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Outcome predictors of pallidal stimulation in patients with primary dystonia: the role of disease duration

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Pallidal deep brain stimulation (DBS) is currently the most effective treatment for advanced, medically refractory dystonia. However, factors predicting clinical outcome are not well defined. We reviewed the clinical records of 39 consecutive patients with medically refractory primary dystonia who underwent pallidal DBS implants. Thirty-five patients were implanted bilaterally and four unilaterally. Seven patients had fixed skeletal deformities (FSD). The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scores at baseline, 3 and 12 months after DBS were used to evaluate clinical outcome. We investigated the outcome predictive role of several demographic and clinical factors. FSD patients had a significantly inferior outcome at 12 months, mostly affected by axial scores. All other patients ($n = 32$) showed a remarkable improvement (median BFMDRS percentage improvement = 87.8). Only disease duration showed a significant correlation with DBS outcome at 3 and 12 months. No other demographic and baseline clinical features predicted DBS outcome. This study confirms that patients with primary, medically refractory dystonia are generally outstanding candidates for pallidal DBS, with the possible exception of axial FSD. Patients with shorter duration of disease may expect a better general outcome. No particular predictive value should be assigned to age at onset, age at surgery, severity of disease, DYT1 status and the presence of phasic or tonic involuntary movements.

Keywords: deep brain stimulation; globus pallidus; dystonia; outcome predictors; disease duration

Abbreviations: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation; FSD = fixed skeletal deformities

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Introduction

Dystonia is a movement disorder characterized by patterned, directional and often sustained muscle contractions that produce abnormal postures or repetitive movements (Tarsy and Simon, 2006). Primary dystonias are by definition unaccompanied by other neurological abnormalities and have no known cause, aside from a few genetic mutations identified to date (Geyer and Bressman, 2006). With the notable exception of dopa-responsive dystonia, pharmacological treatment of primary generalized dystonia is mostly unsatisfactory. As a consequence, surgical attempts to relieve dystonic spasm have targeted both peripheral and CNS structures (Tagliati *et al.*, 2003).

Chronic stimulation of the globus pallidus internus is a safe and effective treatment for advanced, disabling dystonia (Vidailhet *et al.*, 2005; Kupsch *et al.*, 2006). Despite these successful results, the indications of pallidal stimulation for dystonia remain highly empirical. Current experience suggests that primary dystonias respond better than most secondary dystonias (Tagliati *et al.*, 2004), and patients carrying the DYT1 mutation have been reported to be particularly good candidates for this procedure (Coubes *et al.*, 2000; Tagliati *et al.*, 2004). To add uncertainty to patient selection for deep brain stimulation (DBS) in dystonia, the clinical outcome predictors are still poorly defined. The influence on DBS results of factors like age, disease duration and severity, symptom distribution and history of ablative procedures has not been accurately evaluated, due in part to the relatively small size and variable clinical presentation of the studied cohorts.

In order to better define demographic and clinical outcome predictors of pallidal stimulation for primary dystonia, large and homogeneous study populations are needed. To this purpose, we reviewed DBS results obtained

in a large cohort of primary dystonia patients implanted by the same neurosurgeon (R.L.A.) and followed almost exclusively by the same neurologist (M.T.).

Methods

Subjects

Thirty-nine consecutive patients with medically refractory primary dystonia who underwent stereotactic pallidal DBS surgery between December 2000 and January 2007 were included in the study. Similar to previous series (Vidailhet *et al.*, 2005), patients were diagnosed with primary dystonia if they: (i) exhibited a normal neurological examination except for dystonia; (ii) lacked a history of known aetiologies of dystonia such as static encephalopathy, head trauma, ischaemic insults, meningitis/encephalitis and neuroleptic treatments and (iii) had an anatomically normal brain MRI. DBS surgery was offered if they suffered with severe disability despite optimal medical management. Patients with untreated psychiatric disturbances or cognitive dysfunction were not offered surgery. Patients with secondary dystonia or history of prior central ablative procedures (i.e. thalamotomy/pallidotomy) were excluded from this study.

