HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2016 May 25.

Published in final edited form as:

Parkinsonism Relat Disord. 2015 February ; 21(2): 116–119. doi:10.1016/j.parkreldis.2014.11.013.

Temporal profile of improvement of tardive dystonia after globus pallidus deep brain stimulation

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Abstract

Background—Several case reports and small series have indicated that tardive dystonia is responsive to globus pallidus deep brain stimulation. Whether different subtypes or distributions of tardive dystonia are associated with different outcomes remains unknown.

Methods—We assessed the outcomes and temporal profile of improvement of eight tardive dystonia patients who underwent globus pallidus deep brain stimulation over the past six years through record review. Due to the retrospective nature of this study, it was not blinded or placebo controlled. Results: Consistent with previous studies, deep brain stimulation improved the overall the Burkee–Fahn–Marsden motor scores by 85.1 ± 13.5%. The distributions with best responses in descending order were upper face, lower face, larynx/pharynx, limbs, trunk, and neck. Patients with prominent cervical dystonia demonstrated improvement in the Toronto Western Spasmodic Torticollis Rating Scale but improvements took several months. In four patients the effects of deep brain stimulation on improvement in Burke Fahn Marsden score was rapid, while in four cases there was partial rapid response of neck and trunk dystonia followed by was gradual resolution of residual symptoms over 48 months.

Conclusion—Our retrospective analysis shows excellent resolution of tardive dystonia after globus pallidus deep brain stimulation. We found instantaneous response, except with neck and trunk dystonia where partial recovery was followed by further resolution at slower rate. Such outcome is encouraging for using deep brain stimulation in treatment of tardive dystonia.

Keywords

Drug-induced movement disorders; Basal ganglia; Axial dystonia; DBS; Antiemetic; Dopamine receptor blocker

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The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

1. Introduction

Tardive syndromes are chronic, disabling, and often irreversible complications of treatment with dopamine receptor blocking agents [1]. Patients with tardive syndromes may have primarily dystonic movements, referred to as tardive dystonia (TD), which predominantly involves axial musculature including neck, face, jaw, and trunk [2]. Pharmacotherapeutic options include anticholinergics, baclofen, propranolol, benzodiazepine, tetrabenazine, and botulinum toxin but TD is often intractable [1,2]. Deep brain stimulation (DBS) surgery of the globus pallidus, pars interna (GPi) has been used to treat complicated TD cases. Several case reports and a few case series have shown more than 80% improvement of dystonia [3–8]. We hypothesized, based on preliminary observations, that specific distributions of dystonia in TD might be more responsive to DBS therapy. In order to address this question we measured the improvement in motor function of specific involved body parts at six-month intervals post DBS for up to six-years.

2. Materials and methods

2.1. Patients

We assessed the response of all TD patients (3 men and 5 women) from our center who were treated with GPi DBS (Table 1) over the last six years. The average age was 48.2 ± 10.6 years and the average duration of TD prior to surgery was 5.4 ± 2.8 years. In all cases, TD was attributed to prior antipsychotic drug administration, both typical and atypical, as well as antiemetics. The dystonia was not satisfactorily treated with pharmacotherapy, three patients were treated unsuccessfully with botulinum toxin injections in the neck, and one (patient 8) had undergone prior unilateral pallidotomy. Treatment with tetrabenazine was attempted in two patients without success. However, tetrabenazine was avoided in six patients who had underlying depression. Distribution of dystonia was as follows: all patients had cervical dystonia; six had truncal dystonia; four experienced dystonia involving speech, swallowing, lower face, and arms; two had blepharospasm; and one crural dystonia.

2.2. Clinical assessment

The response of DBS surgery on distribution of dystonia was quantitatively measured by motor components of the BurkeeFahneMarsden (BFM) dystonia rating scale at the time of each visit [9]. At least one assessment was done prior to DBS surgery. Post-operatively BFM motor rating scale was assessed at month 1, 2, 3, and then at every six month for six years. The average BFM motor component score prior to DBS was 25.64 ± 12.65. The patients with cervical dystonia were also assessed by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [10].

2.3. Surgery and post operative DBS programming

Six patients had DBS surgery performed bilaterally; one patient had left pallidotomy prior to right-sided DBS surgery, and one patient had unilateral (right) DBS surgery for cervical and left appendicular dystonia. The DBS electrodes were stereotactically placed using MRI imaging and micro-electrode mapping [11]. Three-dimensional anatomical models of basal ganglia were optimized to MRI scans using a proprietary algorithm. These models were

used to facilitate the accuracy of electrophysiological mapping and lead placement with a minimal number of microelectrode penetrations. We initiated DBS programming approximately four weeks post surgery. Patients were programmed at one month, three months and then at every six-month intervals. None of the patients had persistent side-effects related to DBS. During programming and mapping, as a standard of care, we assessed for extent of capsular as well as sensory side-effects induced by DBS.

