Two Cases of Monozygotic Twins with Early-onset Isolated (DYT1) Dystonia Effectively Treated with Bilateral Globus Pallidus Internus Stimulation

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Abstract

Early-onset isolated (DYT1) dystonia is one of the most common forms of primary dystonia in childhood, and deep brain stimulation of the globus pallidus internus (GPI-DBS) is a highly effective treatment for it. However, the effectiveness of GPI-DBS in monozygotic twins with DYT1 dystonia has never been reported globally. Here, we report the cases of monozygotic twins with DYT1 dystonia who were treated using GPI-DBS, and we include a literature review. The younger brother showed an abnormal gait, with external rotation of the right lower leg at 6 years old. The symptoms gradually became so severe that he had difficulty walking on his own at 9 years of age. Treatment with levodopa-carbidopa partially resolved his symptoms, but most of the symptoms remained. Meanwhile, the older brother developed dystonia in both upper limbs at 8 years of age, with gradual symptom progression. At 13 years of age, they were diagnosed with DYT1 dystonia. Bilateral GPI-DBS was performed in both patients at 16 years of age. Their symptoms remarkably improved after surgery. The Burke-Fahn-Marsden dystonia rating scale (BFMDRS) movement score was reduced from 52 to 2 points for the younger brother and from 35 to 1 point for the older brother. Even if monozygotic twins have the same genes, the onset and severity of symptoms might vary in accordance with differences in epigenomic profiles. However, GPI-DBS treatment was very effective for the two cases; thus, we should consider the surgical interventions for each patient.

Keywords: DYT1 dystonia, monozygotic twins, deep brain stimulation of the globus pallidus internus

Introduction

Dystonia is a movement disorder that is characterized by sustained, long, or intermittent skeletal muscle contractions.1 The incidence of primary dystonia is 16.43 per 100,000.1 For associated mechanisms, the direct pathway involving basal ganglia is excited, and the indirect pathway is inhibited, resulting in increased excitation in the cerebral cortex.2 Hereditary dystonia is a disease that causes dystonia symptoms due to a genetic disorder, and it is also characterized by a low penetrance, even in cases where there is a dominant inheritance pattern. Thus, it may be diagnosed as a solitary dystonia without genetic predisposition, and de novo mutations are common.3,4

Approximately 20 DYT dystonia causative genes have been reported to date. Among them, early-onset isolated (DYT1) dystonia is inherited as an autosomal dominant trait with a penetrance rate of 30%-40%, and it accounts
Patient 1: The younger brother

This patient was born at 37 weeks gestation, with a birth weight of 2,238 g, and he was the second-born of twins. At approximately 6 years and 7 months of age, the patient showed an abnormal gait related to his lower right leg. His symptoms gradually developed into generalized dystonia. He had increasing difficulty walking and required assistance to walk at 9 years of age (Fig. 1A, B). At 13 years of age, the patient was positive for the DYT1-TOR1A mutation via genetic analysis.

Neuroradiological examinations were performed to reveal his pathological conditions. There were no abnormal findings found on the head magnetic resonance imaging (MRI), 99mTc-etylcysteinate dimer cerebral single-photon emission computed tomography (ECD SPECT), or somatosensory evoked potential (SSEP) scan. A dopamine transporter (DAT)-scan showed mildly reduced uptake in the dorsal part of the left putamen. He started levodopa at 9 years of age, but the single agent did not work well enough. At 12 years of age, we changed the levodopa to levodopa/carbidopa, and his symptoms improved well. After that, it was difficult to adequately control his symptoms even with increased doses of this medication, so at 16 years of age, he underwent bilateral GPI-DBS (Boston Scientific Inc., Marlborough, MA, USA). The preoperative Burke-Fahn-Marsden dystonia rating scale (BFMARDS) motor and disability scores were 52/120 and 17/30, respectively. The first electrode position was placed at the bottom of GPI by referring to the perioperative MRI (short tau inversion recovery; STIR), the Schaltenbrand and Wahren stereotactic atlas, and the intraoperative microelectrode recordings (MER). The final coordinates of the first contact...
Monozygotic Twins with DYT1 Dystonia Treated with GPi-DBS

