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KRACK, Paul, *et al*.

ORIGINAL ARTICLE

Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease

Paul Krack, M.D., Ph.D., Alina Batir, M.D., Nadège Van Blercom, M.D., Stephan Chabardes, M.D., Valérie Fraix, M.D., Claire Ardouin, M.A., Adnan Koudsie, M.D., Patricia Dowsey Limousin, M.D., Ph.D., Abdelhamid Benazzouz, Ph.D., Jean François LeBas, M.D., Ph.D., Alim-Louis Benabid, M.D., Ph.D., and Pierre Pollak, M.D.

ABSTRACT

BACKGROUND

Although the short-term benefits of bilateral stimulation of the subthalamic nucleus in patients with advanced Parkinson's disease have been well documented, the long-term outcomes of the procedure are unknown.

METHODS

We conducted a five-year prospective study of the first 49 consecutive patients whom we treated with bilateral stimulation of the subthalamic nucleus. Patients were assessed at one, three, and five years with levodopa (on medication) and without levodopa (off medication), with use of the Unified Parkinson's Disease Rating Scale. Seven patients did not complete the study: three died, and four were lost to follow-up.

RESULTS

As compared with base line, the patients' scores at five years for motor function while off medication improved by 54 percent ($P<0.001$) and those for activities of daily living improved by 49 percent ($P<0.001$). Speech was the only motor function for which off-medication scores did not improve. The scores for motor function on medication did not improve one year after surgery, except for the dyskinesia scores. On-medication akinesia, speech, postural stability, and freezing of gait worsened between year 1 and year 5 ($P<0.001$ for all comparisons). At five years, the dose of dopaminergic treatment and the duration and severity of levodopa-induced dyskinesia were reduced, as compared with base line ($P<0.001$ for each comparison). The average scores for cognitive performance remained unchanged, but dementia developed in three patients after three years. Mean depression scores remained unchanged. Severe adverse events included a large intracerebral hemorrhage in one patient. One patient committed suicide.

CONCLUSIONS

Patients with advanced Parkinson's disease who were treated with bilateral stimulation of the subthalamic nucleus had marked improvements over five years in motor function while off medication and in dyskinesia while on medication. There was no control group, but worsening of akinesia, speech, postural stability, freezing of gait, and cognitive function between the first and the fifth year is consistent with the natural history of Parkinson's disease.

From the Departments of Clinical and Biological Neurosciences (P.K., A. Batir, N.V.B., S.C., V.F., C.A., A.K., P.D.L., A. Benazzouz, A.-L.B., P.P.) and Magnetic Resonance Imaging (J.F.L.), Joseph Fourier University, Grenoble, France. Address reprint requests to Dr. Krack at the Department of Clinical and Biological Neurosciences, Département de Neurologie, Centre Hospitalier Universitaire de Grenoble, BP 217, 38043 Grenoble CEDEX 9, France, or at paul.krack@ujf-grenoble.fr.

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Levodopa is the standard treatment for Parkinson's disease but causes long-term motor complications despite other pharmacologic interventions.[1] In 1998, we reported that the first series of patients with Parkinson's disease who were treated with bilateral stimulation of the subthalamic nucleus[2] had improvement in motor function while off medication one year after surgery. We also reported an associated improvement in on-medication dyskinesia and off-medication dystonia.[3,4] These findings have been confirmed by other groups,[5,6] but little information about the long-term outcome of this therapy has been published. We report here the results of a five-year prospective cohort study of the first 49 patients with advanced Parkinson's disease whom we treated in our center with bilateral stimulation of the subthalamic nucleus.

METHODS

PATIENTS

We studied the first 49 consecutive patients who received implants at our institution from 1993 through 1997 for bilateral stimulation of the subthalamic nucleus. The selection criteria were clinically diagnosed Parkinson's disease, severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication, an age under 70 years, no surgical contraindications, and no dementia or major ongoing psychiatric illness. The ethics committee of Grenoble University, in France, approved the study, and all the patients gave written informed consent.

SURGERY

We located the subthalamic nucleus by contrast ventriculography, magnetic resonance imaging (MRI), and electrophysiological recordings and stimulation. The quadripolar electrodes (DBS 3387 and 3389, Medtronic) were implanted bilaterally in a single operation in all but the first three patients, in whom the second electrode was implanted from 1 to 12 months after the first. All patients underwent MRI postoperatively for the assessment of surgical complications. A few days after implantation of the electrodes, a programmable pulse generator (Itrel II, Medtronic) was implanted subcutaneously on each side of the brain while the patients were under general anesthesia. Stimulation settings and medication were progressively adjusted.