Thirty-five patients had early-onset dystonia (<26 years) (Geyer and Bressman, 2006). Twenty-five tested positive for the DYT1 gene defect. Thirty-five were implanted bilaterally; four were treated unilaterally based on the anatomical distribution of their symptoms. Seven patients had fixed skeletal deformities (FSD), in all cases scoliosis, at the time of surgery. This group was analysed separately and compared to the rest of the cohort. Table 1 summarizes the demographical characteristics of the two subgroups (i.e. those with and without FSD) in our study.

Clinical evaluation and outcomes measures

We reviewed retrospectively the clinical records of all 39 subjects, including videotaped evaluations, with the approval of the Mount Sinai School of Medicine (MSSM) Institutional Review Board (IRB #05-0589). The severity of dystonia was evaluated at baseline (2 weeks before surgery) and 3 and 12 months postoperatively using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (Burke *et al.*, 1985). Postoperatively, patients were evaluated only while actively stimulated. Results were normalized by calculating the percentage change of the BFMDRS according to the formula:

$$\frac{\text{Baseline BFMDRS score} - \text{Postoperative BFMDRS score}}{\text{Baseline BFMDRS score}} \times 100$$

Medications taken into account were: dopaminergic drugs (levodopa, dopamine agonists), anticholinergics, antispasmodic drugs (baclofen) and benzodiazepines. Twelve patients were receiving botulinum toxin injections before surgery. Injections were suspended during the first 12 months of stimulation.

In addition to the BFMDRS scores, we also recorded the presence of phasic movements and/or tonic posturing in each body segment. A body segment that exhibited rapid, repetitive movements was categorized as 'phasic'; a segment exhibiting sustained contractions and abnormal postures was categorized as 'tonic' (Ahlskog *et al.*, 2000). We reserved the term 'fixed' for chronic dystonic contractions associated with tendonous or skeletal deformities. Patients were then divided into predominantly phasic or predominantly tonic groups based on the number of body segments exhibiting those respective symptom subtypes.

In order to determine preoperative predictors of response to pallidal DBS, we analysed the correlation of the postoperative percent change in the BFMDRS with several demographic (age at surgery, gender) and clinical features at baseline. The clinical features examined included age at onset of dystonia, disease duration, presence of the DYT1 gene mutation, presence/absence of skeletal deformities, degree of motor disability and predominance of axial symptoms.

Neurosurgical procedure and DBS programming

All subjects included in this study underwent microelectrode-guided, frame-based stereotactic implantation of DBS leads (model 3387, Medtronic) by one surgeon (R.L.A.), as described previously (Shils *et al.*, 2002; Alterman *et al.*, 2007). Postoperative brain MRI was routinely performed to confirm placement of the leads in the posteroventral globus pallidus internus. In accordance with the United States Food and Drug Administration Humanitarian Device Exemption regulating the use of DBS for dystonia (HDE# H020007), starting in 2004 patients were operated upon with the approval of either the Beth Israel Medical Center, NY (April–September 2004) or the MSSM IRB (February 2005 to January 2007).

Device programming was conducted in a standardized fashion. As previously published (Alterman *et al.*, 2007), we systematically analysed the four available contacts on each lead in monopolar configuration in order to map clinical responses (when present) and the tolerability of stimulation. Ventral contacts (0 and 1) were preferentially,

Table 1 Demographic characteristics of the two subgroups of patients included in the study

	N	Sex (M/F)	Age at onset	Age at surgery	Disease duration	DYT1+ (*n*)
FSD	7	6/1	11.9 ± 5.1 (6–19)	28.9 ± 18.0 (15–63)	17.0 ± 14.3 (7–44)	3
PTD	32	20/12	14.3 ± 11.4 (3–50)	28.3 ± 16.0 (10–58)	14.0 ± 12.3 (1–40)	22

FSD = fixed skeletal deformities; PTD = primary torsion dystonia without FSD. Data are reported as Mean ± SD (range) unless otherwise specified.

but not exclusively, used for initial therapy. Adjustments were performed thereafter in order to maximize clinical benefit and/or reduce adverse effects (Kumar, 2002).

Statistical analysis

Statistical analyses were performed with the JMP® statistical package, version 5.1 (SAS Institute, Inc., Cary, NC, USA). ChiSquare was used to test demographic homogeneity among groups regarding gender and DYT1 status. Average BFMDRS percentage improvement of the FSD group was compared with the rest of the sample by means of Wilcoxon tests. To look for factors that were predictive of improvement both at 3 and at 12 months, we used the Spearman correlation coefficient for quantitative variables (age at onset, age at surgery, disease duration and total scores or subscores for the movement and disability scales) and the Wilcoxon test for categorical variables (gender, skeletal deformities, DYT1 status, phasic/tonic dystonia predominance). Variables relating to improvement after surgery were included in stepwise multiple linear regression. Statistical tests were two-tailed and $P < 0.05$ was considered to be statistically significant.

