Deep Brain Stimulation for Primary Generalized Dystonia

Long-term Outcomes

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Background: Pallidal deep brain stimulation (DBS) is the best therapeutic option for patients with disabling primary generalized dystonia (PGD) that is refractory to medications. However, little is known about its long-term effects.

Objective: To describe long-term clinical outcomes in patients with PGD who underwent pallidal DBS.

Design: Case series.

Setting: University hospital.

Patients: Thirty consecutive patients with at least 2 years’ follow-up after pallidal DBS for intractable PGD.

Interventions: Pallidal DBS and annual follow-up examinations up to 8 years after DBS implantation.

Main Outcome Measures: Clinical outcome as measured by changes in the Burke-Fahn-Marsden dystonia scale, incidence and prevalence of adverse events, total electrical energy delivered, and implantable pulse generator longevity.

Results: Twenty-three patients were followed for 3 years, 13 for 4 years, 9 for 5 years, 5 for 6 years, 5 for 7 years, and 1 for 8 years after DBS. Overall improvement at 1 year was maintained in all at successive yearly examinations. There were no intraoperative complications; hardware-related adverse events were infrequent. Rare stimulation-related adverse events primarily affected speech. Implantable pulse generators were replaced every 24 months on average in patients who received initial stimulation at 130-Hz frequency. No battery was replaced, for up to 48 months, in 20 patients initially stimulated using 60 Hz. Clinical outcome did not depend on high energies of stimulation.

Conclusions: Pallidal DBS is a safe and effective treatment for PGD, with improvement sustained for up to 8 years in 1 patient. Low energies of stimulation, although they did not affect clinical outcome, were associated with longer battery life.


METHODS

During the past decade, deep brain stimulation (DBS) at the internal globus pallidus (GPi) has emerged as the best therapeutic option for patients with disabling primary dystonia that is poorly responsive to pharmacologic treatment. A growing number of retrospective case series and prospective trials demonstrate the short-term efficacy of pallidal DBS in primary dystonia; however, few studies have examined the long-term effects in large cohorts. Because many patients with primary dystonia undergo implantation in childhood or adolescence, the long-term results of this intervention are of great interest. In this study, we investigated the long-term safety and efficacy of pallidal DBS in 30 consecutive patients with primary generalized dystonia (PGD) who were followed for at least 2 years after pallidal DBS surgery.

We reviewed the clinical records, including videotaped evaluations, of 30 consecutive patients with PGD implanted with pallidal DBS by the same neurosurgeon (R.L.A.) and almost exclusively followed by the same neurologist (M.T.) for a minimum of 2 years. No patients were lost to follow-up. The Mount Sinai School of Medicine institutional review board approved this study. Clinical outcomes at 1-year follow-up were previously published.

Diagnosis of PGD was defined by (1) a negative history of static encephalopathy, head trauma, cerebral ischemia, meningitis/encephalitis, neuroleptic treatments, or other causes of secondary dystonia; (2) the absence of neurologic findings other than dystonia, as determined by a movement disorders specialist (M.T.); and (3) normal findings on magnetic resonance imaging of the brain. Patients with PGD were offered DBS surgery if their symp-
toms were poorly controlled by standard medications and they were free of cognitive dysfunction or untreated psychiatric disturbances.

Twenty patients were male and 10 were female; their mean (SD) age at onset was 14 (10) years and at surgery was 28 (17) years. Twenty-seven patients had early-onset dystonia, and 20 tested positive for the DYT1 gene defect. Twenty-eight patients underwent bilateral implantation, 2 unilateral. Six patients (3 of them DYT1+) had fixed skeletal deformities (FSDs) at the time of surgery, in all cases scoliosis. Patients with FSDs were evaluated separately from the others because orthopedic deformities are unresponsive to stimulation, which creates a limit to possible improvement. The PGD and FSD groups were similar in mean (SD) age at onset of dystonia (14 [12] vs 13 [3] years) and at DBS surgery (28 [17] vs 31 [19] years). There was a higher prevalence of male patients in the FSD group (5 [3] vs 25 [17]%; P=.027). One patient with FSD underwent corrective spinal surgery 1 year after pallidal DBS.