ASSESSMENTS

Patients were evaluated preoperatively and postoperatively at one, three, and five years with use of the Unified Parkinson's Disease Rating Scale.[7] Unblinded assessments were performed when patients had taken no medication for 8 to 12 hours (off medication)[8] and during periods of maximal clinical benefit after the administration of a dose of liquid levodopa that was 50 percent higher than the usual morning dose of dopaminergic treatment (on medication).[9] Postoperatively, patients were assessed during stimulation.

Neuropsychological tests included the Mattis Dementia Rating Scale[10] for global cognitive assessment and an assessment of frontal-lobe dysfunction.[11] Mood was assessed with the Beck Depression Inventory.[12] In addition, patients were interviewed annually by the same neuropsychologist, a method that permitted detailed assessment of behavioral abnormalities. Apathy was diagnosed according to the definition of Marin,[13] and dementia according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[14]

STATISTICAL ANALYSIS

The primary outcome measures were the scores on part II (activities of daily living) and part III (motor examination) of the Unified Parkinson's Disease Rating Scale at base line and at the clinical end points of one year, three years, and five years. The secondary outcome measures were the subscores on part III (limb tremor, limb rigidity, limb akinesia, speech, postural stability, and gait) and part IV (the dyskinesia items) of the Unified Parkinson's Disease Rating Scale, the scores on the Schwab and England scale of global activities of daily living,[15] the results of neuropsychological tests, and the dose of dopaminergic treatment and stimulation settings at one year, three years, and five years.

Data are presented as means ±SD. Repeated-measures analysis of variance was used to predict motor scores on the basis of two independent variables: medication status (on or off medication), and time (length of follow-up). So as to avoid a type I error when conducting multiple analyses over time, a P value of 0.005 was considered to indicate statistical significance with use of the Bonferroni correction method. For post hoc comparisons of base-line data with data at year 1 and at year 5, we used the Student's t-test or the Wilcoxon signed-rank test.

RESULTS

Table 1 shows the characteristics of the patients at base line. Of the 49 patients who underwent bilateral stimulation of the subthalamic nucleus, 7 could not be evaluated at five years: 3 patients died and 4 were lost to follow-up (2 lived overseas and 2 were unable to return for the five-year follow-up for personal reasons).

Table 1. Base-Line Characteristics of the 49 Patients.*

Characteristic	Value
Sex (no. of patients)	
Male	24
Female	25
Age (yr)	
Mean	55.0±7.5
Range	34–68
Duration of disease (yr)	14.6±5.0
Levodopa plus decarboxylase-inhibitor therapy (no. of patients)	49
Dose of levodopa (mg/day)	1100±567
Dopamine-agonist therapy (no. of patients)	43
Dose of levodopa-equivalent medication (mg/day)†	1409±605

* Plus–minus values are means ±SD.
† The dose of levodopa-equivalent medication was calculated as the dose of dopamine agonist plus levodopa.[6]

OFF-MEDICATION EVALUATION

With stimulation in the off-medication state, the total score on part III of the Unified Parkinson's Disease Rating Scale, a standardized evaluation of all the motor signs of the disease, improved from the base-line value (55.7±11.9) by 66 percent at one year, 59 percent at three years, and 54 percent at five years. (Scores on the scale range from 0 to 108, and a reduction in scores indicates an improvement in function.) As compared with base line, at five years the scores for tremor improved by 75 percent, those for rigidity by 71 percent, and those for akinesia by 49 percent (Table 2). Postural stability and gait also improved. The score for speech improved only during the first year and then progressively worsened, returning to the base-line score at five years.

