusion. To avoid the risk of embolization, the surgeon opens the carotid to remove the clot from the neck, and the team uses that as an access point to deploy endovascular techniques — either aspiration or stent retrieval — to remove the clot in the brain.
- Multimodal treatment of inaccessible intracranial vascular lesions. Drilling a burr hole through the skull to directly access the venous sinus, or surgically exposing intracranial arteries or veins, can allow access to dural fistulas and other vascular lesions when traditional routes are not available, providing an opportunity to treat and cure these complex lesions.



SPINE DISEASE

Spinal Fusion with Pedicle Screw Instrumentation, Iliac Fixation and Multilevel Osteotomies for Adult Scoliosis with Sagittal Plane Imbalance

CT navigation, neuromonitoring and blood management help minimize considerable risks.

By Jason Savage, MD, and R. Douglas Orr, MD

Presentation

A 72-year-old woman presented to Cleveland Clinic reporting severe back pain and radiating leg pain (right greater than left) with standing and walking. Her symptoms had been present for approximately five years and had steadily worsened over the past six to 12 months. She also reported worsening posture and an inability to stand upright for more than 10 to 15 minutes at a time.

She had exhausted nonoperative treatment options, including multiple rounds of physical therapy, several targeted epidural steroid injections and appropriate nonsteroidal anti-inflammatory medications. She was seen by several surgeons outside of Cleveland Clinic who told her “nothing could be done” to help with the pain, as surgery was too risky to consider in her case. Nevertheless, she was quite debilitated by her symptoms and remained interested in moving forward with surgical intervention.

Evaluation and Preoperative Workup

X-rays as well as MRI, CT and dual-energy X-ray absorptiometry scans were taken as part of the diagnostic workup. Scoliosis X-rays revealed a 55-degree convex right adult scoliosis with sagittal plane imbalance and high pelvic tilt, as well as multilevel lateral recess and foraminal stenosis (Figures 1 and 2). CT showed advanced degenerative changes with “vacuum disks” throughout the lumbar curve.

In view of the patient’s worsening symptoms and radiographic findings, she elected to proceed with surgery. An extensive multidisciplinary preoperative evaluation was done to ensure that she was optimized for the procedure. At Cleveland Clinic, this typically involves evaluation by endocrinology (bone health evaluation and management of diabetes if present), the perioperative medicine team (blood pressure management, risk stratification, smoking cessation, weight loss program, etc.), anesthesiology and physical therapy (“prehabilitation”). The surgical team oversees the entire perioperative process but relies heavily on these other specialists to minimize complications and optimize outcomes.

Surgery

The goals of surgery were to decompress the neural elements, correct the scoliosis and restore coronal and sagittal plane alignment (age-appropriate alignment objectives were used).

We performed a T4-sacrum posterior spinal fusion with pedicle screw instrumentation, iliac fixation and multilevel posterior column osteotomies (Schwab grade 2). Intraoperative CT navigation was used to place the pedicle screw instrumentation (Figure 3). Electrophysiological neuromonitoring with somatosensory evoked potentials and transcranial motor evoked potentials was used to ensure safety of the neural elements during placement of the screws and correction of the spinal deformity.

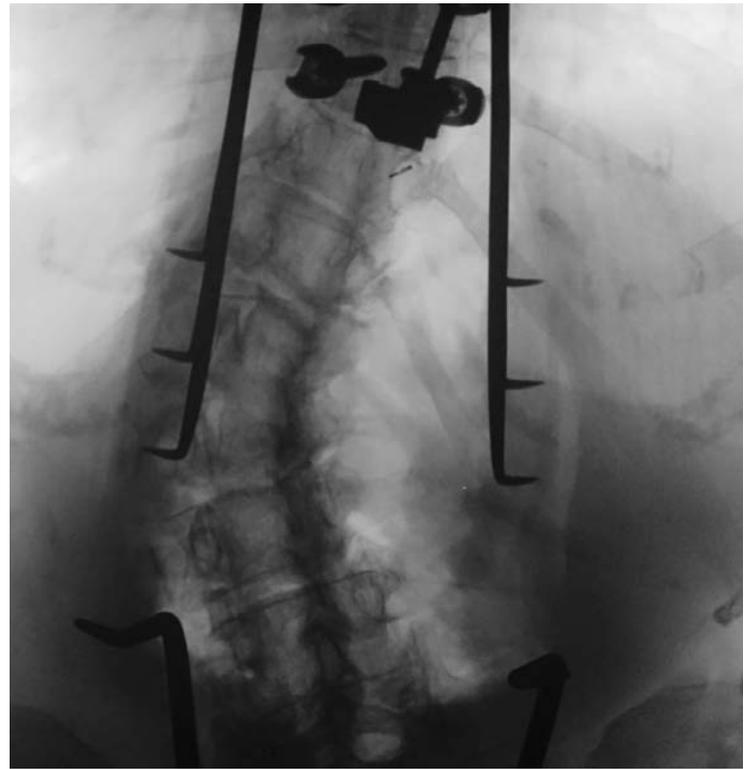
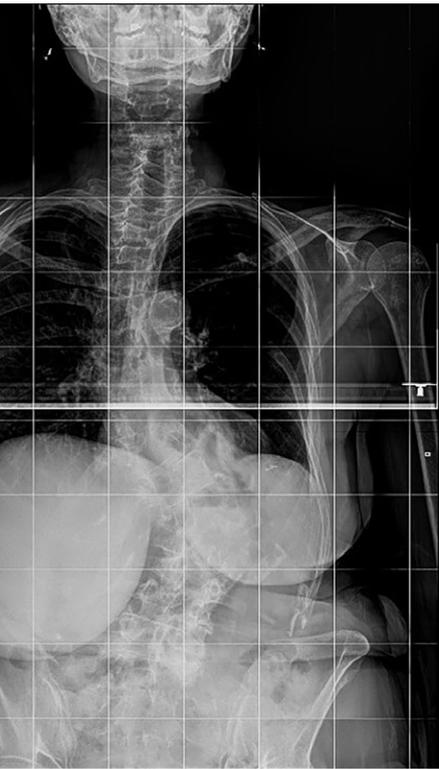
The osteotomies were performed throughout the apex of the curve to mobilize the spine. Compression, distraction and cantilever forces were used to correct the curvature and improve the overall alignment, and 6.0-mm titanium rods were used to hold the improved new posture. A third rod was used to provide more stability across the area of curve correction and across the lumbosacral junction. Local bone graft, allograft and bone morphogenetic protein were used for the fusion.

The operation was completed in approximately six hours (staff surgeon with spine surgery fellow) with an estimated blood loss of 800 mL. Tranexamic acid (TXA) and other blood management strategies were used to minimize blood loss and optimize fluid resuscitation during the procedure.

Outcome

The patient was extubated in the operating room, went to the recovery room and was taken to the regular nursing floor for postoperative care. She mobilized with physical therapy on postoperative day 1 and was discharged home on day 5.

Her postoperative X-rays revealed good correction of her deformity and restoration of her overall coronal and sagittal plane alignment



FIGURES 1 AND 2 (TOP LEFT AND MIDDLE).

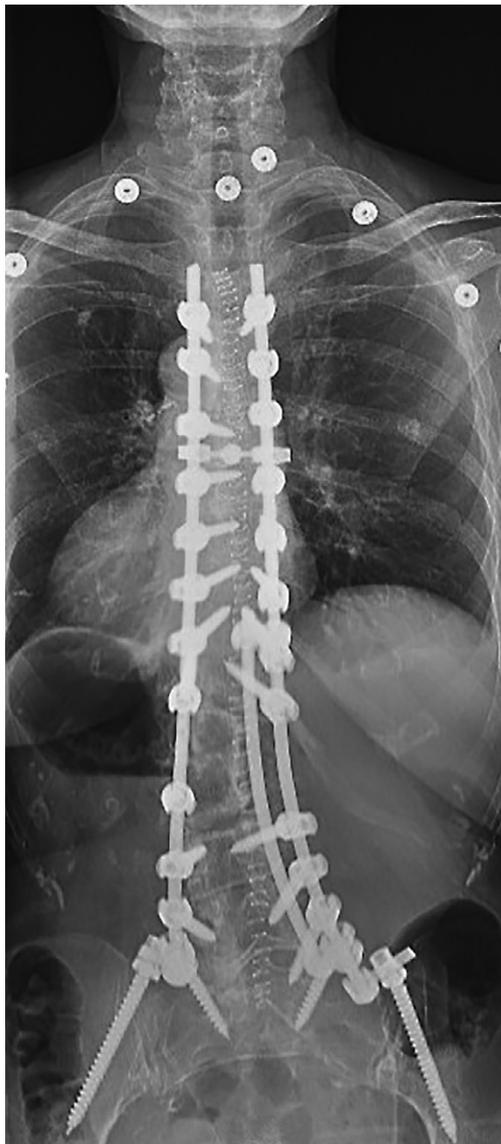
Preoperative X-rays showing convex right adult scoliosis with sagittal plane imbalance and high pelvic tilt along with multilevel lateral recess and foraminal stenosis.