Fig. 2 Patient 2’s posture before and after surgery. He showed dyskinesia symptoms during movement, and in particular, he was observed to throw his left leg forward in a twisting motion while walking (A, B). After surgery, his symptoms markedly improved (C, D). The postoperative location of the bilateral deep brain stimulation (DBS) electrode for Case 2 (white arrow). The right 1st electrode (E), right 2nd electrode (F), left 1st electrode (G), and left 2nd electrode (H).

were as follows: on the right side, 6 mm anterior, 20 mm lateral, and 3 mm ventral to the midcommissural point (MCP); and on the left side, 3.4 mm anterior, 20.3 mm lateral, and 3 mm ventral to the MCP. The DBS electrodes were placed as planned in the fusion images between postoperative computed tomography (CT) scan and preoperative MRI (Fig. 1E-H).

After stimulation, the dystonia symptoms almost disappeared, and the patient was completely independent without the use of a wheelchair (Fig. 1C, D). The BFMDRS motor score was 1/120, and the disability score was 1/30 at 19 months after surgery. The current stimulation parameters were as follows: right side, cathode; first and second contact, anode; pulse generator, 3.8 mA, 180 μs, 130 Hz; and left side, cathode; first and second contact, anode; and pulse generator, 4.0 mA, 220 μs, and 130 Hz. The patient was taking 1,200 mg of levodopa before surgery, but the dose was able to be reduced to 800 mg at discharge, and this treatment was discontinued 5 months after surgery.

Patient 2: The older brother

This patient was born at 37 weeks gestation, and his weight was 2,212 g. At 8 years and 9 months of age, symptoms in his upper limbs suddenly appeared, such as the inability to wash his hair or to wash himself when taking a bath. Thereafter, he had difficulty writing and dressing or undressing. Although he could maintain his posture at rest, he had dystonia that was induced by movement in both the upper and lower limbs. At 13 years of age, genetic testing showed a positive result for the DYT1-TOR1A mutation.

A head MRI, 99mTc-ECD SPECT, and DAT-scan showed no obvious abnormal findings. He also started taking levodopa at 9 years of age. With medical treatment, his symptoms improved considerably, and his gait became stable. However, the upper limb symptoms and throwing his left leg when walking persisted (Fig. 2A, B), so he decided to undergo GPi-DBS. The preoperative BFMDRS motor and scores were 35/120 and 11/30, respectively. At 16 years of age, he underwent bilateral GPi-DBS (Boston Scientific Inc., Marlborough, MA., USA), and the surgery was performed using the same procedure as described above for the first case. The final coordinates of the first contact were as follows: on the right side, 5.1 mm anterior, 21.4 mm lateral, and 3 mm ventral to the midcommissural point (MCP); and on the left side, 4.1 mm anterior, 19.8 mm lateral, and 3 mm ventral to the MCP. The DBS electrodes were placed as planned in the fusion images between postoperative computed tomography (CT) scan and preoperative MRI. (Fig. 2E-H).

Thirteen months after surgery, the dystonia symptoms had almost disappeared, and the BFMDRS motor and disability scores were 2/120 and 1/30, respectively (Fig. 2C, D). The current stimulation parameters were as follows: right side, cathode; first and second contact, anode; pulse generator, 3.7 mA, 150 μs, 130 Hz; and left side, cathode; first and second contact, anode; and pulse generator, 3.5 mA, 260 μs, and 130 Hz. The levodopa dose was 1,000 mg before surgery, but it was gradually reduced after discharge, and medical treatment was completely stopped at 6 months after surgery.

