Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results

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Object. Primary generalized dystonia (PGD) is a medically refractory disease of the brain causing twisting or spasmodic movements and abnormal postures. In more than 30% of cases it is associated with the autosomal DYT1 mutation. Continuous electrical stimulation of the globus pallidus internus (GPi) has been used successfully in the treatment of PGD. The aim of this study was to examine the long-term efficacy and safety of deep brain stimulation (DBS) in the treatment of PGD in children and adults with and without the DYT1 mutation.

Methods. Thirty-one patients with PGD were selected for surgery. Electrodes were bilaterally implanted under stereotactic guidance and connected to neurostimulators that were inserted subcutaneously. Efficacy was evaluated by comparing scores on the clinical and functional Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) before and after implantation.

The efficacy of stimulation improved with time. After 2 years, compared with preoperative values, the mean (± standard deviation) clinical and functional BFMDRS scores had improved by 79 ± 19% and 65 ± 33%, respectively. At the 2-year follow-up examination the improvement was comparable in patients with and without the DYT1 mutation in both the functional (p = 0.12) and clinical (p = 0.33) scores. Children displayed greater improvements in the clinical score than adult patients (p = 0.04) at 2 years of follow up. In contrast, there was no significant difference in functional scores between children and adults (p = 0.95).

Conclusions. Electrical stimulation of the GPi is an effective, reversible, and adaptable treatment for PGD and should be considered for conditions refractory to pharmaceutical therapies.

KEY WORDS • dystonia • deep brain stimulation • globus pallidus • DYT1

Abbreviations used in this paper: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation; GPi = globus pallidus internus; IPG = implantable pulse generator; MR = magnetic resonance; PGD = primary generalized dystonia.

YSTONIA is a condition in which a pathological process occurring in the basal ganglia induces a decrease in the inhibition of the brain cortex. In the most severe forms there is an early onset and rapid development of dystonic symptoms during childhood. Patients face a high risk of a severe handicap and, in a few cases, life-threatening complications.

Many phenotypic descriptions have been reported, but only three so far have been connected with mutations. One form, called levodopa-responsive PGD, is treatable with medication and is thus not suitable for DBS. The second is a recurrent autosomal-dominant mutation known as 946del GAG, which has been isolated to the DYT1 gene on chromosome 9q32–34. The third is an autosomal-dominant mutation of the sarcomere gene on chromosome 7q21 (SGCE), which is responsible for myoclonic–dystonia (DYT11). Apart from these forms, the origins of most dystonic syndromes remain unknown and they present with a high degree of phenotypic polymorphism.

Pharmacological treatment for PGD (other than levodopa-responsive PGD) is usually ineffective, both in suppressing abnormal movements and in slowing disease progression. Various surgical approaches have been attempted, but have proved to be poorly effective in the long term. Bilateral pallidotomy has recently been reconsidered to be a possible treatment for the more severe forms of PGD. Its long-term efficacy has not been clearly established, however, and its use remains controversial, especially in children.

Deep brain stimulation therapy involving electrical stimulation of the GPi is effective in the treatment of akinetic hypertonic disorders and the levodopa-induced dyskinesia associated with PD. Using this method, electrodes are implanted bilaterally in the brain under stereotactic guidance and connected postoperatively to neurostimulators implanted subcutaneously.

We first used DBS to treat PGD in 1996. The patient was an 8-year-old girl who had been maintained in a state of general anesthesia for 8 weeks. Under these exceptional circumstances, GPi stimulation was attempted as a last resort,
based on the established efficacy the technique had shown in the treatment of levodopa-induced dyskinesia in patients with PD. As a result of the success of this first surgery, the technique has been developed for use in patients with PGD and has been applied successfully at several different centers.

In this study 31 patients with advanced PGD were treated using long-term bilateral electrical stimulation of the GPi. Our aim was to examine the long-term efficacy and safety of the technique in children and adults with and without the DYT1 mutation.

**Clinical Material and Methods**

**Patient Population**

Between November 1996 and June 2001, 31 patients with PGD (12 adults and 19 children; 14 male and 17 female patients) were surgically treated consecutively. All patients met the criteria for PGD outlined by Fahn. These diagnostic criteria were applied by at least two neurologists. The mean age of the patients at onset of dystonia was 17.8 ± 9.5 years (minimum 6 years, maximum 42 years). The mean duration of follow up was 42.1 ± 14.8 months (minimum 24 months, maximum 78.5 months). The mean duration of the disease at the time of surgery was 9.7 ± 7.8 years. Informed written consent was obtained from all patients or their families as appropriate.