FIGURE 3 (TOP RIGHT).

Representative image from the intraoperative CT guidance used in placement of the pedicle screw instrumentation.

FIGURES 4 AND 5 (BOTTOM).

Postoperative X-rays showing good correction of the deformity with restoration of overall coronal and sagittal plane alignment.



(Figures 4 and 5). Her preoperative leg pain has completely resolved. Her back pain has significantly improved, and her functional outcome scores (EuroQol 5D [EQ-5D™], Oswestry Disability Index, Short-Form Health Status Survey [SF-36]) continue to improve relative to preoperative levels.

It is now approximately one year since her operation, and she can walk up to a mile and play with her grandchildren, which she could not do before the surgery. She is now looking forward to an upcoming international trip.

Discussion

Patients with adult spinal deformity often have significant pain and disability, which is typically related to neurologic symptoms and sagittal plane malalignment. In general, patients who do not respond to nonoperative care have significant improvement in patient-reported outcome measures postoperatively.

Nevertheless, operations in these patients are associated with significant risk, as it is estimated that approximately 40 percent of patients will have a complication after surgery to correct adult spinal deformity.¹ Risks include, but are not limited to, wound infection, urinary tract infection, medical complications, malpositioning and/or failure of instrumentation, nonunion, and proximal junctional kyphosis or failure.

In view of these risks, it is typically best that these large surgeries be performed at centers that treat a high volume of deformity cases and that employ an interdisciplinary protocol and approach in such cases. An in-depth understanding of adult spinal deformity, including age-appropriate alignment parameters/objectives, is critical for the preoperative planning and successful execution of surgical reconstruction. Intraoperative tools such as CT navigation and neuromonitoring, along with multidisciplinary preoperative assessment and the use of TXA and other blood management strategies, help minimize complications in these high-risk cases.

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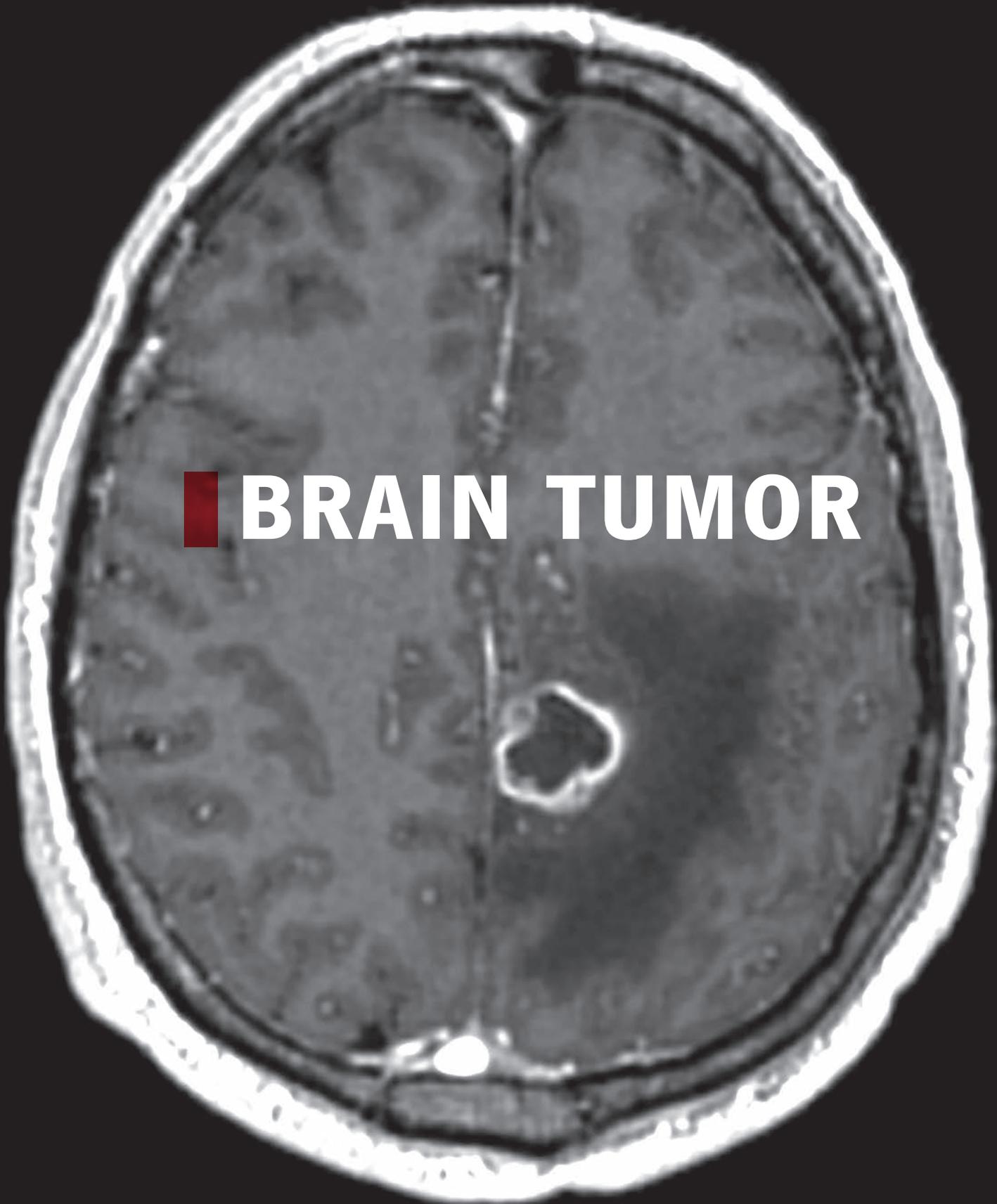
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5 Pillars of Standout Spine Care

Beyond its expertise in complex cases like this one, Cleveland Clinic's Center for Spine Health is shaped by at least five other factors that set it apart:

- 1) Volume-based experience, derived from 6,000 surgical/interventional spinal procedures performed annually.
- 2) Commitment to data-informed practice through routine collection of performance measures from patients and providers using Cleveland Clinic's homegrown Knowledge Program[®] tool. This electronic platform feeds data to the patient's EMR, providing a longitudinal view of health and function over the course of care.
- 3) Orientation to value-based care, exemplified by Cleveland Clinic's innovative Back on TREK program using physical and behavioral therapy to restore function in patients with chronic low back pain without reliance on medications or procedures.
- 4) Judicious use of advanced technology. Examples include the O-arm[®] Surgical Imaging System at multiple locations, expanding uses of spinal surgical robotics and other minimally invasive procedures, regular use of stereotactic radiosurgery for metastatic spine tumors, and emerging applications of artificial intelligence to inform surgical decision-making.
- 5) Research-driven practice stemming from the center's dedicated Spine Research Laboratory and participation in an abundance of multicenter and investigator-initiated treatment trials.



BRAIN TUMOR



Tumor Ablation with Chemo-Radiotherapy Consolidation Yields Rare Durable Remission of Glioblastoma

No evidence of residual tumor or recurrence at 6.5 years of follow-up.

By Gene Barnett, MD, MBA, and Manmeet Ahluwalia, MD

History and Presentation

A 48-year-old right-handed man presented with recent onset of motor and cognitive dysfunction. He had begun to have vague symptoms of dizziness and unsteadiness about two weeks earlier. Initially these were attributed to a resolving sinus infection, but approximately one week before presentation his wife began to notice more significant cognitive symptoms. He then had a falling episode while in the shower and was taken to an outside emergency department, where a CT scan revealed a left medial parietal mass. He was placed on dexamethasone and levetiracetam and then sought a second opinion at Cleveland Clinic.

