ONLINE FIRST

Ten-Year Outcome of Subthalamic Stimulation in Parkinson Disease

A Blinded Evaluation

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Objective: To assess the 10-year motor outcome of deep brain stimulation of the subthalamic nucleus (STN-DBS) in patients with Parkinson disease (PD).

Design: Patients with PD with bilateral STN-DBS were assessed according to the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease protocol and videotaped at baseline and 1, 5, and 10 years after surgery. An independent rater blinded to stimulation and medication condition scored the 10-year video assessments.

Setting: Movement Disorders Centre, Toronto Western Hospital, University Health Network, University of Toronto.

Patients: Eighteen patients with advanced PD and 10-year follow-up of STN-DBS.

Intervention: Bilateral STN-DBS surgery.

Main Outcome Measures: The primary outcome was the change in blinded Unified Parkinson's Disease Rating Scale (UPDRS) motor scores/subscores between the no medication/stimulation condition vs the no medication/no stimulation condition at 10 years. Secondary outcomes were the changes in blinded UPDRS motor scores between the medication/no stimulation and medication/stimulation conditions, UPDRS II scores, UPDRS IV dyskinesia and motor fluctuations scores, and anti-PD medication dose (levodopa equivalent daily dose) at different points.

Results: In the 18 patients available for follow-up at 10 years, STN-DBS still significantly improved the UPDRS total motor score ($P=.007$) and resting and action tremor ($P<.01$ and $P=.02$, respectively) and bradykinesia ($P=.01$) subscores. The UPDRS II scores in the medication and no medication conditions, UPDRS IV dyskinesia and motor fluctuations scores, and the levodopa equivalent daily dose were also significantly reduced compared with baseline. Axial signs showed the most progressive decline in stimulation and levodopa response over the years.

Conclusion: This class III study provides evidence that stimulation-induced motor improvement was sustained overall at 10 years, although part of the initial benefit wore off mainly because of progressive loss of benefit on axial signs over time.

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SINCE THE FIRST APPLICATION OF deep brain stimulation of the subthalamic nucleus (STN-DBS) for Parkinson disease (PD),[1] several clinical studies have established its effectiveness and safety.[2-8] Randomized controlled trials[9-11] have shown that STN-DBS is superior to the best medical treatment in controlling motor complications and improving quality of life. The motor improvement induced by STN stimulation has been reported to be sustained for up to 5 to 8 years after surgery,[4-8] although part of the initial benefit progressively deteriorates, mainly because of worsening of axial signs. To date, studies with postoperative follow-up for longer than 8 years[8] are lacking. The objective of this study was to evaluate the main effects of STN-DBS at 10 years after implant, with particular focus on blinded assessment of motor effects.

METHODS

SUBJECTS

Forty-one patients with advanced PD underwent bilateral STN-DBS surgery at the Toronto Western Hospital between 1996 and 2000. Eighteen of these patients were available for follow-up at 10 years. Inclusion crite-

ria at the time of surgery[2] were diagnosis of PD according to UK Brain Bank Criteria,[12] disease duration longer than 5 years, severe motor fluctuations and/or disabling levodopa-induced dyskinesia despite optimization of medical therapy, and age younger than 70 years. Exclusion criteria were dementia, major active psychiatric disorders, and other major contraindication to surgery (eg, coagulopathies, uncontrolled hypertension, malignancies).[2] All patients were implanted bilaterally with a quadripolar DBS electrode (Model 3387; Medtronic, Minneapolis, Minneapolis) under local anesthesia, using magnetic resonance imaging–guided stereotactic surgery, intraoperative microrecording, and macrostimulation, as previously described.[2] Postoperative brain magnetic resonance imaging was performed in all patients to confirm the electrode position. A few days later, 1 (Kinetra; Medtronic) or 2 programmable pulse generators (Itrel II o Soletra; Medtronic) were implanted under general anesthesia and connected subcutaneously to the electrodes. Stimulation settings and medications were progressively adjusted after surgery.