3. Results

3.1. Clinical outcome

Fig. 1 summarizes the course of improvement in total BFM score after DBS surgery in all patients. Each colored line represents one patient, while the gray thick line depicts the population average. After the first follow-up visit at one month, the total BFM improved, compared to baseline, by 43.6 ± 41.9%. The BFM continued to improve over time. The improvement in average motor BFM was 85.1 ± 13.5% achieved after 48-month visit.

Patient 2 developed unusual late fluctuations in the severity of dystonia as reflected by the motor component of BFM score (light green (in web version) dashed line in Fig. 1A,B). The worsening of scores was correlated with the onset of severe depression. Although less robust in comparison to our entire cohort, the improvement in his BFM score was, nonetheless, 66% from the 60th month going forward.

Speech, swallowing and mouth dystonia had significant improvement by the third month. Upper limb dystonia improved in 18 months, while lower extremities had improvement in 48 months. Cervical and truncal dystonia also had early response, but sometimes they required multiple programming sessions over 48 months before satisfactory responses were achieved. Improvement in BFM motor subscore for speech and swallowing function was 83.3 ± 23.6% and for mouth dystonia was 87.5 ± 25%. The BFM motor score for upper limb dystonia improved by 88.9 ± 19.2%, and legs improved by 87.5 ± 17.7%. Cervical and truncal dystonia improved by 77.1 ± 34.4% and 95.5 ± 5.33%, respectively. The rate of improvement in BFM was varied among patients. Fig. 2 depicts examples of three trends. All subscores of BFM scales rapidly improved within one month in patient 3 (Fig. 2A). Patient 4 had rapid improvement in trunk, but mouth and neck dystonia gradually improved (Fig. 2B). Patient 5 had gradual improvement in neck and trunk over a more prolonged course (Fig. 2C).

We also measured the effect of DBS on the TWSTRS in four patients with prominent cervical dystonia. Fig. 3 illustrates the trend of total TWSTRS demonstrating gradual improvement in these patients. Clinically the benefit was noticed at 24 months. The total TWSTRS score improved by 62.0 ± 23.9% at 36 months.

3.2. Effects of DBS stimulation parameters on outcome in TD

We used monopolar stimulation setting in all subjects. The distance of the active electrode contact for best outcome from the midcommisural point was 20.6 ± 1.5 mm in the axial, 2.9 ± 1.7 mm in sagittal, and −1.1 ± 1.2 mm in coronal planes. At the best BFM outcome the

average stimulation frequency was 84.5 ± 30.4 Hz, amplitude was 3.8 ± 0.4 V, and pulse-width was 141.8 ± 40.4 μs.

4. Discussion

We followed eight TD patients at six month intervals following GPi DBS for up to six years demonstrating a substantial response in all cases. It is well known that remission rate for TD is generally low [1,12]. Since our patients had the disorder for 1–9 years prior to surgery, it is unlikely that the changes were the result of spontaneous remission. Several single case reports and a case series with comparable number of patients to ours have also shown an excellent improvement in TD as measured by more than 80% reduction in motor component of BFM score [3–8]. However, none of these prior studies assessed the rate of improvement during frequent sampling intervals, nor did they examine the response of particular distributions of dystonia. We were able to assess how quickly dystonia responded after initiation of DBS and whether the improvement continued over time or plateaued as well as addressing the unanswered question as to whether DBS more readily improved TD with a particular distribution. We found that improvement in blepharospasm was rapid, arm dystonia improved within 18 months and legs within 48 months. The most challenging distributions were cervical and truncal dystonia. Both types took up to 48 months and several programming sessions were required before achieving meaningful improvement. There was one TD patient who had late fluctuations in response which might be attributed to the onset of depression.

Previous case reports showed rapid improvement of TD within hours to months [4–6,13]. Three of our patients (Patients 1, 3, and 8) had substantial improvement (95%, 93%, and 83% respectively) at first month visit. This outcome was consistent with previous case reports [4–6,13]. On the contrary it was not the case in the remaining five patients. The improvement in these patients was slow, but after multiple DBS programming sessions their TD eventually improved comparably with other patients. We suspect that disparity between current series of eight patients and previous single case-reports could be a consequence of sampling bias of single reports that were published because of excellent and rapid outcome. Nevertheless, we must emphasize that although delayed in some cases, our patients also had excellent outcome after GPi DBS.