Results

The baseline clinical characteristics of the study cohort are summarized in Tables 2 and 3. The cohort had homogeneous features, with the exception of FSD patients, who exhibited higher axial scores at baseline (mean ± SD; 18.5 ± 6.4 versus 11.8 ± 6.6, $P < 0.05$). No other clinical or demographic differences at baseline were found between patient groups. Following surgery and device activation, every patient experienced a progressive improvement in motor function, which is reflected in their BFMDRS motor and disability score percentage changes (Table 2).

Dystonic patients with FSD had a significantly poorer outcomes at 12 months ($P < 0.01$; Fig. 1). This was due to the poor resolution of limb and particularly axial symptoms (Table 3). Therefore, we excluded this subgroup of patients from further outcome analysis, focusing on the remaining 32 patients without FSD.

Among demographic features, only the patient's age at surgery correlated with clinical outcome at 3 and 12 months ($P < 0.01$). Patients older than 21 years at surgery ($n = 17$) improved, on average, 38 percentage points less than patients younger than 21 ($n = 15$) 3 months after surgery ($P < 0.01$) and 15 percentage points less at 1 year ($P < 0.01$).

Total and segmental BFMDRS scores at baseline, 3 and 12 months after surgery are listed in Tables 2 and 3. There was no correlation between BFMDRS score or segmental subscores at baseline and DBS outcomes at 3 months and 12 months. Among clinical variables, only disease duration significatively correlated with clinical outcome at 3 ($P < 0.01$) and 12 months ($P < 0.05$). In addition, disease duration also showed a significant negative correlation with disability scores at 12 months ($P < 0.05$, Spearman test). Patients with disease duration longer than 15 years ($n = 12$) improved 49% less than patients with shorter disease duration ($n = 20$) at 3 months ($P < 0.001$) and 13% less at 1 year ($P < 0.05$; Fig. 2A and B). As disease duration and age at surgery are related, we used multiple regression analysis to identify, which factor had a stronger predictive value. Disease duration was the only resulting independent variable correlated with DBS outcome ($P < 0.001$; Fig. 2C).

DYT1-positive patients ($n = 22$) were, on average, younger at symptom onset (10.5 ± 6.0 years versus 22.5 ± 15.8, $P < 0.01$) and younger at surgery (22.7 ± 13.3 years versus 40.7 ± 14.8, $P < 0.01$) than DYT1-negative patients ($n = 10$). There were no other significant differences in the demographic or baseline clinical characteristics of these two groups, with the exception of a higher prevalence of speech and swallowing involvement in DYT1-negative subjects (7/10 versus 7/22; $P < 0.05$). DYT1-positive patients exhibited a greater BFMDRS percentage improvement both at 3 months (72.0 ± 23.0 versus 47.0 ± 30.8, $P < 0.05$) and 1-year (88.4 ± 12.4 versus 78.0 ± 15.0, $P < 0.05$; Fig. 3A and B) after surgery. However, when patients were stratified by disease duration, this difference was lost (Fig. 3C–F).

Seven patients presented with predominantly phasic symptoms; 25 had predominantly tonic dystonia. We found no outcome disparity between phasic predominant and tonic predominant patients at either 3 or 12 months of follow-up.

Twenty-six subjects (81%) were taking one or more medications before surgery. In addition, one patient had a functioning baclofen pump (which was explanted after surgery). One year after surgery, nine patients (28%) had completely discontinued medications. No demographical or baseline clinical features predicted medication reduction or their discontinuation.

Stimulation settings at 12 months were grossly similar to those used at 3 months of follow up. We predominantly used a monopolar configuration both at 3 (68/74 leads; 33 single, 35 double) and 12 months (67/74 leads; 19 single, 44 double, 4 triple); the rest of the electrodes were set at a bipolar configuration (one simple bipolar and five tripolar at 3 months; two simple bipolar, five tripolar at 12 months). At 3 months, mean voltage was 2.8 V (±0.4 SD), mean pulse width was 217.2 ms (±71.6 SD) and mean frequency was 82.7 (±32.2 SD). At 12 months, mean voltage was 3.0V (±0.4 SD), mean pulse width was 226.6 ms (±72.0 SD) and mean frequency was 76.9 Hz (±26.9 SD).

