

## Deep brain stimulation of globus pallidus internus for DYT1 positive primary generalized dystonia

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Received: 13 June 2013

Accepted: 9 Oct 2013

Published: 1 Mar 2014

### Abstract

**Background:** Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is recommended as a promising technique for the management of the primary generalized dystonia (PGD) with DYT1 gene mutation. We present the first report of DBS results in Iranian patients with DYT1 positive PGD.

**Methods:** Nine patients who suffered from severely disabling DYT1 positive PGD consecutively were recruited for the study between 2008 and 2010. The patients underwent bilateral deep brain stimulation of the GPi in a single procedure. The mean follow up duration was  $8.8 \pm 2.2$  months. The efficacy of the intervention was evaluated by comparing pre- and post operative scores of patients with Burke-Fahn-Marsden's dystonia Scale (BFMDRS). Statistical analysis was performed using SPSS 11.0 software.

**Results:** Of 9 patients six were female with the mean age of  $15.2 \pm 5.5$  years old (range: 8- 25 years old). The mean for Burke-Fahn-Marsden's Dystonia Rating Scale (BFMDRS) score was  $47.22 \pm 14.1$  before surgery and  $12.3 \pm 8.2$  after follow up, which significantly improved ( $P=0.0001$ ). The mean stimulation parameters at the last visit were at a frequency of  $152.2 \pm 32.4$  Hz (range 130- 230 Hz), a voltage of  $2.6 \pm 0.7$  V (range 1.1- 4), and a pulse width of 60  $\mu$ sec. No complication was observed during follow up.

**Conclusion:** Bilateral DBS of the GPi has an encouraging result for the management of DYT1 positive PGD and is recommended as a safe technique for the treatment of these patients. Shorter pulse width in stimulation parameters is suggested for DYT1 dystonia patients.

**Keywords:** Deep brain stimulation, Globus pallidus internus, DYT1 dystonia.

**Cite this article as:** Miri Sh, Ghoreyshi E, Shahidi Gh. A, Parvaresh M, Rohani M, Saffari M. Deep brain stimulation of globus pallidus internus for DYT1 positive primary generalized dystonia. *Med J Islam Repub Iran* 2014 (1 Mar). Vol. 28:18.

### Introduction

Primary generalized dystonia (PGD) is a progressive neurological disorder characterized by involuntary, prolonged muscle contractions and abnormal twisting postures in young adults (1). The most frequent cause of early onset primary dystonia is an autosomal dominant disease due to mutation in DYT1 gene locus on chromosome 9q34, which encodes for an abnormal torsin A protein (2,3). Since pharmacotherapy

usually has a limited efficacy in suppressing the disease progression, surgical approaches have been considered for the treatment of severe forms of PGD (4). Pallidotomy improves the symptoms, but it has severe side effects (5). Unilateral pallidotomy cannot adequately resolve generalized symptoms, and bilateral pallidotomy may cause serious complications such as cognitive impairment, dysarthria, dysphagia, and limb weakness (5,6). Other surgical tech-

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nique is a bilateral deep brain stimulation (DBS) by implanting electrodes in the Globus Pallidus Internus (GPi) which is particularly recommended for patients with DYT1-positive dystonia (4,7).

The intervention showed encouraging results in different reports from various countries (4,8). However, no study in Iran has demonstrated the outcome of DBS in primary generalized dystonia with DYT1 mutation. The present study aimed to evaluate the efficacy and safety of the bilateral DBS of GPi for the management of 9 Iranian patients with advanced DYT1 positive dystonia.

### Methods

Between January 2008 and December 2010, nine consecutive patients (six females) who suffered from DYT1 positive dystonia underwent bilateral globus pallidus internus DBS at the department of Neurosurgery of Rasool-Akram teaching hospital, Iran University of Medical Sciences, Tehran, Iran. The study was approved by the ethics committee of the university. All patients and their families provided written informed consent for the surgical procedure and follow up examinations.

The diagnosis of dystonia was based on the Fahn's criteria for PGD by two expert neurologists (9). All patients harbored genetically proven DYT1 mutation and their neurological examination was normal except for dystonia. Brain MRIs were normal with no focal lesion and secondary causes of dystonia were excluded. Psychiatric disorders and cerebral atrophy were other exclusion criteria.

The mean for age at surgery was  $15.2 \pm 5.5$  years (range: 8- 25 years) and for duration of the disease  $7.3 \pm 5.1$  years (range: 1- 17 years). The patients had a disabling form of PGD which was refractory to medical treatment with anticholinergic medications, benzodiazepines, neuroleptics, or baclofen.

