Bilateral Pallidal Stimulation for X-Linked Dystonia Parkinsonism

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Objective: To report the clinical benefits of bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi) in a patient with X-linked dystonia parkinsonism (XDP).

Main Outcome Measures: The primary outcome measures were the Burke-Fahn-Marsden Dystonia Scale (BFMDS) severity and disability scores, and the secondary outcome measure was the Unified Parkinson Disease Rating Scores.

Results: At the 1-year postoperative follow-up, there was 80.4% improvement in the BFMDS severity score and 66.7% improvement in the BFMDS disability score.

Conclusion: Bilateral GPi DBS seems to be very effective in improving dystonia in XDP.

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UBAG, or X-Linked Dystonia parkinsonism (XDP; DYT-3 [monogenetic form of dystonia]), is a rare genetic disorder that affects men and, rarely, women, with maternal roots from the Philippine island of Panay. The disorder most commonly presents in the third to fourth decade of life with progressive, severe dystonia dominating the first 10 to 15 years of illness; it is later replaced by parkinsonian features.1,2 Parkinsonism as a presenting feature is relatively uncommon. Those with onset of segmental dystonia usually progress to generalized dystonia within 5 or 6 years.1,2

Report of a Case

A 37-year-old Filipino man born on the Philippine island of Panay first presented with blepharospasm in 2005. The dystonia rapidly spread to involve the entire face and neck and affected his speech, with concurrent development of limb rigidity and bradykinesia (video 1, http://www.archneurol.com). During the subsequent year, the dystonia spread to involve his trunk and limbs, resulting in progressive gait dysfunction. Molecular genetic testing confirmed the clinical diagnosis of XDP by demonstrating a mutated allele (T) at DSC3 and a mutated allele (G) at DSC12 on the X chromosome.7

The patient had been treated with botulinum toxin A injections for the orofacial and cervical dystonia (2 sessions of 400 IU each) with only partial relief, 12 mg/d of trihexyphenidyl, 75 mg/d of tetrabenazine, 15 mg/d of baclofen, 3.5 mg/d of clonazepam, 1 mg of lorazepam as required, and 100 mg/d of trazodone. Despite the above treatment he...
became severely disabled and was unable to care for himself, thus requiring admission to a nursing home. He was considered for DBS surgery for medically intractable dystonia.

When we first evaluated the patient in December 2007, he presented with severe generalized dystonia. His Burke-Fahn-Marsden Dystonia Scale (BFMDS) severity score was 67 (range, 0-120, with higher scores indicative of worse dystonia). Dystonia was present at rest in his limbs, face, neck, and trunk. He presented with frequent arching of the trunk (opisthotonus) and laryngeal stridor. He used a wheelchair, and a seatbelt was used to prevent him sliding from his chair. He required assistance for all basic activities of daily living. In addition to dystonia, he also presented with parkinsonian features (hypomimia, bradykinesia, and limb rigidity). His Unified Parkinson Disease Rating Scale (UPDRS) part III (motor) score was 40 of a possible 108. Neuropsychiatric assessment revealed mild executive dysfunction with impairment in visuospatial reasoning, sequencing, and working memory. Findings of brain and cervical spine magnetic resonance imaging (1.5 T) were normal.

The dystonia continued to progress until the time of surgery (preoperative BFMDS severity and disability scores were 13% and 4% worse, respectively, compared with 6 months earlier) (video 2; Table). The patient also developed swallowing difficulty, necessitating placement of a gastrostomy tube for feeding. At this time, 100 mg/d of trazodone had been added to his treatment regimen.

