Letter to the Editor

Low frequency subthalamic nucleus electrical stimulation relieves the symptoms of DYT1-dystonia: a case description

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Introduction

Primary DYT1-dystonia is the most common form of hereditary dystonia. It is an autosomal dominant movement disorder caused by mutation of the *TOR1A* gene (1,2). Its response to drug therapy is usually transient and unsatisfactory, and botulinum toxin injections are rarely indicated (3,4). Many groups have reported the long-term efficacy of high frequency deep brain stimulation (DBS) on the globus pallidus internus (GPi) and subthalamic nucleus (STN) as a treatment for dystonia in pediatric patients, especially DYT1-dystonia patient (5-10). Two recent meta-analyses suggest that DBS targeting the GPi is effective in treating primary dystonia, especially early onset DYT1-dystonias (11,12). However, the efficacy of low frequency DBS, especially low frequency STN-DBS, has rarely been documented. Here, we report on a boy with primary DYT1-dystonia who was treated with 60 Hz STN-DBS after the failure of high frequency STN and GPi-DBS. The patient obtained remarkable improvement and now behaves normally in daily life. This is the first report of a beneficial effect of low frequency STN-DBS in patients with DYT1-dystonia, in view of the limited efficacy in the only report on the treatment of DYT1-dystonia with low frequency STN-DBS (13).

Case description

Our patient is an 11-year-old Chinese boy who is a primary school student. He experienced the first emergence of right arm spasm at the age of six, and a *TOR1A* gene mutation was detected in the same year, which presented as a 907_909delGAG heterozygous mutation. At present, his chief complaint was severe muscle spasm inflicting both arms, right leg, back, and waist, which made him lean to the left and involuntarily tilt his head backward (observable in Video S1). His face, throat, and left arm were spared. He experienced his worst period of disease the year before the operation, with a Burke-Fahn-Marsden dystonia rating scale (BFMDRS) score of 39. His walking and writing were heavily affected, which made him drop out of school. He did not receive any medical treatment prior to the operation. Neurological examination showed an intermittent increase in muscle tension in both upper limbs, waist, back, and right lower limb. There was no obvious abnormality in his medical and psychosocial history. No secondary causes such as trauma, infections (e.g., encephalitis), or medication adverse effects (e.g., tardive dyskinesia) were found. The patient's father was also a DYT1-dystonia patient with the same *TOR1A* gene mutation, but his symptom was not so serious, that he can live a normal life (observable

Table 1 Clinical report of symptoms before and after treatment

Variables	Baseline	GPi-DBS stim on (8 months)	GPi-DBS stim off (8 months)	STN-DBS HFS	STN-DBS LFS	Two years of follow-up
BFMDRS						
The movement scale	29	25	32.5	9.25	1	1
Disability scale	10	10	11	6	1	1
Stimulation parameters [contact voltage (V)/pulse width (us) /frequency (Hz)]						
L	–	C+2-3-, 3.0/90/130	–	C+0-3-, 1.85/60/135	C+0-3-, 2.3/60/60	C+0-3-, 2.3/60/60
R	–	C+9-10-, 3.0/90/130	–	C+8-11-, 1.5/60/135	C+8-11-, 2.3/60/60	C+8-11-, 2.3/60/60

GPi, globus pallidus internus; DBS, deep brain stimulation; STN, subthalamic nucleus; HFS, high frequency stimulation; LFS, low frequency stimulation; BFMDRS, Burke-Fahn-Marsden dystonia rating scale; L, left; R, right.

in Video S2). The diagnosis was made carefully by neurological physicians according to the patient's typical symptoms, history of present illness, neurological examination, family history, and *TOR1A* gene mutation.

After rigorous preoperative assessments of his condition, the indication for a DBS procedure was confirmed by neurosurgeons experienced in hyperkinetic movement disorders. The operation was carried out by experienced neurosurgeons of the functional neurosurgery department in Beijing Tiantan Hospital. All procedures performed in this study were in accordance with the ethical standards of the ethics committee of Beijing Tiantan Hospital and the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's father for publication of this case report and the accompanying images and videos. A copy of the written consent is available for review by the editorial office of this journal. The patient underwent bilateral implantation of electrodes (3387 Medtronic, Minneapolis, MN, USA) into the GPi under local anesthesia using a Leksell microstereotactic system (Elekta Instrument AB, Stockholm, Sweden) working with preoperative magnetic resonance imaging (MRI) and computed tomography. Then, the implantable pulse generator (IPG) was implanted in the subclavicular area under general anesthesia. The coordinates of the left and right GPi were (115.3, 104.7, 109.1) and (81.2, 104.2, 109.3), respectively. The preoperative MRI was shown in Figure S1. The IPG was turned on one month after the operation. The programming parameters were adjusted according to his complaints. A standardized videotape assessment and validated rating scale BFMDRS were used to document dystonia severity. As shown in *Table 1*, the patient's preoperative BFMDRS score was 39 (29 and 10 respectively for the movement scale and disability scale). After 8 months of high frequency GPi-DBS [left (L): C+2-3-, 3.0 V/90 us/130 Hz, right (R): C+9-10-, 3.0 V/90 us/130 Hz], his symptoms showed no improvement and had become more severe (43.5 in stim-off condition and 35 in stim-on condition), with the face and neck symptoms worsened. Furthermore, reconstruction of the electrodes using the Lead-DBS toolbox (14) showed a non-ideal electrode location, with implantation outside the GPi (*Figure 1A*).