The presence of the mutation 946del GAG was used to screen directly for the DYT1 mutation. The DYT1 mutation was found in 14 of 31 patients.

**Study Design**

In this study we examined the effect of time and the presence of the DYT1 mutation on functional and clinical outcomes following DBS in adults (> 17 years of age) and children (≤ 17 years of age).

Before implantation 25 of 31 patients were receiving medication. After implantation the patients continued to receive their preoperative medication, at least until the end of the 1st year. In 14 patients medication was then decreased gradually and discontinued by the end of the 2nd year.

**Clinical Examination**

Dystonic movements and abnormal postures were assessed using the BFMDRS. This scale consists of two parts: Part I (clinical assessment) and Part II (functional assessment). Higher scores represent higher levels of disability. Part I is used to quantify the dystonia by reference to nine different body areas by rating both the triggering factor of the dystonic movement and its extent and severity on a scale of 0 to 120. Part II is used to quantify the patient’s abilities with regard to activities of daily living and reflects the quality of life on a scale of 0 to 30. Patients were examined by two physicians (P.C. and L.C.) who arrived at a consensus opinion. Examinations were performed immediately before implantation of the electrodes, daily during the postoperative hospital stay, monthly during the 1st year, and at intervals of 3 months thereafter. The pre- and postoperative absolute scores of the BFMDRS were assigned. Benefits of the procedure were shown by the following equation: (preoperative score − postoperative score)/preoperative score × 100.

**Surgical Procedure**

The operation was performed after induction of standard general anesthesia. Bilateral implantation of a pair of electrodes, each comprising four contacts conventionally numbered 0 (distal) to 3 (proximal) (DBS 3389; Medtronic, Inc., Minneapolis, MN), was performed in each patient in a single session under strict-profile radioscopic control. General anesthesia was mandatory to eliminate intraoperative dystonic movements that could result in displacement within the stereotactic frame with the consequent compromise of the high precision required, and to maintain constant hemodynamic conditions. The MR-compatible Leksell ste reotactic frame was applied and the posteroventral portion of the GPi was located by means of axial, sagittal, and coronal MR images. Dedicated software (Val de Grâce Hospital, Paris, France) was used to calculate the cartesian target coordinates (x, y, and z) and the trajectory angles (α and β). We placed the upper border of Contact 1 on the target. In our protocol, it has been validated to be the most efficient. The target was chosen vertically on the axial slice at the level of the anterior commissure and horizontally at the junction between the two posterior quarters of the GPi. The coordinates (x, y, and z) were then automatically calculated using dedicated software. The best electrode trajectory was selected to be in the direction of the coronal suture and as vertical as possible to avoid vessels, ventricles, and sulci. On reconstructed images, viewed perpendicular to the electrode trajectory, we checked the position of each contact inside the GPi. Finally, we examined whether the trajectory projected onto the external border of the optic tract. The same planning was performed on both sides.

Afterward, in the operating room, the stereotactic electrode–guiding device was installed and a 14-mm burr hole was made at the level of the predetermined trajectory. No microelectrode recording was used. Electrode implantation was achieved under a real-time strict-profile radioscopic control. The distal connectors of the electrodes were placed subcutaneously and the patient, still in a state of general anesthesia, was transported back to the MR imaging unit, where an immediate postoperative stereotactic image was obtained to verify the electrode’s position, detect any error caused by MR imaging distortions, and identify any hemorrhagic complications. The electrode coordinates were checked to ensure that they were on the selected target. This demonstrated the safety and accuracy of the entire procedure with an overall precision to within less than 1.015 mm (the size of the pixel). No hemorrhage was detected on the postoperative MR images.

