

Successful bilateral pallidal stimulation in a patient with isolated lower limb dystonia coexistent with Langerhans cell histiocytosis and coeliac disease

Skuteczna obustronna stymulacja części wewnętrznych gałek białych u chorej na izolowaną dystonię kończyn dolnych ze współistniejącą histiocytozą i celiakią

Michał Sobstyl¹, Mirosław Ząbek¹, Sebastian Dzierżęcki¹, Zbigniew Mossakowski², Krzysztof Szczałuba³

¹Klinika Neurochirurgii i Urazów Ośrodkowego Układu Nerwowego, Centrum Medyczne Kształcenia Podyplomowego w Warszawie

²Oddział Neurochirurgii, Wojewódzki Szpital Bródnowski w Warszawie

³Poradnia Genetyczna, Zakład Genetyki Medycznej, Instytut Matki i Dziecka w Warszawie

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Abstract

The authors report a case of bilateral globus pallidus internus (GPi) stimulation for treatment of medically intractable isolated lower limb dystonia. The 14-year-old girl developed dystonic movements in her left lower limb. At the age of 17, the patient was handicapped by dystonic movements in her lower limbs, and became wheelchair-bound. Pharmacological therapy and botulinum toxin injection resulted in transient and modest benefit. Moreover, the patient was diagnosed with histologically proven coeliac disease and Langerhans cell histiocytosis. Genetic testing revealed the presence of DYT-1 mutation. The 17-year-old girl underwent bilateral implantation of deep brain stimulation leads. Bilateral GPi stimulation resulted in remarkable improvement of phasic dystonic movements, and dystonic posture of lower limbs. Over 2 years postoperative follow-up, the patient is able to walk independently. Bilateral GPi stimulation appears to be an effective treatment modality for isolated lower limb dystonia.

Key words: movement disorders, lower limb dystonia, pallidal stimulation, functional neurosurgery.

Streszczenie

Autorzy przedstawiają przypadek chorej poddanej obustronnej stymulacji części wewnętrznej gałki białej z powodu izolowanej dystonii kończyn dolnych. U 14-letniej dziewczynki zaobserwowano ruchy dystoniczne obejmujące początkowo lewą kończynę dolną. Stopniowo ruchy dystoniczne objęły również prawą kończynę dolną. W wieku 17 lat dystonia w znacznym stopniu upośledzała życie chorej, która poruszała się wyłącznie na wózku inwalidzkim. Farmakoterapia i wstrzyknięcia toksyny botulinowej przyniosły niewielką i przejściową poprawę. Badanie genetyczne wykazało obecność mutacji DYT-1. Chorą skierowano do leczenia operacyjnego. W wieku 17 lat przeszła operację obustronnej implantacji elektrod do głębokiej stymulacji mózgu. Obustronna stymulacja GPi przyczyniła się do znacznego zmniejszenia ruchów dystonicznych i wymuszonego dystonicznego ustawienia kończyn dolnych. Podczas dwuletniej obserwacji pacjentka zaczęła chodzić samodzielnie. Obustronna stymulacja GPi wydaje się skuteczną metodą leczenia izolowanej dystonii kończyn dolnych.

Słowa kluczowe: choroby ruchu, dystonia kończyn dolnych, stymulacja gałki białej, neurochirurgia czynnościowa.

Correspondence address: Dr Michał Sobstyl, Klinika Neurochirurgii, Centrum Medycznego Kształcenia Podyplomowego, ul. Marymoncka 99, 01-813 Warszawa, e-mail: mrsob@op.pl

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Introduction

Pallidal stimulation is now a well-established treatment modality for primary generalized dystonia (PGD) [1-4]. Among patients with PGD, most benefit has been observed in those harbouring DYT-1 mutation [1-3]. Furthermore, striking improvement has also been noted in patients with PGD without DYT-1 mutation [5]. A patient with secondary generalized dystonia can also gain functional benefit under chronic bilateral GPi stimulation, although the outcome is less predictable than in patients with PGD. Recent reports have indicated that patients with medically intractable cervical dystonia or segmental dystonia (Meige's syndrome) can improve under chronic bilateral GPi stimulation [6-8].