The study was approved by the University Health Network Research Ethical Board. All patients gave their informed written consent.

STUDY DESIGN

Patients were assessed preoperatively and postoperatively at 1, 5, and 10 years according to the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease protocol,[13] using the Unified Parkinson's Disease Rating Scale (UPDRS).[14] All motor assessments were videotaped. Before surgery, patients were evaluated after an overnight withdrawal of dopaminergic drugs and after an acute levodopa challenge using approximately 150% of the morning anti-PD medication dose.[13] Postoperatively, patients were assessed in 4 conditions: no medication/stimulation, no medication/no stimulation, medication/no stimulation, and medication/stimulation, using the same dose of levodopa used in the preoperative challenge.[7,13] Each condition was maintained for about 60 minutes before the clinical assessments. This interval was adopted since the first postoperative follow-up because it was considered the best compromise to allow reliable assessments and minimize patient discomfort.[7] The 10-year video assessments were scored by a blinded rater (A.C.), with the exception of rigidity (unblinded scored). Dopaminergic drugs and doses were recorded at each point and converted into levodopa equivalent daily dose (LEDD).[9] Adverse events were systematically documented.

STATISTICAL ANALYSIS

The primary outcome measure was the change in blinded UPDRS motor scores between the no medication/stimulation and no medication/no stimulation conditions at 10 years. Subscores for tremor at rest (item 20), action tremor (item 21), rigidity (item 22), bradykinesia (items 23-26 and 31) and axial signs–speech (item 18), posture (item 28), gait (item 29), and postural stability (item 30) were studied separately. Secondary outcomes were changes in blinded scores between the medication/no stimulation and medication/stimulation conditions and in the unblinded UPDRS motor scores at 1, 5, and 10 years compared with baseline. Changes in the UPDRS Part I and II scores (total and axial scores: item 5, speech; item 13, falling; item 14, freezing; and item 15, walking) were also calculated. Changes in the UPDRS IV scores were used to compare motor fluctuations (UPDRS IVb, calculated as the sum of items 35, 36, 37, 38, and 39) and levodopa-induced dyskinesia (UPDRS IVa, calculated as the sum of items 32, 33, and 34) at 1, 5, and 10 years. Further analysis included changes in LEDD and changes in the stimulation settings at 1, 5, and 10 years compared with the preoperative status.

Linear regression analysis was used to investigate the impact on the primary outcome of age and disease duration at surgery, preoperative response to levodopa, side of disease at onset, symptoms at disease onset, previous brain surgeries (such as pallidotomy), preoperative LEDD, and preoperative gait and postural stability scores (with and without medication).

The Wilcoxon signed rank test was used for numeric data and the χ^2 test, for categorical variables. $P < .05$ was considered significant. Statistical analysis was performed using the JMP statistical package, version 5.1 (SAS Institute Inc, Cary, North Carolina). Values are given as mean (SD) (range), unless otherwise specified.

RESULTS

Of the 41 patients operated on between 1996 and 2000 at Toronto Western Hospital, the 10-year data were available from only 18 patients (12 men and 6 women; mean [SD] age at onset, 39.6 [6.6] years; mean [SD] age at surgery, 52.9 [7.9] years; mean [SD] disease duration, 13.4 [4.8]). Seven of the 18 patients included had previous pallidotomy. Of the remaining 23 patients (17 men and 6 women; mean [SD] age at onset, 47.4 [9.6] years; mean [SD] age at surgery, 61.2 [10.2] years; mean [SD] disease duration, 13.7 [4.9]), 12 were dead (3 of aspiration pneumonia, 2 of sepsis, 1 of gastric cancer, 1 of arrhythmia, 1 of stroke, and 1 of cerebral bleeding secondary to head trauma) and 11 were lost at follow-up (9 were living abroad and unable to come back for the assessments and 2, for unknown reasons). When comparing baseline characteristics of patients available for the study and those of patients lost at follow-up, age at disease onset and at surgery were significantly higher in the group of patients lost at follow-up ($P = .02$ and $P = .02$, respectively). No differences were found in the 2 groups when comparing disease duration and sex.