There were no intraoperative haemorrhages and no adverse neurological sequelae were observed. Nine patients experienced adverse events including five device infections (two of these in the same patient); in each case, the infected device components were removed and re-implanted following an appropriate course of intravenous antibiotics. There were two extension cable fractures, one scalp erosion

Table 2 Clinical features at baseline and at 3 and 12 months post-DBS

	BFMDRS total score			% BFMDRS improvement		% drugs reduction		Disability score		
	Baseline	3 months	12 months	3 months	12 months	3 months	12 months	Baseline	3 months	12 months
FSD	54.0 ± 18.6 (28–77)	27.3 ± 11.0* (8.5–39)	21.6 ± 10.2§ (11–36)	51.7 ± 10.0 (37–70)	61.1 ± 9.4# (50–76)	30.8 ± 24.4 (0–67)	41.2 ± 31.8* (0–92.5)	12.0 ± 5.8 (3–21)	6.1 ± 2.8 (2–10)	5.8 ± 4.7 (3–13)
PTD	40.3 ± 22.2 (9–81.5)	14.1 ± 12.5 (0–56.5)	5.3 ± 4.8 (0–21)	64.1 ± 27.7 (0–100)	85.2 ± 14.0 (50–100)	36.0 ± 34.8 (0–100)	68.7 ± 35.8 (0–100)	9.7 ± 5.5 (3–24)	4.3 ± 3.3 (1–16)	3.0 ± 2.5 (0–10)

FSD = fixed skeletal deformities; PTD = primary torsion dystonia without FSD. Data are reported as Mean ± SD (range). The total score for the movement subscale of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which can range from 0 to 120, is the sum of individual scores of nine body regions and represents the severity of motor disability related to dystonia. The total disability score can range from 0 to 30 and is the sum of individual ratings for seven activities: speech, handwriting, and the degree of dependence with respect to hygiene, dressing and feeding, swallowing and walking. A high score indicates worse disability.*$P < 0.05$; §$P < 0.01$; #$P < 0.001$.

Table 3 BFMDRS sub-scores at baseline, 3 and 12 months

	Face			Speech and Swallowing			Axial			Limbs		
	Baseline	3 months	12 months	Baseline	3 months	12 months	Baseline	3 months	12 months	Baseline	3 months	12 months
FSD	7.2 ± 3.8 ($n = 3$)	2.8 ± 3.0	0.6 ± 1.7	4.8 ± 5.2 ($n = 7$)	1.3 ± 1.1	0.5 ± 0.8	18.5 ± 6.4 ($n = 7$)*	12.0 ± 4.5§	11.0 ± 4.7#	28.4 ± 13.8 ($n = 7$)	12.7 ± 9.0	9.8 ± 6.9*
PTD	4.3 ± 4.0 ($n = 11$)	2.1 ± 2.8	1.0 ± 1.8	4.3 ± 3.4 ($n = 14$)	2.4 ± 2.9	1.4 ± 2.0	11.8 ± 6.6 ($n = 25$)	4.1 ± 4.9	1.3 ± 2.3	27.7 ± 16.2 ($n = 32$)	9.0 ± 9.7	3.3 ± 3.3

FSD = fixed skeletal deformities; PTD = primary torsion dystonia without FSD. Data are reported as Mean ± SD (no. of patients with symptoms). *$P < 0.05$; §$P < 0.01$; #$P < 0.001$.

