Subthalamic Stimulation in Parkinson Disease

A Multidisciplinary Approach

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Background: High-frequency stimulation of the subthalamic nucleus constitutes a therapeutic advance for severely disabled patients with Parkinson disease.

Objective: To evaluate the efficacy and safety of continuous bilateral high-frequency stimulation of the subthalamic nucleus in patients with Parkinson disease.

Design: A prospective study of patients with Parkinson disease treated at a university hospital.

Patients and Methods: Electrodes were implanted bilaterally in the subthalamic nucleus of 23 consecutive patients with Parkinson disease who responded well to levodopa but had severe motor complications. There were 16 men and 7 women (mean ± SEM age, 53 ± 2 years) who had a mean ± SEM disease duration of 14.7 ± 1.0 years. Targets were determined by 3-dimensional magnetic resonance imaging, combined with intraoperative electrophysiologic recordings and stimulation.

Results: Six months after surgery, motor disability, levodopa-induced motor fluctuations, dyskinesias, and the daily dose of levodopa equivalent decreased significantly by 67%, 78%, 77%, and 61%, respectively, compared with the preoperative state. No significant morbidity was observed, except transient depression in 4 patients.

Conclusions: The beneficial effects of subthalamic stimulation depend on (1) the criteria used for patient selection, (2) the precision with which the subthalamic nucleus is targeted (dependent on the 3-dimensional magnetic resonance imaging and the intraoperative electrophysiologic and clinical assessments), and (3) the long-term postoperative adjustment of stimulation variables.

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Despite the development of new antiparkinsonian drugs, the management of advanced forms of Parkinson disease (PD) represents a therapeutic challenge. Recent improvement in the understanding of the anatomical-functioned organization of the basal ganglia has highlighted the crucial role played by the dysfunction of the internal globus pallidus and the subthalamic nucleus (STN) in the pathophysiological features of the disease. Alternative therapies, such as pallidotomy, have been proposed, indicating a renewed interest in functional stereotactic neurosurgery. Continuous high-frequency stimulation of the STN was recently reported to constitute a highly effective treatment of advanced forms of PD. This is confirmed in the present study. Electrodes were implanted bilaterally for continuous stimulation of the STN in 23 disabled patients with PD who were highly responsive to levodopa but had severe motor complications. The method associated 3-dimensional stereotactic magnetic resonance imaging (MRI) with intraoperative microelectrode recording and stimulation.

RESULTS

Six months after surgery, activities of daily living (UPDRS part II) improved by 66% (UPDRS part II score, from 30 ± 3 to 10 ± 2; P < .001) and 55% (UPDRS part II, from 11 ± 2 to 5 ± 1; P = .01) in the off and on drug conditions, respectively. The Hoehn and Yahr motor disability score in the off drug condition decreased by 58% (from 4.3 ± 0.2 to 1.8 ± 0.3; P < .001). The severity of motor fluctuations decreased by 78% (UPDRS part IVB score, from 4.5 ± 0.2 to 1.0 ± 0.3; P < .001) and dyskinesias by 77% (UPDRS part IVA score, from 7.0 ± 0.5 to 1.6 ± 0.4; P < .001). The daily dose of antiparkinsonian medication was reduced by 61% (levodopa...
PATIENTS AND METHODS

Between January 1, 1996, and December 31, 1998, 85 of the 500 patients with PD who were referred to Fédération de Neurologie, Paris, France, were considered for STN neurosurgery. Fifty-three are still awaiting surgery. We report the results of the first 23 consecutive patients (16 men and 7 women; mean age, 53 ± 2 years) after 6 months of clinical follow-up. At inclusion, all had an advanced form of the disease (Hoehn and Yahr score, while not taking medication, 4.3 ± 0.2; duration of the disease, 14.7 ± 1.0 years). Levodopa still effectively reduced parkinsonian motor disability, which improved by more than 60% according to part III of the Unified Parkinson’s Disease Rating Scale (UPDRS)\(^5\) following the administration of a single dose of levodopa (usual morning dose of levodopa plus 30 mg). Despite optimized drug treatment based on a combination of levodopa and dopamine agonists (daily dosage of levodopa equivalent to 1340 ± 120 mg),\(^6\) all patients had disabling motor fluctuations (UPDRS part IVB score, 4.5 ± 0.3) and levodopa-induced abnormal involuntary movements (UPDRS part IVA score, 7.0 ± 0.5). None of the patients had cognitive decline, major depression, or significant abnormalities on a brain MRI scan. All patients gave informed written consent, and the protocol received the approval of the local ethics committee.