PRIMARY OUTCOME

In the no medication condition with blinded assessment at 10 years, STN-DBS showed a significant effect in improving the UPDRS total motor score (25.3%), resting and action tremor subscores (85% and 87.5%, respectively), and bradykinesia subscores (23.1%) when compared with no stimulation (**Table 1**).

SECONDARY OUTCOMES

In the medication/no stimulation condition with blinded assessment at 10 years, there was no significant improvement of UPDRS total motor score when compared with the no medication/no stimulation condition. A significant improvement was observed only in rigidity (33.8%). In the medication/stimulation condition, there was a significant improvement of the UPDRS total motor score (28.0%) and resting and action tremor (100% and 87.5%, respectively), rigidity (52.7%), and bradykinesia (19.7%) subscores (Table 1).

Unblinded UPDRS total motor scores and subscores before and after surgery at 1, 5, and 10 years are re-

Table 1. Blinded UPDRS Motor Scores and Subscores in the 4 Different Conditions of Assessment at the 10-Year Follow-up

Score	Mean (SD)						
	No Medication/ No Stimulation	No Medication/ Stimulation	*P* Value	Medication/ No Stimulation, Mean (SD)	*P* Value[a]	Medication/ Stimulation, Mean (SD)	*P* Value[b]
UPDRS III total	48.6 (11.7)	36.3 (12.7)	.007	39.6 (13.1)	.06	35.0 (13.1)	.005
Resting tremor	2.0 (3.6)	0.3 (0.8)	.01	0.4 (0.9)	.06	0.0 (0.0)	<.001
Action tremor	0.8 (1.2)	0.1 (0.3)	.02	0.2 (0.5)	.06	0.1 (0.2)	.007
Rigidity	7.4 (3.5)	5.1 (2.8)	.06	4.9 (3.4)	.04	3.5 (2.4)	<.001
Bradykinesia	23.8 (5.5)	18.3 (6.5)	.01	21.1 (6.1)	.21	19.1 (6.8)	.04
Axial signs	13.4 (6.1)	11.6 (6.0)	.33	11.8 (6.2)	.46	11.1 (6.1)	.25
Speech	2.6 (1.2)	2.4 (1.2)	.77	2.6 (1.2)	.92	2.7 (1.1)	.83
Arising from chair	2.3 (1.4)	1.8 (1.4)	.25	1.8 (1.4)	.28	1.6 (1.3)	.13
Posture	1.7 (1.0)	1.6 (0.9)	.69	1.7 (1.1)	>.99	1.7 (1.0)	.96
Gait	2.3 (1.5)	1.9 (1.6)	.49	1.8 (1.3)	.35	1.7 (1.4)	.25
Postural stability	2.7 (1.2)	2.6 (1.3)	.86	2.4 (1.3)	.54	2.3 (1.3)	.45

Abbreviation: UPDRS III, Unified Parkinson's Disease Rating Scale Part III.
[a] *P* value obtained comparing the medication/no stimulation with the no medication/no stimulation scores.
[b] *P* value obtained comparing the medication/stimulation with the no medication/no stimulation scores.