Bilateral GPi DBS was performed under general anesthesia in June 2008 using standard stereotactic and microelectrode techniques, as described previously. Briefly, a stereotactic frame (Leksell model G; Elekta Instrument, Atlanta, Georgia) was applied to the patient’s head with local anesthetic; this was followed by magnetic resonance imaging (1.5-T magnet; General Electric, Milwaukee, Wisconsin). The anterior and posterior commissures were identified using axial T2-weighted images and 3-dimensional inversion recovery axial images. Images were transferred to a neuronavigation station and reformatted using the FrameLink 4.1 software (Mach 4.1 SNT StealthStation; Medtronic Inc, Minneapolis, Minnesota). Using StealthStation software, target coordinates for the most posteroventral part of the GPi were obtained. Microelectrode recordings were used to map the targets, starting 15 mm anterosuperior to the final targets, using 2 microelectrodes simultaneously advanced at steps of 0.5 mm. Microstimulation (1-second train of 0.2-millisecond pulses at 300 Hz and currents of 1-100 µA) was carried out at regular intervals. Intraoperative microrecordings were recorded and stored for analysis with Spike2 software (Cambridge Electronic Design, Cambridge, England).

Once the target was localized, bilateral DBS electrodes (3387; Medtronic Inc) were implanted at the sites, and a dual-channel implantable pulse generator (Kinetra; Medtronic) was placed in the right subclavicular region during the same surgical session. Postoperative brain magnetic resonance imaging confirmed the location of

### Table. Dystonia and Parkinsonism Scores Before and After GPi DBS Surgery at the 3-, 6-, and 12-Month Follow-ups

<table>
<thead>
<tr>
<th>Time Point</th>
<th>BFMDS Severity</th>
<th>BFMDS Disability</th>
<th>UPDRS Part I</th>
<th>UPDRS Part II</th>
<th>UPDRS Part III</th>
<th>UPDRS Part IV</th>
<th>Stimulation Parametersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>67</td>
<td>20</td>
<td>40</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1 wk</td>
<td>87</td>
<td>21</td>
<td>4</td>
<td>25</td>
<td>40</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>After surgery</td>
<td>3 mo</td>
<td>33 (62.0)</td>
<td>9 (55.0)</td>
<td>28 (30.0)</td>
<td>3.8 Right, 3.4 left</td>
<td>130</td>
<td>3.8 Right, 3.4 left</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>20.5 (76.0)</td>
<td>9 (57.0)</td>
<td>38 (2.6)</td>
<td>4.0 Bilaterally</td>
<td>185</td>
<td>4.0 Bilaterally</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>17 (80.4)</td>
<td>7 (66.7)</td>
<td>0 (100)</td>
<td>8 (68)</td>
<td>38 (2.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BFMDS, Burke-Fahn-Marsden Dystonia Scale; GPI DPS, globus pallidus internus deep brain stimulation; NA, not applicable; UPDRS, Unified Parkinson Disease Rating Scale.

After the initial programming, the patient was stimulated using the 2 most ventral contacts bilaterally in double monopolar configuration (−0 and −1, −4 and −5, case +). The pulse width was set at 60 microseconds.

b Range, 0 to 30, with higher scores indicative of increased disability.

![Figure 1. Postoperative coronal T2-weighted magnetic resonance image demonstrating the electrode locations in the posterolateral globus pallidus internus.](https://jamanetwork.com/)
the electrodes in the GPi (Figure 1).11 Because of the severity of dystonia and inspiratory stridor, stimulation was started within a few hours of the operation. Stridor started to improve within 1 day of continuous stimulation, whereas phasic dystonic movements showed improvement a few days later. He continued to slowly improve with subsequent programming sessions during hospitalization (1 month).

At the 3-month follow-up after surgery, the patient’s generalized dystonia had improved remarkably (62% improvement in BFMDs severity score compared with before surgery) (video 3; Table; Figure 2 and Figure 3). He stopped taking baclofen. A swallowing assessment at that time showed mild improvement but not enough to start oral feeding. Soon after this follow-up, the Kineta was accidentally switched off. The patient noticed worsening of his symptoms within a few hours, reaching his preoperative state 48 hours later, with recurrence of stridor and marked generalized dystonia (video 4). After switching back on the implantable pulse generator, improvement was seen within minutes, with further improvement occurring during the next 24 hours.

