Procedural Treatments for Movement Disorders

The Philadelphia Neurologic Society explores the journey from thalamotomy to MR-guided focused ultrasound for movement disorders.

By Gordon Baltuch, MD, PhD

Getting Started

When I began training at the Montreal Neurological Institute, treatment of movement disorders was primarily medical. The only surgeries we were doing were thalamotomies using ventriculograms and leucotomes to make leucotomies in the thalamus in people with Parkinsonian tremor. We were doing deep brain stimulation (DBS), but it was for treatment of intractable pain and the treated individuals had access to the leads to do the programming themselves.

After completing my neurosurgery training, I worked clinically in Europe, and I remember thinking we would do a pallidotomy for a patient with a movement disorder and being surprised at hearing, "No, we're doing stimulation." At the time, neurosurgeons in Europe had moved away from thermal lesioning and were pursuing neuromodulation approaches. I then had a huge opportunity to spend some time with Professor Alim Louis Benabid—the first neurosurgeon to win the Lasker award—for pioneering DBS for movement disorders.

After that, I was fortunate to have the opportunity to come to Pennsylvania Hospital and develop a program in the US for DBS. Since then we've treated 1,300 people, mostly at the subthalamic nucleus (STN) or globus pallidus inferior (GPi) for Parkinson's disease (PD). The others treated were individuals with essential tremor or dystonia with a few investigative procedures for other conditions.

Showing Safety and Efficacy for Deep Brain Stimulation

Initially, the work was observational in that we would do a few procedures; follow those people to see what outcomes occurred; write about the results, positives, and negatives; and send it to a journal so others could learn about what we observed. In 2002, we published the original cases of bilateral stimulation of the subthalamic nucleus (STN) showing some really, really positive results.[1] We were among the first people to report on safety data for DBS—the morbidity and mortality in our first group of patients.

Eventually, the field realized we needed more rigorous studies comparing outcomes after DBS with outcomes after medical therapy alone. In a trial at 13 sites, DBS was compared to best medical care with a primary outcome measure of time with and without dyskinesia after 6 months of treatment. The trial also compared outcomes of stimulating the STN vs the GPi.

Early in the trial, it became clear that the number of hours without dyskinesia was significantly increased in those treated with DBS compared with very little change in the time without dyskinesia for those treated medically. Ultimately, the trial was stopped because the results with DBS were so good that it was not ethical to continue treating participants with medicine alone.

In some ways, this was surprising because a participant in the surgical arm of the trial had died from a hemorrhage. We were concerned that this would completely shut down our ability to continue with DBS—I figured, "Okay, that's it, we're going to get shut down; we're done, this is done." But, in fact, the safety and efficacy data showed, with class I evidence, that the benefits of DBS for treatment of PD outweighed the risk.[2]

Finding the Best Target

There was controversy in the field at the time about the best target for DBS. In the US, there was a preference for STN; in Switzerland, there was a preference for GPi; and in France, there was a focus on the STN. In general, most people were targeting the STN, however data showed no significant difference between the 2 targets—both gave the same increased benefit over standard medical care at the time.[3] Because there was some dogmatism about what the right target was at this time, it was a valuable learning opportunity.

In a particular case, we were treating a participant with severe tremor during his off state. We learned in the operating room that he had been randomized to receive stimulation to the GPi, and I was very concerned that this might not help his tremor. A mentor pushed me to remember the primary outcome of the trial was time in the on state without dyskinesia and suggested that the individual probably didn't have tremor in the on state and that we should go ahead. Staying focused on the outcomes allowed us to include the participant in the trial and learn that the targets were equally effective at controlling dyskinesia in the on state.

We do see advantages and disadvantages of each target, however. An advantage of stimulating the STN is that, usually, medications can be decreased afterwards, and for individuals for whom that is goal, this can be important. We still have observational evidence that stimulating STN is better for treating tremor and may be better for treating gait freezing. A disadvantage of stimulating the STN is that it is a smaller anatomic target and programming the stimulator can be more challenging. There is some evidence that cognition and mood can worsen, and medication has to be reduced carefully, which may be difficult and even undesirable for some individuals.

In contrast, the GPi is a larger anatomic area that requires less programming finesse. It seems to be better for dystonia and reduction in medication is not required. Less medication can be advantageous or disadvantageous depending on the individual being treated. Stimulation of GPi seems to be less effective for gait freezing.

Deep Brain Stimulation Case Examples

A woman, age 52, with PD and symptoms of bradykinesia and severe dystonia in the off state that responds only to medication is someone for whom I would strongly consider GPi stimulation. A man, age 78, with a 50-year history of PD and disabling dyskinesia with some cognitive impairment is also a good candidate for GPi stimulation, just to improve the dyskinesia and not have to adjust medication. Some individuals who have STN stimulation develop severe dystonia in the off period and can have contralateral stimulation of the STN or GPi stimulation added to help with the off-state dystonia. For patients who have stimulation of STN or GPi and still develop gait freezing, stimulating an additional target may be helpful but is very difficult; other options should be considered first. For patients with advanced PD and motor fluctuations who are on a high dose of levodopa equivalent and experience severe depression when medication is decreased, great care is needed. For these individuals, there is a risk of stimulating STN and subsequently dropping medication after good motor benefits, only to see patients become severely depressed and even suicidal. For these people, GPi stimulation is a better strategy. Great care should be taken whenever dopaminergic medications are decreased.