In comparison with the base-line score (30.4± 6.6), the total score with stimulation on part II of the Unified Parkinson's Disease Rating Scale (which assesses activities of daily living; range of scores, 0 to 52) improved by 66 percent at one year, 51 percent at three years, and 49 percent at five years; the worsening between one year and five years was significant ($P<0.001$) (Table 2). All changes from base line to one year indicated an improvement in parkinsonism, and all changes from one to five years a worsening. The scores on the Schwab and England scale, which measures activities of daily living, range from 0 to 100 percent (with 100 percent indicating normal function). The scores dramatically improved postoperatively in the off-medication condition (Fig. 1). Five years after surgery, most patients were independent in their activities of daily living in the off-medication condition (mean score on the Schwab and England scale, 73 percent), whereas before surgery most had been fully dependent on a caregiver (mean score on the Schwab and England scale, 33 percent). Before surgery, 35 of the 49 patients (71 percent) had painful dystonia while off medication; 8 of 43 patients (19 percent) had dystonia at one year, and 14 of 42 patients (33 percent) had dystonia at five years.

ON-MEDICATION EVALUATION

A levodopa test could not be performed in two patients at three years and in three patients at five years who had stopped dopaminergic treatment. These patients could not tolerate a levodopa challenge. For the remaining patients, motor function and activities of daily living in the on-medication state did not improve after stimulation of the subthalamic nucleus. Between the first and the fifth year, there were no significant changes in individual scores for tremor and rigidity, but scores for akinesia, speech, postural stability, and freezing of gait worsened ($P<0.001$ for each comparison), resulting in a worsening of the total score for motor function ($P<0.001$) and the total score for activities of daily living ($P<0.001$), as assessed on the Unified Parkinson's Disease Rating Scale. Activities of daily living as assessed by the Schwab and England scale were unchanged. Compared with base line, the severity of the disability related to dyskinesia decreased by 58 percent, and the duration of dyskinesia by 71 percent (Table 3).

NEUROPSYCHOLOGICAL EVALUATION

There were no significant changes on the Beck Depression Inventory (maximal score, 63; a higher score indicates more severe depression). The average score on the Mattis Dementia Rating Scale (maximal score, 144; a higher score indicates better function) was worse at five years, reflecting progres-

Table 2. Effect of Bilateral Stimulation of the Subthalamic Nucleus on Off-Medication UPDRS Subscores.*

Subscale	Range of Possible Scores	Base Line (N=49)	1 Year after Surgery (N=43)	3 Years after Surgery (N=42)	5 Years after Surgery (N=42)	P Value	
		Score				5 Years after Surgery vs. Base Line	5 Years after Surgery vs. 1 Year after Surgery
Motor examination							
Total	0–108	55.7±11.9	19±11.1	22.8±11.6	25.8±12.3	<0.001	<0.001
Tremor	0–28	5.2±4.8	1.3±1.8	0.9±1.5	1.3±1.7	<0.001	0.91
Rigidity	0–20	13.4±3.4	3.6±3.5	3.5±2.0	3.9±3.0	<0.001	0.52
Akinesia	0–32	18.5±5.7	6.9±5.8	8.8±5.7	9.5±6.2	<0.001	0.004
Speech	0–4	1.9±1.0	1.3±1.0	1.8±1.0	1.9±1.0	0.56	<0.001
Postural stability	0–4	2.5±0.9	0.9±0.9	1.3±0.9	1.4±1.0	<0.001	0.09
Gait	0–4	3.1±0.8	1.0±1.0	1.2±1.1	1.5±1.1	<0.001	0.04
Activities of daily living							
Total	0–52	30.4±6.6	10.3±6.9	14.8±6.0	15.6±8.5	<0.001	<0.001
Writing	0–4	3.5±0.7	2.2±1.2	2.6±1.2	2.2±1.4	<0.001	0.72
Freezing of gait	0–4	2.6±0.2	0.7±1.0	1.3±1.2	1.4±1.2	<0.001	<0.001

* Plus–minus values are means ±SD. UPDRS denotes the Unified Parkinson's Disease Rating Scale. A reduction in scores indicates an improvement in function. Off-medication evaluations were performed when the patient had taken no antiparkinsonian medications for 8 to 12 hours. Writing and freezing of gait are complex motor functions that are not represented in the motor scores.

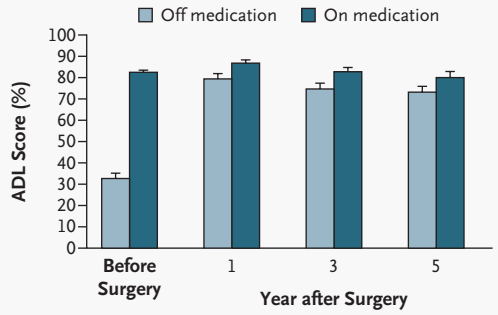

Figure 1. Off-Medication and On-Medication Scores on the Schwab and England Scale for Activities of Daily Living (ADL) at Base Line and One, Three, and Five Years after Surgery.

