ORIGINAL ARTICLE

Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia

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ABSTRACT

BACKGROUND

Severe forms of dystonia respond poorly to medical treatment. Deep-brain stimulation is a reversible neurosurgical procedure that has been used for the treatment of dystonia, but assessment of its efficacy has been limited to open studies.

METHODS

We performed a prospective, controlled, multicenter study assessing the efficacy and safety of bilateral pallidal stimulation in 22 patients with primary generalized dystonia. The severity of dystonia was evaluated before surgery and 3, 6, and 12 months postoperatively during neurostimulation, with the use of the movement and disability subscores of the Burke–Fahn–Marsden Dystonia Scale (range, 0 to 120 and 0 to 30, respectively, with higher scores indicating greater impairment). Movement scores were assessed by a review of videotaped sessions performed by an observer who was unaware of treatment status. At three months, patients underwent a double-blind evaluation in the presence and absence of neurostimulation. We also assessed the patients' quality of life, cognition, and mood at baseline and 12 months.

RESULTS

The dystonia movement score improved from a mean (±SD) of 46.3±21.3 before surgery to 21.0±14.1 at 12 months ($P<0.001$). The disability score improved from 11.6±5.5 before surgery to 6.5±4.9 at 12 months ($P<0.001$). General health and physical functioning were significantly improved at month 12; there were no significant changes in measures of mood and cognition. At the three-month evaluation, dystonia movement scores were significantly better with neurostimulation than without neurostimulation (24.6±17.7 vs. 34.6±12.3, $P<0.001$). There were five adverse events (in three patients); all resolved without permanent sequelae.

CONCLUSIONS

These findings support the efficacy and safety of the use of bilateral stimulation of the internal globus pallidus in selected patients with primary generalized dystonia.

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N Engl J Med 2005;352:459-67.

Dystonia is a clinical syndrome characterized by sustained muscle contractions causing twisting and repetitive movements or abnormal postures.[1] Primary generalized dystonia is a severe motor disease, causing physical and social incapacity in patients with normal cognitive function. Pharmacologic treatments have limited efficacy, and injections of botulinum toxin are useful only in restricted areas (e.g., the face and neck). Thus, surgical approaches merit investigation. Thalamotomy[2] and pallidotomy[3] may induce variable and unstable responses[4] and unacceptable adverse effects, including speech difficulties and cognitive disturbances.[5] In contrast, deep-brain stimulation targeting the internal globus pallidus is a reversible procedure with low morbidity.[6-10]

Although a beneficial effect of bilateral stimulation of the internal globus pallidus has been reported in children with primary generalized dystonia,[11,12] little information is available on its effects in adults. Data from case reports[13-21] or small groups of patients[22,23] with primary generalized dystonia are scattered or embedded in reports of heterogeneous groups of patients, including those with secondary[16,18,21,23] or focal[15,18] disease. Moreover, the ability to draw conclusions from these reports is limited by variations in selection criteria, stimulation settings,[11,12,14,21] evaluation of the clinical outcomes, and the duration of follow-up.[12,18,22] In addition, in the absence of a controlled, blinded evaluation, the possibility that observed benefits are due to a placebo effect cannot be excluded. Therefore, we conducted a prospective, multicenter study to determine the effects of bilateral pallidal stimulation on motor impairment, functional disability, and the quality of life in patients with primary generalized dystonia, using standardized and blinded assessments.

METHODS

PATIENTS

Twenty-two patients were recruited in France: 10 in Grenoble, 9 in Paris, and 3 in Lille. The inclusion criteria were as follows: clinically diagnosed primary generalized dystonia with a combination of segmental crural dystonia (involving one leg and the trunk) and the involvement of any other segment (the cranium, neck, or upper or lower limbs); the absence of any secondary cause, including birth injury, head trauma, and neuroleptic treatments; a normal neurologic examination except for dystonia; normal findings on magnetic resonance imaging (MRI) of the brain; the absence of psychiatric disturbances; normal cognitive function, as reflected by a score of at least 24 on the Mini–Mental State Examination (MMSE; lower scores indicate cognitive impairment)[24]; and severe impairment in the ability to perform the activities of daily living despite optimal medical management. All patients were tested for the *DYT1* mutation in the torsin A gene.[25]