The Burke-Fahn-Marsden Dystonia Rating Scale motor (BFMDRS-M) and disability (BFMDRS-D) subscales were used to evaluate the severity of dystonia at baseline (ie, within 2 weeks of surgery) and at each yearly follow-up visit. Reviews of videotaped evaluations were systematically performed for BFMDRS-M scoring by one of us (I.U.I.), who was blinded to the follow-up time of the taped segment. The BFMDRS-M score (range, 0-120) is the sum of 9 body region subscores, which define the follow-up time of the taped segment. The BFMDRS-D score (range, 0-120) is the sum of 9 body region subscores, which were grouped into 4 anatomical areas: face (eyes and mouth), speech and swallowing, and limbs. The total BFMDRS-D score (range, 0-30) is the sum of individual ratings for 7 activities: speech, handwriting, and the degree of dependence with respect to hygiene, dressing, feeding, swallowing, and walking. Higher scores indicate worse motor impairment and disability. Postoperatively, patients were evaluated only while receiving stimulation. Stimulation was never interrupted either electively or because of intolerable programming-related adverse events.

At each yearly follow-up, the clinical responses to stimulation were normalized by calculating the percentage change in the BFMDRS scores, relative to baseline, according to the following formula:

\[
\frac{\text{[Baseline BFMDRS \[Sub\]score} - \text{Postoperative BFMDRS \[Sub\] score]} \times 100\%
\]

Stimulation variables, including the active contact(s), amplitude in volts, pulse width (PW) in microseconds, and frequency in hertz, and indicators of implantable pulse generator (IPG) longevity (impedance, current drain, and battery voltage) were recorded at each follow-up visit. Total electrical energy delivered in 1 second (TEED$_{1\text{second}}$) was calculated according to the following formula:\(^\text{11}\)

\[
\frac{\text{[Voltage}^2 \times \text{Frequency} \times \text{PW}] \times \text{Impedance}} \times 1 \text{ Second}
\]

Daily intake of the following medications was monitored at each follow-up: dopamine agonists (levodopa and dopamine agonists), anticholinergics, antidepressants (eg, bupropion), and benzodiazepines. Twelve patients (including all 6 with FSDs) were receiving botulinum toxin injections before surgery. Medical therapy was progressively tapered based on a clinical judgment related to the degree of improvement. Medication reduction was calculated for every follow-up visit as the average percentage reduction in every antidystonia drug achieved by each patient.

**NEUROSURGICAL PROCEDURE AND DBS PROGRAMMING**

Each patient underwent frame-based, magnetic resonance imaging, and microelectrode-guided stereotactic implantation of DBS leads (model 3387; Medtronic Inc, Minneapolis, Minnesota) by one surgeon (R.L.A.), as described previously.\(^\text{12}\) Microelectrode recordings were used to refine these anatomically defined coordinates. A minimum 7-mm span of GPi was required for implantation. The presence of kinesthetic responses was observed in most cases but was not required for implantation. After exiting the GPi, the recording electrode was advanced an additional 2 to 3 mm in search of the optic tract. Again, a recordable response to the passing of light before the eyes of a patient was desirable but was not required for implantation. The DBS lead was implanted so that the deepest contact (0) lay at the inferior border of the GPi. Postoperative brain magnetic resonance imaging was routinely performed to confirm lead positioning within the posteroventral segment of the GPi. After 2004, patients were operated on with the approval of either the Beth Israel Medical Center, New York, Committee on Scientific Activities (April 1 to September 30, 2004) or the Mount Sinai School of Medicine institutional review board (February 1, 2005 to January 31, 2006) in accordance with the US Food and Drug Administration Humanitarian Device Exemption regulating the use of DBS for dystonia.

Device programming was conducted in a standardized manner as previously described.\(^\text{10}\) In brief, we systematically analyzed the 4 contacts on each lead in monopolar configuration to map clinical responses (when present) and the tolerability of stimulation, up to 4 V. The ventral-most contacts were preferentially, but not exclusively, used for therapy. After the initial programming session, adjustments were performed to maximize clinical benefit or reduce adverse effects.\(^\text{13}\)

Beginning in March 31, 2004, we almost exclusively used 60-Hz stimulation as initial frequency of stimulation.\(^\text{9}\) At the same time, we started using shorter PWs, never longer than 210 microseconds. This methodological shift created 2 subpopulations of patients: group 1 included 9 patients who received initial stimulation at a frequency of 130 Hz and were progressively titrated to long PWs; group 2 included 20 patients who were initially stimulated using 60 Hz and lower PWs. One patient had staged implants, the first of which was set at 130 Hz but later switched to 60 Hz after his second implantation. All hardware-related adverse events were identified, and their incidence was calculated in electrode-years, defined as the number of years with an electrode implanted.\(^\text{10,13}\)