Clinical Tips

- Consider talking to patients about surgical options before they are needed to help people become more comfortable with neurosurgery as an option
- Understand that neurosurgery may be frightening for people and be willing to bring it up as an option gently and more than once as part of an ongoing conversation
- Even a person who is convinced they would never have neurosurgery may benefit from a exploratory visit to a neurosurgeon to learn more
- Efficacy and safety of deep brain stimulation for Parkinson's disease (PD) motor symptoms are proven
- Efficacy and safety of MR-guided focused ultrasound are proven for essential tremor and tremor in PD and indications are still growing

Long-Term Outcomes

Initially, there was some hope that DBS might be disease-modifying—that is, that it could provide neuroprotection or slow progression. The first cohort was followed for 3 years and motor symptoms were still improved but nonmotor symptoms continued to progress. Cognitive decline, which is the big challenge, continues. We've followed a group of 400 individuals with PD treated with DBS. Mortality at 10 years is approximately 50%.[4]

Some people died from cancer, some from heart disease, but the vast majority had a cause of death related to the nonmotor complications of PD. Among the survivors, about half had high levels of disability—struggling to prepare their own meals or run simple errands. That said, the procedures did allow some people, who came in with advanced PD, to maintain at least some function for 10 to 20 years and possibly live longer than they would have without the procedure. Overall, what we see is that there is benefit for motor but not nonmotor symptoms, and that onset of cognitive decline is related to mortality. There are risks of the procedure, including hemorrhage, infection, and equipment failure, and for many individuals, the potential benefits outweigh the risks.

A New Direction or a Step Backward?

In my first exposure to magnetic resonance-guided focused ultrasound (MRgFUS), I was asked to comment on a paper presented at the American Association of of Neurologic

Surgeons.[5] Decades after leaving thalamotomy behind, thermally lesioning the thalamus made a comeback for the treatment of pain, which had been among the first indications for DBS. Unlike before when a probe or leucotome was used, with MRgFUS, the lesions is specifically localized with MRI. The ultrasound machine that creates the soundwaves that generate the heat for a thermal lesion is used like a thermostat to measure the temperature generated. In this manner, the shape, size, and location of the lesion are controlled.

Eventually, the technique was used to treat essential tremor and the benefits have been proven in randomized controlled trials. The advantages are that the procedure is noninvasive, can be done on an outpatient basis, and doesn't require implantation of hardware or programming of software. For individuals with comorbidities, who may have contraindications to DBS, it is viable option that is approved by the Food and Drug Administration for treatment of essential tremor or tremor in PD. Studies for the use of MRgFUS for treatment of other PD motor symptoms has also begun. An initial study showed results similar to DBS of the STN.[6]

New Frontiers

Gene Delivery

While we were developing DBS and MRgFUS, others were focused on biologicals as treatment for central nervous system (CNS) diseases and the challenge of delivering biologicals to the CNS. A clinical trial[a] brings this together with magnetic resonance tomomography (MRT). Using MRT, a gene vector labeled with contrast agent can be observed during injection into the putamen to ensuredelivery and placement of the vector and gene. Outcomes of delivering gene therapy vs sham will be compared.

Depression

We participated in sham-controlled small studies using DBS to treat people with treatment-resistant depression.[7] Although we didn't see a benefit, I believe that may have been because some participants who should have been excluded because of suicidality may not have been. We also noticed among the people our site treated, it took longer for improvement to occur than the time frame used to measure outcomes in the trial. The problem of inducing hypomania and mania also occurred, and when it did, participants did not want to have the stimulation decreased and that produced other problems. At our site, we operated on 8 patients and at 5 years of follow up saw some people doing very well. Although this trial was discontinued for lack of benefit, I hope another generation of people might consider DBS for refractory depression—such a large and devastating illness in our society—to study this again.

Conclusion

Seeing people who are essentially immobile get up from their chairs and walk after treatment with DBS or MRgFUS is among the highlights of my career. I have been fortunate to be here in Philadelphia, supported by colleagues in my department, whose efforts have allowed me to research these new techniques. We've taken small steps toward solving the grand challenge of CNS diseases and are at the frontier of bigger steps to come. What this work has taught me is that we should not limit ourselves to only what we know but should always consider the ways we can expand the options for improving our patients' lives. ■

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a. VY-AADC02 for Parkinson's Disease With Motor Fluctuations (NCT 03562494).