STUDY DESIGN

The patients served as their own controls and were evaluated while taking their usual treatments. Clinical assessment was performed before surgery and 3, 6, and 12 months after surgery. With the use of a standardized protocol, patients were videotaped wearing a cap to conceal evidence of prior surgery (an example is shown in the Supplementary Appendix, available with the full text of this article at www.nejm.org). The patients' movements on the videos (presented in random order and with the patients' family names removed to preserve anonymity) were scored by an independent expert using the movement subscale of the validated Burke–Fahn–Marsden Dystonia Scale,[26] and the patients completed questionnaires assessing their degree of disability. At the three-month follow-up visit, movement was evaluated with and without neurostimulation (in random order) on separate days. Both the patient and the neurologist who performed these assessments were unaware of the patient's neurostimulation status. The electrical variables of deep-brain stimulation were set 10 hours before video and clinical assessment. If unacceptable worsening occurred within the 10 hours before evaluation, the neurostimulator could be turned to the therapeutic-stimulation settings. The patient was videotaped just before the neurostimulator was activated. At 6 and 12 months postoperatively, evaluations were conducted with the neurostimulator activated.

The study was approved by the ethics committee of Pitié–Salpêtrière University Hospital, Paris. All the patients provided written informed consent.

SURGERY

Leads were implanted bilaterally in one session with the patient under local anesthesia (3 patients) or general anesthesia (19 patients) according to institutional protocols. The posterolateral ventral part

of the internal globus pallidus was identified either by stereotactic brain MRI or by MRI with ventriculography and intraoperative electrophysiological recording. At the end of the surgical procedure, an electrode with four contacts (DBS-3389, Medtronic) was implanted and then connected to a neurostimulator (Kinetra, Medtronic) implanted in the subclavicular region while the patient was under general anesthesia.

Before the implantation of the neurostimulator, all but one patient underwent postoperative MRI to confirm that there was adequate electrode-contact localization at the posterolateral ventral part of the internal globus pallidus and to rule out surgical complications. The mean (±SD) coordinates of the most ventral contact of the electrodes were established as X mm lateral to the midline, Y mm anterior to the posterior commissure, and Z mm below the anterior–posterior commissure line (right hemisphere: X=20.1±1.6 mm, Y=15.0±3.0 mm, and Z=4.3±1.7 mm; left hemisphere: X=20.1±1.9 mm, Y=14.5±2.5 mm, and Z=4.4±1.7 mm). We used one or two ventral contacts as the cathode with monopolar polarity and a frequency of 100 to 185 Hz. The voltage and pulse width were adjusted according to the clinical effect.[27]

CLINICAL EVALUATION

The Burke–Fahn–Marsden Dystonia Scale was used to evaluate the effects of neurostimulation. It has a nonlinear scoring system and includes a movement scale with nine subscales (one for each body part) and a disability scale (Table 1).[26] The disability scores were obtained by having the patient answer a questionnaire at each examination. The health-related quality of life was assessed before surgery and at the 12-month follow-up visit with a validated French version of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional roles, pain, and vitality; scores on each scale can range from 0 (worst) to 100 (best).[28] Cognitive function[24] and mood[29] were also assessed before surgery and 12 months postoperatively, by means of the MMSE and the Beck Depression Inventory, respectively.

STATISTICAL ANALYSIS

The primary outcome measures were the scores on the movement and disability subscales of the Burke–Fahn–Marsden Scale preoperatively and at 3, 6, and 12 months. The secondary outcome measures were the dystonia scores at 3 months (with and without neurostimulation), the quality of life at 12 months as reflected by the SF-36 scores, use of other medical therapies, neurostimulation settings, and adverse events.

Data at baseline and at month 12 were compared with the use of a Wilcoxon signed-rank test for matched pairs. Repeated measures across time were compared with the use of a linear mixed model (analysis of variance with random effects), with a random effect for the patient and a fixed effect for time.[30] When the results of the global comparison were significant, pairwise comparisons were performed with the Tukey–Kramer adjustment for multiple comparisons. To look for factors that were predictive of improvement at month 12, we used the Wilcoxon test for categorical variables (sex and *DYT1* status) and the Spearman correlation coefficient for quantitative variables (age, duration of disease, and total scores or subscores for the movement and disability scales).

All statistical tests were two-tailed. P values that were less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of the SAS statistical package, version 8.1 (SAS Institute).

