Stimulation of the globus pallidus internus in a patient with DYT1-positive primary generalized dystonia: a 10-year follow-up

DYSTONIA is a syndrome characterized by involuntarily sustained muscle contractions that result in twisting, repetitive movements, and abnormal posture. Dystonia is typically classified by age of onset, origin, and affected body region. When the cause of dystonia is unknown, it is referred to as idiopathic or primary dystonia. Primary dystonia can be familial or sporadic in nature. Several gene mutations have been identified including the DYT1 gene, which codes for an abnormal torsinA protein on chromosome 9q34. This mutation is autosomal dominant and usually affects individuals early in life.

Primary generalized dystonia is a disabling condition with symptoms presenting in young adults. Pharmacotherapy is usually ineffective and the disease tends to progress. Targeting of the GPi for medication-induced dyskinesias in individuals with Parkinson disease renewed interest in the GPi as a target for dystonia. Deep brain stimulation of the GPi has become the site of choice particularly in patients with DYT1-positive primary generalized dystonia. Based on numerous case reports and case series, early surgical intervention has been recommended before permanent neuromusculoskeletal deficits develop.

Case Report

History. This patient was a healthy, right-handed male who at 15 years of age noticed involuntary contractions of his right hand after fracturing his right arm. “Winged scapula” was noted on his right side at age 16 years. Involuntary movements in the right leg appeared at age 17 years, which spread into the trunk and right arm. Over the next 6 months the patient’s movements became more bilateral and proximal. Violent extension and torsion of the trunk backward forced the patient into becoming bedridden.

His family history was not significant for any movement disorder or neurological disease. The patient was an only child of unrelated healthy parents of non-Ashkenazi background.

Examination and Treatments. Routine laboratory workup including complete blood count, erythrocyte sedimentation rate, electrolytes, liver function, uric acid, and thyroid function tests were all within normal limits. Copper, ceruloplasmin, serum, and urine amino acids were also within normal limits. Brain and cervical spine MR imaging showed normal results. A dystonia gene panel

Case Report

History. This patient was a healthy, right-handed male who at 15 years of age noticed involuntary contractions of his right hand after fracturing his right arm. “Winged scapula” was noted on his right side at age 16 years. Involuntary movements in the right leg appeared at age 17 years, which spread into the trunk and right arm. Over the next 6 months the patient’s movements became more bilateral and proximal. Violent extension and torsion of the trunk backward forced the patient into becoming bedridden.

His family history was not significant for any movement disorder or neurological disease. The patient was an only child of unrelated healthy parents of non-Ashkenazi background.

Examination and Treatments. Routine laboratory workup including complete blood count, erythrocyte sedimentation rate, electrolytes, liver function, uric acid, and thyroid function tests were all within normal limits. Copper, ceruloplasmin, serum, and urine amino acids were also within normal limits. Brain and cervical spine MR imaging showed normal results. A dystonia gene panel
(Athena Diagnostics) was positive for the GAG946 deletion mutation in the DYT1 allele 1.

The patient had trials of numerous medications, including carbidopa/levodopa, baclofen, trihexyphenidyl, benztrapine, valproic acid, risperidone, and tetrabenazine, but none provided significant relief. Haloperidol did offer modest relief but caused mild drug-induced parkinsonism, which later resolved when the drug was discontinued.

After consultation with neurosurgery, and after extensive discussion with the family, the patient elected to proceed with GPi DBS. The basis for this treatment was humanitarian because the procedure was not FDA approved in the US for the treatment of dystonia at that time.

Operation. This study was approved by the institutional review board at Allegheny General Hospital and was accepted as a humanitarian exemption trial. Prior to surgery, a head CT scan with 2-mm slices in a Cosman-Roberts-Wells frame were fused with the MR images, using software provided by the StimPilot system (Medtronic, Inc.). Targeting and stereotactic coordinates determined by fused CT and MR images were compared with the Schaltenbrand-Wahren atlas. The GPi target was 3 mm anterior to the midcommissural line, 20 mm lateral to that point, and 4 mm below the midcommissural point. The patient was positioned supine, the frames were secured, and surgery proceeded after injection of a local anesthetic with no sedation.