Five days after implantation the electrodes were connected to two neurostimulators (Itrel II or III; Medtronic, Inc.), which were implanted subcutaneously within the abdominal area through a subcostal, linear, 4-cm-long incision. Telemetric programming of the neurostimulator was performed by the physician following implantation and subsequently after each follow-up examination. The neurostimulator was initially set for continuous bilateral stimulation at a pulse rate of 130 Hz, a pulse width of 450 μsec, and a voltage of 0.8 V, with Contact 1 as the cathode positioned in the targeted volume and the case as the anode (monopo-
Deep brain stimulation of the GPi in patients with dystonia

### Results

At the time of surgery, all 31 patients were severely disabled in their performance of daily activities (Tables 1 and 2). After GPi stimulation, the patients’ dystonic movements and abnormal postures decreased considerably and their motor functions greatly improved (Fig. 1). For all 31 patients, improvement was highly significant at each follow-up examination: 3 months, 6 months, 1 year, and 2 years, for functional and clinical BFMDRS scores (p < 0.0001 for all the tests).

In patients with the DYT1 mutation (the DYT1-positive group), changes in the BFMDRS functional (maximum possible score 30) and clinical (maximum possible score 120) scores over time were highly significant (p = 0.0014 and p < 0.0001, respectively) as well as in patients without the mutation (p = 0.0006 and p = 0.0002, respectively) (Tables 1 and 2).

Changes in the functional and clinical BFMDRS scores over time were highly significant in children (p = 0.0004 and p < 0.0001, respectively) as well as in adult patients (p = 0.006 and p = 0.0003, respectively) (Tables 1 and 2). At the 2-year follow up the relative difference was not statistically significant in the DYT1-positive and DYT1-negative groups in either the functional (p = 0.33) or clinical (p = 0.12) scores (Table 3). Children were more improved (relative variation) than adult patients according to the clinical score (p = 0.04) at the 2-year follow up. In contrast, there was no significant difference between children and adults according to the functional score (p = 0.95) (Table 3).

At the 2-year follow up there was no significant difference between children with or without the DYT1 mutation with regard to clinical improvement (p = 0.1). Functional improvement, however, was significantly greater in children who had the DYT1 mutation than those without the mutation (p = 0.03). In the adult population, there was

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### Statistical Analysis

The mean pre- and postoperative absolute scores of the BFMDRS and the rate of improvement ((preoperative score – postoperative score)/preoperative score × 100) were calculated, as well as the associated standard deviations according to the clinical and functional parts of the BFMDRS for all patients. These data were calculated a second time in several subgroups of patients, which were defined according to the presence of the DYT1 mutation and the age of the patients (>17 years of age and ≤ 17 years of age).

The effect of time on the clinical and functional scores of the BFMDRS was tested using a multivariate repeated-measures analysis of variance. The findings of a significant overall time effect was followed by post hoc analyses with an overall probability value of 0.05. Patient age and the effect of the DYT1 mutation were tested using a t-test or the nonparametric Mann–Whitney U-test, depending on the normality of the distributions.

The statistical software SAS Enterprise version 6.12/UNIX (proc univariate, proc glm, proc test, proc npar1way; SAS Institute, Cary, NC) was used for the statistical analysis.

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### TABLE 1

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Preop Value</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>2 Yrs</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>all (31 patients)</td>
<td>59.1 ± 26.4</td>
<td>17.7 ± 20.0</td>
<td>15.3 ± 15.6</td>
<td>12.6 ± 14.0</td>
<td>12.9 ± 13.2</td>
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<tr>
<td>% improvement</td>
<td>72.0 ± 24.9</td>
<td>74.8 ± 21.2</td>
<td>78.6 ± 23.1</td>
<td>79.0 ± 19.2</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>DYT1-positive (14 patients)</td>
<td>62.6 ± 26.1</td>
<td>20.7 ± 27.3</td>
<td>12.8 ± 17.2</td>
<td>9.9 ± 14.4</td>
<td>12.4 ± 15.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>score</td>
<td>72.3 ± 33.6</td>
<td>82.4 ± 19.2</td>
<td>84.6 ± 21.2</td>
<td>83.0 ± 16.8</td>
<td>0.0002</td>
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<tr>
<td>% improvement</td>
<td>56.3 ± 27.1</td>
<td>15.6 ± 11.7</td>
<td>17.4 ± 14.4</td>
<td>14.9 ± 13.7</td>
<td>13.4 ± 12.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>DYT1-negative (17 patients)</td>
<td>57.9 ± 28.5</td>
<td>24.2 ± 23.5</td>
<td>21.5 ± 18.8</td>
<td>18.9 ± 17.1</td>
<td>18.9 ± 17.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>% improvement</td>
<td>71.8 ± 15.6</td>
<td>68.6 ± 21.3</td>
<td>73.7 ± 24.0</td>
<td>75.8 ± 20.9</td>
<td>15.6 ± 12.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>children (19 patients)</td>
<td>59.8 ± 25.8</td>
<td>13.5 ± 16.9</td>
<td>11.4 ± 12.2</td>
<td>8.7 ± 10.4</td>
<td>9.2 ± 8.3</td>
<td>—</td>
</tr>
<tr>
<td>score</td>
<td>78.4 ± 25.8</td>
<td>81.9 ± 14.3</td>
<td>84.8 ± 17.6</td>
<td>84.7 ± 13.6</td>
<td>—</td>
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</tbody>
</table>