RESULTS

The clinical characteristics of the patients are summarized in Table 1. The median age of the patients at surgery was 30 years (range, 14 to 54). The median age at the onset of dystonia was 8 years (range, 5 to 38), and the median duration of the disease was 18 years (range, 4 to 37). Seven patients had the *DYT1* mutation.

Three months after the initiation of bilateral pallidal neurostimulation, the Burke–Fahn–Marsden movement score was significantly lower than the preoperative value (P<0.001). The improvement in scores persisted at subsequent evaluations, with a mean decrease of 51 percent at month 12 (P<0.001) (Fig. 1A and video, available with the full text of this article at www.nejm.org). A total of 11 patients had an improvement in the movement score of more than 50 percent at month 3, 13 at month 6, and 14 at month 12. In two patients, motor symptoms worsened (by 10 percent and 34 percent at month 12). The seven patients who had an improvement of more than 75 percent at one year had diffuse phasic, hyperkinetic involuntary movements preoperatively.

Table 1. Clinical Characteristics of the Patients.*

Patient No.	Sex	Age at Onset	Duration of Disease	Site of Initial Symptom†	*DYT1* Status†	Movement Score		Disability Score		Treatments‡	
						Baseline	12 Mo	Baseline	12 Mo	Baseline	12 Mo
			yr								
1§	F	22	20	F	–	51.0	23.5	10	3	BDZ	Anti-SP
2	M	10	21	F	–	32.0	29.0	9	6	—	—
3	F	5	10	LL	–	56.0	8.0	9	3	45 mg of THP + BDZ	40 mg of THP
4	F	34	19	UL	–	34.0	8.0	12	5	DA	DA + BDZ
5	M	30	16	LL	–	19.0	9.0	6	2	10 mg of THP	4 mg of THP
6	M	38	4	UL	–	35.5	12.0	8	4	30 mg of THP + BDZ	30 mg of THP + BDZ
7	M	13	37	LL	–	31.5	7.0	6	4	BDZ	BDZ
8	F	30	21	UL	–	39.0	14.0	12	8	6 mg of THP + BDZ	4 mg of THP + BDZ
9	M	7	9	UL	–	30.0	4.0	8	1	15 mg of THP + TBZ	—
10	F	8	26	UL	–	19.0	25.5	7	8	—	BDZ
11	F	7	26	LL	–	102.5	34.0	21	14	10 mg of THP + BDZ	—
12	F	8	11	LL	–	39.0	28.0	8	4	20 mg of THP + BDZ	20 mg of THP + BDZ
13	F	10	17	UL	–	62.0	4.5	14	2	10 mg of THP, BDZ, anti-SP, + DA	—
14	M	8	10	LL	–	42.0	46.0	12	13	30 mg of TRP	15 mg of TRP
15	M	6	18	LL	–	37.0	28.0	11	6	20 mg of THP + TBZ	20 mg of THP + TBZ
16	F	9	9	UL	+	25.0	0.0	8	0	15 mg of THP + anti-SP	15 mg of THP + anti-SP
17	M	7	29	UL	+	59.5	43.5	14	10	BDZ + TBZ	BDZ
18	M	8	32	UL	+	61.0	30.0	19	12	BDZ	BDZ + anti-SP
19	F	8	18	LL	+	42.0	29.0	8	5	15 mg of THP + anti-SP	12 mg of THP
20	M	5	17	UL	+	95.5	41.0	28	19	BDZ, anti-SP, + TBZ	BDZ
21	F	7	23	LL	+	58.5	7.0	18	3	40 mg of THP, BDZ, + TBZ	15 mg of THP + BDZ
22	M	9	21	UL	+	44.5	32.0	8	7	150 mg of THP, BDZ, + anti-SP	30 mg of THP, BDZ, + anti-SP

* The total score for the movement subscale of the Burke–Fahn–Marsden Dystonia Scale, which can range from 0 to 120, is the sum of individual scores for each body region and represents the severity of motor disability related to dystonia. The individual score is based on the product of the severity factor (i.e., quantification proportional to severity of dystonia,) and the provoking factor (i.e., the circumstances in which dystonia appears) — for example, a score of 1 indicates that it is task-specific and a score of 4 that dystonia persists at rest, with a "down weighting" of 0.5 in the scores for the eyes, mouth, and neck. The total disability score can range from 0 to 30 and is the sum of individual ratings for seven activities: speech (a score of 0 indicates the patient is easily understood, and a score of 4 the presence of almost complete anarthria), handwriting (a score of 0 indicates legible handwriting, and a score of 4 inability to grasp a pen), and the degree of dependence with respect to hygiene, dressing, and feeding (a score of 0 indicates normal ability, and a score of 4 complete dependence), swallowing (a score of 0 indicates normal ability, and a score of 4 marked difficulty swallowing soft food and liquids), and walking (a score of 0 indicates normal ability, and a score of 6 wheelchair-bound).

