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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.4–6 One potential reason for
this is that there is often prominent oromandibular dystonia, which is
less responsive to DBS.7 Furthermore, deterioration of dystonic
symptoms 1–3 years after implantation has been reported in DYT6
patients.4,5

Status dystonicus (SD) represents the severe end of a deteriorating
spectrum of dystonia.8 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.”9 To date, there
is no consensus on the optimal treatment protocol for SD8,10–12
but early surgical intervention may be a valuable addition to the medical
armamentarium for its cessation.8,13 Here we report the case of an
11-year-old DYT6 patient with unexpected and rapid clinical deterio-
ration 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 post-
operatively (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 con-
tractions. This was accompanied by metabolic derangements (creatine
kinase levels up to 920 IU/L), exhaustion, pain, sleep disturbance, dys-
phagia, and cachexia. Based on the criteria described by Allen et al.,11
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), baclofen (12.5 mg/day), gabapentin (900 mg/
day), and trihexyphenidyl (8 mg/day) had only limited effect. Never-
theless, 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>
<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>Disability</td>
<td>26</td>
<td>14</td>
<td>29</td>
<td>30</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Movement</td>
<td>71</td>
<td>69</td>
<td>90</td>
<td>108</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Total</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></th>
<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>22.4</td>
<td>2.7</td>
<td>-2.9</td>
<td>22.6</td>
<td>3.1</td>
<td>-2.8</td>
</tr>
<tr>
<td>Second surgery</td>
<td>20</td>
<td>3</td>
<td>-4</td>
<td>20</td>
<td>3</td>
<td>-4</td>
</tr>
</tbody>
</table>

Target coordinates relative to anterior commissure - posterior commissure line midpoint in millimeters.

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 in the basal-ganglia-thalamic circuit (BGTC) model for dystonia,14 DBS induced increased GPe activity might disrupt the increased BGTC synchronized oscillations in dystonia. However, the optimal DBS target for dystonia is the posteroverventrolateral GPi. In the literature, target coordinates vary from 18 to 22 mm lateral from the midline.16–18 In our patient, the electrodes were placed too lateral (left 23.1 mm/ right 24.4 mm). The reversal of SD by repositioning of the electrodes highlights the importance of optimal electrode placement.

The case also illustrates the unpredictable clinical effect of DBS in DYT6. This is in line with previous studies focusing on the response of DYT6 patients to pallidal DBS. Two of these studies describe DYT6 patients who initially responded well to pallidal stimulation, but after 1–3 years of stimulation regression occurred requiring lead reposition.15

Noteworthy, in this case study, changes in clinical condition of the patient seem to be reflected better by the BFMDRS-M scores than by the BFMDRS-D scores. For example, the BFMDRS-M score 1 year after the first implementation (69) hardly differs from the preoperative BFMDRS-M score (71), while daily functioning was clearly improved, or days,8 while BFMDRS-D scores reflect disability for a longer period of time. This observation is paralleled by the results of a previous literature.

In conclusion, this case study demonstrates that severe SD in DYT6 dystonia can be reversed by relocation of pallidal DBS electrodes, highlighting the importance of optimal electrode placement. Prospective multicenter studies with systematic follow-up are needed to investigate the optimal timing and patient selection for pallidal DBS in SD.

References