Forty-six electrodes were implanted according to our standard procedure.\(^3,\(^4\) Briefly, the surgical procedure was planned based on a preoperative 3-dimensional T1-weighted MRI scan, performed stereotactically with a Leksell frame fixed to the patient’s head. The STN was visualized directly on multiplanar reformatted coronal T2-weighted images. The coordinates of the center of the nucleus were first determined using the T2-weighted images with respect to the posterior and anterior commissures and then transcribed to stereotactic coordinates of the frame using the 3-dimensional T1-weighted acquisition. A double oblique extraventricular trajectory was used to avoid blood vessels visualized by 3-dimensional preoperative angiographic MRI. Surgery was performed under local anesthesia. Neuronal activity was recorded, and the effects of high-frequency (130-Hz) stimulation were assessed with 5 exploratory electrodes implanted in a 250-mm\(^3\) volume around the MRI-defined target.\(^2,\(^7\) The optimal functional target was defined by the pattern of electrical activity characteristic of the STN\(^8\) and the effectiveness with which the lowest intensity stimulation decreased parkinsonian signs without inducing adverse effects. The definitive quadripolar electrodes (model 3389-28; Medtronic, Minneapolis, Minn) were implanted bilaterally, during the same surgical session, using the same procedure. The operation lasted from 7 to 12 hours (mean, 9 hours). An MRI scan of the brain was performed the day after surgery to identify the final position of the electrodes. Within 5 days, the electrodes were connected to a subcutaneous programmable pulse generator (model ITREL II; Medtronic) in the subclavicular area. The choice of the electrode contacts used for stimulation (4 contacts per electrode covering a distance of 7.5 mm), frequency (0-185 Hz), amplitude (0-10.5 V), and pulse width (60-420 microsecond) were fine-tuned by telemetry in view of continuous stimulation.

Clinical evaluations were performed the month before and 6 and 12 months after surgery. Before surgery, the patients were evaluated while taking and while not taking medication (referred to as on and off medication) with the motor score of the UPDRS: the off medication state (the baseline score) was defined by withdrawal of antiparkinsonian drugs for at least 12 hours; the on medication state evaluation was performed after a single dose of levodopa (100-300 mg, the patient’s usual morning dose, plus 50 mg) when parkinsonian signs were maximally improved. After surgery, patients were examined in 4 conditions: off medication and off stimulation, after stimulation was stopped for 12 hours; off medication and on stimulation, after stimulation was turned on for half an hour; on medication and off stimulation; and on medication and on stimulation. The off and on drug conditions were similar to those before surgery.

Results were expressed as mean ± SEM. Data were analyzed using the paired t test or the Mann-Whitney rank sum test. \(P \leq 0.05\) was considered statistically significant.

equivalent, 520 ± 120 mg; \(P < 0.01\)). There was no further need for drug treatment in 3 patients. In the 23 patients, continuous monopolar stimulation at 2.7 ± 0.4 V was applied through 1 (\(n = 40\)) or 2 (\(n = 6\)) contacts of the 46 electrodes, with a frequency of 155 ± 29 Hz and a pulse width of 60 (\(n = 43\)) or 90 (\(n = 3\)) microsecond.

The effects of the administration of a single dose of levodopa on parkinsonian motor disability (UPDRS part III) before and after surgery, with and without bilateral optimal stimulation of the STN, are shown in the Figure. Before surgery, levodopa induced a 71% improvement in the parkinsonian motor score. After surgery, the patients were first examined after stimulation was stopped for 12 hours (off stimulation); the motor scores off levodopa for more than 12 hours and on levodopa at the time of maximal clinical improvement were not significantly different from those estimated before surgery. When evaluated after stimulation had been turned on for half an hour (on stimulation), the motor scores on stimulation and off levodopa were not different from those observed after the administration of levodopa in the absence of STN stimulation (off stimulation and on levodopa), but improved by 67% compared with the baseline score (off medication) before surgery. The administration of levodopa during stimulation resulted in an improvement of 81% compared with the baseline score before surgery, which was significantly better than without levodopa. In the 11 patients who were followed up for 12 months after surgery, the UPDRS scores (parts II, III, and IV) were similar to those obtained at 6 months (not shown).

No adverse events, such as hemorrhage, infarction, or infection, occurred as a direct result of surgery, except for a subdural aeroma in most patients. At the end of the implantation procedure, 3 patients experienced a confusional state that spontaneously resolved within 1 day. Transient adverse effects directly related to stimu-
Evaluation were observed in all patients. Abnormal involuntary movements, such as chorea, ballismus, or dystonia, were observed during stimulation through the electrode contacts that improved parkinsonian disability (“therapeutic contacts”). The severity of dyskinesias increased as the intensity of the stimulation increased. They appeared, however, at a voltage threshold that was higher than those that improved parkinsonian motor symptoms and could, therefore, be avoided. The threshold of appearance of the dyskinesias varied among the patients but tended to increase with time after surgery in most. In 2 patients, stimulation alone (on stimulation and off levodopa) afforded less improvement than levodopa alone (off stimulation and on levodopa) (Figure). In one of these patients, the brain MRI scan showed that the electrodes were 1 mm medial to each STN. In the other patient, the left electrode was located at the periphery of the posterior part of the STN, whereas the tip of the right electrode was dorsal to the STN (not shown). In a third patient, the moderate camptocormia, festinating gait, and hypophonia observed before surgery were not improved, although stimulation with and without levodopa provided a 58% and a 71% improvement, respectively, in the baseline parkinsonian motor score (UPDRS part III). Stimulation through contacts that did not improve parkinsonian disability produced miscellaneous adverse effects, the most common of which were paresthesia, dysarthria, dystonic contractions, and diplopia. All these adverse events were transient and reversible when voltage was reduced or the stimulator was switched off. The results of a neuropsychological evaluation revealed no significant changes 6 months after electrode implantation (the detailed evaluations are reported elsewhere). Despite major improvements in parkinsonian motor disability, 4 patients experienced depression within the 2 months that followed surgery. Depression was severe in 2 patients (with a suicide attempt in 1) and moderate in the other 2, and disappeared in 3 patients after 2 months of treatment with antidepressant serotonin reuptake inhibitors and in 1 patient after the electrical variables were changed.