Discussion

We report the cases of DYT1 dystonia patients who were monozygotic twins and whose symptoms were dramati-
Table 1  Demographic data from published cases of monozygotic twins with dystonia and a genetic disorder

| Case            | Genetic disorder         | Sex  | Onset       | First neurological symptoms                              | Dystonia site   | Treatment                                | Outcome                        |
|-----------------|--------------------------|------|-------------|----------------------------------------------------------|-----------------|------------------------------------------|--------------------------------|
| Pavone 2020.14  | ATP1A3 mutation          | F    | 0-24 months | Head deviation, hypertonia in the upper limbs            | Upper limbs     | Flunarizine                              | Reduced paroxysmal motor attack in adult |
|                 |                          | F    | 0-24 months | Head deviation, hypertonia in the upper limbs            | Four limbs      | Flunarizine                              | Reduced muscle strength and tonus in adult |
| Zúñiga-Ramírez 2019.15 | ATP1A3 mutation         | M    | 2 months    | Hyperkinetic movements                                   | Generalized dystonia | GPI-DBS                                  | Improvement of BFMDRS: from 50 to 28 |
|                 |                          | M    | 2 months    | Hyperkinetic movements                                   | Generalized dystonia | Levodopa/cardiodopa                      | Improvement                    |
| Hoei-Hansen 2014.11 | ATP1A3 mutation         | M    | 5 months    | Abnormal eye movements and hemiplegic bouts              | Tongue          | N/D                                      | N/D                            |
|                 |                          | M    | 5 months    | Abnormal eye movements and hemiplegic bouts              | Tongue          | N/D                                      | N/D                            |
| Yosunkaya 2010.19 | P492R mutation           | M    | 3 months    | Diffuse dystonia, hypokinesia, and tremor in the upper limbs | Generalized dystonia | Levodopa/selegiline                      | Improvement                    |
|                 |                          | M    | 3 months    | Diffuse dystonia, hypokinesia, and tremor in the upper limbs | Generalized dystonia | Levodopa/selegiline                      | Improvement                    |
| Castiglioni 2013.17 | PRRT2 mutation          | M    | 10 years    | Arm stretching following movements                        | Dystonia was not mentioned | Carbamazepine                          | Improvement                    |
|                 |                          | M    | 10 years    | Action-induced dystonia                                   | Left upper and lower limbs | Haloperidol                          | Improvement                    |
| Foncke 2010.12  | SCA14 mutation           | M    | Teens       | Myoclonus of the leg and dystonia of the trunk           | Trunk and lower legs | N/D                                      | N/D                            |
|                 |                          | M    | Teens       | Myoclonus of the leg and dystonia of the trunk           | Trunk           | N/D                                      | N/D                            |
| Nardoci 2003.16 | GTP cyclohydrolase deficiency | F    | 1 month     | Rigidity and tremor                                       | Generalized dystonia | Levodopa/cardiodopa                     | Improvement                    |
|                 |                          | F    | 1 month     | Rigidity and tremor                                       | Generalized dystonia | Levodopa/cardiodopa                     | Improvement                    |
| Urbizu 2010.18  | SLC2A1 missense          | M    | 5 years     | Clumsy gait                                              | Both legs        | Ethosuximide Ketogenic diet              | Improvement                    |
|                 |                          | M    | 5 years     | Clumsy gait                                              | Both legs        | Ethosuximide Ketogenic diet              | Improvement                    |

M, male; F, female; GPi-DBS, deep brain stimulation of the globus pallidus internus; BFMDRS, Burke-Fahn-Marsden dystonia rating scales; GTP, Guanosine-5′-triphosphate; N/D, no data

Dystonia in monozygotic twins with genetic disorders

Some cases of dystonia were in monozygotic twins with a genetic disorder (Table 1). There were three pairs of twins with ATP1A3 mutations, one pair with GTP-cyclohydrolase deficiency, one pair with the PRRT2 mutation (no description for DYT10), one pair with the spinocerebellar ataxia type 14 (SCA14) mutation (DYT11 negative), one pair with the SLC2A1 missense mutation, and one pair with the P492R mutation in the tyrosine hydroxylase gene. In many cases, the age of onset, symptoms, and clinical course were similar. Only one patient...
Monozygotic Twins with DYT1 Dystonia Treated with GPi-DBS