Table 2. Unblinded UPDRS Motor Scores and Subscores in the No Medication Condition With and Without Stimulation at Baseline and the 1-, 5-, and 10-Year Follow-ups

Score	Mean (SD)						
		No Stimulation			Stimulation		
	Baseline	1 y	5 y	10 y	1 y	5 y	10 y
UPDRS III total	50.2 (13.3)	45.21 (11.8)	49.3 (11.7)	49.5 (10.3)	28.7 (9.5)[a]	32.2 (10.9)[a]	38.8 (9.7)[b,c]
Resting tremor	6.6 (4.5)	5.0 (4.2)	5.5 (4.1)	2.7 (3.2)[b,d]	1.3 (1.7)[a]	1.6 (1.8)[a]	0.8 (1.1)[a]
Action tremor	3.0 (1.8)	2.4 (2.4)	2.5 (1.7)	2.0 (1.3)	0.7 (1.2)[a]	1.2 (0.9)[a]	1.4 (0.9)[a]
Rigidity	8.7 (3.8)	8.5 (3.2)	7.1 (3.9)	7.4 (3.5)	6.0 (3.4)	4.5 (4.0)[a]	5.1 (2.8)[a]
Bradykinesia	20.2 (5.5)	21.1 (4.8)	21.6 (5.0)	24.1 (4.8)[b]	14.0 (5.2)[a]	14.2 (4.6)[a]	18.6 (5.4)
Axial signs	10.9 (5.4)	8.4 (3.8)	12.1 (4.1)	13.0 (4.8)	6.4 (3.7)[b]	9.5 (4.5)	11.4 (4.9)
Speech	1.7 (0.9)	1.7 (0.9)	2.1 (0.7)	1.9 (1.0)	1.8 (0.8)	1.9 (0.7)	2.0 (1.0)
Arise from chair	1.6 (1.5)	0.8 (0.7)	1.9 (1.2)	2.3 (1.4)	0.4 (0.7)[b]	1.3 (1.3)	2.0 (1.2)
Posture	1.9 (0.9)	1.1 (0.8)[b]	2.0 (0.7)	1.9 (0.8)	1.0 (0.8)[b]	1.7 (0.7)	1.8 (0.8)
Gait	2.1 (1.2)	1.7 (0.8)	2.2 (1.0)	2.4 (1.0)	1.2 (0.9)[b]	1.7 (1.1)	2.1 (1.2)
Postural stability	2.0 (1.4)	1.2 (1.0)	1.8 (1.2)	2.6 (1.2)	0.8 (1.0)[a]	1.3 (1.3)	2.2 (1.3)

Abbreviation: UPDRS III, Unified Parkinson's Disease Rating Scale Part III.
[a] *P* value < .01, comparison with baseline scores.
[b] *P* value < .05, comparison with baseline scores.
[c] *P* value < .05, comparison with 5-year scores in no medication/stimulation condition.
[d] *P* value < .05, comparison with 5-year scores in no medication/no stimulation condition.

ported in **Table 2** and **Table 3**. Overall, the open assessments confirmed the significant effectiveness of STN-DBS in improving the UPDRS total motor scores and resting and action tremor and rigidity subscores at 5 and 10 years. However, stimulation and medications (alone or together) did not ameliorate the axial signs at the 5- and 10-year end points. In the medication/no stimulation condition at 5 and 10 years, the UPDRS total motor scores (–33.2% and –62.4%, respectively) and subscores for bradykinesia (–46.2% and –86.7%, respectively), axial signs (–53.6% and –101.8%, respectively), speech (–50.6% and 66.6%, respectively), and posture (–80% both at 5 and 10 years) significantly deteriorated compared with the medication preoperative scores.

Table 4 reports the results related to UPDRS Parts I, II, and IV and LEDD at baseline and the 1-, 5-, and 10-year follow-ups. In the no medication condition, STN stimulation significantly improved the UPDRS II scores at 1, 5, and 10 years and the freezing score at 10 years. In the medication condition, speech scores significantly worsened with stimulation at 1, 5, and 10 years, whereas falling scores worsened only at the 10-year follow-up. Compared with before surgery, at each point there was a significant stimulation effect in reducing dyskinesia and motor fluctuations subscores and LEDD (46.2% at 1 year, 43.0% at 5 years, and 36.3% at 10 years).