Data are means ±SD. After surgery, evaluation was performed with bilateral stimulation activated. Scores range from 0 to 100 percent (with a score of 100 percent indicating normal function). A score above 70 percent indicates complete independence in activities of daily living. A score of 70 percent or lower indicates that patients need the help of a caregiver. Off-medication scores were improved at one, three, and five years (P<0.001 for all three comparisons).

sive dementia in three patients according to DSM-IV criteria (Table 4), but the changes were not significant (131±18 vs. 136±10 at base line, P=0.07). The average score for frontal-lobe function (maximal score, 50; a higher score indicates better function) tended to be worse at five years (37.3±11.2 vs. 40.4±9.2 at base line, P=0.03).

MEDICATIONS AND STIMULATION SETTINGS

Postoperatively, the requirement for levodopa (or equivalent medication) decreased significantly, from a levodopa-equivalent daily dose of 1409±605 mg at base line to 584±366 mg at one year, 526±328 mg at three years, and 518±333 mg at five years (P<0.001, by analysis of variance). At five years, 11 of 42 patients were no longer taking levodopa and 3 were not taking any dopaminergic drugs. After the first year, there were no significant changes in voltage (one year, 2.8±0.6 V; five years, 3.1±0.4 V; P=0.007, by analysis of variance), frequency (one year, 143±19 Hz; five years, 145±19 Hz), or pulse width (one year, 61±6 μsec; five years, 64±12 μsec). Monopolar stimulation with the use of a single contact from the quadripolar electrode was applied in

Table 3. Effect of Bilateral Stimulation of the Subthalamic Nucleus on On-Medication UPDRS Subscores.*

Subscale	Range of Possible Scores	Base Line (N=49)	1 Year after Surgery (N=43)	3 Years after Surgery (N=40)	5 Years after Surgery (N=39)	P Value	
		Score				5 Years after Surgery vs. Base Line	5 Years after Surgery vs. 1 Year after Surgery
Motor examination							
Total	0–108	14.3±7.0	11.4±8.9	15.3±9.5	21.1±12.2	0.003	<0.001
Tremor	0–28	0.4±0.8	0.4±0.8	0.1±0.5	0.2±0.5	0.07	0.17
Rigidity	0–20	3.6±2.7	2.1±2.9	2.2±2.9	2.8±2.7	0.27	0.09
Akinesia	0–32	4.4±3.6	3.7±4.4	6.3±5.4	8.4±6.7	0.001	<0.001
Speech	0–4	0.8±0.6	0.9±0.7	1.4±0.9	1.8±0.7	<0.001	<0.001
Postural stability	0–4	1.0±0.7	0.7±0.7	1.0±0.8	1.3±0.9	0.08	<0.001
Gait	0–4	0.5±0.6	0.6±0.8	0.8±1.0	1.0±0.9	0.02	0.04
Activities of daily living							
Total	0–52	7.3±4.2	7.4±4.8	10.7±6.4	14.0±7.0	<0.001	<0.001
Writing	0–4	1.7±1.1	2.0±1.2	2.2±1.2	2.4±1.4	0.008	0.04
Freezing of gait	0–4	0.3±0.7	0.3±0.6	0.7±1.0	1.2±1.2	<0.001	<0.001
Motor complications							
Duration of dyskinesia	0–4	2.1±1.1	0.6±0.9	0.6±0.9	0.6±0.9	<0.001	0.94
Dyskinesia disability	0–4	1.9±0.8	0.7±0.8	0.6±0.6	0.8±0.8	<0.001	0.65

* Plus–minus values are means ±SD. UPDRS denotes the Unified Parkinson's Disease Rating Scale. A reduction in scores indicates an improvement in function. On-medication evaluations were performed during periods of maximal clinical benefit after administration of a suprathreshold dose of levodopa. The numbers of patients who were evaluated in the on-medication and off-medication condition vary because some patients who could stop all dopaminergic treatment postoperatively did not tolerate a levodopa challenge. Duration of dyskinesia represents the portion of the waking day spent with dyskinesia, and dyskinesia disability represents the severity of the dyskinesia as assessed subjectively by the patient.