† The first symptom of the disease was in the face (F), the upper limbs (UL), or the lower limbs (LL). No patient had trunk involvement as the initial symptom.

‡ THP denotes trihexyphenidyl, TRP tropatepine, BDZ benzodiazepines, anti-SP antispastic drugs (dantrolene or baclofen), TBZ tetrabenazine, and DA dopaminergic drugs (levodopa or bromocriptine). Additional treatments (analgesics and antidepressants) are mentioned in the Results section. Daily doses of THP are shown.

§ Patient 1 had a family history of dystonia: her sister had an isolated writer's cramp.

In contrast, the two patients whose dystonia worsened and the two with little improvement (0 to 25 percent) had severe tonic abnormal postures preoperatively.

As compared with baseline values, the majority of movement subscores had decreased at month 3 and remained stable through month 12; the face and speech and swallowing subscores were not significantly changed at follow-up assessments, as compared with preoperative assessments. Twelve months postoperatively, axial and limb subscores had improved by 69 percent and 52 percent, respectively (P<0.001) (Table 2).

The global disability score was improved at month 3 (P<0.001) and continued to improve through month 12 (Fig. 1B). Scores for dressing, eating and swallowing, feeding, hygiene, and walking were improved at month 3 (P<0.001), and writing was improved at month 6 (P<0.001); these improvements remained stable thereafter (Table 2).

The general health and physical functioning subscores for the SF-36 scale improved significantly after surgery (Table 3). Cognition (as measured by the MMSE) and mood (as measured by the Beck Depression Inventory) did not change significantly after surgery.

None of the baseline factors we assessed (sex, age, duration of disease, *DYT1* status, or global scores and subscores for the Burke–Fahn–Marsden Dystonia Scale) were significant predictors of motor improvement one year after surgery.

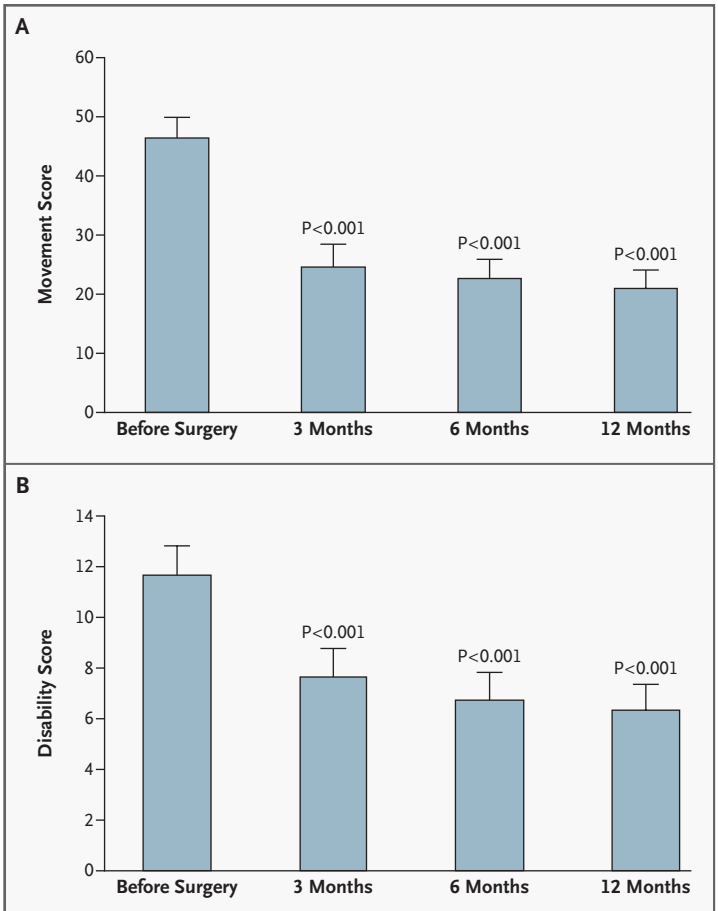

Figure 1. Mean (+SD) Scores for the Movement (Panel A) and Disability (Panel B) Subscales of the Burke–Fahn–Marsden Dystonia Scale before and 3, 6, and 12 Months after Surgery.