Evaluation

When he was seen at Cleveland Clinic, the patient's symptoms had resolved and he was neurologically intact. An MRI showed ring enhancement and extensive edema around the mass, which appeared to be situated in the cingulate gyrus, immediately below the left paracentral lobule and the primary motor and sensory fibers (Figure 1).

Management

Additional imaging, including diffusion tensor imaging for fiber tracking, was obtained. This led to the determination that any

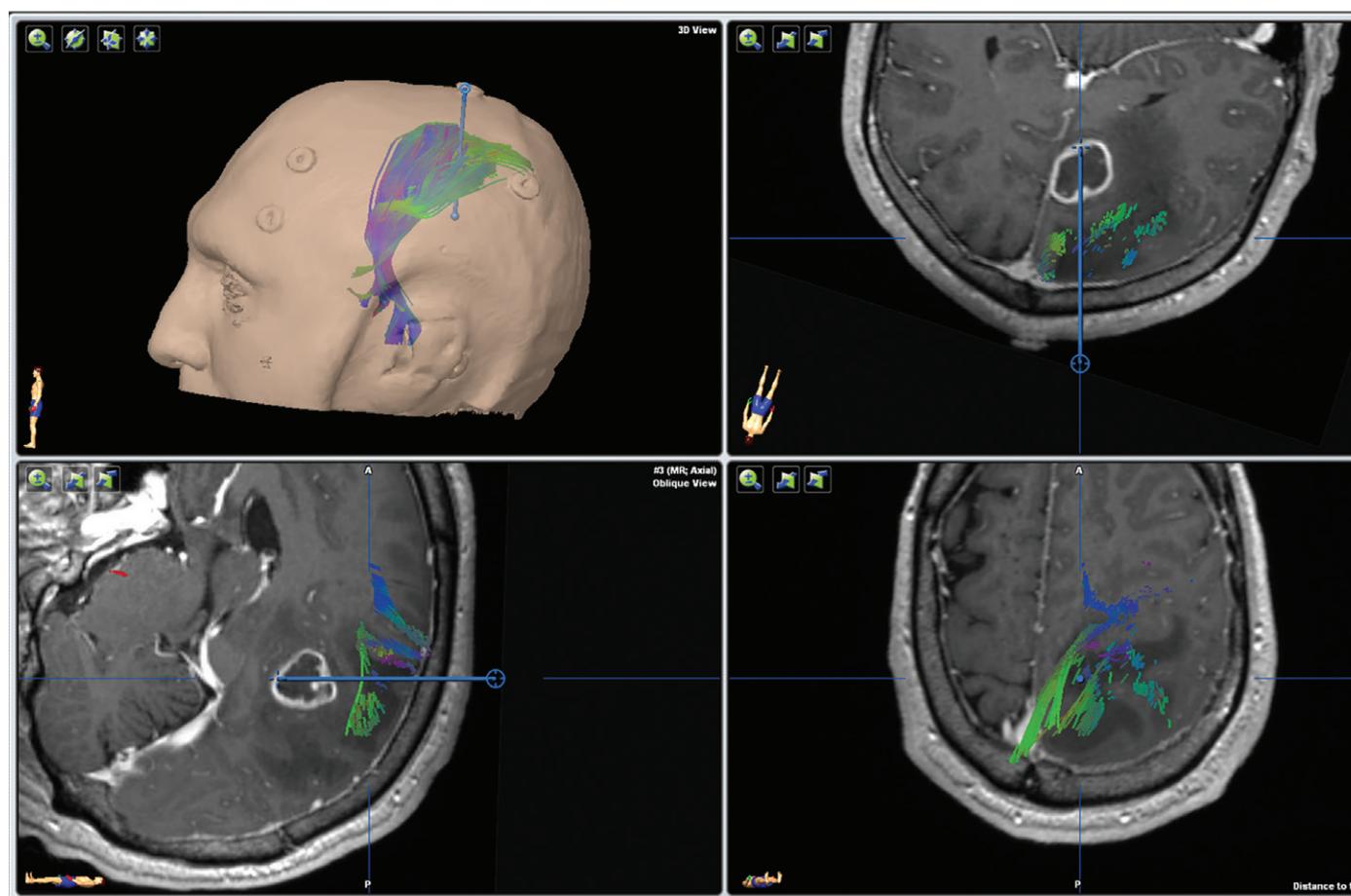


FIGURE 1. Neuronavigation planning for biopsy and laser ablation showing the relationship of the tumor in the cingulate gyrus to overlying motor and sensory projection fibers and the paracentral lobule. Blue lines indicate the surgical trajectory.

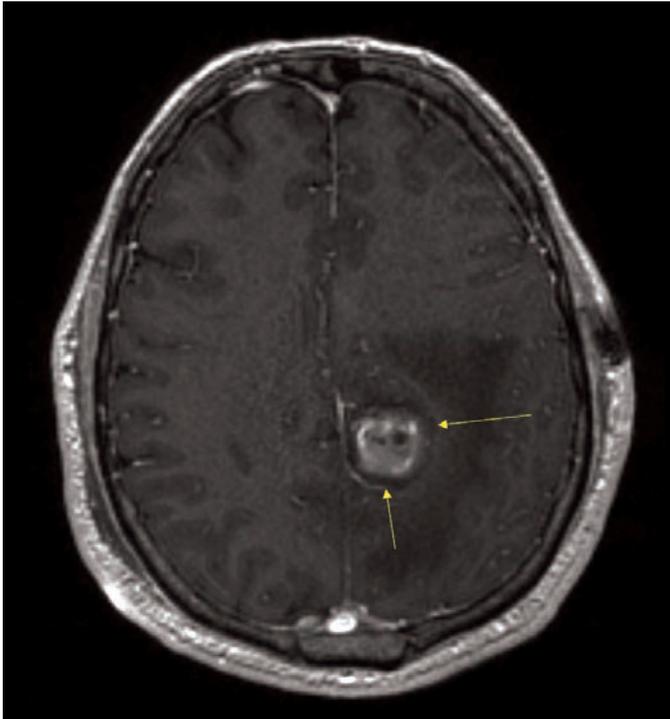


FIGURE 2. MRI taken 24 hours after ablation showing the extent of ablation (thin eggshell of enhancement indicated by arrows) and loss of contrast enhancement (hyperintensities are post-ablation blood and protein products).

conventional surgical approach (including parafascicular surgery) would subject the patient to a very high risk of motor and/or sensory deficits in his right lower limb because of the sensitive and deep location of the tumor. He was offered stereotactic biopsy and what was at the time — i.e., autumn 2011 — a relatively new therapeutic surgical modality, laser interstitial thermal therapy (LITT), which involves a laser probe only a few millimeters wide.

Five days after his fall in the shower, he underwent the minimally invasive LITT procedure and, as had been predicted, had only mild dorsiflexion weakness of his right foot, which resolved within a few weeks.

The following week, his case was reviewed in one of the twice-weekly multidisciplinary brain tumor boards convened by Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. The neuropathologist noted that the patient had a WHO grade IV astrocytoma (glioblastoma) without *IDH-1* mutation and with a Ki-67 labeling index of 9 to 10 percent and chromosomes 1p- and 19q intact (at that time [2011], the *MGMT* gene promoter was not routinely assessed). The neuroradiologist confirmed that the patient's postoperative imaging showed a complete ablation of the enhancing portion of the tumor (Figure 2).