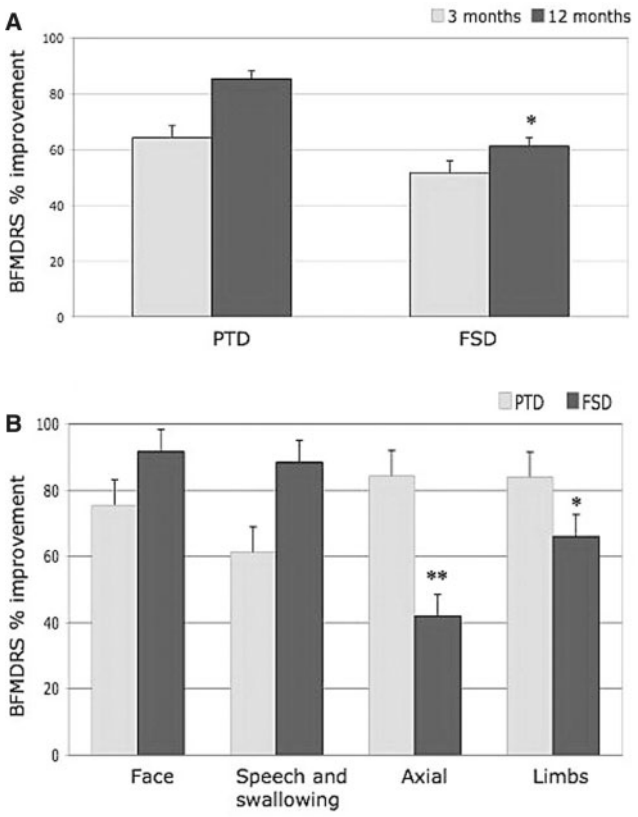

Fig. 1 (**A**) Average Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) percentage change at 3 and 12 months after surgery. FSD = fixed skeletal deformities; PTD = Primary torsion dystonia without skeletal deformities. Patients with FSD had a significantly poorer outcome at 12 months follow-up ($^{*}P < 0.05$). (**B**) Average BFMDRS motor subscores percentage change at 12 months follow-up. Results in patients with FSD (gray bars) were limited by comparatively poorer outcome in axial ($^{**}P < 0.01$) and limbs subscores ($^{*}P < 0.05$). Error bars = Standard error.

without infection and three lead revisions. In all cases there were no long-term neurological repercussions. There were no complications related to revision surgery.

Discussion

This retrospective study confirms previous reports showing that pallidal DBS is a safe and effective therapy for medication refractory primary dystonia (Yianni *et al.*, 2003; Coubes *et al.*, 2004; Vidailhet *et al.*, 2005, 2007; Kupsch *et al.*, 2006; Alterman *et al.*, 2007). Patients without FSD showed a remarkable 85% average improvement in their BFMDRS scores, which is higher than that reported by others (Yianni *et al.*, 2003; Vidailhet *et al.*, 2005; Kupsch *et al.*, 2006). This may due to the fact that our population had much shorter disease duration than did patients in these other studies, a clinical factor that appears to be significantly correlated to DBS outcome. Patients with FSD showed a relatively poorer outcomes 12 months after surgery (61%), as their results were negatively weighed by the axial BFMDRS subscores, whose improvement was limited to 40%.