Table 4. Neuropsychological Evaluation.*

Neuropsychological Test	Base Line		1 Year after Surgery		3 Years after Surgery		5 Years after Surgery		P Value
	No. Tested	Score	No. Tested	Score	No. Tested	Score	No. Tested	Score	
Mattis Dementia Rating Scale	44	136±10	43	135±10	40	136±6	40	131±18	0.07
Beck Depression Inventory	37	15.5±7.3	40	13.4±8.8	39	14.6±9.4	35	14.9±8.3	0.88
Frontal-lobe function	48	40.4±9.2	43	38.7±9.5	40	39.3±10.2	34	37.3±11.2	0.03

* Plus–minus values are means ±SD. Not all patients were evaluated with all the neuropsychological tests at every follow-up visit. On the Mattis Dementia Rating Scale (maximal score, 144) and the frontal-lobe test (maximal score, 50), a higher score indicates better function. On the Beck Depression Inventory (maximal score, 63), a higher score indicates more severe depression. The frontal-lobe test evaluates executive functions that are typically impaired in Parkinson's disease, as demonstrated by the mean base-line score of 40 out of a possible 50, which indicates a mild deterioration in frontal executive functions. Base-line scores on the Mattis Dementia Rating Scale, a global measure of cognitive function, are within the normal range. P values were determined by analysis of variance.

Table 5. Adverse Events Associated with Subthalamic Stimulation.*

Type of Adverse Event†	Transient	Permanent
	number	
First three postoperative months (n=49)		
Related to procedure		
Ballism	1	0
Asymptomatic bleeding detected on MRI	8	0
Intracerebral hemorrhage	0	2
Head trauma (fall in hospital)	0	1
Contusion	3	0
Dementia	0	2
Delirium	12	0
Seizures	2	0
General health complications	6	0
Wound healing problem	4	0
Related to device		
Skin erosion with infection	1	0
Stimulator repositioning	2	0
Related to treatment		
Disabling dyskinesia	NA	4
Weight gain	NA	41 (Mean, 3 kg; maximum, 5 kg)
Eyelid-opening apraxia	0	15
Depression	1	0
Apathy	0	1
Impulsive aggressive behavior	1	0
Hypomania	4	1

90 percent of patients at one year and five years. With these settings, the stimulators had to be replaced in the first five years in only one patient.

ADVERSE EVENTS

There were three deaths. One patient in whom an intracerebral hemorrhage developed during surgery remained bedridden[2] and died three years after surgery. Another patient died of myocardial infarction 11 months after surgery. One patient was severely depressed and had suicidal ideation three months before surgery and committed suicide six months after surgery.

Surgical complications were frequent but mostly temporary (Table 5). Permanent side effects included dementia in two patients. Transient postoperative delirium, ranging from temporospatial disorientation to psychosis, occurred in 12 patients (24 percent) during the first few days after surgery. Device-related complications were rare. One patient had an infection that required temporary removal of the subcutaneous extension lead and pulse generator.

Treatment-related side effects changed with time during the follow-up. At three months, 4 patients, and at five years, 2 patients indicated that they still had disabling dyskinesia (related to dopaminergic treatment, subthalamic stimulation, or both) as compared with 29 patients at base line. Fifteen of 49 patients (31 percent) had eyelid-opening apraxia in the first three months, and this remained a problem in 8 of 42 patients (19 percent) for the duration of follow-up. In the first three months, reversible stimulation-induced dyskinesias commonly developed in patients after an increase in voltage. In the long term, base-line dyskinesias improved.[3,4]

During the first three months after surgery, 41 patients gained weight (mean, 3 kg; maximum,

Table 5. (Continued.)

Type of Adverse Event†	Transient	Permanent
	number	
From three months until five years after surgery (n=42)‡		
Related to device		
Stimulator repositioning	1	0
Related to stimulation		
Eyelid-opening apraxia	0	8
Disabling dyskinesia	5	2
Weight gain	0	39 (Mean, 4 kg; maximum, 16 kg)
Tetanic muscle contraction	0	2
Dysarthria	2	2
Hilarity	1	0
Related to treatment or disease		
Depression	7	0
Suicide attempts	3	0
Hallucinations	2	3
Psychosis	1	0
Dementia	0	3
Apathy	2	5

* Data are expressed as numbers of complications; some patients had more than one adverse event. MRI denotes magnetic resonance imaging, and NA not assessed.

