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Case Reports

Reversal of Status Dystonicus after Relocation of Pallidal Electrodes in DYT6 Generalized Dystonia

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Abstract

Background: DYT6 dystonia can have an unpredictable clinical course and the result of deep brain stimulation (DBS) of the internal part of the globus pallidus (GPI) is known to be less robust than in other forms of autosomal dominant dystonia. Patients who had previous stereotactic surgery with insufficient clinical benefit form a particular challenge with very limited other treatment options available.

Case Report: A pediatric DYT6 patient unexpectedly deteriorated to status dystonicus 1 year after GPI DBS implantation with good initial clinical response. After repositioning the DBS electrodes the status dystonicus resolved.

Discussion: This case study demonstrates that medication-resistant status dystonicus in DYT6 dystonia can be reversed by relocation of pallidal electrodes. This case highlights that repositioning of DBS electrodes may be considered in patients with status dystonicus, especially when the electrode position is not optimal, even after an initial clinical response to DBS.

Keywords: Status dystonicus, deep brain stimulation, DYT6

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Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive, movements, postures, or both. Childhood dystonia is often genetic, and DYT6 is one of the autosomal dominant forms, caused by mutations in the thanatos-associated domain-containing apoptosis-associated protein 1 (THAP1) gene. Clinically, DYT6 is characterized by an early age of onset, with symptoms that frequently start in the craniocervical region and spread to the extremities. Case series on deep brain stimulation (DBS) of the globus pallidus internus (GPI)...
for DYT6 suggest that improvement is to be expected, but less robust and less predictable than DYT1 dystonia. One potential reason for this is that there is often prominent oromandibular dystonia, which is less responsive to DBS. Furthermore, deterioration of dystonic symptoms 1–3 years after implantation has been reported in DYT6 patients.

Status dystonicus (SD) represents the severe end of a deteriorating spectrum of dystonia. Recently, SD has been defined as “a movement disorder emergency characterized by severe episodes of generalized or focal hyperkinetic movement disorders that had necessitated urgent hospital admission because of life-threatening complications regardless of the patient’s neurological condition at baseline.” To date, there is no consensus on the optimal treatment protocol for SD, but early surgical intervention may be a valuable addition to the medical armamentarium for its cessation. Here we report the case of an 11-year-old DYT6 patient with unexpected and rapid clinical deterioration to SD, after a 1-year period of good response to GPi DB.

The SD was reversed by repositioning of the DBS electrodes.

Case report

After a normal birth and development, our patient developed a disturbed walking pattern at the age of 3.5 years. At age 5 he was diagnosed with dystonia and 1 year later a p.Arg29Pro mutation in the THAP1 gene was found and the diagnosis DYT6 dystonia was made. His dystonia gradually progressed to the upper limbs at age 6 and at age 9 he developed generalized dystonia. Despite pharmacological treatment with different medications his symptoms further deteriorated and he was no longer able to attend school. He became wheelchair bound with hardly intelligible speech and developed a severely impaired hand function. The neurological assessment on the Burke–Fahn–Marsden Dystonia Rating Scale Movement (BFMDRS-M) at that time was 71 (range 0–120), and on the disability part of the scale (BFMDRS-D) the score was 21 (range 0–30); see Table 1. After multidisciplinary evaluation, DBS was performed with bilateral pallidal electrodes (model 3387; Medtronic, MN, USA) using direct magnetic resonance-guided stereotactic targeting (Figure 1). A postoperative computed tomography scan showed that the actual electrode positions were more lateral than intended (Table 2). Nevertheless, the patient responded well to the DBS and 1 year after the implantation, he could walk without support, and had a clearly improved hand function and speech (BFMDRS-M 69 and BFMDRS-D 14). However, after the first year the effect of pallidal stimulation decreased and at 15 months postoperatively (age 11 years) his clinical status progressively deteriorated to SD, requiring hospital admission. Constipation was considered as a possible trigger and was treated by laxatives without success. No other possible triggers were identified. Despite symptomatic treatment with trihexyphenidyl (6 mg/day, body weight 30 kg), gabapentin (300 mg/day), and clonazepam (1.0 mg/day) and reprogramming of the DBS settings, he developed severe episodes of generalized dystonic spasms, which progressed to continuous abnormal postures and sustained contractions. This was accompanied by metabolic derangements (creatine kinase levels up to 920 IU/L), exhaustion, pain, sleep disturbance, dysphagia, and cachexia. Based on the criteria described by Allen et al., he was initially diagnosed with grade 3 SD, further deteriorating towards grade 4 SD. Since this is a potentially life-threatening situation, the patient was admitted to an intensive care unit (ICU). On the ICU, pharmacological treatment with high doses of benzodiazepines (up to intravenous midazolam 1 mg/kg/hour and enteral clonazepam 3.6 mg/day, body weight 25 kg), clonidine (intravenous 105 μg/day), chloral hydrate (1,250 mg/day), hydroxyzine (12.5 mg/day), gabapentin (900 mg/day), and trihexyphenidyl (8 mg/day) had only limited effect. Nevertheless, he experienced less discomfort, less pain, and the metabolic derangements resolved. However, he suffered from severe adverse effects, especially drowsiness. When subsequently decreasing the dosages, the dystonic movements and the discomfort became more severe. After 4 weeks on the ICU, his condition deteriorated to a total BFMDRS score of 138 (Table 1). After extensive multidisciplinary and multicenter deliberation it was decided to reposition the pallidal electrodes to a more dorsal and more medial position. Target coordinates of the old and new electrodes are shown in Table 2 and the new target was further refined by micro-electrode recording. After the repositioning of the DBS electrodes the SD ameliorated to a BFMDRS score of 100 after 1 week, and medication dosages were drastically reduced. Six months after the second surgery he was able to walk short distances unaided and attend school without medication (BFMDRS-M 64, BFMDRS-D 15). At present.