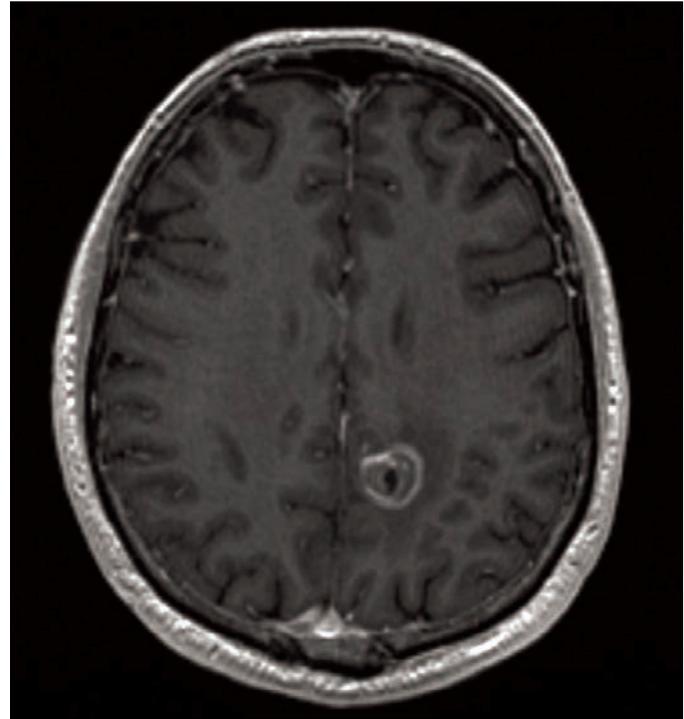


FIGURE 3. Six-month postoperative MRI with contrast showing decreasing rim of ablation enhancement and overall reduction in lesion size.

The brain tumor board recommendation was for external beam radiotherapy (60 Gy to the ablation bed + 2 cm) with concurrent temozolomide, followed by high-dose temozolomide for five days repeated at 28-day cycles. The patient elected to have the chemo-radiation therapy performed at Cleveland Clinic.

Outcome

His first imaging after chemo-radiation showed marked improvement in the appearance of the tumor, which was even better at six-month follow-up (Figure 3). In view of this, his temozolomide therapy was continued for a full year. Serial imaging showed that the tumor remnant continued to decrease, and the patient has remained neurologically normal more than 6.5 years after his surgery, with no evidence of recurrent or residual tumor (Figure 4).

Discussion

Although stereotactic brain biopsy can provide accurate and safe diagnosis of deep brain lesions owing to the small diameter of the biopsy instrument, it does not provide meaningful cytoreduction of tumor cells. In some cases, a safe corridor can be devised via a minimally invasive craniotomy using neuronavigation (with or

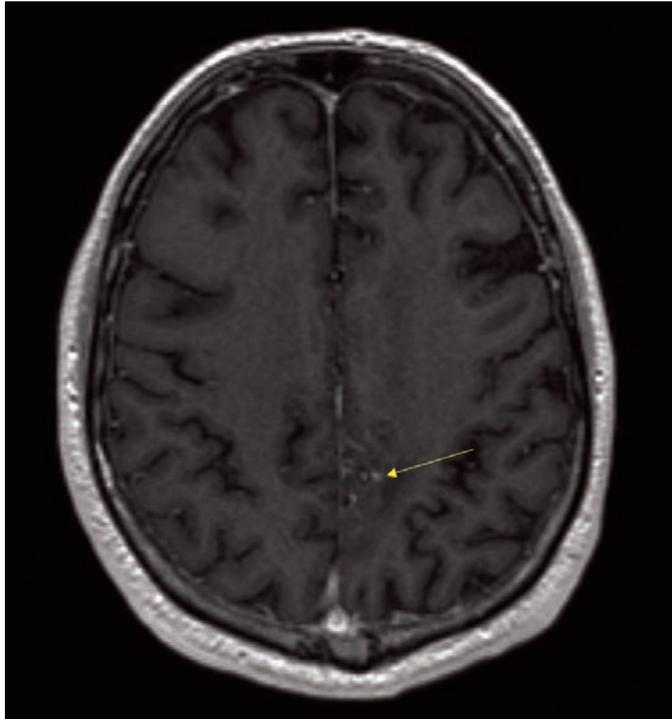


FIGURE 4. MRI with contrast taken 6.5 years after ablation showing a single speck of enhancement (arrow) and no clear evidence of residual or recurrent tumor. The patient has remained asymptomatic.

without tubular retractors), but the location in this case was not accessible without a high risk of sustained functional morbidity for the patient's right lower limb. A noninvasive treatment such as stereotactic radiosurgery eliminates the access issue but has been shown not to improve prognosis as part of the initial management of glioblastoma.

LITT (also known as laser ablation) was a relatively new method of minimally invasive cytoreduction when this patient was treated in 2011, with the first human case of tumor ablation using this system performed at Cleveland Clinic in 2008 (by co-author Dr. Gene Barnett). Nonetheless, early results in the multicenter clinical trial led by Dr. Barnett — along with subsequent clinical experience after LITT was cleared by the FDA for ablation of brain tissues — were very promising and prompted Dr. Barnett to offer this cutting-edge treatment to the case patient, whose prognosis otherwise looked bleak. Tumor ablation followed by consolidation using a multidisciplinary approach combining chemotherapy and radiotherapy has led to a rare, durable remission of the tumor with no evidence of viable residual tumor or recurrence.

An Abundance of Advanced Alternatives for Brain Tumor Patients

The early and innovative use of LITT in this case is one example of an array of novel, cutting-edge treatments — investigational and otherwise — that are routinely available to patients at Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. The center has been a pioneer in the following therapies in addition to LITT:

- Convection-enhanced delivery via the Cleveland Clinic-developed Cleveland Multiport Catheter (CMC), a four-port device for therapeutic delivery by bypassing the blood-brain barrier
- Tumor-treating fields for glioblastoma
- Immunotherapy of brain tumors
- Precision medicine-based approaches
- Two-staged stereotactic radiosurgery for large brain metastases

Additionally, the center offers stereotactic radiosurgery with the new Leksell Gamma Knife® Icon™, which allows stereotactic referencing with a mask rather than just a rigid screwed frame. And patients have access to a broad range of clinical trials of experimental therapies, including major multicenter and consortium-based investigations plus Cleveland Clinic-initiated clinical and translational studies.

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MOVEMENT DISORDERS

Treating the Patient, Not the Disease: A Physician's Long Journey to DBS for His Refractory Early-Onset Parkinson Disease

Recognizing patient readiness for interventions can be central to success.

By Hubert H. Fernandez, MD

History

"Dr. X" was one of the most skilled and highly regarded physicians in his field and a rising clinical star when, in 2008, he noticed a decrease in dexterity of his right arm and some curling of his right foot. He was only 37 years old.

Fearing Parkinson disease (PD), he left his home in Northeast Ohio and sought consultation at a leading academic medical center elsewhere in the country. Unfortunately, the diagnosis of PD was confirmed.

He was first started on levodopa, which resulted in dramatic improvement. Soon, however, the dose had to be increased as he started experiencing wearing-off symptoms. The dose was escalated rapidly, until even the highest dosage could not provide meaningful and lasting benefit. Ropinirole was soon added, up to the highest recommended amount, without much benefit. He was then placed on rasagiline, then pramipexole, then entacapone.

In a short span of two years, he was taking four PD medications around the clock yet was still experiencing tremors, stiffness, predictable wearing off, sudden "off" spells, foot dystonia and peak-dose dyskinesias. The solution offered was to add more medications. He was then unable to work as a physician and decided to retire and return home to Cleveland with his family.

Presentation and Evaluation

When Dr. X first presented to me in 2010, he was experiencing every type of motor fluctuation, including levodopa-induced dyskinesias. He was stiff and bradykinetic, with resting tremors in all limbs and postural instability. Within 30 minutes of taking levodopa, his foot curled, his arms started flailing, he began sweating profusely, he was barely audible and his mood dramatically worsened.

FIGURE 1 (LEFT). Neurosurgeon Andre Machado, MD, PhD, during surgery for deep brain stimulation of the globus pallidus internus.

My first visit with Dr. X took more than two hours. He needed to understand what motor fluctuations were, how over- and under-medicated states presented, and how some of his symptoms required reducing his medications while others required an increase. These nuances had not been explained to him at his previous facility.

Initial Management

Over the next 12 months, Dr. X's regimen was simplified, which provided some relief of his wearing-off symptoms, but his dyskinesias remained. He was most bothered by the off-spell symptoms, when suddenly he would not be able to speak, walk and sometimes think.

In 2011, we offered deep brain stimulation surgery (DBS) as a potential treatment to relieve him of his wearing-off periods and dyskinesias. He had several concerns, however: *What if my personality changes? Can you guarantee success? Will I remain sharp? What exactly will it treat?* He was clearly not ready for surgery.