Concerning the parameters of stimulations, most of the setting changes were made in the first few years to optimize the stimulation[15] (change in contacts of stimulation in 7 patients, switch from bipolar to monopolar stimulation in 3 patients, switch to bipolar stimulation in 1 patient, and increase of amplitude in 4 patients and frequency in 3 patients). Minimal changes were made in the stimulation settings between the 5- and the 10-year points (shift from monopolar to bipolar stimulation in 1 patient, change of contact in 1 patient, amplitude increase of 0.1 V

Table 3. Unblinded UPDRS Motor Scores and Subscores in the Medication Condition With and Without Stimulation at Baseline and the 1-, 5-, and 10-Year Follow-ups

	Mean (SD)						
		No Stimulation			Stimulation		
Score	Baseline	1 y	5 y	10 y	1 y	5 y	10 y
UPDRS III total	22.6 (9.8)	28.3 (11.3)	30.1 (11.9)[a]	36.7 (14.0)[b]	21.3 (8.5)	24.2 (8.1)	32.7 (12.1)[b,c]
Resting tremor	0.8 (1.4)	0.9 (1.6)	1.1 (1.6)	0.1 (0.5)[d]	0.3 (0.7)	0.1 (0.3)	0.0 (0.1)[a]
Action tremor	1.1 (1.1)	1.0 (1.6)	1.3 (1.1)	1.1 (0.9)	0.2 (0.4)[b]	0.6 (0.8)	0.6 (0.7)
Rigidity	4.9 (2.4)	6.1 (3.3)	4.4 (3.3)	4.9 (3.4)	4.8 (3.2)	2.7 (2.1)[a]	3.5 (2.4)
Bradykinesia	9.8 (4.1)	13.7 (5.9)	13.9 (5.9)[a]	18.3 (7.3)[b,d]	10.2 (4.9)	11.6 (3.9)	17.0 (6.7)[b,c]
Axial signs	5.6 (3.8)	6.1 (3.7)	8.6 (4.6)[a]	11.3 (5.2)[b]	5.6 (3.5)	8.1 (4.4)	10.8 (5.4)[b]
Speech	1.2 (0.8)	1.5 (1.0)	1.8 (0.5)[b]	2.0 (0.9)[a]	1.6 (0.9)	1.9 (0.5)	2.1 (0.9)
Arise from chair	0.6 (0.9)	0.4 (0.6)	1.1 (1.2)	1.8 (1.2)[b]	0.4 (0.6)	0.9 (1.2)	1.7 (1.3)[b]
Posture	1.0 (1.0)	0.8 (0.9)	1.8 (0.8)[a]	1.8 (0.9)[a]	0.6 (0.8)	1.7 (0.7)[a]	1.8 (0.9)[a]
Gait	0.9 (1.0)	1.2 (1.0)	1.4 (1.1)	2.1 (1.0)[b]	1.1 (1.0)	1.2 (1.1)	2.0 (1.2)[a]
Postural stability	0.9 (1.0)	0.7 (0.9)	1.3 (1.3)	2.1 (1.3)[a]	0.6 (1.0)	1.5 (1.2)	2.1 (1.4)[b]

Abbreviation: UPDRS III, Unified Parkinson's Disease Rating Scale Part III.
[a] P value $<.05$, comparison with baseline scores.
[b] P value $<.01$, comparison with baseline scores.
[c] P value $<.05$, comparison with 5-year scores in medication/stimulation condition.
[d] P value $<.05$, comparison with 5-year scores in medication/no stimulation condition.