Table 2  Demographic data for the present cases and three previous cases of patients with early-onset isolated (DYT1) dystonia

| Case         | Blood relationship | Sex | Onset (years) | Site of initial symptom | Main symptoms                                | Treatment                  | Outcome                      |
|--------------|--------------------|-----|---------------|-------------------------|-----------------------------------------------|----------------------------|------------------------------|
| Gasser 1998.21 | Dizygotic twins   | M   | 16           | Right hand             | Action-induced dystonia of the right hand     | N/D                        | The therapeutic effect was not mentioned. |
|              |                    | M   | 17           | Right hand             | Writer’s cramp on the left hand               | N/D                        | The therapeutic effect was not mentioned. |
| Opal 2002.22 | Siblings           | F   | 20           | Right leg              | Trunk tremor, dystonic posturing, and gait    | Levodopa/carbidopa, clonazepam, pramipexole | Slow progression             |
|              |                    | F   | 12           | Left leg               | Head and hand tremors, spasms of tongue       | Clonazepam, trihexyphenidyl hydrochloride, orthopedic surgery | Slow progression             |
| Bereznaï 2007.20 | Siblings        | M   | 12           | Right lower leg        | Generalized dystonia                          | Levodopa                   | No progression               |
|              |                    | M   | 12           | Writer’s cramp         | Generalized dystonia                          | Levodopa                   | No progression               |
| Present case | Monozygotic twins | M   | 6            | Lower limbs            | Generalized dystonia                          | Levodopa, GPi-DBS           | Significant improvement      |
|              |                    | M   | 8            | Upper limbs            | Generalized dystonia                          | Levodopa/carbidopa, GPi-DBS | Significant improvement      |

M, male; F, female; N/D, no data; BFMDRS, Burke-Fahn-Marsden dystonia rating scales; GPi-DBS, deep brain stimulation of the globus pallidus internus

with the ATP1A3 mutation underwent DBS surgery, and the other patient presented mild symptoms but did not require a surgery.13 There were no reports of surgery that was performed on both twins or DYT1 dystonia cases in monozygotic twins.

**DYT1 dystonia in dizygotic twins and sibling cases**

There was one report of dizygotic twins and two reports of sibling cases with DYT1 dystonia (Table 2). Among the three case reports, one report showed the same age of disease onset for both twins (12 years), while the other two reports showed age differences between the twins, as follows: 16 and 17 years old; and 20 and 12 years old. The initial symptom was dominant in the right upper extremity in one case but had different onset sites in two cases, as follows: right lower extremity and left lower extremity; and right lower extremity and writer’s cramp. All reports showed that the symptoms developed in other areas of the body, and the same treatment resulted in some symptom improvement. In the present case, the age at onset and that of the first symptom were different between the twins, and the same treatment, including surgery, was more effective than that in the previous reports (Table 2).

**Surgery treatment for DYT1 dystonia**

As mentioned above, several reports indicated that GPi-DBS was effective in cases that are refractory to drug treatment.20 The therapeutic effect of GPi-DBS was reported in 47 DYT1 dystonia patients.22 The average stimulation conditions were as follows: amplitude, 3.1 V; pulse width, 168 μs; and frequency, 72 Hz. The BFMDRS motor score improved by 74% (47 patients) at 1 year postoperatively, and 61% of patients were able to stop receiving medical treatment. Although the stimulation frequency was somewhat lower than that in the present case, the effectiveness of GPi-DBS was similar in both because medical treatment could be reduced or stopped. However, symptoms have been reported to worsen 5-10 years after surgery,20 so long-term follow-up is required.

**Conclusions**

We report the first cases of monozygotic twins with DYT1 dystonia that was successfully treated using bilateral GPi-DBS. Although the clinical course of the disease and the treatment effect were similar in both twins, the disease onset, clinical symptoms, and disease severity were different between the twins, as in most dystonia cases. Appropriate treatments with medication and surgery are considered on a case-by-case basis for a long-term follow-up period. GPi-DBS is highly effective in most cases of DYT1 dystonia. It is important to carefully observe the patient’s symptoms and the disease course in each case, and, if DYT1 dystonia is suspected, appropriate treatment should
be administered.

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Abbreviations

GPI-DBS, deep brain stimulation of the globus pallidus internus; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; DAT, dopamine transporter; BFMDRS, Burke-Fahn-Marsden dystonia rating scales; MER, microelectrode recording; MCP, midcommissural point.

Ethics Approval

All procedures performed in the studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or the national research committee (IRB#1911-023) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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