† Ballism is severe dyskinesia of the proximal limbs. Disabling dyskinesia is defined as a score on the dyskinesia disability item of the Unified Parkinson's Disease Rating Scale that is greater than 2 (range, 0 to 4), indicating interference with motor function, as assessed at base line, three months, one year, three years, or five years. Transient worsening of dyskinesia after changes in medication or stimulation were not systematically assessed. Eyelid-opening apraxia refers to an involuntary forceful closure of the eyelids. Tetanic muscle contraction indicates tonic muscle contractions that can be restricted to a single muscle or that include larger muscle groups leading to an abnormal posture. (This side effect is related to diffusion of the current to the pyramidal tract. Dysarthria, similarly, can be related to diffusion of the current to corticobulbar fibers.)

‡ Three patients died during the follow-up period, and four were lost to follow-up.

5 kg). Patients on average gained another kilogram within the first year; thereafter, weight was stable. In the immediate postoperative period, transient hypomania developed in 8 percent of the patients. With longer follow-up, other psychiatric disorders occurred, including transient depressive episodes (17 percent) and transient apathy (5 percent), which were responsive to antidepressants, an increase in dopaminergic medication, or both. Permanent apathy occurred in the immediate postoperative period in one patient, who was dependent on levodopa and in whom the dose of levodopa was drastically decreased after surgery. Apathy that did not respond to dopaminergic treatment occurred in five patients (12 percent), as did dementia in three patients (7 percent) between the third year and the fifth year of follow-up.

DISCUSSION

In patients with advanced Parkinson's disease who were followed prospectively, long-term bilateral stimulation of the subthalamic nucleus led to significant postoperative improvements in all parkinsonian motor signs that were assessed while the patients were off dopaminergic medication except speech. The improvements over base line were sustained five years after surgery. Tremor and rigidity improved substantially at one year and remained stable at five years. Akinesia also improved at one year, but this improvement was not completely sustained over time. Painful off-period dystonia disappeared at five years in most patients. Five years after surgery, most patients were independent in their activities of daily living when assessed off medication.

Before surgery, all patients had depended on a caregiver.

When the patients were assessed while receiving dopaminergic medication, the duration of dyskinesia and the severity of the associated disability substantially decreased at one year and remained stable at five years. However, on-medication motor signs of parkinsonism were not improved after surgery; akinesia, speech, postural stability, and freezing of gait all worsened between years 1 and 5. This decline was reflected in a mild deterioration in the scores for activities of daily living in the on-medication state, despite the ongoing reduction in the duration and severity of dyskinesia.

The deterioration when the patients were on medication in axial symptoms, including speech, postural stability, and freezing of gait, is characteristic of the natural history of Parkinson's disease[16] and has been attributed to the increasing severity of cerebral nondopaminergic lesions.[17] The effect of levodopa on akinesia, rigidity, and tremor tends to remain stable over time,[17,18] whereas gait, postural stability, and dysarthria worsen and become less responsive to levodopa. Since we did not have a simultaneously treated control group, we speculate that the deterioration that we observed in our patients is what one would have expected in the absence of specific treatment.

We reduced the dose of dopaminergic medication during the first year and kept it stable thereafter. Stimulation settings were stable after the first year and throughout the study period, indicating that clinically important tolerance to stimulation does not develop in patients who undergo such treatment.

The frequency of symptomatic hematomas in this cohort is similar to that reported in patients who undergo microelectrode-guided stereotactic neurosurgery.[19] Although high rates of complications such as electrode fracture, electrode dislocation, and stimulator malfunction have previously been reported with deep-brain stimulation,[20,21] no clinically significant problems related to the hardware occurred in our cohort, except for inadvertent and reversible deactivation of the stimulator.

Five patients had cognitive decline: two immediately after the surgery, and three in whom progressive dementia developed between the third and fifth postoperative years. In the remaining patients, the dementia score remained stable. Because stimulation has no clinically relevant effects on cognition,[11,22] the cases of progressive cognitive deterioration probably reflect the natural history of long-standing Parkinson's disease.

