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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

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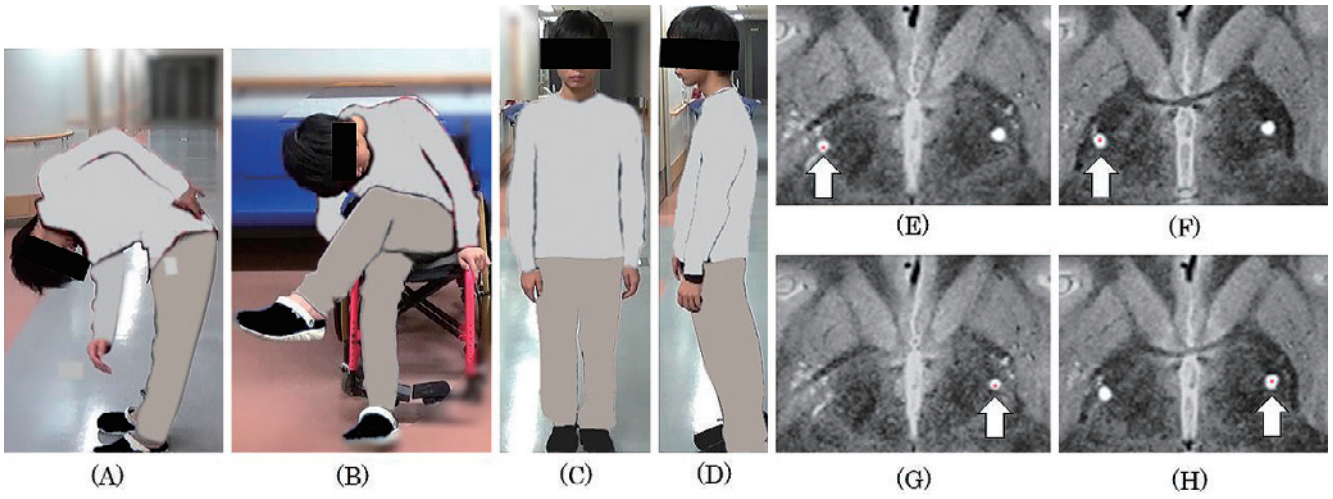

Fig. 1 Patient 1' s posture before and after surgery. He presented with dyskinesia symptoms, with lateral and forward flexion in the upright position (A). He showed the same torsion dyskinesia when he was raising his legs before surgery (B). After surgery, he was able to hold his posture in the upright position and no longer required a wheelchair (C, D). Postoperative computed tomography (CT) images were combined with preoperative magnetic resonance imaging (MRI) using a Stealth Station. The deep brain stimulation (DBS) electrodes were placed bilaterally in the globus pallidus internus (GPi; white arrow); the right 1st electrode (E), right 2nd electrode (F), left 1st electrode (G), and left 2nd electrode in Case 1 (H).

for 50% of primary dystonias in childhood.[4-6] DYT1 dystonia begins in the extremities and progresses to become generalized dystonia.[1] The treatment includes medication (e.g., anticholinergics, antiepileptics, and levodopa), botulinum toxin, and stereotactic brain surgery.[7,8] When drug therapy is ineffective, deep brain stimulation of the globus pallidus internus (GPi-DBS) might be a feasible option, having a response rate of 50%-92%.[9,10]

Thus, clarifying the differences in these clinical and therapeutic processes is important because they vary, even for the same gene of hereditary dystonia.[11,12] Currently, there are few reports of monozygotic twins with dystonia and a genetic disorder, and there are no reports of DBS surgery in both twins. Hanaoka et al. report a case of twins with DYT1 dystonia, in which symptoms improved for a period with levodopa treatment but subsequently worsened.[13] We have treated the first cases of with DYT1 dystonia in monozygotic twins using bilateral GPi-DBS, and indeed, the results of the treatment were as expected as in previous reports. However, there has never been a report globally on twin cases treated with surgery; thus, here, we report the clinical findings and the treatment course for a case of DYT1 in twins, along with a literature review.

Case Report

The informed consent from all the participants were obtained. Because Hanaoka et al. previously reported the detailed course of these two patients,[13] here, we have briefly described their clinical course and focused on the surgical interventions.