Table 4. UPDRS I, II, and IV Scores at Baseline and the 1-, 5-, and 10-Year Follow-ups

	Mean (SD)			
	Baseline	1 y	5 y	10 y
Total UPDRS I score	3.4 (1.8)	2.6 (1.8)	2.6 (1.7)	4.3 (1.9)[a]
Total UPDRS II score, no medication	28.2 (6.8)	18.8 (7.7)[b]	18.2 (7.6)[b]	21.5 (6.6)[b]
Speech	1.8 (1.1)	1.9 (1.2)	2.1 (0.9)	2.1 (1.2)
Falling	0.8 (1.2)	0.9 (1.3)	1.0 (1.2)	1.3 (1.3)
Freezing	2.0 (1.3)	0.8 (1.1)[c]	1.1 (1.3)	1.0 (1.1)[c]
Walking	2.8 (1.0)	2.0 (0.9)[c]	2.7 (1.6)	2.1 (1.2)
Total UPDRS II score, medication	11.0 (7.3)	12.2 (6.6)	14.5 (7.5)	17.9 (7.9)[c]
Speech	0.8 (1.0)	1.4 (1.2)	1.7 (0.9)[b]	1.9 (1.2)[b]
Falling	0.4 (0.8)	0.7 (1.2)	0.9 (1.2)	1.4 (1.5)[c]
Freezing	0.7 (1.0)	0.6 (1.0)	0.8 (1.1)	0.9 (1.2)
Walking	1.2 (0.9)	1.3 (1.0)	1.7 (1.0)	1.9 (1.4)
Total UPDRS IVa score	3.2 (2.6)	1.4 (2.1)[c]	1.2 (1.6)	1 (1.5)[b]
Dyskinesia duration	1.6 (1.2)	0.8 (1.0)[c]	0.5 (0.5)[b]	0.6 (0.7)[b]
Dyskinesia disability	1.3 (1.2)	0.5 (0.9)[c]	0.4 (0.7)[c]	0.2 (0.5)[b]
Total UPDRS IVb score	4.9 (1.6)	2.6 (2.1)[b]	3.5 (1.5)[c]	2.6 (1.9)[b]
Early morning dystonia	0.5 (0.5)	0.4 (0.5)[c]	0.5 (0.5)	0.4 (0.5)
No medication duration	2.1 (0.9)	1.1 (0.9)[b]	1.2 (0.7)[b]	0.8 (0.5)[b]
LEDD, mg	1237.8 (547)	665.6 (311.4)[b]	705.6 (272.5)[b]	788.9 (485.5)[b]

Abbreviations: LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale.
[a] P value $<.05$, compared with 5-year scores.
[b] P value $<.01$, compared with baseline scores.
[c] P value $<.05$, compared with baseline scores.

in 4 patients, amplitude decrease of 0.2 V in 1 patient, and frequency decrease in 1 patient). In 3 patients with worsening axial signs after 5 years, a decrease of frequency of stimulation to 60 to 80 Hz was tried, with no change in axial symptoms but worsening of tremor and bradykinesia subscores in 2 patients. One of these patients had slight improvement of speech and gait; thus, frequency was kept reduced. Mean (SD) amplitude at 10 years was 3.0 (0.7) V for the right STN and 3.2 (0.4) V for the left STN, whereas at 5 years, amplitude was 2.8 (0.8) V for the right STN and 3.1 (0.4) V for the left STN. Mean (SD) frequency was 168.3 (25.1) Hz and 162.4 (35.9) Hz at 5 and 10 years, respectively. Mean (SD) pulse width was 73.3 (18.5) microseconds and 74.1 (18.7) microseconds at 5 and 10 years, respectively.

No preoperative factors were found to be associated with a positive 10-year outcome. However, a preoperative higher score for gait in the no medication condition was inversely correlated with long-term motor outcome ($P=.002$).