Realizing that wearing off was his biggest problem, I offered him participation in a clinical trial of apomorphine (an injectable dopamine agonist that works quickly, thereby promising to "rescue" him from his off spells). While this provided temporary relief, it became unsustainable when he began requiring several injections per day.

DBS was offered again, but the same fears remained. He asked if there were any treatment beyond brain surgery or more pills and injections. By 2012, Cleveland Clinic was one of the leading sites testing a then-investigational therapy, levodopa intestinal gel — a liquid form of levodopa delivered directly through the small intestine via an external pump. Dr. X was one of the first patients in Ohio to try this medication, and it was a success. A dramatic improvement in his motor fluctuations was achieved, which sustained him for several years.

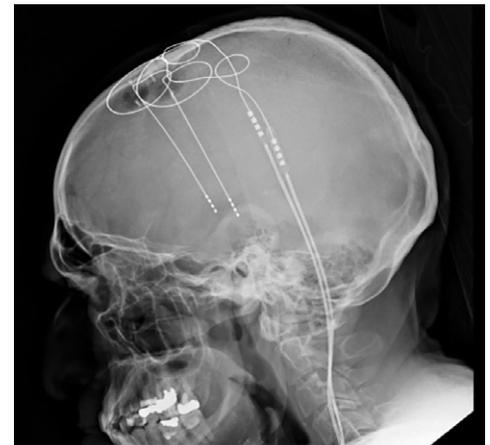
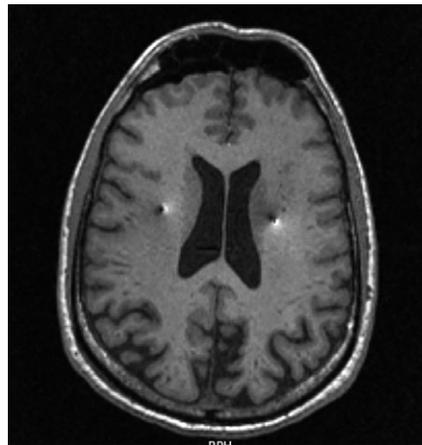


FIGURE 2 (TOP LEFT). A meeting of the Center for Neurological Restoration’s multidisciplinary movement disorders team, which includes neurologists, neurosurgeons, psychiatrists, psychologists, neuropsychologists, ethicists, nurses and trainees, to determine whether a patient is an ideal candidate for DBS and which type of surgery to offer. **FIGURE 3 (TOP RIGHT).** Cleveland Clinic’s intraoperative MRI suite allows precise DBS targeting while the patient is asleep. **FIGURE 4 (BOTTOM).** Postoperative imaging of Dr. X showing DBS implantation in the globus pallidus internus.

Readying the Patient for DBS

However, by 2016, he was again disabled by the motor fluctuations, and this time the dyskinesias were more violent, sometimes displacing him from his chair. He was almost ready for DBS, but he and his family still had questions. I went to his house to meet his wife, children and parents to discuss the procedure and answer all their concerns. Dr. X then met neurosurgeon Andre Machado, MD, PhD (Figure 1), who explained all the technical aspects of DBS implantation surgery.

Dr. X’s case was then presented to the entire movement disorders team in Cleveland Clinic’s Center for Neurological Restoration (Figure 2), which collectively concluded that Dr. X was indeed an ideal candidate for DBS surgery.

Because of his troublesome dyskinesias, fear of personality change and concern for cognitive impairment, the team felt that the globus pallidus internus (GPI) was a better DBS target than the subthalamic nucleus. Because both sides of his body were equally affected and he was young, otherwise physically healthy and cognitively sharp, the team felt that DBS was best performed bilaterally and simultaneously. But because he was extremely anxious, he was offered DBS under general anesthesia using our intraoperative MRI suite (IMRIS). This state-of-the-art technology, offered by only a few centers in the world, allows precise DBS targeting while a patient is asleep, with use of an MRI scanner built into the operating room (Figure 3), in contrast to traditional microelectrode recordings that can be performed only when the patient is awake.

In 2017, seven years after his first consultation at Cleveland Clinic, Dr. X finally underwent bilateral GPi DBS under general anesthesia. Figure 4 shows his postoperative imaging studies.

Outcome

Three months after adjustment of his DBS settings, Dr. X's levodopa intestinal gel pump was discontinued and he was converted back to oral levodopa. After two more months, he is now sustained solely on oral levodopa plus amantadine, with almost no wearing-off symptoms, "near normal" motor control (in Dr. X's own words) and minimal dyskinesias. At our most recent office visit, his wife said, "I have my husband again."

Discussion

PD is a complicated illness that requires listening intently to the patient, as symptoms can stem from any of several causes — the disease itself, lack of medication or too much medication. Because younger patients, like Dr. X, are at higher risk of developing motor fluctuations, it is especially critical to pay attention to their responses to medication. Absent such monitoring, the result can be an unnecessarily rapid escalation of medication, which then fuels further motor fluctuations in a vicious cycle.

Fortunately, we now have options, and our patients live longer and more fulfilling lives. Our Center for Neurological Restoration offers one of the nation's most recognized clinical trial programs, and Dr. X participated in two of the trials we offered for PD. While this bought him time, after several years even the best pharmacological treatments have limitations.

DBS is perhaps one of the greatest advances in neurology — and even medicine more broadly — because of its ability to restore motor function in a patient with PD. However, DBS is not for everyone. It is a highly technical procedure that carries its own risks and can be intimidating for any patient.

While Dr. X was likely to have benefited from DBS in the third or fourth year of his illness, he was not emotionally and psychologically ready. Sometimes patients need to go through "the process" at their own pace before finally deciding to go for it. It took six years, more than 20 visits, enrolling Dr. X in two clinical trials and meeting his family at his house before I was able to convince him the time was right. And it took the collective mind of our entire movement disorders team to determine the best target, staging and surgical procedure that respected and alleviated Dr. X's concerns. Finally, it took the expertise of a highly experienced neurosurgeon, Dr. Machado, to place the DBS leads in the right target.

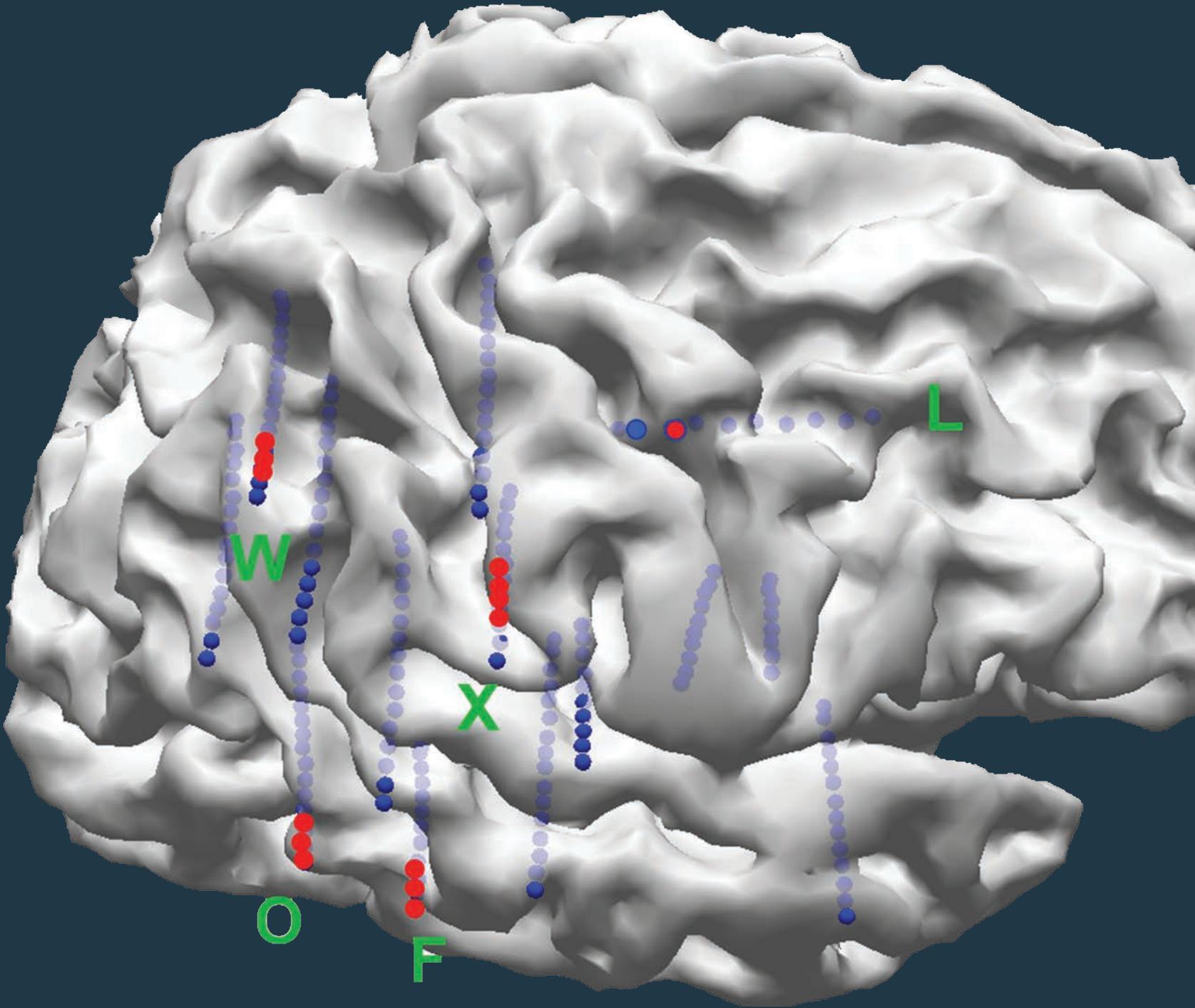
More Resources on Tap for Movement Disorders