Pallidal stimulation is also very effective in ameliorating dystonic features in advanced stages of Parkinson's disease [9]. Early morning foot dystonia responds very favourably to GPi stimulation [10].

Foot or lower limb dystonia is very often the initial site in young-onset dystonia. It is usually primary and spreads to other body parts. Primary generalized dystonia in early childhood is associated with DYT-1 mutation. The symptoms usually appear in childhood or early adulthood. The mean age of onset is approximately 12 years. Symptom onset involving a lower limb is also associated with an increased likelihood that the condition will quickly evolve to generalized dystonia.

The management of patients with PGD is challenging. The pharmacological treatment has a very limited influence on dystonic movements and dystonic posturing. Botulinum toxin injections can be applied only locally. The dystonic movements produce musculoskeletal deformities involving the foot or the cervical or lumbar spine. To avoid such complications in patients with PGD, an early surgical approach is warranted.

In this article, we present a young patient with isolated lower limb dystonia without dystonic movements in other body parts. The isolated dystonia confined only to both feet resulted in total inability to walk. After three and a half years of her illness she was physically handicapped only by lower limb dystonia. Genetic testing revealed the presence of DYT-1 mutation. This clinical picture of the presented positive DYT-1 case with onset in a lower limb is rather unusual. There was no spread of dystonia to other body parts and both feet were equally affected by dystonic movements. Moreover, the patient suffered from histiocytosis and coeliac disease. These two entities can also be associated with various movement disorders [11,12]. In the presented case, genetically proven

for DYT-1 mutation, the dystonic features have a rather genetic background. This case demonstrates that dystonia confined only to feet can severely handicap the individual without the spread of dystonic movements to other body parts.

Case report

This 17-year-old right-handed woman with negative family history of movement disorders and no other neurological disease was referred to our neurosurgical department for consideration of pallidal stimulation due to medically intractable young-onset lower limb dystonia. The first symptoms were noticed at the age of 14 as increased tension in the left foot only after walking. The first admission to a paediatric ward was made to elucidate muscle spasm involving only the left foot, with small foot inversion, and curling of the big toe of the left foot. The neurological examination was unremarkable besides inappropriate dystonic posturing of the left foot. The laboratory tests indicated only increased inflammatory markers. She was seen by a neurologist who prescribed hydroxyzinum. This treatment improved the patient's symptoms. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were normal. An EEG was also unremarkable. She was diagnosed as having vegetative dystonia. To exclude spinal pathology of atypical left foot posturing, MRI of the entire spine was done, which was unremarkable. After 10 months, the right foot started to be affected by dystonic movements. During the second admission the right foot was inverted and all the toes were curled. The right foot was more affected than the left. The patient experienced walking difficulty for the first time. The electromyography and electroneurography examinations were normal. A battery of laboratory tests including mitochondrial antibodies, smooth muscle antibodies, gastric cell antibodies, and antinuclear antibodies was performed. All antibody values were within the normal range. Combi-test was negative. The psychological testing and psychiatric consultations were unremarkable. The diagnosis of young-onset dystonia involving only the feet was made. The patient was put on levodopa + benserazide (62.5 mg) with the daily dose titrated up to 4 tablets a day. The levodopa treatment brought only transient and modest benefit lasting 2 months. Benzodiazepine was initiated but also with slight effect. Laboratory examinations were within the normal range beside visibly increased inflammatory markers. To exclude an active inflammatory process, tests