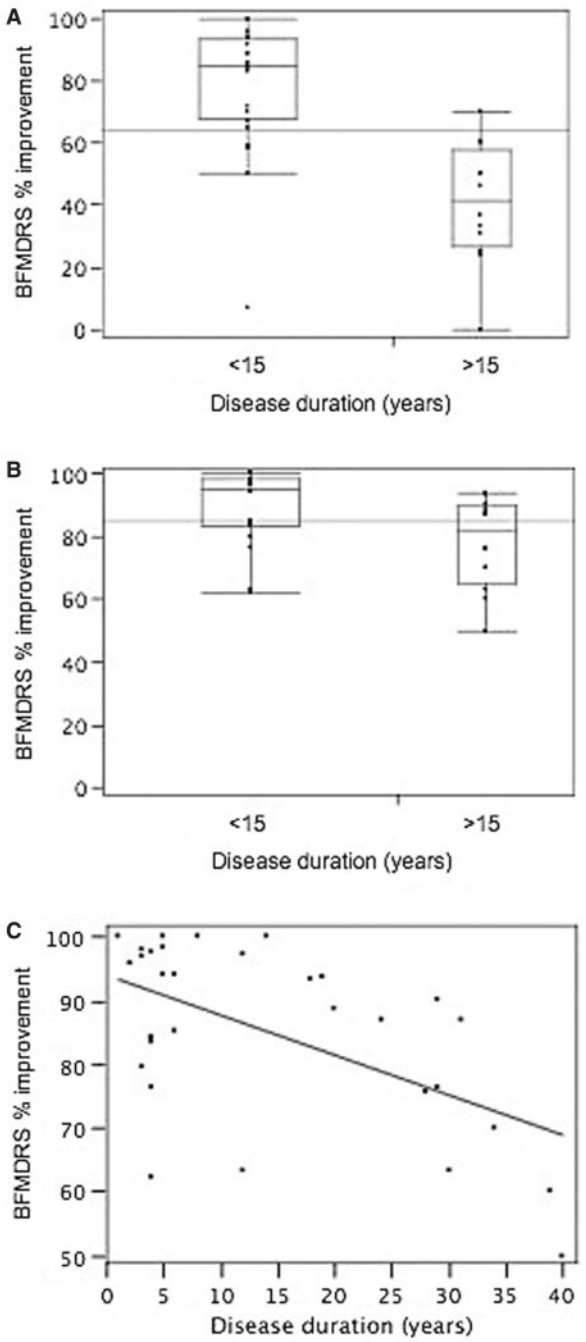

Fig. 2 Effect of disease duration on Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) percentage improvement in 32 patients with primary dystonia without skeletal deformities. Patients with disease duration longer than 15 years ($n = 12$) improved significantly less than patients with shorter disease duration ($n = 20$) both at 3 months (2*a*, $P < 0.001$) and at 1-year follow-up (2*b*, $P < 0.05$). Disease duration was the only independent factor significantly correlated with DBS outcome at one-year follow up (2*c*; $r^2 = 0.32$, $P < 0.01$).

Despite the consistent positive results reported with surgical therapy for torsion dystonia, surgical outcome