After careful deliberation, the original electrodes were removed. In the second operation (8 months after the first operation), we attempted to implant the electrodes into the GPi again, but we didn't find typical GPi electrophysiological signals during microelectrode recording (Figure S2). During the temporary electrical stimulation, the patient showed facial paresthesia. Considering that more and more researches have confirmed the effectiveness of STN-DBS in the treatment of primary dystonia (6,15,16), and that STN-DBS enables lower power consumption, which is suitable for his non-rechargeable IPG. Bilateral STN-DBS surgery was performed, which obtained informed consent from the patient's father. The coordinates of the left and right STN were (109.7, 101, 108.5) and (87.1, 101, 108.5), respectively. Electrode reconstruction showed an ideal electrode location (shown in *Figure 1B*). High frequency STN-DBS (L: C+0-3-, 1.85 V/60 us/135 Hz, R: C+8-11-, 1.5 V/60 us/135 Hz) sometimes greatly relieved the patient's symptoms (8.5 on the BFMDRS), but the relief did not last, and his symptoms frequently recurred within a short time (22 on the BFMDRS), usually of several hours to several days. So, the patient has been in a state

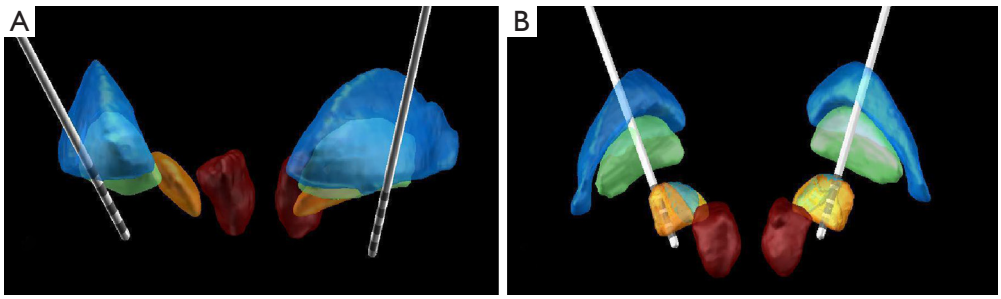

Figure 1 Reconstruction images of electrode location in STN and GPi using the Lead-DBS toolbox. (A) Non-ideal electrode location of GPi-DBS. (B) Ideal electrode location of STN-DBS. Blue: GPe; green: GPi; yellow: STN; red: red nucleus. STN, subthalamic nucleus; GPi, globus pallidus internus; DBS, deep brain stimulation; GPe, external globus pallidus.

of repeated remission and recurrence of dystonia, which exhausted the patient and his families. After a long period (6 months) of unfavorable treatment attempts with high frequency STN-DBS, and in view of some favorable results using low frequency STN-DBS in Parkinson's disease (PD) and dystonia (17,18), low frequency STN-DBS (L: C+0-3-, 2.3 V/60 us/60 Hz, R: C+8-11-, 2.3 V/60 us/60 Hz) was employed. This allowed stable improvement to be achieved (2 on the BFMDRS), which has been persisting for 2 years. In addition, stimulation-induced dyskinesia (SID) occurred in the early stage of stimulation. After many attempts of various monopolar and bipolar stimulation modes, the current double monopolar stimulation mode was employed, which can not only achieve satisfied dystonia improvement, but also avoid SID. No other surgery-related, stimulation-related, or device-related complication was reported. The patient obtained remarkable and persistent improvement and now behaves normally in daily life. The BFMDRS scores and videos of the patient at various follow-up time points (before and after DBS surgery) are presented in *Table 1* and Video S1, respectively.