Microelectrode recordings were started 15 mm above the target, and the most posteroventral part of the GPi was found 2 mm deeper than the intended target. The DBS electrodes (model 3387, Medtronic, Inc.) spanned the entire GPi. Macrostimulation was performed using 0 and 3 electrode combination with a pulse width of 90 μsec, frequency of 185 Hz, and voltages of up to 6 V. There were no visual, sensory, or other symptoms during this intraoperative trial stimulation. The electrode was secured with a bur hole cap and coiled in the subgaleal space with intraoperative fluoroscopy to ensure that the electrodes had not moved from their original target. On Day 3 after placement of the left GPi electrode, an IPG was placed in the left subclavicular space with intraoperative fluoroscopy to ensure that the electrode was placed 5 months later in the same manner.

**Programming of the DBS Device.** Initial programming was started within 12 hours of IPG placement. A movement disorder nurse and physician team used standard protocols to program the IPG. Initially, the patient underwent 3-month follow-up visits for approximately 1 year and is now being seen every 6 months. At these visits, he is assessed by a multidisciplinary team that includes a movement disorders neurologist, neurosurgeon, and nurse. The UDRS, Burke-Fahn-Marsden Dystonia Rating Scales, and standardized videotaping were used prior to surgery and during the 10 years of follow-up.

Follow-Up Course. The greatest adjustment in stimulation parameters was seen in the first 3 years (Table 1). Three years after electrode implantation, stimulation parameters have not required significant adjustments (Table 1). The time to stabilization of dystonic symptoms was approximately 12 months after the right GPi electrodes were implanted.

The patient has had 10 left IPG changes on the more symptomatic side and 5 IPG changes on the right over 10 years (Fig. 1). After 3 IPG changes in 13 months, a Kineta IPG (Medtronic) was inserted (Fig. 1). The patient has required on average 1 IPG change annually on the left side.

There have been minimal changes in stimulation parameters in the right hemisphere with low-voltage requirements resulting in fewer IPG changes (Fig. 1). The more symptomatic side, the left, has required higher voltages. After implantation of the Kineta IPG, the frequency of IPG changes has decreased. Kineta batteries are double the power of the comparative Soleta batteries (Medtronic).

There have been no significant complications, neurological deficits, infection/erosion, or system malfunctions. However, 4 years after initial IPG placement, we noticed increased rigidity and more cramping on the right side with the development of diaphoresis. In the left subclavicular IPG, we observed extremely high impedances, and chest radiography revealed disconnection of that generator. After revision surgery, these worsening symptoms resolved and the patient has had no further episodes of symptom recurrence.

**TABLE 1: Stimulation parameters during the 10-year period after implantation of the DBS device**

<table>
<thead>
<tr>
<th>Date</th>
<th>Contact</th>
<th>Amp (V)</th>
<th>Frequency (Hz)</th>
<th>Pulse Width (μsec)</th>
<th>Date</th>
<th>Contact</th>
<th>Amp (V)</th>
<th>Frequency (Hz)</th>
<th>Pulse Width (μsec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/4/00</td>
<td>3+0−</td>
<td>4.9</td>
<td>185</td>
<td>270</td>
<td>8/8/00</td>
<td>3+0−</td>
<td>2.8</td>
<td>185</td>
<td>120</td>
</tr>
<tr>
<td>1/23/01</td>
<td>2+0−</td>
<td>4.0</td>
<td>185</td>
<td>330</td>
<td>1/23/01</td>
<td>3+0−</td>
<td>3.2</td>
<td>185</td>
<td>120</td>
</tr>
<tr>
<td>4/3/01</td>
<td>2+1−</td>
<td>4.5</td>
<td>185</td>
<td>330</td>
<td>4/3/01</td>
<td>3+0−</td>
<td>3.7</td>
<td>185</td>
<td>120</td>
</tr>
<tr>
<td>8/28/01</td>
<td>3+1−</td>
<td>5.5</td>
<td>185</td>
<td>330</td>
<td>8/28/01</td>
<td>3+0−</td>
<td>4.1</td>
<td>185</td>
<td>120</td>
</tr>
<tr>
<td>3/24/03</td>
<td>3+2+1−</td>
<td>6.0</td>
<td>130</td>
<td>330</td>
<td>1/8/02</td>
<td>3+0−</td>
<td>4.1</td>
<td>185</td>
<td>150</td>
</tr>
<tr>
<td>5/4/04</td>
<td>3+2+1−</td>
<td>5.8</td>
<td>130</td>
<td>330</td>
<td>5/4/04</td>
<td>3+0−</td>
<td>4.1</td>
<td>185</td>
<td>180</td>
</tr>
<tr>
<td>1/5/05</td>
<td>3+2+1−</td>
<td>5.8</td>
<td>130</td>
<td>330</td>
<td>1/5/05</td>
<td>3+0−</td>
<td>4.1</td>
<td>185</td>
<td>180</td>
</tr>
<tr>
<td>2/19/10</td>
<td>3+2+1−</td>
<td>5.8</td>
<td>130</td>
<td>330</td>
<td>2/19/10</td>
<td>3+0−</td>
<td>4.1</td>
<td>185</td>
<td>180</td>
</tr>
</tbody>
</table>
Stimulation of the GPi in DYT1-positive generalized dystonia