The total movement score (Panel A) is the sum of individual scores for each body region and represents the severity of motor disability related to dystonia; scores can range from 0 to 120, with higher scores indicating more severe disability. The individual score is based on the product of the severity factor (i.e., quantification proportional to the severity of dystonia) and the provoking factor (i.e., the circumstances in which dystonia appears). The total disability score (Panel B) can range from 0 to 30 and is the sum of individual ratings for seven activities of daily living: speech (a score of 0 indicates the patient is easily understood, and a score of 4 the presence of almost complete anarthria), handwriting (a score of 0 indicates legible handwriting, and a score of 4 inability to grasp a pen), and the degree of dependence with respect to hygiene, dressing, and feeding (a score of 0 indicates normal ability, and a score of 4 complete dependence), swallowing (a score of 0 indicates normal ability, and a score of 4 marked difficulty swallowing soft food and liquids), and walking (a score of 0 indicates normal ability, and a score of 6 wheelchair-bound).

EVALUATION OF NEUROSTIMULATION AT THREE MONTHS

Two of the 22 patients were not able to complete 10 hours of evaluation owing to unacceptable worsening of dystonia in the absence of neurostimulation. The neurostimulator had to be turned to the therapeutic-stimulation settings after three hours in one patient because of breathing difficulties (preoperative movement score, 95.5; score at three months without neurostimulation, 84.0; and score at three months with neurostimulation, 51.5) and after seven hours in the other patient because of recurrent dystonic spasms (preoperative score, 102.5; score at three months without neurostimulation, 66.5; and score at three months with neurostimulation, 51.0).

In all patients, the total score for the Burke–Fahn–Marsden movement subscale was worse in the absence of neurostimulation than in the presence of neurostimulation (34.6±22.3 vs. 24.6±17.7, P<0.001), although the scores did not revert to preoperative values (46.3±21.3, P<0.001) (Table 2). All subscores except speech were poorer in the absence of neurostimulation than in the presence of neurostimulation. At three months, neurostimulation did not significantly change the total score for the Burke–Fahn–Marsden disability scale (Table 2).

Table 2. Effect of Bilateral Pallidal Stimulation on Burke–Fahn–Marsden Subscores 3, 6, and 12 Months after Surgery.*

Scale	Possible Range	Baseline	3 Months		6 Months	12 Months
			Stimulation	No Stimulation		
Movement						
Neck and trunk (axial)	0–24	12.5±7.9	4.9±5.2†	8.4±6.3‡	5.3±4.7†	3.9±4.1†
Upper and lower limbs	0–64	28.5±16.3	16.4±15.0†	22.0±17.5‡	14.8±12.3†	13.6±12.2†
Face (eyes and mouth)	0–16	2.1±2.5	1.3±2.2	1.9±2.5§	1.3±1.8	1.3±2.1
Speech and swallowing	0–16	2.8±3.9	2.0±2.8	2.4±3.4	1.9±2.5	2.2±2.8
Total		46.3±21.3	24.6±17.7†	34.6±22.3	22.6±14.9†	21.0±14.1†
Disability						
Speech	0–4	1.3±1.3	1.2±1.3	1.2±1.3	1.1±1.3	1.3±1.3
Writing	0–4	2.0±1.1	1.6±1.1	1.7±1.0	1.2±1.1¶	1.2±0.9¶
Feeding	0–4	1.6±0.9	0.7±0.9†	1.1±1.2	0.5±0.7†	0.5±0.7†
Eating and swallowing	0–4	1.1±1.0	0.5±0.8¶	0.7±0.8	0.6±0.7¶	0.5±0.7¶
Hygiene	0–4	1.4±0.8	0.7±0.8†	0.8±1.0	0.5±0.7†	0.5±0.7†
Dressing	0–4	1.3±0.9	0.7±0.7†	0.8±0.9	0.6±0.8†	0.5±0.8†
Walking	0–6	3.0±1.6	2.1±1.4†	2.5±1.5	2.0±1.5†	2.0±1.5†
Total		11.6±5.5	7.6±5.2†	8.8±6.2	6.7±5.2†	6.5±4.9†

* Plus–minus values are means ±SD. For all comparisons, lower scores indicate less dystonia.
† P<0.001 for the comparison with the baseline score.
‡ P<0.001 for the comparison with the score obtained during stimulation.
§ P<0.05 for the comparison with the score obtained during stimulation.
¶ P<0.01 for the comparison with the baseline score.