Discussion

An important finding in this case was that 60 Hz STN-DBS provided significant and continuous relief of dystonia, which has been persisting for 2 years. To the best of our knowledge, this is the first report of a beneficial effect of low frequency STN-DBS in patients with DYT1-dystonia. In this report, we not only confirm the efficacy of STN-DBS, but also provide evidence for the validity of low frequency STN-DBS in the treatment of DYT1-dystonia.

DYT1-dystonia is an autosomal dominant disease that typically begins at school age, with a mean onset of approximately 12 years old. Characteristically, it initially affects a unilateral arm or leg, then subsequently spreads to additional limbs and/or the trunk. Up to 50% of affected subjects may ultimately develop general involvement (1,2). Our patient was a typical DYT1-dystonia patient, presenting with typical clinical manifestations and a *TOR1A* gene mutation, and demonstrated general involvement with multiple body parts being implicated. GPi-DBS is now a mature treatment for DYT1-dystonia, with long-term efficacy of over 60% (19-21). STN-DBS has also been reported to be a valid treatment for several patients with primary dystonia (6,15,16). As in PD patients, high frequency stimulation is the traditional stimulation mode in dystonia, but low frequency stimulation has also been tried in a few studies. Merola *et al.* (17) reported an improvement in residual involuntary movement (including dyskinesia and dystonia) after switching stimulation frequency from 130 to 80 Hz in PD patients. However, a moderate worsening of parkinsonian symptoms was observed in a portion of patients, requiring a return to 130 Hz STN-DBS. Furthermore, Ostrem *et al.* (13) reported that high frequency STN-DBS was more effective than low frequency STN-DBS in primary dystonia (5 cranial cervical dystonia and 2 DYT1-dystonia patients). Thus, the efficacy of low frequency STN-DBS has not been confirmed. The patient in our case obtained a stable improvement of 95.4% on the BFMDRS (from 43.5 to 2), similar to that reported for high frequency STN-DBS (more than 50% on long-term follow-up) (6,15-17), and a higher improvement rate than achieved using low frequency STN-DBS in primary dystonia (16.6%) (13), which gives support to the validity of low frequency STN-DBS for DYT1-dystonia.

Along with the increasing application of low frequency

DBS, there is growing interest in the effects of varying frequencies in basal ganglia DBS for the treatment of movement disorders, although the frequency-dependent mechanism of action has not been clarified. It may be that a specific frequency of stimulation interferes with the pathogenesis of dystonia, or it could be that the electrical activity of basal ganglia neural circuits could be differently modulated by different frequencies of stimulation (17). In the present case, GPi-DBS failed because of a non-ideal electrode location, which may be due to an error of stereotactic system or human operation error. Patients with dystonia had lower beta power but higher low frequency and high gamma power than PD, and its mean firing rate was lower compared to PD (22-24). Local field potential activity less than 10 Hz has been observed in coherence with dystonic movement (25,26). It has been hypothesized that stimulation frequencies exceeding the firing rate and the mean oscillatory activity of the target in dystonia (~50 Hz) would be enough to modulate this abnormal electrical activity and dystonic movements (25,26), which may be the reason why 60 Hz STN-DBS is effective for this patient. However, we cannot provide a reason for the limited success of the high frequency STN-DBS. This may be due to the individual specific local field potential and single unit activity in the patient's cortico-basal ganglia-thalamic circuits. These electrophysiological activities responded well to low frequency STN-DBS, but not to high frequency STN-DBS. In addition, the double monopolar stimulation mode of this patient may also be one of the reasons for its different stimulation strategy.

The SID that occurred in the early stage of stimulation is a common stimulation-induced adverse effect of STN-DBS, which usually predicts better clinical outcomes on chronic stimulation and this dyskinesia generally disappears within several months. SID is usually caused by stimulating the ventral part of STN, while stimulating the area above the STN (zona incerta area) can exert a direct anti-dyskinesia effect (27,28).

Some limitations must be considered in this study. The results from a single case may not be applicable to patients in other settings. Besides, the rater who scored the BFMDRS was not blinded to the patient's before and after DBS surgery status.

In conclusion, this case can serve as evidence that low frequency STN-DBS has promise for treating patients with DYT1-dystonia, and that it may be the direction of future programming for some patients with primary dystonia, although the underlying mechanism requires further study.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-56/coif). FM reports that he receives funding from National Natural Science Foundation of China (81971070). JZ reports that he receives funding from National Natural Science Foundation of China (81671104, 81830033, 61761166004) and Beijing Municipal Administration of Hospitals' Ascent Plan (DFL20150503). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the ethics committee of Beijing Tiantan Hospital and the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's father for publication of this case report and the accompanying images and videos. A copy of the written consent is available for review by the editorial office of this journal.