* — = not applicable.
† Values are expressed as means ± standard deviations. The highest (worst) possible clinical BFMDRS score is 120. A reduction in score indicates an improvement in dystonia. The percentages of improvement are calculated based on the patient’s best possible gain according to the following formula: (preoperative score – postoperative score)/preoperative score × 100.
‡ Based on an analysis of variance. A probability value less than 0.05 is considered significant.
We observed one case of delayed unilateral infection \((\text{Staphylococcus epidermidis})\) of an IPG in a bedridden 6-year-old patient. After induction of general anesthesia the system was removed. It was reimplanted 6 months later, leading to a clinical improvement. No additional adverse events were observed.

**DISCUSSION**

Our data confirm the efficacy at 2 years of follow up of GPi stimulation in patients suffering from severe forms of dystonia. The stereotactic operation was performed with the patient in a state of general anesthesia and without microelectrode recording. The accuracy of this method for GPi targeting has been previously evaluated.\(^{29}\) This approach is especially appropriate in patients with dystonia.\(^{29}\) Since DBS was first proposed for treating the most severe cases of generalized dystonia, its superior efficacy in PGD, compared with secondary generalized dystonia, has been reported.\(^{8,16,17}\)

Most series have been composed of a limited number of patients\(^{16}\) and have had short follow-up periods;\(^{32}\) however, this treatment seems to be efficient in most cases of primary dystonia, whatever the topography of the symptoms may be (from spasmodic torticollis to generalized dystonia). Of course, additional studies are necessary to confirm the long-term results.

In our experience, the risk of delayed infection of the implanted system appears to be the main potential complication of this technique. Great care must be taken to eradicate any chronic dental granuloma before operation, especially in bedridden children with a poor general condition. Using the MR-based surgical protocol developed at our center, however, we have encountered a lower rate of surgery-related morbidity than those associated with other forms of surgery.\(^{9}\)

Hemorrhage of the intracerebral tract has previously been reported,\(^{24}\) but none occurred in the present study. This was probably a result of the careful use of MR imaging during the planning stage, which enabled blood vessels to be locat-

**TABLE 2**

*Functional BFMDRS scores in 31 patients with PGD who were treated by long-term neurostimulation of the GPi*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Preop Value</th>
<th>Postop Value*</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>2 Yrs</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>all (31 patients)</td>
<td>score 16.5 ± 7.8</td>
<td>8.8 ± 8.1</td>
<td>8.3 ± 8.2</td>
<td>6.9 ± 7.5</td>
<td>6.3 ± 6.9</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>DYT1-positive (14 patients)</td>
<td>score 16.8 ± 6.9</td>
<td>6.6 ± 6.9</td>
<td>6.2 ± 7.0</td>
<td>4.5 ± 5.8</td>
<td>4.2 ± 4.6</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>50.1 ± 32.1</td>
<td>51.5 ± 36.1</td>
<td>60.1 ± 34.1</td>
<td>65.2 ± 33.0</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DYT1-negative (17 patients)</td>
<td>score 16.4 ± 8.7</td>
<td>10.7 ± 8.8</td>
<td>10.1 ± 8.9</td>
<td>8.9 ± 8.2</td>
<td>8.0 ± 8.2</td>
<td>0.0006</td>
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</tr>
<tr>
<td>% improvement</td>
<td>40.7 ± 25.7</td>
<td>41.2 ± 32.6</td>
<td>50.9 ± 27.7</td>
<td>58.2 ± 32.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adults (12 patients)</td>
<td>score 14.4 ± 8</td>
<td>6.8 ± 5.9</td>
<td>6.8 ± 5.2</td>
<td>6.3 ± 5.3</td>
<td>4.8 ± 4.3</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>51.7 ± 26.5</td>
<td>47.4 ± 32.6</td>
<td>55.9 ± 25.9</td>
<td>69.1 ± 23.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>children (19 patients)</td>
<td>score 17.9 ± 7.5</td>
<td>10.1 ± 9.2</td>
<td>9.4 ± 9.6</td>
<td>7.3 ± 8.7</td>
<td>7.2 ± 8.2</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>49.2 ± 35.9</td>
<td>54.1 ± 38.8</td>
<td>62.8 ± 38.8</td>
<td>62.8 ± 38.3</td>
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</table>