The natural history of TD, as reported in large cohorts in the literature, is that the remission rate is less than 15% and this occurs on average by 2.6 years after discontinuation of offending agent [1,12]. Likelihood of their spontaneous remission is minimal. Two additional facts reassured us that the response we observed was due to the deep brain stimulation and not the natural course of the disease. In our patients TD was present for one to nine years, but it resolved within months after deep brain stimulation surgery. In three patients response was almost instantaneous, while in others rapid partial response was followed by slow resolution of residual TD. One of our patients whose pulse generator battery was near the end of life, had dramatic re-emergence of TD. Such recurrence of symptoms rapidly resolved after battery replacement. Spontaneous natural recovery of TD cannot describe any of these phenomena.

Our study also has following caveats. It is a retrospective, non-blinded study. Although we believe unlikely in this case, non-blinded studies have potential of placebo effects or investigator bias. Number of subjects in our study were comparable to previous (largest) study, but even larger size prospective randomized trial comparing DBS with best medical therapy is clearly justified.

5. Conclusion

We found excellent improvement in TD after GPi DBS and the better outcome is correlated with higher voltage and longer pulsewidth of electrical stimulation. Although TD affecting the neck and trunk may have delayed benefit compared to other body regions, they too ultimately may respond favorably. These observations, however, could be biased due to the relatively small number of patients in our study. Similar studies with larger cohorts are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Shaikh had fellowship grant from Dystonia Medical Research Foundation. The Emory movement disorders division receives educational grant from Medtronic, Inc. Dr. Gross and Dr. Jinnah serve as a consultants to Medtronic, Inc. and receive compensation for these services. Medtronic develops products related to the research described in this paper. Dr. Factor serves as consultant for Merz, Chelsea Therapeutics, UCB, Neurocrine, Lundbeck, Avanir, Auspex. Dr. Factor has grants from Sangamo, TEVA, Ipsen, Allergan, Medtronics, Auspex, Genzyme, Michael J. Fox Foundation, and NIH (Grant No. U10 NS077366). Dr. Factor receive royalties from Demos, Blackwell Futura for textbooks, Uptodate, and Neurotherapeutics as guest editor. Dr. Factor has funding from Sartain Lanier Family Foundation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.11.013.

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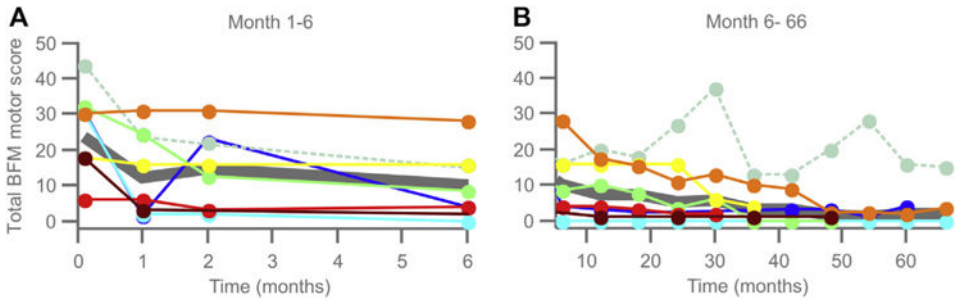

Fig. 1.

Trend of change in total of motor component of Burke–Fahn–Marsden (BFM) dystonia rating scale. The value of BFM is plotted on *y*-axis. The *x*-axis logarithmically depicts corresponding time in month. The thin lines illustrate individual subjects, while the thick gray line depicts average total BFM score of the population. Panel A depicts the trend of BFM score for upto six months, and panel B depicts BFM score between 6 and 66 months.

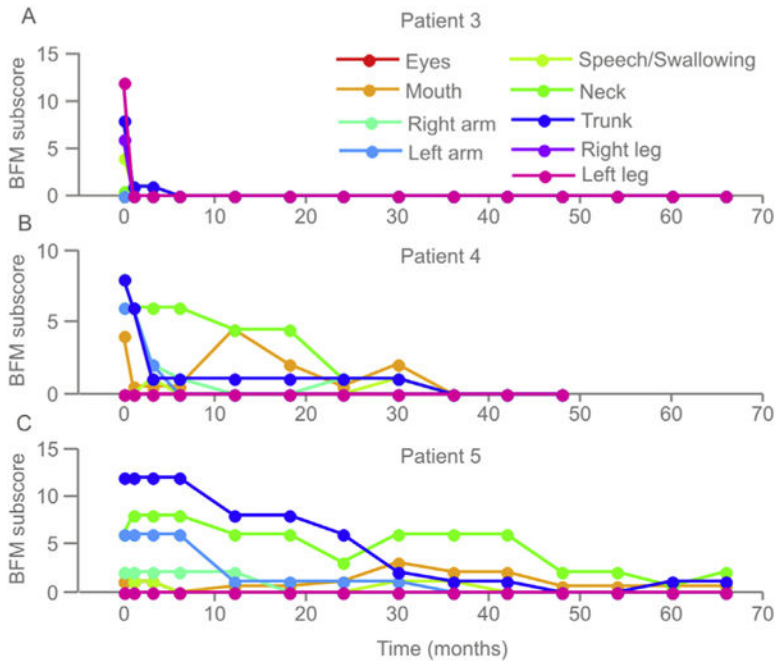

Fig. 2.