There was a dramatic decrease in his UDRS score within 4 months after placing the left GPi electrode, in contrast to the rapid progression of his dystonia during the previous year. This was seen clearly clinically and supported on his UDRS scores (Fig. 2 and Video 1).

Video 1. The video is composed of 5 sections: 1) 1 week prior to left pallidal stimulation; 2) 5 months after left pallidal stimulation; 3) almost 6 months after left pallidal and 1 week after right pallidal stimulation; 4) 5 years after bilateral hemisphere stimulation; and 5) 10 years after bilateral stimulation. Click here to view with Windows Media Player. Click here to view with Quicktime.

Within 3 months of Stage 1 surgery, the patient experienced a dramatic improvement, was able to return to school, and could function independently. After contralateral GPi electrode placement, additional improvement occurred in all postoperative dystonia rating scores, and this improvement has persisted over a 10-year period. The frequency with which the batteries required changing has stabilized (accounting for change in battery type) in the last 5 years.

The patient continues to be fully independent; he is currently employed full time and has a very active lifestyle. His only minor symptoms include a mild dysarthria and a subtle rigidity while walking, none of which impedes his daily activities (Video 1). His current medication regimen includes Klonopin (3 mg daily) and Artane (1 mg daily), unchanged for the past 7 years.

Discussion

Deep brain stimulation of bilateral GPi has shown promising results.2–5,9,13,14,16,17,21,22,26 Younger individuals who are DYT1 positive have exhibited greater improvements in Burke-Fahn-Marsden Dystonia Rating Scale scores from 50% to greater than 80% compared with individuals with DYT1-negative primary generalized dystonia (40% to 70%). These gains improve maximally within 1–2 years after pallidal stimulation.4,5,10 In these studies and others, children appear to benefit more after early intervention, before permanent dystonic posturing ensues, and surgical intervention is strongly advocated.4,5,23 Deep brain stimulation has proven to be efficacious and is reversible and adaptable, allowing for maintenance of symptoms over time as well as the ability to capture new symptoms that may develop.9,11–13,15–17,21 There are no comparison studies between pallidotomy and DBS of the bilateral GPi for dystonia. Such studies, we believe, may provide further evidence that DBS of GPi may be the preferred treatment for DYT1-positive individuals with dystonia.

Conclusions

In this case report, symptom control has been maintained for more than 10 years. Based on the stabilization of energy requirements, it appears that the previously noted rapid progression of dystonia in this patient has been arrested.

Disclosure

Dr. Oh is a consultant for Boston Scientific and received research support from Medronic for the current study. Dr. Whiting is a consultant for Medtronic.

Author contributions to the study and manuscript preparation include the following. Conception and design: Whiting. Acquisition of data: Baser, Angle. Analysis and interpretation of data: Oh, Cheng. Drafting the article: Alcindor.

References