When comparing baseline conditions between patients with previous pallidotomy and those without, no

significant differences were found in LEDD (mean [SD], 1429.8 [603.5] milligrams vs 1103.5 [490.4] milligrams), UPDRS total motor scores in the no medication condition (mean [SD], 46.8 [14.1] vs 52.6 [12.8]), axial signs subscores (mean [SD], 11.2 [5.7] vs 10.6 [5.5]), and UPDRS IVa and b scores (mean [SD], 2.3 [1.7] vs 3.8 [2.9], and 5.1 [1.2] vs 4.7 [1.9], respectively). At 10 years, no differences between the 2 groups were found in LEDD (mean [SD], 971.4 [551.4] milligrams vs 672.7 [424.3] milligrams), UPDRS III scores in the no medication/stimulation condition (mean [SD], 42.1 [7.1] vs 36.7 [10.8]), axial subscores under stimulation (mean [SD], 11.4 [4.7] vs 11.4 [5.1]), the percentage of improvement that was stimulation induced (mean [SD], 17.1 [10.6] vs 23.0 [20.9]), and UPDRS IVa and b scores (mean [SD], 1.7 [2.1] vs 0.5 [0.7] and 3.0 [1.8] vs 2.3 [2.0], respectively).

Adverse events at the 1-, 5- and 10-year points are listed in the eTable (http://www.archneurol.com). There was a trend toward a loss of weight over the years (mean [SD], 98.0 [18.5] kg at 1 year, 87.8 [20.6] kg at 5 years, and 82.2 [23.1] kg at 10 years), even if weight was still increased compared with before surgery (mean [SD], 80.9 [22.8] kg). Most neuropsychiatric issues occurred and were solved during the first 2 years after surgery (4 cases of depression and 1 suicide attempt). Three patients newly developed impulse control disorders 5 to 6 years after surgery, possibly related to treatment with dopamine agonists. Of 3 other patients who had preoperative impulse control disorders, 1 improved after surgery. Five patients developed visual hallucinations after the 5-year follow-up, whereas in another 3 patients, there was a progressive cognitive decline culminating in dementia (diagnosed with clinical examination and formal neuropsychological assessment). Eyelid opening apraxia was successfully managed with botulinum toxin injections. Between the 5-year and 10-year assessments, there were 2 device-related infections (right electrode removal 7 years after surgery in 1 patient, right internal pulse generator removal in another patient).

The mean (SD) time until the first battery replacement was 5.9 (1.6) years. Twelve patients needed a second battery replacement 4.2 (0.6) years later.

COMMENT

To our knowledge, this is the first class III study (in which the outcome was independently assessed by a rater who was not part of the treatment team) focusing on 10-year postoperative motor outcomes of bilateral STN-DBS in advanced PD. At the 10-year follow-up, there was a significant stimulation effect on the UPDRS total motor scores even without medication. During the blinded assessments, STN stimulation significantly improved the UPDRS total motor scores and tremor and bradykinesia subscores. On the short-term blinded evaluations, the combination of stimulation and medication added little to the motor outcomes over that seen with stimulation alone.

Motor fluctuations, dyskinesia, and activities of daily living were also improved by stimulation in the long-term follow-up, although there was some decline in the stimulation benefit over the years. The stimulation decay became more evident after 5 years of continuous STN-DBS, as revealed by the significant worsening of the 10-year UPDRS total motor scores and bradykinesia subscores in the medication/no stimulation and medication/stimulation conditions when compared with the 5-year follow-up.

As previously reported,[4-8] axial signs showed the most striking progressive loss of stimulation benefit over time. Taking into account the significant progressive and parallel loss of the levodopa response on axial scores, the decline in DBS benefit could be due to the natural progression of PD.[6] However, since stimulation but not medication alone was able to improve tremor and bradykinesia at the blinded assessments, different mechanisms of action of DBS and levodopa or some interaction between them in the long-term could be hypothesized. Our patients showed a remarkable progressive loss of levodopa response over the years. This phenomenon has been previously observed and analyzed in shorter follow-ups.[7,16] Besides the growing impact of the nondopaminergic features on the motor scores due to the progression of PD, other factors might contribute to these observations, such as changes in the short-term and long-term levodopa response and in the postsynaptic striatal dopamine receptors.[16] In addition, a simple short-term levodopa challenge performed in a study setting might not reflect the real response to levodopa, especially after the significant LEDD reduction after surgery. Interestingly, freezing was improved by stimulation but not by medication at the 10-year follow-up.