**STATISTICAL ANALYSIS**

Statistical analysis was performed using a software package (JMP version 5.1; SAS Institute Inc, Cary, North Carolina). \(\chi^2\) analysis was used to test the demographic homogeneity between study groups regarding sex and DYT1 status. The Wilcoxon signed-rank test for matched pairs was used to compare BFMDRS-M and BFMDRS-D scores at each follow-up and at baseline. A pair represented data obtained in the same individual at different time points (eg, 3 years vs baseline, 3 years vs 1 year, etc). By comparing repeated measures across time, we could evaluate the efficacy and consistency of the DBS outcome and exclude the bias created by the fact that not every patient reached the same time end point. In addition, BFMDRS subscore percentage improvement was calculated and compared by means of 1-way analysis of variance. A Pearson correlation coefficient was calculated to investigate the relationship between clinical outcome and demographic features and the correlation between DBS settings, clinical improvement, and time to IPG replacement. A \(P<.05\) was considered to be statistically significant.
RESULTS

All 30 patients experienced significant improvement in motor function as measured using the BFMDRS-M and the BFMDRS-D. The BFMDRS-M score improved a mean (SD) of 79.6% (17.7%) (range, 40%-100%) at 1 year and 82.5% (15.3%) (range, 49%-100%) at 2-year follow-up; the BFMDRS-D score improved a mean (SD) of 69.2% (22.3%) (range, 7%-100%) at 1 year and 77.6% (16.8%) (range, 57.8%-100%) at 2-year follow-up (Table). Twenty-three patients were followed for 3 years after DBS, 13 for 4 years, 9 for 5 years, 5 for 6 years, 5 for 7 years, and 1 for 8 years. Overall clinical improvement was maintained at every successive examination and was still greater than 80% in the 5 patients who reached 7 years of follow-up (the Table and Figure 1).

Transient clinical regression was observed in patients whose batteries reached end of life or whose hardware malfunctioned. The time course of this regression was not captured by this study design, which included only a review of annual follow-up data. Two patients showed lasting regression exceeding 10%. In 1 case, generalization of previously achieved improvement was attributed to unsuccessful stimulation adjustments, which later recovered (Figure 1A). In another case, we observed axial and lower limb dystonia deterioration after a hip fracture (Figure 1C).

The 6 patients with FSDs showed consistently less improvement than those without FSDs, with the mean response ranging from 50% to 75%. Predictably, clinical improvement in this group was limited mainly by poorer responses in the axis and lower limbs. Patients with FSDs showed slower progression to maximum benefit (Figure 1C), but their clinical response was similarly maintained across time. One patient with FSDs underwent successful spinal surgery 1 year after DBS was implanted. After scoliosis correction, this patient further improved, reaching similar benefit of motor symptoms as patients with PGD (ie, 55% before and 93% after spinal surgery) (Figure 1C).

Except for SS, all body sites improved similarly at every time end point. The grand mean (SD) improvement was 91.2% (8.5%) for face scores, 90.5% (4.5%) for axial scores, and 88.5% (5.4%) for limb scores, whereas SS improved significantly less at every follow-up after DBS (48.3 [8.8]; P < .05). Of 15 patients with positive SS scores at baseline, 10 had spasmodic dysphonia (1 associated with dysphagia) and 5 had speech dystartha (4 associated with dysphagia). Two patients with spasmodic dysphonia showed no benefit, and a third worsened after DBS, as did 1 patient with dystartha. Lack of SS improvement was not related to any demographic or clinical features.

Most devices were set to a monopolar configuration at each follow-up: 54 of 58 leads at year 1 (18 single, 33 double, and 3 triple), 41 of 44 at year 3 (6 single, 31 double, and 4 triple), and 16 of 18 at year 5 (2 single, 12 double, and 2 triple); the remaining electrodes were set in a bipolar configuration (1 simple bipolar and 3 tripolar at 1 year, 1 simple bipolar and 2 tripolar at 3 years, and 1 simple bipolar and 1 tripolar at 5 years). Of the 100 active contacts used for effective stimulation at 1-year follow-up, contact 0 was used 15% of the time; contact 1, 38%; contact 2, 31%; and contact 3, 16%. No difference was found between active contacts used on the left and right sides. These percentages remained constant during the following years.

Demographic and baseline clinical characteristics did not differ between group 1 (130 Hz and long PW) and group 2 (60 Hz and shorter PW), except for a higher male to female ratio in group 2 (16 to 4 vs 4 to 5 in group 1). No significant difference in clinical outcome was found at any yearly follow-up between the 2 groups (Figure 1A and B). Higher energies of stimulation translated into 39 IPG replacements in group 1. The mean (SD) IPG lifetime in this group was 24 (6) months. In contrast, no IPG replacements have yet been required in the group receiving 60-Hz stimulation, at up to 48 months of follow-up in 2 patients, except for 1 IPG that was replaced after 40 months for device malfunction. As expected, time to IPG replacement strongly correlated with TEED1-second and IPG current drain (Figure 2A and B). However, there was no correlation between TEED1-second and clinical outcome (Figure 2C).