* Values are expressed as means ± standard deviations. The highest (worst) possible functional BFMDRS score is 30.

**FIG. 1.** Changes in functional (upper) and clinical (lower) BFMDRS scores over time in 31 patients with PGD treated by DBS. The first measurement value in each figure represents the preoperative score.
ed with precision, and the direct visual control of the cortical puncture through the 14-mm burr hole at the time of electrode insertion. In addition, electrode implantation was accomplished via a single track without the use of microelectrode recordings or ventriculography.

The postimplantation clinical BFMDRS scores were higher in children than in adults. This can largely be ascribed to the chronic deterioration in health over time with special attention to the omnipresent skeletal deformities that had been induced by dystonia. The most frequent of these were scoliosis and talipes varus and equinus, which often required separate management. This finding is a strong argument in favor of an early operation, especially for early-onset forms of dystonia, because surgery may enable us to limit or prevent such deformities.

In a few instances it was possible to observe the effect of discontinuation of stimulation (for example, at times when an IPG unexpectedly switched off, during a period in which the IPG was turned off to obtain sleep electroencephalograms, or in the one case in which the IPG had to be removed as a result of infection). In all such cases symptoms recurred within 1 week and disappeared quickly on reactivation of stimulation.

A delay in the response of dystonic symptoms to DBS after the initial implantation of the electrode was observed consistently; we hypothesized that this could be explained by a progressive reorganization of the damaged neuronal network either inside or outside the Gpi.

Deep brain stimulation was initially developed for use in adults. Nevertheless, its conservative, adaptable, and reversible nature renders it particularly suitable for the treatment of children, who show a remarkable tolerance of the therapy. Placement of the IPG in the abdominal area seems preferable: the thickness of the skin and fatty tissues contribute to better incision healing and overall outcome. Furthermore, it appears that growth does not interfere with stimulation and the implantation of a single 90-cm extension can compensate adequately for the growth of the child.

No displacement of electrodes over time was observed; this can probably be ascribed to the fact that the growth potential of the brain and cranium is limited after a child is 3 years of age.

In conclusion, the results of this study indicate that continuous electrical stimulation of the Gpi should be considered a highly efficient therapy for PGD, on the grounds of both efficacy and safety. It can be proposed at the initial phase of the disease to limit the functional consequences and to improve the prognosis for functional recovery.

### References


### Table 3

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Improvement (%)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1-positive (14 patients)</td>
<td>83.0 ± 16.8</td>
<td>0.12</td>
</tr>
<tr>
<td>DYT1-negative (17 patients)</td>
<td>75.8 ± 20.9</td>
<td>0.04</td>
</tr>
<tr>
<td>adults (12 patients)</td>
<td>70.1 ± 23.6</td>
<td></td>
</tr>
<tr>
<td>children (19 patients)</td>
<td>84.7 ± 13.6</td>
<td></td>
</tr>
<tr>
<td>DYT1-positive (3 patients)</td>
<td>62.5 ± 5.3</td>
<td>0.54</td>
</tr>
<tr>
<td>DYT1-negative (9 patients)</td>
<td>72.7 ± 27.1</td>
<td></td>
</tr>
<tr>
<td>children</td>
<td>88.5 ± 14.2</td>
<td>0.10</td>
</tr>
<tr>
<td>DYT1-positive (11 patients)</td>
<td>79.3 ± 11.5</td>
<td></td>
</tr>
<tr>
<td>DYT1-negative (8 patients)</td>
<td>44.5 ± 34.8</td>
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</table>

* The effects of patient age and the DYT1 mutation were examined.
† Comparison study. A probability value less than 0.05 is considered significant.

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