Dr. X's case touches on some but not all resources for patients with movement disorders offered by Cleveland Clinic's Center for Neurological Restoration, which has achieved the first multisite designation as a Parkinson's Disease Center of Excellence by the Parkinson's Foundation. The designation covers our PD programs in Cleveland; in Weston, Florida; at Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas; and at Cleveland Clinic Abu Dhabi. Here's a sampling of our programs' resources:

- Experience with DBS in over 1,000 patients to date for treatment of PD, essential tremor and dystonia
- Additional functional neurosurgery options for selected tremor patients, such as radiosurgery with the new-generation Leksell Gamma Knife® Icon™
- A new high-intensity focused ultrasound system at our main campus to offer surgery without a scalpel for patients with difficult-to-treat tremors
- One of the most comprehensive clinical trial programs in the U.S., offering access to trials for all stages of PD as well as for tremors, dystonia, Huntington's disease and more
- Multidisciplinary patient management conferences to assess patients' appropriateness for DBS or other options, drawing on the expertise of movement disorder neurologists, neurosurgeons, neuropsychologists, neuroradiologists and others
- Forward-leaning offerings for patient support and convenience, such as shared medical appointments for newly diagnosed PD patients, virtual visits for established patients and a support group for young-onset PD patients

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■ EPILEPSY



Multimodality Evaluation Enables Epilepsy Control in a Patient with Periventricular Nodular Heterotopias

Resulting localization of a single focus paves the way for effective laser ablation.

By Imad Najm, MD, and Dileep Nair, MD

History and Presentation

A 35-year-old right-handed woman was referred to Cleveland Clinic's Epilepsy Center for possible surgical management of her pharmacoresistant epilepsy. Her seizures had started at age 31. She had failed multiple antiepileptic medications (total of six), and an MRI of her brain showed multiple periventricular nodules (Figure 1).

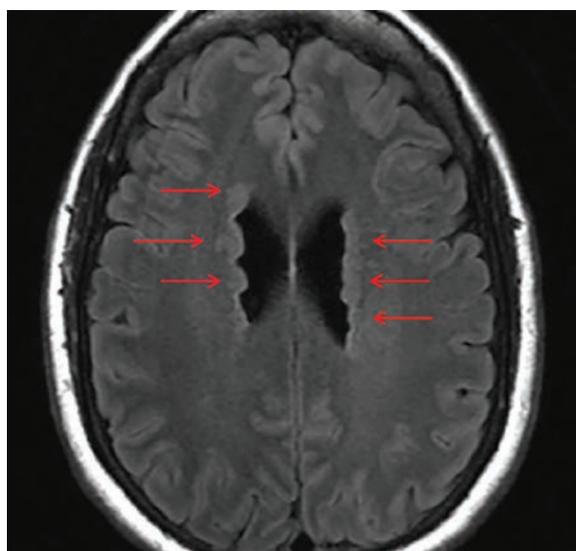


FIGURE 1. Brain MRI showing multiple periventricular nodules (arrows) prior to the patient's presentation at Cleveland Clinic.

The patient described multiple seizure types that included staring with unresponsiveness, difficulty finding words, euphoric feelings and episodes of muffled hearing followed by blurry vision that at times evolved into secondary generalized tonic-clonic convulsions.

Noninvasive Evaluation

She underwent a complete noninvasive evaluation that included video EEG monitoring, 3-Tesla MRI, FDG-PET scan, MEG and ictal SPECT. As detailed in Table 1, these tests revealed multiple areas of possible epileptic abnormalities, with the right hemisphere affected more than the left.

TABLE 1. Areas of Possible Epileptic Abnormalities on Noninvasive Evaluation

Test	Result
Video EEG monitoring	Interictal: right fronto-temporal, right centro-temporo-parietal, bi-occipital (right > left) Ictal: right hemisphere, bi-occipital (right > left)
MRI	Gray matter heterotopias, right and left lateral ventricles, bilateral frontal lobes
PET	FDG uptake in known bilateral heterotopias
MEG	Right frontal operculum, right parietal operculum spikes
Ictal SPECT	Multiple areas of activation including the right basal medial temporo-occipital junction and the right mid-parasagittal medial frontal, right posterior dorsal frontal and left deep lateral parietal regions

SEEG Evaluation

On the basis of these results, the multidisciplinary team in our patient management conference recommended a stereoelectroencephalography (SEEG) evaluation with extensive coverage of the right hemisphere:

- Periventricular nodules
- Frontal lobe
- Perisylvian region
- Temporal lobe
- Temporo-occipital regions (including mesial temporo-parieto-occipital junction)

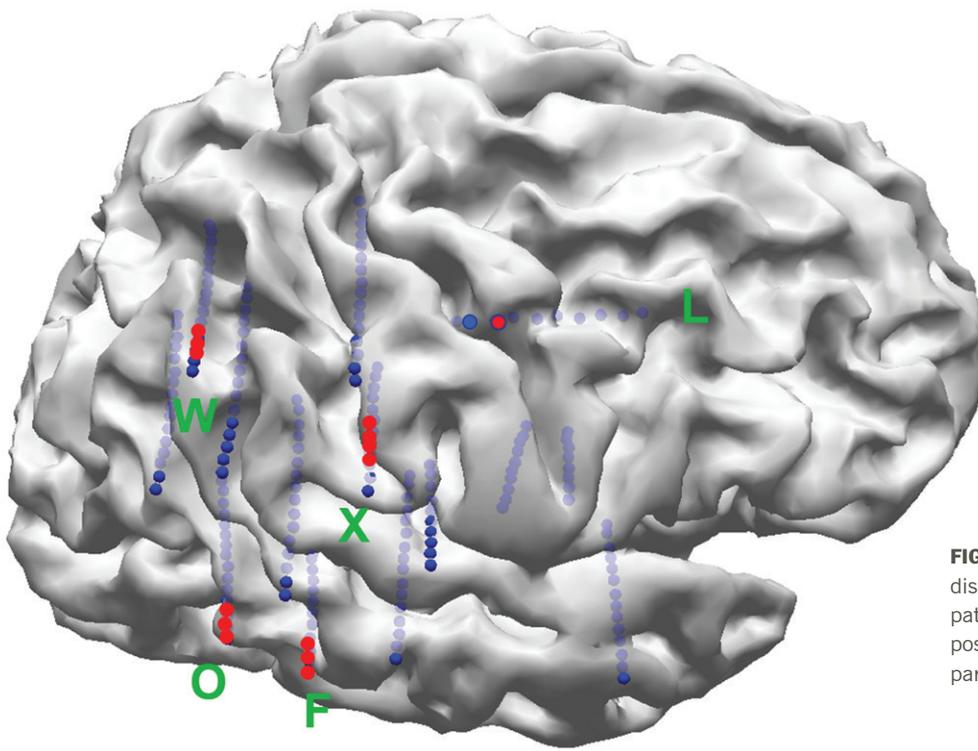


FIGURE 2. SEEG implantation map showing distribution of interictal spikes and ictal patterns in one of the right nodules, the right posterior perisylvian region and the right parietal area.

