# 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.

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**METHODS**

**Clinical Evaluation and Selection Criteria**

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.8,9

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 pa-
tients underwent bilateral implantation, 2 unilateral. Six pa-
tients (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
was a higher prevalence of male patients in the FSD group (5
1 to 1 vs 15 to 9; \(P < .027\)). 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 vid-
earthed 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
was set at 130 Hz but later switched to 60 Hz after his sec-
tal implantation. All hardware-related adverse events were
identified, and their incidence was calculated in electrode-
ond implantation.14,15 patients who were initially stimulated using 60 Hz and lower
were progressively titrated to long PWs; group 2 included 20
patients who were preferentially, but not exclusively, used for therapy.

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

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

Statistical analysis was performed using a software package
(JMP version 5.1; SAS Institute Inc, Cary, North Carolina). \(x^2\)
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
calculate and 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 mea-
ures across time, we could evaluate the efficacy and consist-
sity 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 cal-
culated 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.

**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, Min-
esto) by one surgeon (R.L.A.), as described previously. Microelectrode recordings were used to refine these anatomi-
cally derived 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. Post-
operative brain magnetic resonance imaging was routinely
performed to confirm lead positioning within the posterovent-
ral 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 Sep-
tember 30, 2004) or the Mount Sinai School of Medicine insti-
tutional 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. In brief, we systematically
analyzed the 4 contacts on each lead in monopolar configura-
tion to map clinical responses (when present) and the toler-
ability 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 per-
formed to maximize clinical benefit or reduce adverse effects.

Beginning in March 31, 2004, we almost exclusively used
60-Hz stimulation as initial frequency of stimulation. At the
same time, we started using shorter PWs, never longer than
210 microseconds. This methodological shift created 2 sub-
populations 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 sec-
tal 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.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using a software package
(AMEND version 3.1; SAS Institute Inc, Cary, North Carolina). \(x^2\)
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
calculate and 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 mea-
ures across time, we could evaluate the efficacy and consist-
sity 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 cal-
culated 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% (20.1%) (range, 12.5%-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, generalized deterioration 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 dysarthria (4 associated with dysphagia). Two patients with spasmodic dysphonia showed no benefit, and a third worsened after DBS, as did 1 patient with dysarthria. 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 tripo- lar at 1 year, 1 simple bipolar and 2 tripo lar at 3 years, and 1 simple bipolar and 1 tripo lar 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.

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

**COMMENT**

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 average 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 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. We did not observe the high incidence of slipped and fractured DBS leads previously reported in patients with dystonia. 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. 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 TEED1 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 TEED1 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.

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


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