Table 1. BFMDRS Scores at Different Time Points

<table>
<thead>
<tr>
<th>BFMDRS Scores</th>
<th>May 2014</th>
<th>June 2015</th>
<th>December 2015</th>
<th>January 2016</th>
<th>February 2016</th>
<th>October 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before 1st Surgery</strong></td>
<td><strong>1 Year after 1st Surgery</strong></td>
<td><strong>Status Dystonicus</strong></td>
<td><strong>Before 2nd Surgery</strong></td>
<td><strong>After 2nd Surgery</strong></td>
<td><strong>3 Years after 1st Surgery</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td>26</td>
<td>14</td>
<td>29</td>
<td>30</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td><strong>Movement</strong></td>
<td>71</td>
<td>69</td>
<td>90</td>
<td>108</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>97</td>
<td>83</td>
<td>119</td>
<td>138</td>
<td>100</td>
<td>79</td>
</tr>
</tbody>
</table>

The first deep brain stimulation implantation was in May 2015, the second in February 2016. For privacy reasons, the patient and his parents did not give permission to provide supplemental videos.
the duration after the repositioning of the electrodes is 24 months, and
the clinical condition of the patient is still gradually improving.

During the first surgery the goal was to place electrodes in the
posteroventrolateral GPi. However, Figure 1 shows that the electrodes
were actually positioned within the external segment of the globus
pallidus (GPe). The new electrodes were placed more medially in the
posteroventrolateral GPi. The stimulation parameters after the initial
implantation were bilateral monopolar stimulation of the most ventral
contacts (pulse width 90 ms, frequency 130 Hz, and voltage 2.5 V).

In the first year after the initial implantation, voltages were bilaterally
increased to 3.5 V. Nine months after the initial implantation stimula-
tion parameters were switched to a big bipolar stimulation field (0–/3+
and 8–/11+), with pulse width of 90 ms, a stimulation frequency of
130 Hz, and a voltage of 4.0 V on both sides. During the SD, the
stimulation frequency was changed into 180 Hz on both sides without
clinical effect. After the repositioning the stimulation parameters were
contacts 1–/2+ and 8–/9+, pulse width 210 ms, frequency 130 Hz,
and a voltage of 5.4 V for both sites.

### Table 2. Electrode Positions Relative to the Midcommissural Point

<table>
<thead>
<tr>
<th>X left</th>
<th>Y left</th>
<th>Z left</th>
<th>X right</th>
<th>Y right</th>
<th>Z right</th>
</tr>
</thead>
<tbody>
<tr>
<td>First surgery</td>
<td>22.4¹</td>
<td>2.7</td>
<td>–2.9</td>
<td>22.6¹</td>
<td>3.1</td>
</tr>
<tr>
<td>Second surgery</td>
<td>20</td>
<td>3</td>
<td>–4</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>

¹Realized lateral coordinate left 23.1 mm and right 24.4 mm.

![Schematic Depiction of the Electrode Positions](image)

**Figure 1. Schematic Depiction of the Electrode Positions.** (A) Anterior coronal three-dimensional view of initial electrode positions (right 1, left 2) and electrode positions after second surgery (right 3, left 4). Note the position outside the right GPi (R) and barely inside the left GPi (L) of initial electrodes and the improved position after revision surgery. (B) Sagittal view from the right. (C) Sagittal view from the left. Note the improved position of 2 and 4 with at least two contacts within both internal parts of the globus pallidus (GPis). This is achieved by a more frontal burr hole facilitating a more oblique trajectory through the GPi. Anatomical structures and DBS electrodes were drawn into the patients using computed tomography and magnetic resonance imaging in SureTune2 software (Medtronic, MN, USA). R, GPi right; L, GPi left; OT, optic tract; 1, initial electrode right; 2, revised electrode right; 3, initial electrode left; 4, revised electrode left.

### Discussion

This case study demonstrates that medication-resistant SD in DYT6
dystonia can be reversed by repositioning of pallidal electrodes. This is
an important finding, particularly because SD can be life-threatening.⁸

The exact prevalence of SD in childhood is unknown.⁸ Two
comprehensive systematic literature studies describe a total of 133
episodes of SD in 109 patients, the majority of whom were under age
16 years.⁸,¹⁰ Clinically, SD is characterized by the development of
increasingly frequent or continuous severe episodes of generalized
dystonic spasms,¹⁰,¹¹ often complicated by one or more of the follow-
ing: bulbar weakness compromising upper airway patency; exhaustion;
pain; and metabolic imbalances.¹² In two-thirds of cases, a precipitat-
ing factor can be identified.⁸,¹⁰ Important triggers include infection,
pain, constipation, or a medication change.⁸,¹⁰,¹² Addressing these
factors is the first step of a recently proposed multistaged approach to
childhood SD.¹⁰ Neurosurgical intervention for SD appears to have
become more frequent in the management of SD, with reported
percentages ranging from 40% to 66% of SD patients.⁸,¹⁰ In about
70% of these cases, return to pre-SD baseline or further improvements have been reported. However, prospective blinded studies on the treatment of SD with systematic follow-up are missing.

In our case, the initial DBS placement gave some clinical benefit, despite suboptimal electrode localization. Fifteen months after surgery the patient developed severe SD and repositioning of DBS electrodes led to return to the pre-SD baseline condition. The initial response to the first DBS implantation despite the lateral position of the electrodes might be explained by extension of the electrical field into the Gpi. Alternatively, it could also be the effect of GPe inhibition. As proposed previously torsion dystonia. Nat Genet 2009;41:266–271. doi: 10.1038/ng.304