Some recent studies have reported improvement of axial signs by reducing frequency of stimulation to 60 Hz in the long-term follow-up.[17,18] We also tried stimulation frequencies of 60 and 80 Hz in 3 patients who had developed poor control of axial symptoms after several years of stimulation. Worsening of tremor and bradykinesia occurred in response to these changes in 2 patients, whereas a slight improvement in speech and gait were observed in the third patient. Although the effect of different stimulation settings on axial signs is beyond the purpose of this study, our findings suggest that decreasing frequency of stimulation might be useful only in selected patients.

Our findings are overall in line with data from several previous 5-year outcome studies[4-7] and a more recent study in 20 patients with 8 years of follow-up[8] reporting prolonged benefit of rigidity and tremor but progression of axial signs and thus suggesting lack of neuroprotective effects of stimulation.[6,8]

Surprisingly, without stimulation and dopaminergic drugs only bradykinesia worsened at 10 years compared with the preoperative no medication status. On the other hand, tremor was improved compared with baseline, suggesting a different effect of STN-DBS on this sign or reflecting the natural decay of tremor during the progression of the disease.[19,20] This lack of progressive worsening in the UPDRS total motor scores in the no medication/no stimulation condition (preoperatively vs 5 and 10 years postoperatively) is more likely due to the long-lasting effect of stimulation after switching off the stimu-

lator,[21] although this has not been systematically studied in our patients.

Despite the PD progression, STN stimulation allowed a persistent, marked reduction in dopaminergic drug dosages. These data, together with the minimal changes in stimulation settings in the long-term, further support the sustained benefit of stimulation.

None of the preoperative variables, including the preoperative levodopa response, was found to be associated with a better long-term motor outcome.[7] However, given the small sample, the analysis might be lowly powered to detect associations. Outcome of patients who had unilateral previous pallidotomy did not differ from those without pallidotomy, in agreement with our previous observations.[7]

Regarding safety issues, there were no substantial differences in the incidence of adverse effects at 10 years compared with 1 and 5 years. The rate of infection in our group was similar to that previously reported.[4-8] However, 2 patients experienced a serious device-related infection between 5 and 10 years after surgery, requiring the removal of the lead in 1 case and the internal pulse generator in the other. The occurrence of infections should also be considered and ruled out in the long-term follow-up. A trend to lose the weight previously gained soon after surgery was observed in the long-term follow-up. Although the reasons are unknown, this weight loss might be related to disease progression. The 3 patients who developed impulse control disorders at 5 years were all taking dopamine agonists at that time. Discontinuation of drugs allowed impulse control disorder resolution. In the last 5 years of follow-up, the cognitive performance deteriorated to reach the criteria for dementia in 4 patients (the 10-year cognitive function data will be reported in another article focused on this topic). Although lacking a control group of patients with PD without stimulation, these adverse events appear to be more related to PD progression rather than being stimulation induced. Indeed, the Sydney Multicenter Study (an observational study following up a large cohort of patients with parkinsonism over many years) found that around 80% of survivors developed dementia and more than 70% of patients had died after 20 years of disease.[22] Indeed, only 44% of the patients initially enrolled completed our study at 10 years (30% died), confirming the difficulty of conducting long-term follow-up studies in late-stage PD.[7,8] Interestingly, weight gain after STN-DBS tended to decrease in frequency (44.4% of patients at the 10-year follow-up vs 66.6% at 5 year) and severity at 10 years compared with 5 years of follow-up.

Our study has several limitations, including the lack of a control group and double-blinded assessments, the high dropout rate, and the relatively small sample size. Nevertheless, our findings further support the long-term response to STN stimulation in patients with advanced PD, showing a prolonged motor improvement up to 10 years.

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