Brain Stimulation Tops Medication for Parkinson's

BY PATRICE WENDLING
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CHICAGO — Preliminary data from two trials suggest that deep brain stimulation may be superior to the best medical therapy in Parkinson's disease, and that stimulating specific targets may lead to different cognitive and mood outcomes.

Complete data on 230 of 255 patients with idiopathic Parkinson's disease showed that motor functioning at 6 months, based on blinded ratings, improved 35.6% over baseline with deep brain stimulation (DBS), but only 4.5% with the best medical therapy (BMT), Frances M. Weaver, Ph.D., co–principal investigator, reported in a poster at the 12th International Congress of Parkinson's Disease and Movement Disorders.

Time without troublesome dyskinesia increased by 5.1 hours with DBS, compared with no change with BMT.

The 111 DBS patients experienced significant improvement in all aspects of the Parkinson's Disease Questionnaire–39, except for social support, compared with the 119 BMT patients who had little change.

Motor function improved 36% over baseline, but 40% of DBS patients had a serious adverse event, compared with only 11% of patients on medical therapy.

However, these gains must be weighed against the greater risk of serious adverse events following DBS, Dr. Weaver reported on behalf of the Veterans Affairs/National Institute of Neurological Disorders and Stroke (VA/NINDS-01) Study Group.

At least one serious adverse event was experienced by 40% of DBS patients, compared with only 11% of BMT patients.

The Deep Brain Stimulation vs. Best Medical Therapy trial included patients aged 22 years or older (mean age 63 years) with Hoehn and Yahr stage 2 or greater idiopathic Parkinson's disease responsive to L-dopa, but with persistent motor complications. BMT patients received optimized medical therapy, and DBS patients were further randomized to bilateral stimulation of the subthalamic nucleus (STN) or globus pallidus interna (GPi).

The BMT arm was discontinued early as there was sufficient power to compare the primary outcome with the first 255 patients. Most BMT patients proceeded to surgical treatment, Dr. Weaver, of Hines (Ill.) Veterans Affairs Hospital, said in an interview. Results of the DBS target (STN vs. GPi) portion of the trial are expected in 2009.

Results from the prospective, randomized COMPARE (Comparison of Best Medical Therapy and Deep Brain Stimulation of Subthalamic Nucleus and Globus Pallidus for the Treatment of Parkinson's Disease) trial will not end the controversy over which surgical target is best, but will provide the first level 1 evidence that may allow physicians to tailor DBS to the patient's symptoms, said Dr. Michael S. Okun, co–principal investigator.

"We should stop thinking of these comparisons as yes-or-no phenomena, but start to think of where one target might be better than another and match our patients up so they can achieve optimal benefit," he said.

Six-month data on 45 of 52 patients (mean age 61 years) showed no significant difference between 22 STN and 23 GPi patients in seven of the eight subscales of the visual analog mood scale (VAMS), the primary outcome of the study. There was a significant difference between groups on the VAMS anger subscale; the mean change in anger scores was significantly larger with STN than with GPi (5.4 vs. –0.2).

Both groups reported significant improvements in VAMS scores on the tension and tiredness subscales, but the difference between groups was not significant.

Significant worsening of verbal fluency was seen in the STN group but not with GPi (–5.6 vs. 0.4). This was true whether the stimulator was on or off. The pattern of deterioration in the STN group preliminarily suggested a surgical or lesional effect rather than a stimulation-induced effect, said Dr. Okun, codirector of the movement disorders center at the University of Florida, Gainesville, and national medical director for the National Parkinson's Foundation.

Both groups reported being significantly less happy, less energetic, and more confused when stimulation was delivered ventrally or one contact below the optimal stimulation site.

No significant difference was found in motor improvement between the STN and GPi groups (mean 29.9% vs. 26.6%), while medication reduction trended in favor of STN; however, the study was not powered for these outcomes.

There were 95 surgical adverse events with STN vs. 67 with GPi. There was one death because of pneumonia in the STN group, said Dr. Okun, who has received speaking and consulting fees from the National Parkinson's Foundation and Medtronic Inc.