### Neurological evaluations

The patients were assessed preoperatively and "on" stimulation 6 to 9 months after surgery with the Burke-Fahn-Marsden's

dystonia rating scale (BFMDS) by two neurologists expert in movement disorders field (6). Higher scores representative of higher level of disability. The mean duration of follow up after surgery was  $8.8 \pm 2.2$  months (range: 6- 12 months). The mean for the BFMDS scores were compared preoperatively and postoperatively. All evaluations were performed by the same neurologist.

### Surgical intervention and electrical setting

All 9 patients underwent implantation for bilateral GPi electrodes and implantable pulse generator (IPG) in a single session under general anesthesia. The stereotactic system was Leksell/Lerch in all procedures. Magnetic resonance imaging (MRI) was done for visualization of target location (the posteroventral part of the GPi) before surgery and confirmation of the electrode position postoperatively. Then the electrodes were connected to subcutaneous IPG within the chest or abdomen. Surgeries had been performed by the same neurosurgical group.

The IPGs were programmed 2 weeks after surgery in monopolar mode. The initial electrical variables were as follow: frequency 130 Hz; pulse width  $60\mu\text{s}$ ; and amplitude 2 V. In each GPi the deepest electrode was turned on. In order to optimize the settings, variables were gradually changed according to clinical response at the follow up visits.

### Statistical Analysis

The mean and standard deviation of patient's age, disease and follow up duration, in addition to pre- and post-operative BFMDS scores were calculated. According to the normal distribution of data, the paired t-test was used to compare changes of the BFMDS before and after surgery. We correlated post-operative BFMDS with patients' age, disease duration, age at the time of surgery and pre-operative BFMDS. A probability value less than 0.05 was considered to be significant. The SPSS software version 11.0 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

## Results

Demographic characteristics of the patients are shown in Table 1.

Severe disabilities were observed in all patients before surgery. However, the patient's posture, dystonic movements, and motor function considerably improved after DBS - GPi. The BFMDRS movement score significantly improved from  $42.2 \pm 14.1$  (range 20 to 70) before surgery to  $12.3 \pm 8.2$  (range 3 to 28) after surgery (mean follow up:  $8.8 \pm 2.2$  months) ( $p=0.0001$ ). The patients showed a considerable reduction of  $74.4\% \pm 13.5\%$  (range 56 to 92%) in their BFMDRS score.

The percentage of BFMDRS score improvement was not significantly correlated with the age of the disease onset, the duration of symptoms (between onset and surgery), age at the time of surgery, and pre-operative BFMDRS scores ( $p>0.05$ ).

The mean stimulation parameters at the last visit were at frequency of  $152.2 \pm 32.4$  Hz (range 130- 230 Hz), a voltage of  $2.6 \pm 0.7$  V (range 1.1- 4), and a pulse width of 60 $\mu$ sec which all adjusted to the patient's clinical response. The most common used electrodes (contacts) in the patients were 0/1 (left) and 4/5 (right).

No complication was observed in the patients. Neurological deficits, infection, or system malfunctions did not occur in patients.

## Discussion

Medically refractory dystonia patients, who suffer from severe disabilities, are considered for surgical treatment. The DBS of basal ganglia is an appropriate surgical technique for treatment of these patients (10). Efficacy of DBS with globus pallidus internus targeting in primary dystonic patients was shown first in 1999 (11). Stimulation of GPi showed favorable results, especially in patients with DYT1 mutation (10).

In a recent study, Markun et al. reported the rate of improvement in BFMDRS movement scores as much as 61.5% at 1 year after surgery, 64.4% two years, and 70.3% at the mean follow up of 32 months (12). These results were similar to other study by Isaias et al. in 32 patients with PGD (13). In the study of Borggrafe et al. movement score of BFMDRS in PGD patients was  $56.9 \pm 22.7$  before bilateral DBS - GPi and it improved to  $23.7 \pm 23.2$  over a mean period of 13 months after surgery (14). It has been mentioned that among the studied patients, those with DYT1 mutation had higher rate of improvement (77% vs. 44%, respectively) (14). Another study by Cif et al. represented marked improvement in motor score of BFMDRS postoperatively up to 10 years after surgery ( $57.5 \pm 23.9$  vs.  $23.3 \pm 19.2$ ). However, presence of new signs and recurrence of previous signs were

Table 1. Demographics and clinical characteristics of the patients.