against tuberculosis and active carcinogen metabolites were performed. All carcinogen metabolites including alpha-fetoprotein, carcinoembryonal antibody and human hCG were within the normal range. Despite pharmacological treatment the dystonia progressively worsened. The patient was referred for botulinum toxin injections (BTX). After BTX, the patient underwent an extensive rehabilitation course. During physical exercises the patient started complaining of pain localized in the upper thoracic spine. The plain films of the upper thoracic spine revealed left-sided scoliosis. The MRI confirmed compression changes at the T2 and T4 level. The radiological appearance of MRI changes suggested tuberculosis or brucellosis. The blood and cerebrospinal fluid tests excluded these diagnoses. The thin-needle marrow biopsy was done, which was unremarkable. The repeated MRI of upper thoracic spine showed progression of pathology with associated pain. The patient underwent orthopaedic stabilization. The histopathological examination revealed massive infiltration of eosinophilic, plasmatic, lymphoid and histiocytic cells. The diagnosis of Langerhans cell histiocytosis was made. The patient was referred for further chemotherapy, which proved effective. Two months after completing chemotherapy, the patient suffered from chronic diarrhoea. Endoscopic biopsy performed in general anaesthesia revealed coeliac disease. The patient was put on a diet without gluten-containing food. The diarrhoea was significantly improved. During this period the dystonia was confined only to her feet. She was unable to walk and almost all the time she was

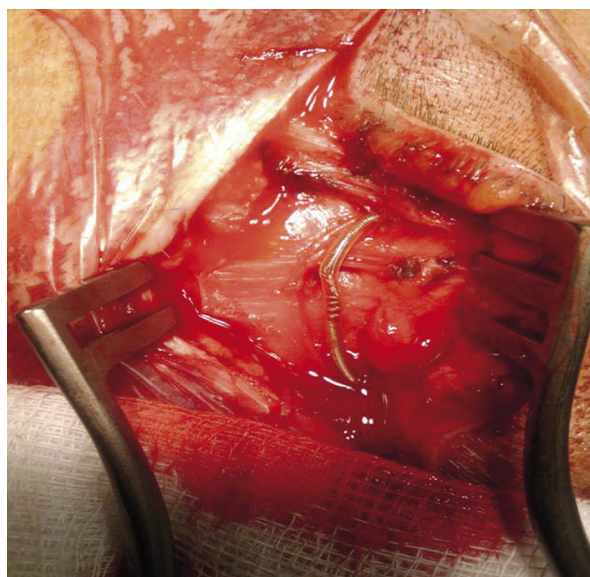


Fig. 1. Broken deep brain stimulation lead near the burr hole secondary to the slippage of the connector to the cervical region

wheelchair-bound during consultation at our department. The patient's feet were severely affected by dystonic movements. Any patient activity aggravated the dystonia and forced the patient to assume a sitting position.

The patient was referred for surgery. The patient and her family member signed written informed consent. The Institutional Review Board of the Postgraduate Medical Centre in Warsaw approved the study. The patient's neurological status before surgery and after it was assessed using the Burke-Fahn-Marsden Dystonia Rating scale (BFMDR) by a neurologist specialized in movement disorders.

In January 2009, the patient underwent implantation of two electrodes in the GPi bilaterally. The stereotactic implantation of deep brain stimulation leads (Model 3387, Medtronic Inc) was performed in general anaesthesia. Standard surgical technique was used, targeting the posteroventral region of GPi, using coordinates based on the midpoint of the AC-PC line. The Leksell G stereotactic head frame was placed on the patient's head and a contrast-enhanced CT scan was obtained. The CT scan was digitally fused with previous noncontrast MRI of the brain to allow targeting based on anatomical structures. The coordinates of posteroventral GPi were chosen as follows: 2 mm anterior to the middle AC-PC point, 20 mm lateral, and 5 mm inferior to the AC-PC line. The targeting was based only on neuroimaging using neuronavigation (Stealthstation, Medtronic Inc). No microrecording was used. The leads were secured using Stimlock bilaterally. The skin was temporarily sutured. The fluoroscopy was performed to check the depth of implanted DBS leads. After removal of the stereotactic head frame, the pulse generators (Soletra) were placed in the subclavicular region. Her pulse generators were programmed on the second postoperative day. The remaining postoperative course was uneventful.