Table 3. Scores for Health-Related Quality of Life, Cognition, and Mood before and 12 Months after Surgery.*

Variable	Before Surgery	12 Months after Surgery	P Value
SF-36 score			
General health	47±24	63±27	0.04
Physical functioning	41±28	62±29	0.007
Physical role	53±43	58±39	0.68
Emotional role	59±48	77±37	0.18
Social functioning	57±36	58±29	0.81
Pain	39±32	56±36	0.12
Vitality	40±24	50±24	0.07
Mental health	54±20	64±23	0.10
MMSE score	28±2	28±2	0.33
Beck Depression Inventory score	11±7	8±8	0.15

* Plus–minus values are means ±SD. Scores for the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) can range from 0 (worst) to 100 (best). Scores for the Mini–Mental State Examination (MMSE) can range from 0 to 30. A score of less than 24 indicates cognitive impairment. Scores for the Beck Depression Inventory can range from 0 to 63, with a score of 20 or more indicating moderate-to-severe depression.

STIMULATION VARIABLES

At three months, all 44 electrodes were set at 130 Hz. At 12 months, 39 were set at 130 Hz, 1 at 100 Hz, and 4 at 185 Hz. The mean voltage was 3.8±0.9 V at 3 months and 3.7±1.0 V at 12 months. The mean pulse width increased from 77±30 μsec at 3 months to 139±130 μsec at 12 months. At 12 months, one contact was used in 29 of the 44 electrodes, and two contiguous contacts were used in 15 electrodes (monopolar stimulation).

MEDICAL TREATMENT

Preoperatively, 20 patients received treatments for dystonia. Fourteen patients received anticholinergic agents (mean dose of trihexyphenidyl, 30 mg; range, 6 to 150; mean dose of tropatepine, 30 mg), 13 received benzodiazepines, 5 received antispastic drugs (dantrolene or baclofen), 5 received tetrabenazine (mean dose, 89±61 mg), 2 received levodopa, and 1 received bromocriptine (Table 1). Additional treatments were analgesics in five patients and antidepressants in five patients.

At 12 months, 18 patients were receiving medi-

cation for dystonia. Ten patients were receiving anticholinergic agents, but at a lower mean dose than that given preoperatively ($P<0.004$; mean dose of trihexyphenidyl, 19 mg; range, 4 to 40; mean dose of tropatepine, 15 mg). Eleven were receiving benzodiazepines, three baclofen, and one tetrabenazine (dose, 25 mg). One patient received analgesic agents, and two received antidepressants.

ADVERSE EVENTS

Five adverse events occurred in three patients in the postoperative period; all resolved rapidly without permanent sequelae. One patient had transient perioperative edema of the frontal lobe that was not clinically evident; in the same patient, a fractured lead that leaked current was replaced. One patient had cutaneous necrosis of the scalp at the site of a resolved skin infection near the connector, and one had a localized skin infection that resolved and a hematoma near the neurostimulator.

DISCUSSION

In patients with primary generalized dystonia, bilateral pallidal stimulation led to a sustained improvement in motor symptoms and disability over a period of one year. The improvement in mean dystonia movement scores was 51 percent, and one third of the patients had an improvement of more than 75 percent, as compared with preoperative scores.

The strengths of our study include its prospective, multicenter design and the use of standardized videos for all motor evaluations, rated by an examiner who was unaware of the patient's preoperative or postoperative status and who used a validated scale (the Burke–Fahn–Marsden Dystonia Scale). The adequacy of the position of the electrodes within the intended target was confirmed by MRI immediately after surgery.