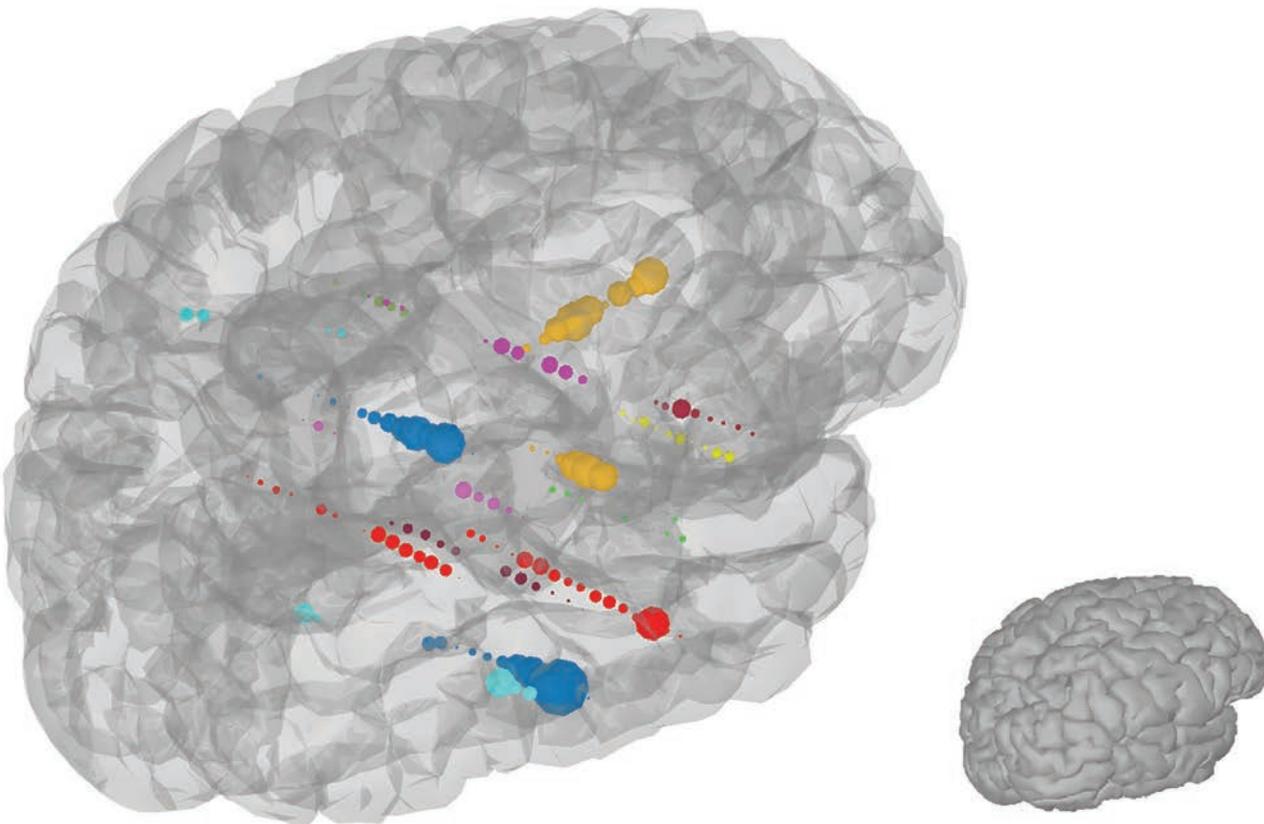


FIGURE 3. Illustration of the connectivity of the surrounding cortex from a seed point in the periventricular nodule that was involved in the ictal onset. Electrode stimulation from the periventricular nodule at low frequencies generates a measure of effective brain connectivity known as cortico-cortical evoked potentials (CCEPs). The regions of greatest connectivity are depicted as larger-sized recording electrodes. This methodology has shown the ability to map the propagation network of seizures. It suggests that the extent of the propagation network is quite broad, which could explain how a relatively restricted epileptogenic zone in the periventricular nodules could give rise to early propagated ictal activity in various parts of the lateral parietal and temporal neocortex.

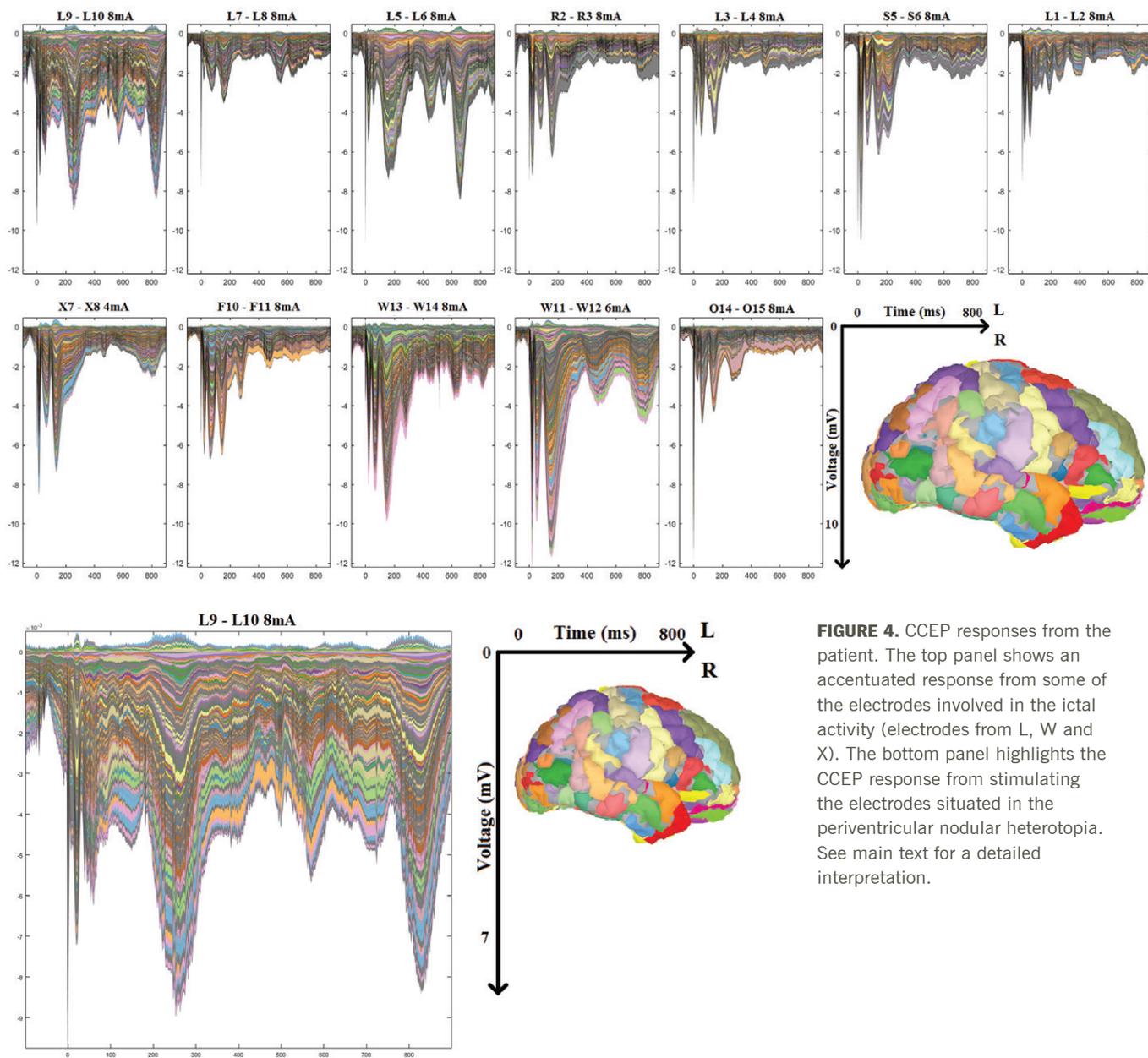


FIGURE 4. CCEP responses from the patient. The top panel shows an accentuated response from some of the electrodes involved in the ictal activity (electrodes from L, W and X). The bottom panel highlights the CCEP response from stimulating the electrodes situated in the periventricular nodular heterotopia. See main text for a detailed interpretation.