Patient's Number	Sex	FH	Age at onset (years)	Onset location	Disease duration (years)	Drug hx	Age at surgery (years)	F/u (mo)	BFMDS score before	BFMDS score after
Case 1	F	-	7	Lt up ex	4	A.ch	11	12	41	3
Case 2	F	-	9	Rt Lo ex	7	A.ch+	16	9	50	8
Case 3	M	+	8	Rt up ex	7	A.ch+ Bz	25	6	70	13
Case 4	F	-	7	Lt up ex	4	A.ch+ A.ep	11	6	44	5
Case 5	M	-	7	Trunk	1	A.ch+ A.ep	8	6	64	28
Case 6	F	-	7	Rt lo ex	7	-	14	11	44	14
Case 7	M	-	9	Rt up ex	3	A.ch	12	8	46	20
Case 8	F	+	8	Rt up ex	11	A.ch	19	11	20	4
Case 9	f	+	9	Rt up ex	12	A.ch	21	11	46	16

F, female; M, male; FH, family history; Mo, months; F/U, follow up; Rt up ex, right upper extremity; Lt up ex, left upper extremity; Rt Lo ex, Right lower extremity; Lt Lo ex, Left lower extremity; Drug hx, Drug history; A.ch, anticholinergics; Bz, benzodiazepines; A.ep, anti epileptics; BFMDS, Burke-Fahn-Marsden's dystonia Scale.

also reported in the study (15). Additionally, in Alcindor et al. report for a patient with DYT1 positive PGD who underwent DBS - GPi, after a 10-year follow up was fully independent and had an active life style (2).

In accordance with findings of previous studies, our study indicates promising results of bilateral DBS - GPi in symptoms improvement of DYT1 positive patients with primary generalized dystonia during a period of 6 to 12 months after surgery. Our patients showed 75% reduction in their BFMDRS score.

We did not include DYT1 negative patients with primary generalized dystonia in the present study. Thus we could not judge about the superiority of DBS- GPi in DYT1 positive patients compare to other PGD patients. Nevertheless, findings of the mentioned studies propose that evaluating PGD patients for DYT1 mutation can help predicting outcome of DBS at consultation before surgery. There are few studies that reject this assumption. For example, according to Coubes and his colleagues, DYT1 positive and negative patients have no significant differences in functional and clinical improvement after DBS procedure (4). Despite the finding of the later study, genetic assessment of PGD patients for DYT1 mutation still seems a valuable diagnostic criteria.

Markun et al. suggested that shorter duration of the disease is another predictor of long-term BFMDRS scores improvement after DBS procedure (12). Furthermore, minor motor impairment before surgery is introduced as a predictor for better improvement after surgery (14). However, our results did not establish any of these correlations which could be due to limitation in number of subjects.

Although DBS is a very effective treatment for DYT1 positive dystonia patients, response of cases to the intervention is variable (12). Accordingly, we observed a wide range of responses. Improvement in BFM scores was between 50% and 92%. This diversity also was observed in the previous studies (2,16,17). This difference could be

due to patient's genetic diversity and heterogeneity or various motor anomalies in patients (16).

According to the results of the Moro's study, higher frequency of stimulation leads to better clinical improvement in pallidal stimulation for dystonia (18). A frequency of 130 Hz is associated with the best clinical improvement in the patients. Higher voltage is also related to significant improvement of clinical symptoms (18). However, due to the risk of delivering excessive charge to the brain and decreasing battery life, voltage may have gradual decline (19). Most of recent studies used stimulation frequencies of 100 to 185 Hz (5,15,19). In our study, frequency and amplitude setting was similar to other studies.

Although it has been reported that increasing pulse width had no significant effect on clinical improvement (18), most of studies implanted long pulse duration (120 to 450  $\mu$ sec) (10,19). Among stimulation parameters, the pulse width setting in our patients was unique and considerably shorter than similar studies. The pulse width equal to 60  $\mu$ sec besides a high frequency (150 Hz) had a reasonable clinical response in the patients. This setting has at least two prominent advantages for the patients: shorter pulse width could extend battery life and it may decrease the side effects. Regarding the tolerability of the setting and good clinical response in the patients, it is advisable to use pulse width of 60  $\mu$ sec in DYT1 positive dystonia patients. Similar to other studies, we used deepest electrodes more commonly in our patients (15,18,19).

Adverse events may occur after the DBS procedure. The rate of complications is different in various studies. In Borggrafe's study, adverse events occurred in 50% of patients and 13% of them underwent another surgery (14). Coubes reported one case of delayed unilateral infection of IPG after DBS which led to system removal (4). Hardware malfunction, including extension of cable disconnection and early IPG dysfunction, in addition to hardware infection

were also observed in another study (15). Nonetheless, increasing rigidity, more cramping and development of diaphoresis were reported 4 years after DBS which led to revision of surgery to resolve symptoms (2). Despite these findings, we observed no complication among our study subjects. One probable cause of this difference could be our short term follow up of patients. This was a limitation in the present study which also made the durability of response to DBS in our DYT1 patients unclear. However, initial therapeutic response was favorable.

### Conclusion

DBS - GPi for DYT1 positive dystonia is a highly effective treatment with rapid response and infrequent complications. Using shorter pulse width in stimulation setting may suggested for DYT1 dystonia patients. Further studies on factors relating to better response and higher improvement rate among these patients is needed.

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