DBS May Prove Beneficial in Early Parkinson's

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Data from new studies suggest that patients with Parkinson's disease might benefit from deep brain stimulation surgery much earlier in their disease course, offering tantalizing hints that early surgery could actually delay progression by protecting the cells that Parkinson's destroys.

Since its 2002 approval for Parkinson's, bilateral subthalamic nucleus stimulation—a form of deep brain stimulation—has been reserved as a last resort for the most severely affected patients: those whose motor symptoms can no longer be controlled by medications because they experience severe side effects of chronic levodopa therapy.

But findings from at least one recent study suggest that early implantation of the electrodes also significantly improves quality of life for patients when some of these issues are just beginning to appear. Experts say this approach might be particularly beneficial for young patients who can be expected to have a long disease course and thus are at greater risk of developing complications of medical treatment.

"The idea behind earlier surgery is not to wait until the last minute, or just consider it a last-ditch effort," Dr. David Riley, director of the Movement Disorders Center at the Neurological Institute of University Hospitals Case Medical Center, Cleveland, said in an interview. "The studies tell us that people who develop motor fluctuations will do better with surgery than with any combination of medications we can develop. Once a patient is spending more than 25% of the day in the 'off' state, we should be considering him or her for DBS surgery."

While anecdotal reports and case series have described the results of earlier DBS surgery, researchers are only now beginning to explore the question systematically, said Dr. Michael Schüpbach, a movement disorders researcher at the Groupe Hospitalier Pitié-Salpêtrière, Paris. His 2007 pilot study examined the issue in a small group of patients with earlier disease (Neurology 2007;68:267-71).

"Our patients in general profited from DBS, not only on the motor symptom level, but in their activities of daily living, their disease-specific quality of life, and their overall psychiatric state," he said in an interview.

The trial, sponsored by Medtronic, included 20 patients with disease duration of 5-10 years, a Hoehn and Yahr stage of 3 or lower, and motor fluctuations during "off" periods for 25% or more of the day. Half of the group received best medical therapy; the other half underwent DBS surgery while continuing on their medication, adjusted as necessary. They were followed for 18 months.

By the end of the follow-up period, Dr. Schüpbach and his colleagues observed several differences between the groups:

► Activities of daily living ratings declined significantly in patients who had been medically treated during their "off" periods, while they improved significantly throughout the study in the DBS group.

► Motor disability scores during "off" periods declined significantly in the medically treated group, dropping 29% by the study's end. In the DBS group, these scores improved by 69% at the same time point.

► By 18 months, medically managed patients experienced a significant 12% increase in their levodopa dosage, whereas their drug-induced motor complications worsened by 15%. Among the DBS patients, however, levodopa dosage decreased by 57% at 18 months, and the severity of drug-induced motor complications lessened by 83%.

► Anxiety and overall psychiatric morbidity improved significantly only in the DBS group. These patients also showed a trend toward improved mood, although the change was not significant.

"While this was only a pilot study that needs confirmation, I think it provided a very strong argument not to withhold surgery for the longest possible time, as we now do," Dr. Schüpbach said.

However, he cautioned, both patients and physicians must carefully weigh the risks and benefits. There were no serious surgical adverse events in his study, but four DBS patients did develop depression, compared with three medically managed patients. "However, with only 20 patients, it's difficult to conclude anything about side effects," Dr. Schüpbach said. "That would take a bigger study, and in fact, we're recruiting for one now."

The EARLYSTIM trial, sponsored by the French government, will include 250 patients at 16 centers in France and Germany. Patients must have a Hoehn and Yahr stage of 2.5 or lower while on medication, and disease duration of more than 4 years. Again, the comparator arms are DBS plus medication, or best medical management alone. The patients will be followed for 2 years.

"We want to include patients with extremely early disease with the goal to keep them functional in their work and social context," Dr. Schüpbach said. "I'm cautiously optimistic that the EARLYSTIM trial will replicate our pilot study."

A smaller trial is also recruiting in the United States. While this study will provide information about the functional benefit of DBS in early Parkinson's, its main goal is to explore the neuroprotective effect of early surgery.