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), ^{99m}Tc-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 (BFMDRS) 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

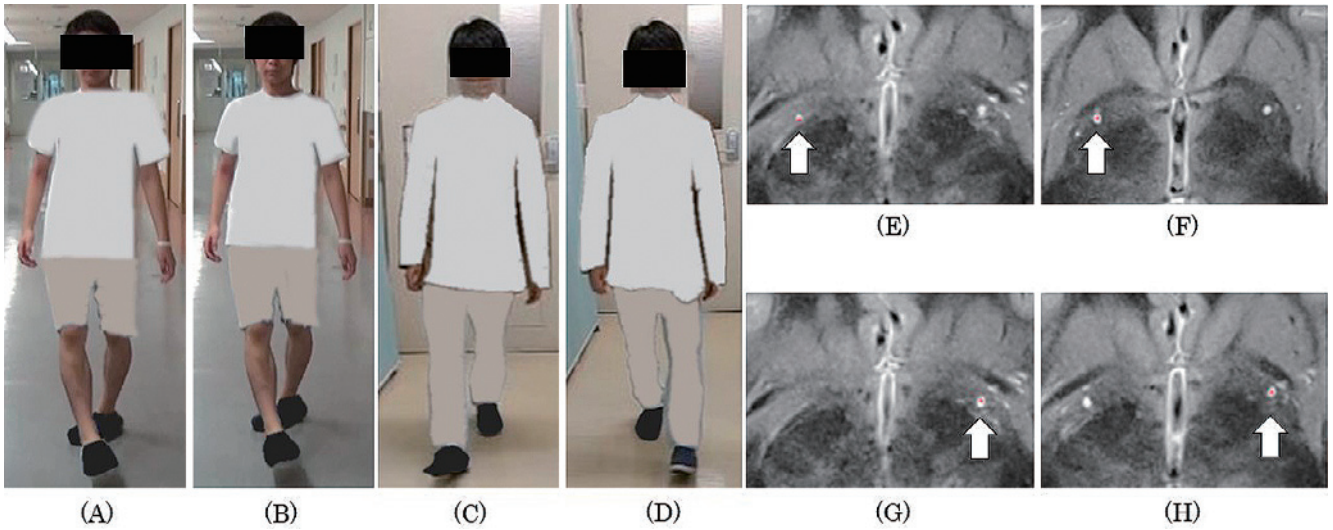

Fig. 2 Patient 2' s posture before and after surgery. He showed dyskinesia symptoms during movement, and in particular, he was observed to throw his left leg forward in a twisting motion while walking (A, B). After surgery, his symptoms markedly improved (C, D). The postoperative location of the bilateral 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, ^{99m}Tc-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 BFMDRS: from 50 to 28
		M	2 months	Hyperkinetic movements	Generalized dystonia	Levodopa/ carbidopa	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	Torsion of his body	Trunk	N/D	N/D
Nardocci 2003.[16]	GTP cyclohydrolase deficiency	F	1 month	Rigidity and tremor	Generalized dystonia	Levodopa/ carbidopa	Improvement
		F	1 month	Rigidity and tremor	Dystonia was not mentioned	Levodopa/ carbidopa	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

cally improved by GPi-DBS. Although the patients were monozygotic twins, there were differences in the age of first onset, site of first symptoms, and degree of severity. They had different symptoms and effects from the use of levodopa, but GPi-DBS was effective for both patients. Symptom control by electrical stimulation might be achieved despite this type of genetic abnormality. In addition, considering that these patients have generalized dystonia and that one electrode was not enough to achieve sufficient improvement, we used two electrodes to achieve the sufficient therapeutic effect.

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,[11,14,15] one pair with GTP-cyclohydrolase deficiency,[16] one pair with the PRRT2 mutation (no description for DYT10),[17] one pair with the spinocerebellar ataxia type 14 (SCA14) mutation (DYT11 negative),[12] one pair with the SLC2A1missence mutation,[18] and one pair with the P492R mutation in the tyrosine hydroxylase gene.[19] In many cases, the age of onset, symptoms, and clinical course were similar. Only one patient

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
Bereznai 2007.[20]	Siblings	M	12	Right lower leg	Generalized dystonia	Levodopa	No progression BFMDRS-M: 17
		M	12	Writer's cramp	Generalized dystonia	Levodopa	No progression BFMDRS-M: 23
Present case	Monozygotic twins	M	6	Lower limbs	Generalized dystonia	Levodopa, GPi-DBS	Significant improvement BFMDRS-M: from 52 to 1
		M	8	Upper limbs	Generalized dystonia	Levodopa/carbidopa, GPi-DBS	Significant improvement BFMDRS-M: from 35 to 2

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.[15] 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).[20-22] Among the three case reports, one report showed the same age of disease onset for both twins (12 years),[20] while the other two reports showed age differences between the twins, as follows: 16 and 17 years old;[21] and 20 and 12 years old.[22] 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.[9,10] 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,[23] 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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