Changes in medication requirements at each follow-up are given in the Table. Seven patients (1 with

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Table. Long-term Clinical Outcome of 30 Patients With PGD After Pallidal DBS

<table>
<thead>
<tr>
<th>Visit Year</th>
<th>Patients (PGD/FSDs), No.</th>
<th>BFMDRS-M, Mean (SD) [Range]</th>
<th>BFMDRS-D, Mean (SD) [Range]</th>
<th>Drug Reductions, Mean (SD) [Range], %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30 (24/6)</td>
<td>44 (23.3) [9-81.5]</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30 (24/6)</td>
<td>3.9 (6.9) [3-33]</td>
<td>79.6 (17.7) [40-100]</td>
<td>10.6 (5.6) [3-24]</td>
</tr>
<tr>
<td>2</td>
<td>30 (25/5)</td>
<td>7.2 (7.5) [24-25.5]</td>
<td>82.5 (15.3) [49-100]</td>
<td>3 (3.0) [0-13]</td>
</tr>
<tr>
<td>3</td>
<td>23 (21/3)</td>
<td>6.7 (7.8) [28-28]</td>
<td>85.5 (14.2) [47-100]</td>
<td>2.4 (2.2) [0-9]</td>
</tr>
<tr>
<td>4</td>
<td>13 (10/3)</td>
<td>8.4 (10.7) [27-27]</td>
<td>84.7 (14.6) [59-100]</td>
<td>2.5 (3.7) [0-13]</td>
</tr>
<tr>
<td>5</td>
<td>9 (6/3)a</td>
<td>10.7 (9.8) [1-24]</td>
<td>83.1 (11.5) [67-99]</td>
<td>2.5 (3.2) [0-10]</td>
</tr>
<tr>
<td>6</td>
<td>5 (3/2)</td>
<td>13.7 (13.0) [33-35]</td>
<td>81.8 (17.1) [56-98.8]</td>
<td>5.6 (8.2) [0-20]</td>
</tr>
<tr>
<td>7</td>
<td>5 (3/2)</td>
<td>13.6 (12.8) [1-33]</td>
<td>82 (16.8) [57-98.8]</td>
<td>5.6 (8.2) [0-20]</td>
</tr>
<tr>
<td>8</td>
<td>1 (1/0)</td>
<td>98.8</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: BFMDRS-M and BFMDRS-D: Burke-Fahn-Marsden Dystonia Rating Scale motor and disability subscales, respectively; DBS, deep brain stimulation; FSDs, fixed skeletal deformities; NA, not applicable; PGD, primary generalized dystonia.

a One patient with FSDs underwent corrective spinal surgery 1 year after DBS implantation.
b One patient had hip fracture 3 months before her 6-month follow-up visit.
FSDs) were not taking any medication at the time of DBS surgery. Twelve of the remaining 23 patients (52%) had discontinued all medications 1 year after surgery, and none had resumed pharmacologic therapy at the time of their last follow-up. One patient with PGD and 3 with FSDs needed botulinum toxin injections 1 year after surgery.

There were no intracerebral hemorrhages or adverse neurologic events in this series of patients. Eight patients (27%) experienced 11 hardware-related adverse events throughout the study, which is equivalent to a complication rate of 4.9% (11 of 225 electrode-years). Adverse events included 5 infections (2 in the same patient), all successfully treated. Two patients experienced a fractured extension cable, both of which were replaced without adverse sequelae. One patient had scalp erosion without infection that was treated with wound revision. One IPG required surgical replacement owing to malfunction rather than battery depletion. In 2 patients, lead position was electively revised because of lack of benefit. There were no complications related to revision surgery. Stimulation-related adverse events were limited to 3 patients (10%) who reported speech difficulties not present at baseline and 1 patient (3%) who reported transient blepharospasm.

The results of this retrospective analysis support the notion that pallidal DBS is a safe and effective treatment for medically refractory PGD. These data show that the symptomatic and functional improvements observed after 1 to 2 years of stimulation were maintained for up to 8 years in 1 patient without significant changes in stimulation variables. In addition, we extend a previous finding that stimulation at 60 Hz yields clinical outcomes equivalent to higher stimulation frequencies while extending the longevity of the IPGs. The retrospective, uncontrolled design is a potential limitation of this study, partially compensated for by systematic videotaped evaluations, which were subsequently reviewed by an examiner blind to the follow-up time of the video segment.