Trend of change in BFM subscores from three patients with TD. Each panel illustrates one patient. Each colored line in a given panel depicts a subscore corresponding to measure of dystonia in respective distribution. Subscores are plotted on the *y*-axis and corresponding time in months is shown on the *x*-axis.

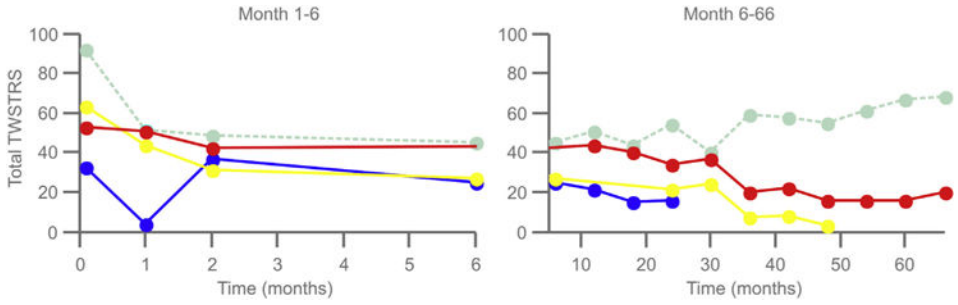

Fig. 3.

Change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Total value of TWSTRS is plotted on the *y*-axis, while the *x*-axis represents the corresponding time interval after DBS surgery. Each trace illustrates one patient. Scores are plotted on the *y*-axis and corresponding time interval after DBS surgery is plotted on *x*-axis. Panel A depicts trend of BFM score for upto six months, and panel B depicts BFM score between 6 and 66 months.

Table 1

Clinical features of TD patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age/Gender	52/F	58/M	52/M	29/M	62/F	47/F	48/F	38/F
Duration of disease prior to DBS	9	4	5	9	1	4	7	4
Offending agents	Chlorpromazine, Trifluoperazine	Aripiprazole	Aripiprazole, Ziprasidone	Aripiprazole, Ziprasidone, Risperdal, Olanzapine	Promethazine	Metoclopramide	Risperidal	Haloperidol
Treatment for dystonia before surgery (maximum daily dose)	Clonazepam 1 mg, Tetrabenazine	Baclofen 60 mg, Lorazepam 1 mg Botilum toxin	Clonazepam 3 mg, Amantadine 300 mg	Botulinum toxin	Clonazepam 2 mg, baclofen 30 mg	Propranolol 60 mg, Trihexyphenidyl12 mg	Ropinirole 2 mg, Clonazepam 1 mg, Tizanidine 2 mg	Tetrabenazine 150 mg, Diazepam 30 mg, Trihexypheidyl 30 mg
Treatment for dystonia after surgery (daily dose)	Clonazepam 1 mg	Baclofen 30 mg, Lorazepam 1 mg, Clonazepam 2 mg	Clonazepam 1 mg, Zolpidem 10 mg	None	Clonazepam 2 mg,	Trihexyphenidyl 6 mg	None	None
Psychiatric treatment after surgery (daily dose)	Duloxetine 60 mg daily	Ecitalopram 10 mg daily	Sertraline 100 mg daily Qutiapine 100 mg daily	Olanzepine 15 mg daily	None	Fluoxetine 40 mg daily	Ecitalopram 5 mg daily	None
Percent improvement in total motor BFM score (time since surgery in months)	87 (48 months)	67 (60 months)	100 (6 months)	100 (36 months)	78 (36 months)	88 (60 months)	67 (30 months)	94 (12 months)
Stimulus parameters for best outcome (Volts, micro-seconds, Hertz)	Left: 3.6, 120, 70 Right: 3.8, 90, 70	Left: 3.6, 180, 60 Right: 3.6, 180, 60	Left: 3.0, 120, 130 Right: 4.5, 90, 130	Left: 3.2, 120, 60 Right: 3.5, 120, 60	Left: 3.2, 120, 60 Right: 3.5, 120, 60	Left: 4.0, 180, 70 Right: 4.0, 210, 70	Left: 3.5, 240, 100 Right: 3.0, 240, 100	Left: Pallidotomy Right: 3.5, 450, 185

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