The patient began to walk independently 4 weeks after surgery. Five months after surgery, the patient experienced rapid recurrence of dystonia in her right foot. The slipped connector caused the breakage of the DBS lead near the burr hole (Fig. 1). The broken left lead was replaced stereotactically in general anaesthesia. The postoperative CT showed proper placement of the new left DBS lead (Fig. 2). The patient regained benefit. The postoperative MRI showed proper placement of the new DBS lead (Fig. 3). The patient's feet preoperatively and postoperatively are shown in Figs. 4 and 5. The preoperative and postoperative functional and motor BFMDRS scores are presented in Table 1. Initial settings of stimulation parameters were as follows: 130 Hz,

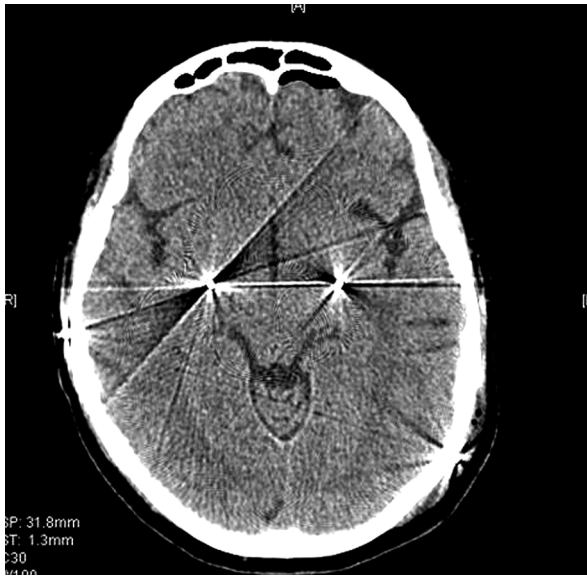


Fig. 2. The postoperative computed tomography after replacement of the left broken deep brain stimulation lead under stereotactic conditions in general anaesthesia

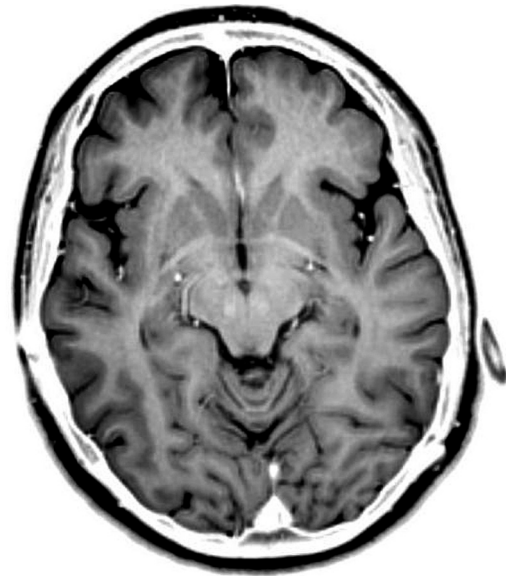


Fig. 3. Postoperative axial magnetic resonance imaging revealing deep brain stimulation leads in the posteroventral GPi implanted just above optic tracts

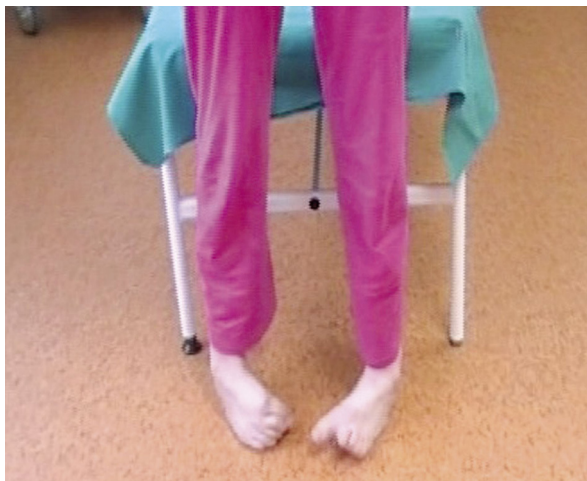


Fig. 4. Preoperative state showing patient's feet. The feet were inverted and all the toes were curled even in resting position. Any movement aggravated dystonia in feet