In our series of patients, bilateral high-frequency stimulation of the STN produced a lasting improvement in parkinsonian motor disability, significantly decreased the doses of antiparkinsonian drugs needed, and markedly reduced motor adverse effects. The results are comparable with those reported by others (Table). The clinical characteristics of the patients did not differ markedly from those in the other series. The patients in the Toronto, Ontario, study were older, and those in the Rome, Italy, cohort had more of a disability. Ventriculography, MRI, or both were used by all, and intraoperative microelectrode recordings by all but one. The differences in technique may, however, explain why the degree of improvement was variable: 33% to 67% for parkinsonian motor disability, 73% to 83% for fluctuations of motor performances, and 64% to 88% for dyskinesias (Table). No vascular complications (intracerebral hematomas or cortical venous infarcts) were observed in our patients, probably because the trajectory of the electrodes was chosen to avoid the major blood vessels and ventricles visualized by preoperative stereotactic 3-dimensional angiographic MRI. Mild and transient adverse effects, however, were observed in a few patients. The origin of the brief confusional state observed in 3 patients during the postoperative period is not known, although the unavoidable exhaustion related to prolonged antiparkinsonian drug withdrawal and the presence of a subdural aeroma may have contributed. The abnormal involuntary movements observed were reversible when stimulation through the optimal therapeutic contact was decreased or stopped. This indicates that the dyskinesias were caused by direct inactivation of the STN. These STN stimulation-induced dyskinesias appear, therefore, to be correlated to the clinical benefit. With time, under continuous treatment by subthalamic stimulation, the voltage threshold at which dyskinesias appeared increased, allowing higher voltages to be used to improve motor disability. This may be a consequence of the reduction in antiparkinsonian drug treatment. Although the pathophysiological basis underlying the change in the susceptibility of subthalamic stimulation to induce dyskinesias is unknown, this observation suggests that continuous high-frequency subthalamic stimulation results in a more physiologic functioning of the basal ganglia. Other stimulation-induced adverse effects, such as paresthesia, were most likely caused by stimulation outside the STN since they were observed with voltages higher than those needed to reduce parkinsonian motor disability.
Given a marked motor improvement and the absence of previous psychiatric disorders, the depression observed in 4 of the 23 patients in the months following surgery is difficult to explain. Levodopa withdrawal or the sudden and dramatic changes in daily living that resulted from an almost total alleviation of parkinsonian disability might be evoked, but a consequence of the stimulation procedure itself cannot be ruled out. We have previously reported a case of acute major depression in a patient when stimulation was delivered in the substantia nigra below the site where stimulation improved parkinsonian symptoms.16 These observations indicate that electrode implantation should be avoided in patients with histories of active depression, and that patients who develop depression after surgery should receive specific treatments if modification of the stimulation variables does not suffice.

CONCLUSIONS

On the strength of our experience, we would like to stress that each step of the stereotactic procedure, from patient selection to the fine-tuning of the stimulation variables, is essential if subthalamic stimulation is to provide optimal results. The choice of appropriate candidates for this neurosurgical procedure is a major issue. Since STN stimulation primarily improves levodopa-responsive motor signs, only patients with severe parkinsonian features markedly improved by levodopa treatment and with severe levodopa-induced motor complications should be selected for the operation, in the absence of other contraindications.6 Selection of patients needs to be conducted with care by experienced neurologists in close cooperation with the other partners of the surgical team. The precision of the targeting is another key issue. Guidance by 3-dimensional stereotactic MRI is a great help in placing the electrodes.3 Direct visualization of the STN on T2-weighted images has shortened the intraoperative electrophysiologic and clinical investigations, likely explaining the reduced duration of the surgical procedure (Table). Despite improvement in MRI identification of the anatomical target, determination of the functional target by analysis of the intraoperative electrophysiologic recordings8 and evaluation of the effects of stimulation on parkinsonian symptoms2 are still mandatory. After surgery, the neurologist has the arduous task of determining the optimal variables of stimulation to be used to continuously treat the patient, to adjust (and if possible to withdraw) antiparkinsonian drug treatment to maintain optimal efficacy. The prerequisite for initiating this new therapeutic approach to PD is to constitute a multidisciplinary medical team, including experienced and well-trained neurosurgeons, neuroradiologists, neurophysiologists, and neurologists.

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REFERENCES