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Supplementary

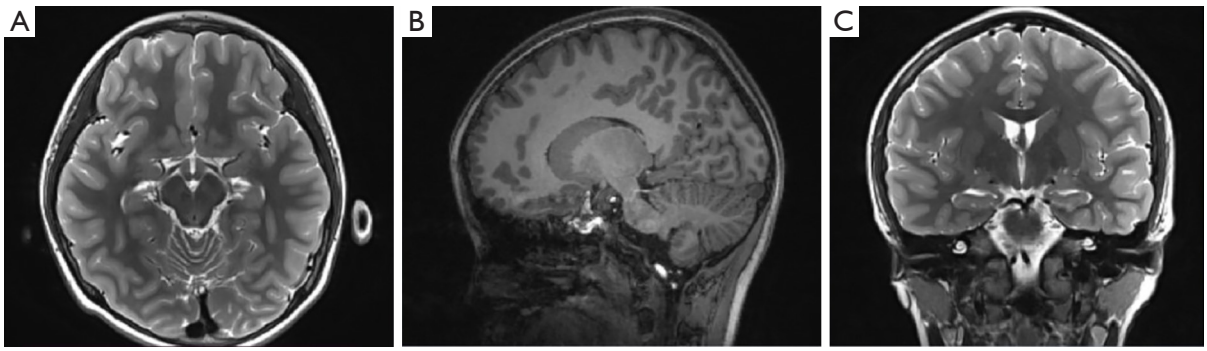

Figure S1 Preoperative MRI of the patient. (A) Axial T2-weighted MRI. (B) Sagittal T1-weighted MRI. (C) Coronal T2-weighted MRI. MRI, magnetic resonance imaging.

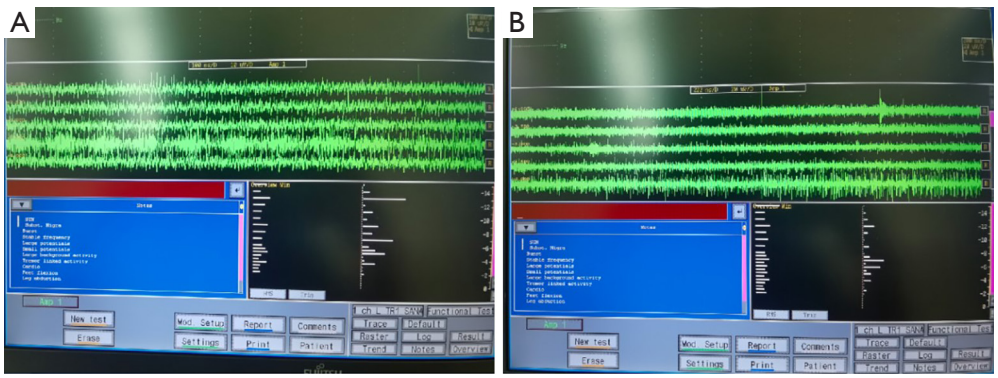

Figure S2 Microelectrode recording results of GPi during the second operation. (A) Left hemisphere. (B) Right hemisphere. GPi, globus pallidus internus.

Video S1 Video of our patient at different follow-up period before and after DBS surgery. Before surgery, his main complaints were serious muscle spasm inflicting two arms, right leg, back and waist, which made him lean to the left, and involuntarily tilt his head back. There was no significant improvement of dystonia after high frequency GPi-DBS, and the symptoms became even more serious. High frequency STN-DBS provided significant improvement, but it didn't last. After it was turned to 60 Hz STN-DBS, stable improvement was achieved, and it has been persisting for 2 years. This video is published with the consent of the patient's father. DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus.

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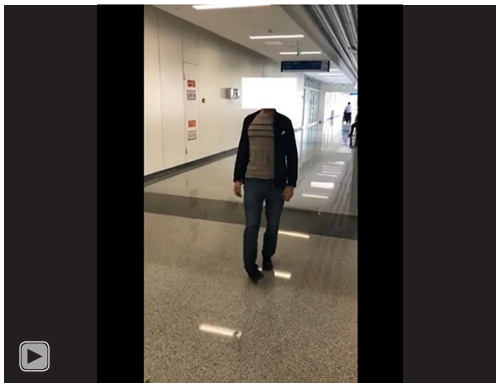

Video S2 Video of the patient's father. The patient's father was also a DYT1-dystonia patient with the same *TOR1A* gene mutation, but his symptom was not so serious, that he can live a normal life. This video is published with the consent of the patient's father.

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