"To date, no therapy—not medication, surgery, stem cell or gene therapy—has been shown to slow the progression of Parkinson's disease," Dr. David Charles, director of the Movement Disorders Clinic at Vanderbilt University Medical Center, Nashville, Tenn., said in an interview. "But recent animal studies have given us some really exciting insight into just how that might be accomplished."

The Medtronic-sponsored Vanderbilt trial, which is just wrapping up its recruitment phase, will include 30 patients randomized to DBS plus medication or medication alone. These patients must have very early Parkinson's, with a Hoehn and Yahr stage of 2 when off medication; the follow-up is 2 years.

The study's main safety end point is the time to a 20% worsening in motor scores. "One concern with early stimulation is that we could somehow worsen Parkinson's disease, or cause some unforeseen problem, by applying the therapy early," Dr. Charles said.

But perhaps more intriguing is the efficacy end point—the reduction in symptoms when the patient is off both medication and stimulation. The level to which symptoms decrease might give researchers insight into whether early DBS slows disease progression. Although he called it "a long shot," Dr. Charles said the two in vivo studies give reason to hope.

In 2006, investigators at Maastricht (the Netherlands) University explored the neuroprotective effect of DBS in rats with a created model of Parkinson's disease—a toxin that killed up to 50% of the dopaminergic cells when injected into the substantia nigra. During the same procedure, some of the rats also underwent implantation of bilateral DBS electrodes. After 1 week, rats who received DBS had 30% more neurons in the substantia nigra than rats who received no treatment—suggesting that the activation of the electrodes had protected the cells from the toxin (Brain Res. 2006;1120:100-5).

"The most exciting study, though, was one performed in monkeys and published last year," Dr. Charles said. "This study is superior, not only in its primate model, but in its Parkinsonian model, which more closely simulates the disease in humans."

The French study, cowritten by DBS pioneer Dr. Alim-Louis Benabid, included 28 macaque monkeys (Brain 2007; 130:2129-45).

Again, the researchers used a toxin to induce symptoms; in some monkeys, the toxic drug was delivered a week before surgery, allowing time for the dopaminergic cells to die off before brain stimulation began. "We know that by the time a patient presents with the first symptoms of Parkinson's, up to 70% of the substantia nigra neurons have already been lost," Dr. Charles said. "This model was more similar to the natural history of the disease in humans."

Monkeys in the experimental group received DBS for about 7 months. At the study's end, they showed up to 24% more nigral cells than did monkeys that had no stimulation.

Dr. Charles explained the theory behind this preservation effect. "Once the substantia nigra begins to degenerate, the subthalamic nucleus becomes hyperactive and increases its output of glutamate, which is toxic to dopamine-manufacturing cells. Although we don't know why the cells begin to die off in the first place, one strategy for protecting them from further depletion could be to reduce the hyperactive output of the subthalamic nucleus; DBS is thought to do that."

Dr. Schüpbach is less enthusiastic about any potentially disease-modifying effect of DBS. "It's an open question at best," he said. "We have more than 10 years of experience with DBS in Parkinson's patients, and we know that they do progress in spite of the treatment—especially with axial symptoms, which don't respond to either medication or simulation."

Neuroprotection will be hard to prove in a small trial, he said. "We considered including it as a secondary outcome in the EARLYSTIM trial. But a power calculation told us that even with 250 patients, we would probably not be able to show a protective effect. If there is one, it would certainly be partial. There is certainly progression in spite of DBS, and it is certainly wrong to recommend it as a neuroprotective treatment without further evidence."

All the researchers, however, agreed that the benefits of DBS should no longer be thought of as a last resort. In an editorial that accompanied Dr. Schüpbach's 2007 study, Dr. Riley noted that even under currently accepted surgical practice, too few people are getting the procedure. "Only a minor fraction of patents with Parkinson's who would benefit from DBS currently experience this treatment," he wrote. Dr. Schüpbach's study "indicates that earlier application of DBS represents an improvement over our current approach to managing Parkinson's."

Dr. Charles said he has received payments from Medtronic lectures and consulting; Dr. Schüpbach said he has no financial ties with the company. ■

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Dr. David Charles checks a patient's deep brain stimulation device. Dr. Charles suspects that DBS reduces the hyperactive output of the subthalamic nucleus.