DBS Beats Medication for Advanced Parkinson's

BY BETSY BATES
Los Angeles Bureau

SALT LAKE CITY — Deep brain stimulation surgery proved far more effective than medical therapy in a large, randomized Parkinson's disease trial in the United Kingdom, adding to mounting evidence that surgery is the best option for many patients with advanced disease.

The PD SURG trial randomized 366 patients with advanced disease to receive subthalamic nucleus deep brain stimulation (183 patients) or medical therapy (also 183) at centers located throughout the United Kingdom.

Interim results were reported at the annual meeting of the American Neurological Association by Dr. Adrian Williams, professor of clinical neurology at Queen Elizabeth Hospital, Birmingham (England) and coordinator of the trial.

"For 25%-30% of the patients, there was a very, very significant improvement in quality of life," he said in an interview at the meeting.

Patients enrolled in the trial had quite extensive disease, with 11 years' mean disease duration. Their main reasons for considering surgery were dyskinesia and severe off-periods, said Dr. Williams.

At 1 year, overall PDQ-39 (Parkinson's Disease Questionnaire) scores were unchanged in patients receiving medication alone, but improved 5.8 points on the 156-point scale in those who received surgery, a highly significant difference ($P = .0002$).

Within this scale, activities of daily living showed a particularly pronounced improvement in patients who underwent surgery, improving, on average 12 points among surgical patients but less than 1 point among patients receiving medical therapy, Dr. Williams noted.

A similarly significant, 8.5-point difference in scores on the 0- to 176-point Unified Parkinson's Disease Rating Scale (UPDRS) favored patients in the surgical arm.

A subset of patients had a dramatic response to surgery, Dr. Williams said.

Nearly a quarter of patients who underwent surgery showed 16-point or greater reductions in their overall PDQ-39 scores, compared with 2% of patients receiving medical therapy. These patients, he said, "tended to be a bit younger, with slightly more aggressive disease."

Their motor involvement tended to be profound at the onset of the study.

As in previous studies, some patients failed to show much improvement following surgery, suggesting the need for identifying clear predictive factors that can tailor interventions to those most likely to benefit, Dr. Williams said.

Surgery was not without risks, with 1% of patients dying and 1% suffering strokes in the surgery arm.

The cost of surgery was about double that of a years' worth of drug therapy, but the magnitude of improvement of some patients would certainly justify the cost.

Dr. Williams stressed the "real world" design of the trial, which attempted true randomization at regional centers rather than "cherry picking by patient or by surgeon." For ethical reasons, patients assigned to the medication arm of the study were offered surgery after 1 year.

The PD SURG trial was supported by the U.K. Medical Research Council and the Parkinson's Disease Society.

The study results parallel findings in two smaller, National Institutes of Health–sponsored trials, one performed with the Department of Veterans Affairs and one coordinated by researchers at the University of Florida, Gainesville. ■

Common Disorders Might Be Early Flags for PD Dementia

BY BETSY BATES
Los Angeles Bureau

SALT LAKE CITY — A number of novel risk factors—many sharing the common denominator of cholinergic dysfunction—emerged as potential early markers of dementia in Parkinson's disease in a longitudinal study of newly diagnosed patients.

Gastrointestinal, urologic, and cardiac disorders emerged as predictors in the massive DATATOP study, a project of the Parkinson Study Group. The study enrolled and extensively studied 740 newly diagnosed, untreated Parkinson's disease (PD) patients for more than 5 years.

The primary objective of the study was to compare deprenyl with tocopherol in the treatment of early PD, with deprenyl showing short-term benefit (Ann. Neurol. 1998;44:[S]160-6).

However, the large database also permitted examination of other questions, such as the progressive emergence of dementia in a relatively young, early-stage population. The mean age of DATATOP participants at enrollment was 61, and their Hoehn-Yahr Parkinson's disease stage averaged 1-2.5 on the 5-stage scale.

Dr. Ergun Y. Uc of the University of Iowa, Iowa City, reported the results in an oral presentation at the annual meeting of the American Neurological Association.

Dementia symptoms developed in 2.4% of 740 subjects in the first 2 years of follow-up and in 5.8% of subjects in the first 5 years, an incidence rate higher than that seen in the general population, but lower than what is usually seen in Parkinson's populations.

The annual incidence rate for dementia development in the group was 12.7 per 1,000. Baseline predictors of dementia included well-known risk factors such as older age, male gender, and Postural Instability and Gait Disorder (PIGD) score, as well as the predictable signal of lower scores on cognitive psychological tests at enrollment.

Several additional risk factors emerged as well, including gastrointestinal, urologic, and cardiac disorders; increased symmetry of Parkinsonism; and impairment of speech and swallowing (bulbar dysfunction).

Gastrointestinal dysfunction emerged as a surprisingly potent risk factor for dementia at an odds ratio of 2.28, just behind male gender, which had an odds ratio of 2.95. Urologic dysfunction was close behind at an odds ratio of 1.99. Increased symmetry of Parkinsonism conferred an odds ratio of 1.44. PIGD scores, at an odds ratio of 1.13, and total motor score, at 1.03, were less important risk factors in this population than previously believed, Dr. Uc said.

Baseline psychological tests such as total recall, delayed recall, and symbol-digit tests were, not surprisingly, the most important factors in predicting development of dementia, he continued.

"Subjects destined to be demented started out 1 standard deviation below normal," he said.

Despite practice effects, which would be expected to improve their scores, "by 4 years they dropped off the cliff," he said.

The average time-to-progression for dementia was 3.3 years after enrollment.

Demented subjects were more likely than other subjects to have a history of falls and gait disturbances, bulbar problems with speech, drooling and swallowing, and functional praxis (difficulties in writing, using utensils, dressing, personal hygiene functions, and turning in bed.)

Dr. Uc suggested that the multifaceted picture of dementia risk points to dysfunction in autonomic cholinergic neurotransmission as a promising target for diagnosis and prevention in patients with early-stage Parkinson's disease. ■

Targeted Deep Brain Stimulation Improves Tic Severity in Tourette

BY PATRICE WENDLING
Chicago Bureau

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, high-frequency bilateral deep brain stimulation was applied 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, said Dr. Mallet, who disclosed no conflicts of interest.

The findings back the theory that Tourette results from dysfunction of the associative-limbic territories of the basal ganglia.

DR. MALLET

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.

A large French multicenter study is 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, the investigators noted.

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. ■

Pages 14a—14b