Sustained motor and quality-of-life improvements in patients with PGD after pallidal DBS has been well documented up to 3 years. Clinical results extending beyond 3 years have been reported in only a few patients. In 1 study, 6 patients with PGD were followed for up to 5 years after pallidal DBS and showed sustained improvement. A single patient with PGD and a BFMDRS improvement of 30% sustained for 7 years after pallidal DBS was described as part of a larger series of patients. Two more patients with PGD followed for 5 and 6 years after pallidal DBS were reported, but their objective scores were limited to 1 and 3 years of follow-up and showed mild decline in motor improvement in both patients.

The present population of patients with PGD without FSDs improved, on average, more than 80% as measured using the BFMDRS-M at each follow-up visit. This remarkable clinical outcome may reflect the young age and short duration of disease of this cohort. Only 2 patients showed significant regression of their maximum clinical improvement, possibly related to unsuccessful stimulation adjustment in 1 case and a severe orthopedic lesion in another. Patients with FSDs showed a lesser degree of improvement, mainly limited by scoliosis. One patient with FSDs experienced additional improvement after corrective spinal surgery, which suggests that correction of FSDs may enhance the clinical outcome of DBS surgery.

No patient experienced an adverse neurologic event during surgery. Hardware- and stimulation-related adverse events were observed in 23% and 13% of patients, respectively. Hardware-related complications, including IPG malfunction, have been reported in long-term follow-up studies with an incidence ranging from 13% to 40%. In the present study, the 4.9% complication rate per electrode-year is at the low end of the 4.3%
to 9.5% range reported in previous works\textsuperscript{14,15,20} that included other targets and disease populations. Given our relatively long cumulative observation time, these data support the observation that the incidence of hardware-related complications decreases with time.\textsuperscript{15} We did not observe the high incidence of slipped and fractured DBS leads previously reported in patients with dystonia.\textsuperscript{21} This is possibly because, at least in part, of the fact that this population included fewer patients with severe mobile cervical dystonia.

Stimulation-related adverse events were virtually limited to speech abnormalities, similar to that reported by other groups.\textsuperscript{3,4,19} In general, SS dystonic abnormalities were the least responsive to DBS, with one-quarter of symptomatic patients showing no improvement or worsening. The SS changes were highly variable throughout the study, possibly owing to the BFMDRS scoring system itself, which lumps in the same category swallowing problems and different speech abnormalities (eg, spasmodic dysphonia and dysarthria). The SS symptoms should be further evaluated in dedicated studies.

As expected, IPG life span was directly related to TEED\textsubscript{1 second} and battery current drain. We could not calculate a formula that would predict the time to IPG replacement based on actual current drain because not all the IPGs were replaced at least once in this cohort. In general, patients treated with lower stimulation frequencies and shorter PWs benefited from longer battery life without experiencing a worse clinical outcome. In fact, no correlation was found between TEED\textsubscript{1 second} and clinical improvement. These findings support other recent studies suggesting that the minimal effective stimulation PW and frequency for PGD may be lower than originally thought.\textsuperscript{6,22}

In conclusion, pallidal DBS is a safe and effective treatment for patients with medically refractory PGD, with

![Figure 2. Effects of DBS energy on IPG longevity and clinical outcomes. Effect of total electrical energy delivered in 1 second (TEED\textsubscript{1 second}) by deep brain stimulation system (A) and current drain (B) on the life span of 39 implantable pulse generators (IPGs). Higher current drain and TEED\textsubscript{1 second} values strongly correlated with shorter IPG life span. C, Correlation between TEED\textsubscript{1 second} and percentage clinical improvement as measured using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). No correlation was found between TEED\textsubscript{1 second} and clinical improvement.](https://www.archneurol.com/content/66/4/469.full.long.pdf)
sustained benefit for up to 8 years after surgery. Stimulation at 60 Hz and shorter PWs seem to achieve sustained clinical outcomes that are equivalent to those obtained using higher energies of stimulation with the added benefit of prolonging battery life. Further work is needed to determine the most efficient long-term stimulation settings for pallidal DBS in dystonia.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Isaias, Alterman, and Tagliati. Acquisition of data: Alterman and Tagliati. Analysis and interpretation of data: Isaias, Alterman, and Tagliati. Drafting of the manuscript: Isaias and Tagliati. Critical revision of the manuscript for important intellectual content: Alterman and Tagliati. Statistical analysis: Isaias and Tagliati. Obtained funding: Tagliati. Administrative, technical, and material support: Alterman. Study supervision: Alterman and Tagliati.

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REFERENCES