At the 6-month postoperative follow-up, further improvement in the patient’s dystonia was noted (Table), formal swallowing evaluation revealed significant improvement, and he was allowed to resume oral intake. Because there was further improvement in dystonia, treatment with tetrabenazine and trazodone was stopped.

At the 1-year follow-up (video 5; Table; Figure 2 and Figure 3), the BFMDs severity score had further improved by 80% compared with before surgery. Clonazepam use was reduced to 2 mg/d. The patient was able to swallow normally and eat solid food, and he no longer required the gastrostomy feeding tube. He was independent in all of his activities of daily living and able to cook his own meals and travel independently using public transportation. While there was no improvement in the UPDRS part III scores with GPi stimulation, there was a significant reduction in the part I and II scores (Table).

Surgical treatment with GPi DBS has been found to be effective for primary generalized and segmental dystonia in a class I clinical trial and in other large studies with blinded assessments.12,13 Genetic types of generalized dystonia such as DYT-1,12,13 DYT-11,14 and parkinsonism15 have been reported to markedly improve after GPi and subthalamic nucleus DBS surgery. Our case adds to the evidence supporting the use of bilateral GPi DBS in patients with severe XDP (DYT-3).

Of the patients in 2 previous reports of GPi DBS in XDP, 1 had a mild form of dystonia predominantly involving the oromandibular region and with relatively slow progression.7 The second patient with XDP with GPi DBS presented with a rapid progressive dystonia parkinsonism that started with blepharospasm (similar to our case). Both of the previous cases, though very different in phenotype, had good clinical response up to 1 year after GPi DBS.7,6

Unlike most primary genetic dystonias in which no pathology is demonstrated in postmortem studies,16 in XDP, neurodegenerative changes including neuronal loss and astrogliosis have been found in the caudate and putamen.3,4 Some studies have suggested that disinhibition of the nigral dopaminergic neurons owing to loss of striosomal GABAergic projection neurons would result in the hyperkinetic dystonia observed in XDP. At a later stage, dopamine-mediated toxic effects on striatal neurons would produce a subsequent striatonigral neurodegeneration, resulting in the dystonia being replaced by parkinsonism.17 Despite these clinicopathological differences to other genetic dystonias, a favorable response to GPi DBS sustained for 1 year in patients with XDP is encouraging. The efficacy of GPi DBS over ablative procedures may be related to a more complex mechanism of DBS in the stimulated structures.

Stimulation of the GPi in our patient was not only effective in improving appendicular, cervical, and truncal dystonia but was also effective in improving less fre-
quent focal types of dystonia such as laryngeal stridor. Obstructed breathing and stridor due to laryngeal adductor dystonia has been described in XDP and can be severe enough to necessitate tracheostomy. The complete remission of stridor under GPi stimulation in our patient indicates that this may be a treatment option for this rare form of dystonia in cases in which other medical options have failed.

As has been reported earlier, the clinical improvement following bilateral GPi stimulation was gradual (Table). In our case there was rapid improvement in appendicular dystonia and a slower improvement in axial symptoms (Figure 2 and Figure 3).

As in the second case of XDP to undergo GPi DBS, the dystonia in our case rapidly worsened when the stimulator was accidentally turned off, further confirming the robust response to GPi DBS in XDP.

Contrary to previous articles, the UPDRS motor part did not show a benefit at the 1-year follow-up (Table). This is a remarkable observation and might support the investigation of another target in patients with XDP for whom parkinsonism is the most important symptom.

In conclusion, bilateral GPi DBS appears to be a safe and effective treatment option for patients with XDP with severe generalized dystonia and poor response to medication. This case report not only confirms the benefits of GPi DBS in XDP but also highlights the effectiveness of bilateral GPi DBS across different phenotypic presentations of dystonia in this disease (such as severe laryngeal dystonia). Long-term follow up is required to know if the benefits are sustained.

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