Our results, obtained from a controlled study of a group of patients meeting strict inclusion criteria, confirm the results obtained in individual patients[16,18,19,23] and open studies.[11,12,22] Moreover, the benefit was observed at three months and was sustained over the course of one year. Motor improvement occurred in most segments of the body (neck, trunk, and limbs); the exceptions were facial movement and speech, which were, on average, less severely affected at baseline and remained essentially unchanged. These differential effects of neurostimulation should be considered when one is selecting patients for surgery.[16,31]

The beneficial effect of deep-brain stimulation was also demonstrated by the double-blind, video-controlled assessment at three months, which demonstrated worsening of the movement scores of all patients in the absence of neurostimulation, as compared with the presence of neurostimulation. Moreover, the two patients who could not complete the 10 hours of blinded evaluation were not receiving neurostimulation at the time. Although the usual pattern of dystonia reappeared in all patients in the absence of neurostimulation, their movement scores did not reach preoperative values, because "washout" effects may not be complete after 10 hours. This postneurostimulation effect suggests that neurostimulation-induced changes in dystonia are related not only to a direct action of the stimulation on neuronal tissue[32,33] but also to structural or functional changes involving plasticity in cortical or subcortical networks.[13] Such a mechanism could also account for the progressive improvement in dystonia over a period of several months that we and others[9,17] have observed.

Despite verifying the adequacy of the placement of electrodes in all patients, we found variability in the response to therapy among patients. The majority had an improvement of at least 50 percent in motor scores, but four patients had limited improvement (25 percent or less) or worsening. Other groups have also reported variability of the response (including therapeutic failure in individual patients), despite correct positioning of the electrodes.[9,17,31] This variability could be related to genetic heterogeneity of disease or to the characteristics of abnormal movements. Although it has been hypothesized that the choice of the target, the location of the electrodes, the location of dystonia, and the *DYT1* status influence the therapeutic outcome,[12,31] we did not identify factors predictive of the magnitude of improvement; however, the ability to identify such predictors was limited by our small sample.

We found in a post hoc analysis that the patients with the greatest improvement were those who had phasic movements, whereas patients who had little or no improvement had severe tonic posturing, although there is still limited ability to assess this variable, owing to the lack of standard criteria for classifying dystonia. Although further studies specifically addressing this question are needed, one could hypothesize that the pattern of dystonia and the underlying pathophysiology may contribute to the variability in the therapeutic outcome.[17,31]

The observed improvement in functional disability in our patients was consistent with a decrease in the severity of dystonia. The benefit pertained to walking, hygiene, feeding, and swallowing and eating by month 3 and to writing by month 6 and was sustained over a period of one year (see the Supplementary Appendix). Our patients also had a concomitant improvement in the health-related quality of life, whereas this finding was only briefly mentioned in a small, retrospective series of heterogeneous patients.[15] In addition, the use of medications to treat dystonia was reduced after surgery.

In contrast to bilateral pallidotomy,[5,17] bilateral pallidal deep-brain stimulation had a good risk–benefit ratio among our patients with dystonia. We did not observe worsening of cognition, mood changes, or any permanent adverse effects. The adverse events that occurred were inherent to deep-brain–stimulation surgery. There was one reversible cerebral adverse event: asymptomatic frontal-lobe edema. The four other adverse events (i.e., leakage of current due to lead fracture, scalp necrosis with resolved infection, hematoma, and infection in the neurostimulator pocket) were related to the hardware and similar to those previously reported.[9,11,15] These types of complications accounted for the 2 to 8 percent rate of complications reported elsewhere for deep-brain stimulation in patients with dystonia.[34] However, our sample was small, and an assessment of the risk of uncommon but serious complications, such as intracerebral hemorrhage, requires a much larger series of patients.

In conclusion, this prospective, double-blind, video-controlled study demonstrated that bilateral stimulation of the posterolateral ventral internal pallidus resulted in a sustained decrease in the severity of dystonia and functional disability and improved the quality of life in adult patients with generalized primary dystonia, without affecting cognition or mood.

Supported by a national grant (PHRC 98) from the Direction Régionale de la Recherche Clinique Assistance-Publique-Hôpitaux de Paris, the INSERM Dystonia French National Network, and an additional unrestricted grant from Medtronic, Minneapolis.

Dr. Benabid reports having received research support from Medtronic, and Dr. Pollak an honorarium for lectures from Medtronic.

We are indebted to the Clinical Research Center in Pitié–Salpêtrière Hospital, Paris, and to the neurologists who referred the patients: A. Alicherif, P. Beauvais, A.R. Bentivoglio, P. Betermiez, M.C. Commare, G. Defer, A. Dürr, P. Jedynak, M. Magid, A. Mendes, M. Verin, A. Vighetto, and D. Zegers de Beyls.