Full results of the COMPARE trial, which was funded by the National Institute of Neurological Disorders and Stroke and the University of Florida, are expected in the fall of 2008.

Additional level 1 evidence on DBS is expected later this year from the double-blind, prospective Deep Brain Stimulation for Parkinson's Disease trial comparing unilateral STN with GPi in 121 patients. Preliminary analysis of motor scores data at 6 months revealed no significant difference between the two target sites (STN and GPi), the trial's principal investigator, Dr. Jerrold Vitek of the Cleveland Clinic Foundation, said in an interview. Data verification is ongoing, and formal analyses will address a number of issues including neuropsychological and psychiatric functioning, quality-of-life parameters, and other secondary variables.

Patients were randomized based on motor symptom symmetry to determine if this factor can be used to decide whether patients require bilateral surgery or whether some may do well with just unilateral stimulation, thereby decreasing the risk and cost of treatment, he said. ■

DBS Improves Tic Severity in Tourette Syndrome Patients

BY PATRICE WENDLING
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CHICAGO — Deep brain stimulation of limbic relays within the basal ganglia circuitry reduced tic severity in patients with Tourette syndrome, according to data from a small double-blind, randomized crossover study.

In three patients with severe and medically refractory Tourette syndrome, researchers applied high-frequency bilateral deep brain stimulation to two structures that form part of the basal ganglia associative-limbic circuits—the centromedian-parafascicular complex (CM-Pf) of the thalamus and the ventromedial part of the globus pallidus interna (GPi).

Patients and investigators were blinded at evaluation to the four stimulation conditions—thalamic, pallidal, simultaneous thalamic and pallidal, and sham.

The greatest lessening of tics was achieved with ventromedial GPi stimulation, coinvestigator Dr. Luc Mallet said at the 12th International Congress of Parkinson's Disease and Movement Disorders. The total Yale Global Tic Severity Scale (YGTSS) score was reduced 65%, 96%, and 74% from baseline in patients 1, 2, and 3, respectively.

CM-Pf stimulation reduced tic severity by 64%, 30%, and 40%, respectively. Combining thalamic and pallidal stimulation did not improve tic reduction in the study (Arch. Neurol. 2008;65:952-7).

In patient No. 2, the best result was obtained after 1 month with stimulation, but the effects decreased after 2 months, even with increased voltage, said Dr. Mallet of Pitié-Salpêtrière Hospital, Paris.

Very good long-term effects were observed in patient No. 1, who was identified with borderline personality disorder before surgery.

The decrease in tic severity was accompanied by a dramatic reduction in self-injurious behaviors and impulsiveness, allowing the patient to start psychotherapy, to improve autonomy and social relationships, and to return to full-time work 2 years after surgery. Although tics are involuntary movements, they are influenced by emotional context, explained Dr. Mallet, who disclosed no conflicts of interest.

In patient No. 2, a stable reduction in tic severity was achieved 27 months after surgery using 20 hours of pallidal stimulation followed by 4 hours off. In patient 3, tic severity was reduced by 74% at 20 months without medication under pallidal and thalamic stimulation.

No neuropsychological, psychiatric, or other long-term adverse effects were observed.

The findings confirm those of open-label studies and case reports, and support the theory that Tourette results from dysfunction of the associative-limbic territories of the basal ganglia, Dr. Mallet said.

"We need further controlled studies to compare the two targets between the thalamus and the pallidum, but this is very encouraging for a proposed treatment for Tourette," he said.

There is a large French multicenter study underway to evaluate ventromedial GPi stimulation in patients with Tourette.

Ventromedial GPi stimulation may be more efficient than CM-Pf because the GPi is a key structure for the output nucleus of the main basal ganglia pathway, whereas the CM-Pf is part of an indirect, internal loop of the basal ganglia circuitry, according to the investigators.

The current study was also by Dr. Marie-Laure Welter and was sponsored by the French National Institute for Health and Medical Research, the University of Pierre and Marie Curie in Paris, and the Public Assistance Hospital of Paris. ■

DATA WATCH