The SEEG evaluation revealed interictal spikes and ictal patterns that were distributed to one of the right nodules, the right posterior perisylvian region and the right lateral parietal area (Figure 2).

These findings suggested two main possibilities: (1) The epileptic activities are multifocal. (2) The epileptic activities are generated in a single area — perhaps one of the periventricular nodules — with spread to the other areas. Surgical intervention would be entertained only if the second hypothesis was confirmed.

CCEP Evaluation and Treatment

To test this hypothesis, we used the cortico-cortical evoked potentials (CCEPs) technique that was developed at Cleveland

Clinic. This technique allows for the testing of connections between various areas in the brain and the direction(s) of those connections. The electrodes that showed epileptic activities were stimulated. CCEPs were elicited in most of the cortical areas with epileptic activity after stimulation of the epileptic periventricular nodule (Figure 3).

Figure 4 shows representative CCEP responses from the patient. The top panel shows an accentuated response from some of the electrodes involved in the ictal activity (electrodes from L, W and X). We believe these accentuated CCEP responses arise in brain regions capable of generating synchronous brain activity, which is one of the hallmarks of epilepsy. The bottom panel highlights

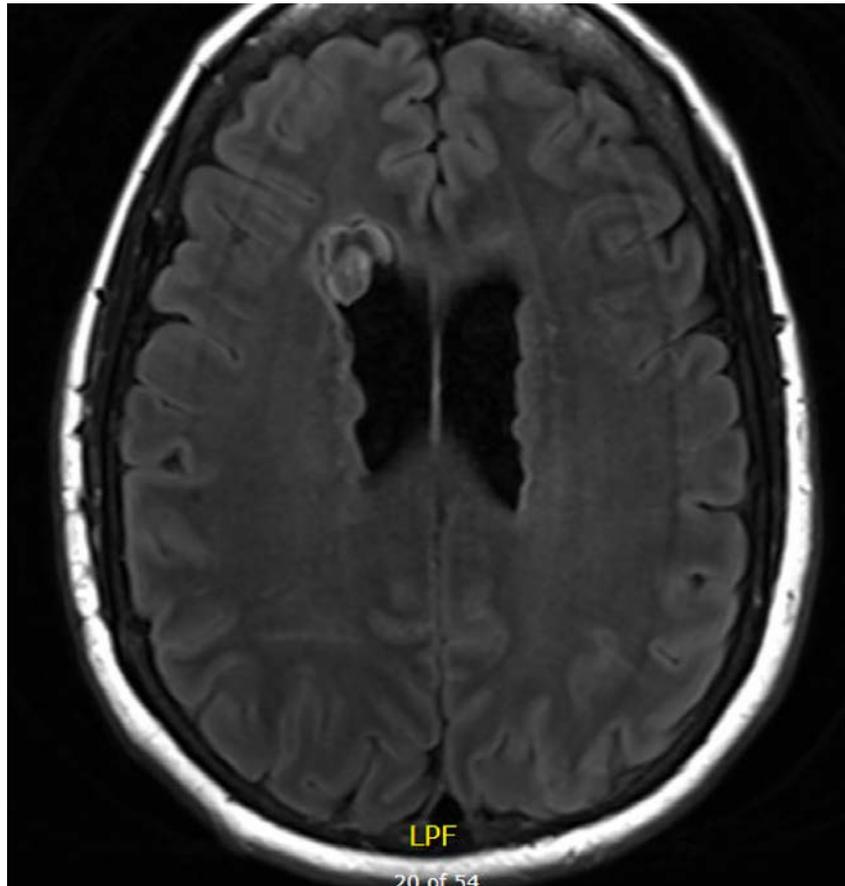


FIGURE 5. MRI taken following laser ablation of the periventricular nodules determined to be involved in the patient’s seizure generation. Note the focal changes (compared with the pre-intervention MRI in Figure 1) due to the ablation.

the CCEP response from stimulating the electrodes situated in the periventricular nodular heterotopia. The color pattern (pink, light blue and light orange) along the largest peaks of this CCEP response shows distribution of response to the posterior perisylvian and right lateral parietal regions shown in the accompanying segmented brain image. This suggests that the periventricular nodule may be the primary generator of the epilepsy and its connections to the outer surface of the brain, explaining the rapid spread of epileptic activity.

These results suggested that the patient had right hemisphere focal epilepsy that likely originated from one of the right lateral ventricle nodules, activating the inferior parietal network. However, independent foci between the two regions cannot be fully ruled out.

The patient underwent laser ablation of the right lateral ventricle epileptogenic nodule (Figure 5), and she has remained seizure-free since 2015.

Discussion

This case illustrates the power of a state-of-the-art multimodality evaluation in patients suffering from pharmacoresistant epilepsy in the setting of periventricular nodular heterotopias. The SEEG method enables the sampling of both deep (periventricular nodules) and cortical areas in a single session. The use of CCEPs to study the connectivity between various brain areas and the directions of those connections helps in uncovering the possibility that there may be a single pacemaker (epileptogenic focus) connected to multiple areas. In turn, the resulting identification and localization of a single focus allows the use of the laser technique for ablation of the deep focus, leading to a higher chance of complete seizure control with low surgical morbidity.

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Expanding CCEPs to New Frontiers

In 2004, Cleveland Clinic's Epilepsy Center published the first of several articles on cortico-cortical evoked potentials (CCEPs), a technique in patients undergoing invasive monitoring for epilepsy surgery that was pioneered by our neurophysiology lab under the direction of Dileep Nair, MD (shown standing in the photo on this page). The technique uses low-frequency cortical stimulation to evoke measurable signals in distant or nearby cortical regions to determine which other brain regions respond. CCEPs offer distinct advantages for invasive monitoring, and their use has been adopted by a number of other epilepsy centers around the world.

Now our Epilepsy Center is spearheading an NIH-funded project to expand this tool's utility by developing a brain atlas of CCEP responses from across hundreds of patients who have undergone epilepsy surgery using stereoelectroencephalography (SEEG).

The research aims to elucidate the complex interactions of brain regions that can be elicited using CCEP studies. Its goal is to find noninvasive strategies to identify the cortico-cortical pathways underlying the pathophysiology of intractable epilepsy — and perhaps other neurological conditions.

This project to map brain connectivity was awarded a five-year R01 grant from the National Institute of Neurological Disorders and Stroke. Cleveland Clinic serves as a principal investigative site along with the University of Southern California.

Findings from more than 150 patients are currently incorporated into the project's brain atlas. We recently described the correlation of ictal SPECT and CCEP connectivity maps in a paper in *Brain* (2017;140:1872-1884). We have since applied these CCEP connectivity maps to inform the use of laser ablation in an individual similar to the patient profiled here, as we report in a paper recently accepted for publication in *Epilepsy & Behavior*. Efforts are now underway to study connectivity across patients to see how brain connectivity informs success in epilepsy surgery. Our research team is also engaged in efforts to study the normal connectivity of the brain based on CCEPs.

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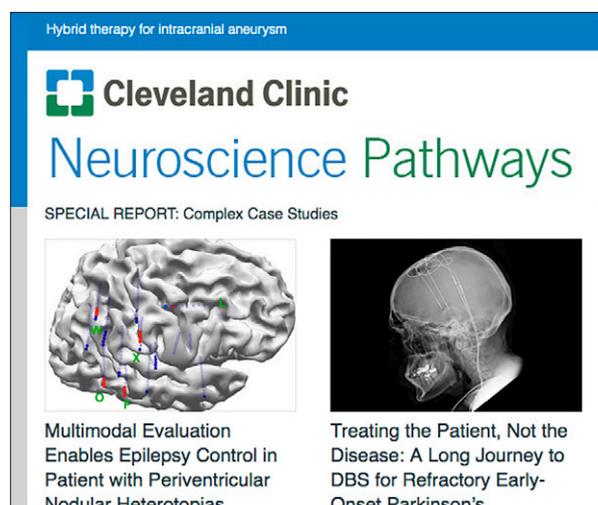


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