Fig. 5. Postoperative state showing patient's feet. The patient's feet are in normal position during standing. There is still occasional curling of the big right toe

Table 1. Preoperative and postoperative Burke-Fahn-Marsden Dystonia Rating (BFMDR) scores in stimulation 'on' condition

BFMDR scores	Before surgery	2 months after surgery	6 months after surgery	12 months after surgery	18 months after surgery	24 months after surgery
Functional BFMDR scores	7	2	7	3	2	2
Motor BFMDR scores	25	8	23	5	3	5

Table 2. Postoperative parameters, active contacts and stimulation mode used 24 months postoperatively

Stimulation parameters at the last follow-up	Voltage (V)	Pulse width (μ s)	Frequency (Hz)	Stimulation mode	Contact(s) active as cathode(s)	Contact(s) active as anodes(s)
Left hemisphere	3.6	210	130	bipolar	0, 1, 2	3
Right hemisphere	3.3	210	130	bipolar	4, 5	6

210 μ s with increasing voltage up to 3.3 V. The stimulation mode was bilaterally bipolar. On the left side, contacts 0, 1, 2 were used as cathodes, and contact 3 as the anode. Contacts 4 and 5 were used as cathodes, and contact 6 as the anode on the right side (Table 2). After 24 months of continuous bilateral GPi stimulation, there was a 72% reduction in functional and a 80% reduction in motor scores of the BFMDR scale. There is still occasional right foot inversion with curling of the right big toe.

Discussion

The typical initial location of primary generalized dystonia is the foot. This location is usually associated with generalization of dystonic movements. The presented case is unique in the clinical picture, because dystonia remained isolated only to the patient's feet. The location and severity of foot dystonia resulted in functional disability. The available pharmacological treatment and BTX proved ineffective in ameliorating dystonic movements confined to the patient's feet. After three and a half years the patient stopped walking and was wheelchair-bound. Her social life and attending school were severely affected by incapacitating dystonia involving only her feet.

GPi stimulation is the most effective treatment modality not only for patients with PGD but also for those with medically intractable focal dystonia [1-3,6,7]. Bilateral GPi stimulation proved to be an effective treatment modality also in our case. Genetic testing revealed the presence of DYT-1 mutation. The patient also suffered from coeliac and Langerhans cell histiocytosis. Both entities were histopathologically confirmed in our case. In the literature, there are reports indicating the presence of movement disorders in patients with coeliac disease [11]. Up to 6% of patients with coeliac disease present with various neurological deficits. The most common symptom in these patients is cerebellar ataxia and, very rarely, dystonia [6]. After putting the patient on a gluten-free diet, dystonia progressed. This patient also harbours

histologically proven Langerhans cell histiocytosis. In our patient the histiocytosis was successfully managed by orthopaedic surgery and further chemotherapy. Although coeliac disease and Langerhans cell histiocytosis were successfully managed, the dystonia progressed to total incapacitation of the patient. The underlying genetic cause of dystonia – the presence of DYT-1 mutation – in the presented case seems to play the pivotal role.

Dystonic movements in the presented case responded very efficiently to bilateral GPi stimulation. GPi procedures are invasive treatment and may be associated with even serious neurological sequelae. This treatment modality should not be delayed and is even warranted earlier in the disease course before musculoskeletal deformities secondary to dystonia develop. Our patient had dystonic posturing of both feet but did not develop deformities in her feet. The early surgical approach prevented the formation of these deformities, which also correlated with functional and motor benefit gained after surgery.

We conclude that bilateral GPi stimulation is an approved target for patients with primary as well as secondary generalized dystonia. Patients with intractable focal or segmental dystonias (cervical dystonia, Meige's syndrome) incapacitating their lives can also dramatically benefit from pallidal surgery. This case supports the observation that dystonia confined to the feet in a patient with positive DYT-1 mutation can respond favourably to bilateral pallidal surgery. This treatment should be undertaken early in the disease course before musculoskeletal deformities develop.

Disclosure

The authors report no conflict of interest.

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