APPENDIX

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REFERENCES

1. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1-10.
2. Andrew J, Fowler CJ, Harrison MJG. Stereotaxic thalamotomy in 55 cases of dystonia. Brain 1983;106:981-1000.
3. Vitek JL, Zhang J, Evatt M, et al. GPI pallidotomy for dystonia: clinical outcome and neuronal activity. Adv Neurol 1998;78:211-9.
4. Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 1997;12:865-70.
5. Ford B. Pallidotomy for generalized dystonia. Adv Neurol 2004;94:287-99.
6. Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P. Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord 1998;13:Suppl 3:119-25.
7. Jankovic J. Re-emergence of surgery for dystonia. J Neurol Neurosurg Psychiatry 1998;65:434.
8. Lang AE. Surgical treatment of dystonia. Adv Neurol 1998;78:185-98.
9. Krauss JK. Deep brain stimulation for dystonia in adults: overview and developments. Stereotact Funct Neurosurg 2002;78:168-82.
10. Lozano AM, Abosch A. Pallidal stimulation for dystonia. Adv Neurol 2004;94:301-8.
11. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalized dystonia by stimulation of the internal globus pallidus. Lancet 2000;355:2220-1.
12. Cif L, El Fertit H, Vayssiere N, et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. J Neurosug Sci 2003;47:52-5.
13. Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 1999;53:871-4.
14. Vesper J, Klostermann F, Funk T, Stockhammer F, Brock M. Deep brain stimulation of the globus pallidus internus (GPI) for torsion dystonia — a report of two cases. Acta Neurochir Suppl 2002;79:83-8.
15. Bereznai B, Steude U, Seelos K, Botzel K. Chronic high-frequency globus pallidus internus stimulation in different types of dystonia: a clinical, video, and MRI report of six patients presenting with segmental, cervical, and generalized dystonia. Mov Disord 2002;17:138-44.
16. Tronnier VM, Fogel W. Pallidal stimulation for generalized dystonia: report of three cases. J Neurosurg 2000;92:453-6.

17. Vercueil L, Krack P, Pollak P. Results of deep brain stimulation for dystonia: a critical reappraisal. Mov Disord 2002;17:Suppl 3:S89-S93.
18. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery 2004;54:613-9.
19. Katayama Y, Fukaya C, Kobayashi K, Oshima H, Yamamoto T. Chronic stimulation of the globus pallidus internus for control of primary generalized dystonia. Acta Neurochir Suppl 2003;87:125-8.
20. Kupsch A, Klaffke S, Kuhn AA, et al. The effect of frequency in pallidal deep brain stimulation for primary dystonia. J Neurol 2003;250:1201-5. [Erratum, J Neurol 2004; 251:1031.]
21. Krauss JK, Loher TJ, Weigel R, Capelle HH, Weber S, Burgunder JM. Chronic stimulation of the globus pallidus internus for treatment of non-dYT1 generalized dystonia and choreoathetosis: 2-year follow up. J Neurosurg 2003;98:785-92.
22. Yianni J, Bain P, Giladi N, et al. Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 2003;18:436-42.
23. Vercueil L, Pollak P, Fraix V, et al. Deep brain stimulation in the treatment of severe dystonia. J Neurol 2001;248:695-700.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
25. Bressman SB, Sabatti C, Raymond D, et al. The DYT1 phenotype and guidelines for diagnostic testing. Neurology 2000;54:1746-52.
26. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35:73-7.
27. Kumar R. Methods for programming and patient management with deep brain stimulation of the globus pallidus for the treatment of the advanced Parkinson's disease and dystonia. Mov Disord 2002;17:Suppl 3:S198-S207.
28. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF 36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
29. Beck AT. Beck depression inventory. San Antonio, Tex.: Psychological Corporation, 1997.
30. McCulloch CE, Searle SR. Longitudinal data. In: McCulloch CE, Searle SR, eds. Generalized, linear, and mixed models. New York: John Wiley, 2001:187-221.
31. Volkmann J, Benecke R. Deep brain stimulation for dystonia: patient selection and evaluation. Mov Disord 2002;17:Suppl 3:S112-S115.
32. Dostrovsky JO, Lozano AM. Mechanisms of deep brain stimulation. Mov Disord 2002;17:Suppl 3:S63-S68.
33. Vitek JL. Mechanisms of deep brain stimulation: excitation or inhibition. Mov Disord 2002;17:Suppl 3:S69-S72.
34. Hariz MI. Complications of deep brain stimulation surgery. Mov Disord 2002;17:Suppl 3:S162-S166.

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