Psychiatric problems, including depression or mania, have been reported by several groups in patients treated with stimulation of the subthalamic nucleus.[23-26] These complications may be related to preexisting psychiatric illness, surgery-related stress, changes in medication, alterations in social life that are associated with improvements in motor function, and the mismatch between the final outcome of treatment and the patient's expectations.[23] Changes in the limbic circuit may also contribute to psychiatric problems.[27] Hypomania occurred in five cases, all in the immediate postoperative period, and may be explained by the synergistic psychotropic effects of stimulation of the subthalamic nucleus and levodopa.[27] In contrast, depression usually occurred several months postoperatively, coinciding with the reduction in dopaminergic medication, and was generally reversible by increasing the dose of the dopaminergic treatment. Although one patient was known to have had severe depression with suicidal ideation before surgery, it is possible that the reduction in the dose of dopaminergic medication contributed to his suicide six months after surgery.

Patients who experienced apathy in the initial postoperative months responded to dopaminergic treatment, with the exception of one patient who was addicted to levodopa and who was not allowed to increase his medication to preoperative levels. Although stimulation of the subthalamic nucleus had no overall effect on mood, modifications in the characteristics of the stimulation or in dopaminergic treatment can affect mood substantially in individual patients, and this possibility needs to be considered in postoperative management.[28]

Permanent apathy became apparent in five patients after the third postoperative year, a development that paralleled a decrease in frontal cognitive function in four of the patients and thus may relate to the natural progression of the disease. After the immediate postoperative period, only three patients had hallucinations (those with a parallel cognitive decline), and only one had transient psychosis, a frequent complication in comparable populations of patients with parkinsonism that are treated medically.[29,30]

The Schwab and England scale has been used in other studies to assess the effects of surgical treatment in patients with Parkinson's disease in both on-medication and off-medication states.[8,15] Although there has been no direct comparison be-

tween long-term outcomes of bilateral stimulation of the subthalamic nucleus and those of other surgical therapies in patients with advanced Parkinson's disease, improvements of the magnitude that we observed on the Schwab and England scale have not, to our knowledge, been previously reported. Thalamotomy and deep-brain stimulation of the thalamus have resulted in long-term improvement in tremor, but not in akinesia[31,32] or in activities of daily living.[33,34] Unilateral pallidotomy results in sustained improvement in contralateral dyskinesia, but ipsilateral symptoms do not improve, and initial improvement in gait and akinesia diminishes progressively with time. Most patients remain dependent on a caregiver when they are in the off-medication state.[35-37]

Data on long-term outcomes of bilateral pallidotomy or pallidal stimulation are sparse, and follow-up is restricted to small series of patients and does not exceed three years.[38-40] The reported rates of persistent fatigue, speech disorder, drooling, and dysphagia[41] are higher than those with bilateral stimulation of the subthalamic nucleus. Psychiatric problems, including postoperative depression and changes in personality, behavior, and executive functions, have also been reported.[42]

Stimulation of the subthalamic nucleus makes possible a reduction in the dose of dopaminergic treatment, whereas thalamic surgery and pallidal surgery do not. Although stimulation of the subthalamic nucleus requires very close follow-up of the patient by a clinician experienced with this approach,[28] once a good balance is achieved between the amount of stimulation and dopaminergic treatment, therapeutic adjustments are infrequent, as shown by the stable treatment settings and the low number of complications beyond the first postoperative year.

Our study has limitations. Patients and evaluators were not blinded, and there was no placebo group. Placebo effects in Parkinson's disease, however, are rarely sustained in repeated testing.[43,44] Furthermore, no placebo effect was observed in two double-blind, controlled studies of neurosurgical interventions for Parkinson's disease.[6,45] Because in our study the evaluation period was nine years, assessments were done by different investigators. However, the reliability is good among the various neurologists using the Unified Parkinson's Disease Rating Scale,[46] especially considering the magnitude of the changes observed in motor scores over time.

Our findings show that the efficacy of stimulation of the subthalamic nucleus in reducing off-medication motor symptoms and levodopa-induced dyskinesia in relatively young patients with severe Parkinson's disease is largely maintained five years after surgery. However, over time there is deterioration in akinesia, axial symptoms, and cognitive problems that is consistent with the progression of the underlying disease. Stimulation of the subthalamic nucleus seems most useful for relatively young patients who have motor complications from levodopa treatment and who are independent in activities of daily living in their best on-medication state. Those patients who already have disabling motor signs that are resistant to levodopa, or who have cognitive deterioration, are not good candidates for this treatment.

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