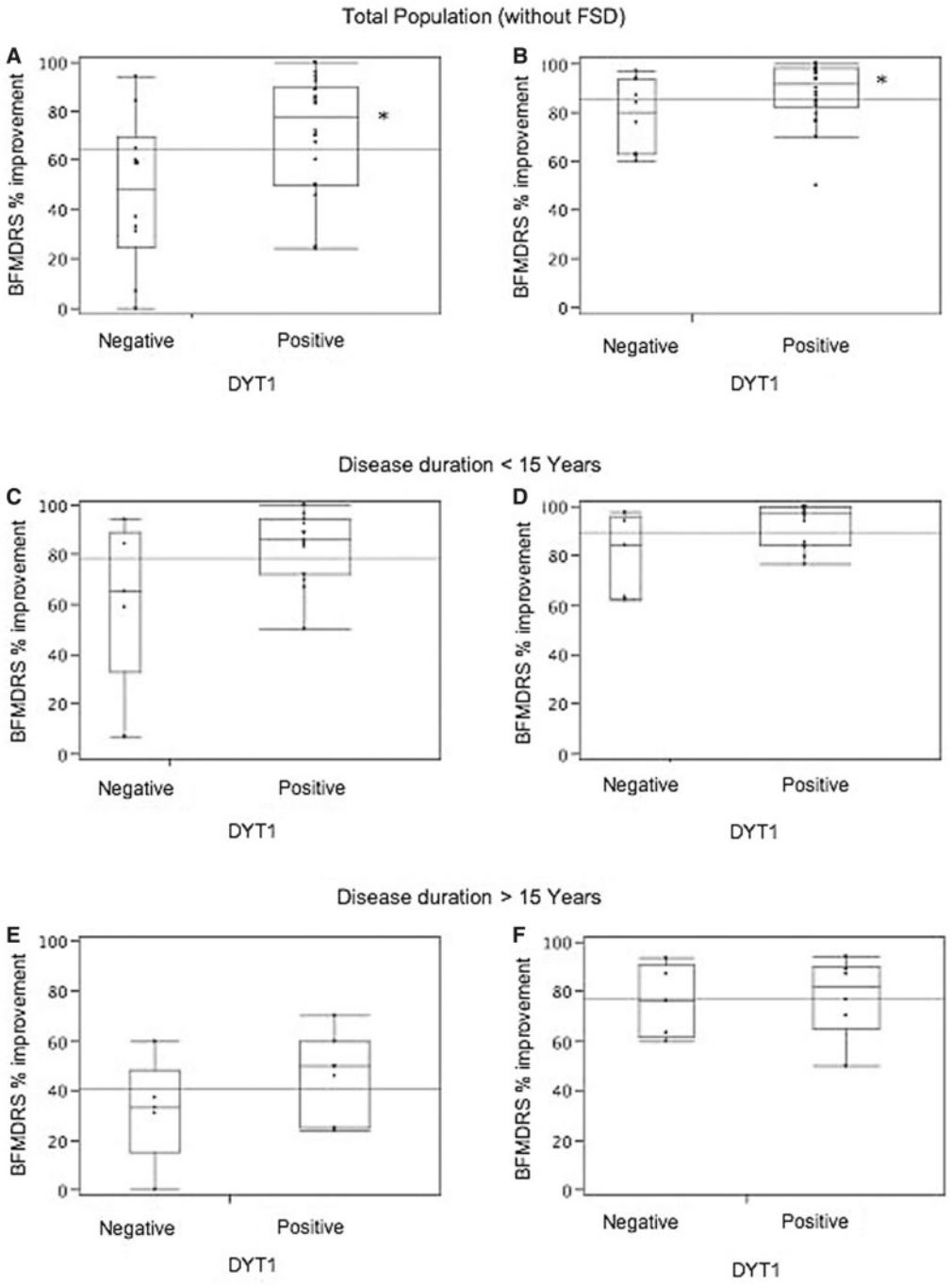

Fig. 3 Boxplot distribution of Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) percentage improvements at 3 months (**A**, **C**, **E**) and 12 months (**B**, **D**, **F**) for DYT1-positive ($n = 22$) and negative subjects ($n = 10$) without fixed skeletal deformities. DYT1-positive subjects showed significantly better outcomes than DYT1-negative subjects at 3 months (**A**) and 1 year (**B**) after pallidal DBS ($^*P < 0.05$). However, this difference became less prominent and lost statistical significance when subjects were stratified by disease duration. Results observed in subjects with less than 15 years disease duration are displayed in boxplot **C** (3 months follow-up) and **D** (1 year follow-up). Results observed in subjects with more than 15 years disease duration are displayed in boxplot **E** (3 months follow-up) and **F** (1 year follow-up). BFMDRS percentage improvement was consistently lower in subjects with longer duration of disease independent of DTY1 status. In each figure the horizontal line represents the grand mean of the population. FSD = fixed skeletal deformities.

predictors have been addressed sparingly. When thalamotomy was the preferred surgical treatment (Cooper, 1976; Tasker *et al*., 1988), the best results were reported in patients with idiopathic disease, predominant distal limbs involvement and little or no axial dystonia (Cooper, 1976; Tasker *et al*., 1988). The more contemporary literature regarding DBS initially suggested that the DYT1 gene mutation is a positive outcome predictor (Coubes *et al*., 2000, 2004;

Yianni *et al.*, 2003). However, two prospective studies failed to associate pallidal DBS results with any pre-surgical variable, except possibly the presence of phasic or hyperkinetic movements (Vidailhet *et al.*, 2005, 2007; Kupsch *et al.*, 2006).

The most remarkable result emerging from our study is the negative influence of disease duration on outcome. In particular, disease duration longer than 15 years seems to strongly predict a slower improvement and overall worse (though still satisfactory) DBS outcome. A negative influence of disease duration was previously suggested, but not clearly demonstrated possibly because of the variable clinical background of the cohort (Yianni *et al.*, 2003). Other studies failed to find a correlation between duration of disease and outcome, in one case possibly due to selection criteria that specifically excluded patients with short disease durations (Kupsch *et al.*, 2006), and in another to the relatively advanced median age of the study population (Vidailhet *et al.*, 2005). The predictive role of disease duration is of particular interest in light of current models proposing that the therapeutic effect of DBS is mediated by a gradual brain reorganization or plasticity (Vitek, 2002; Detante *et al.*, 2004; Krauss *et al.*, 2004; Tisch *et al.*, 2007). It is tempting to speculate that the severity of aberrant plasticity in dystonia may be correlated with disease duration, making complete resolution of symptoms by DBS more difficult the more longstanding the aberrancy.

Neither age at surgery nor severity of disease correlated with clinical outcome in our cohort. While we confirmed the particularly favourable DBS results previously described in younger patients (Coubes *et al.*, 2004; Alterman *et al.*, 2007), multiple regression analysis showed that age at surgery served merely as a proxy for disease duration. The fact that disease severity at baseline, as measured by the BFMDRS, did not correlate with clinical outcome, suggests that patients with disabling, medically refractory, primary dystonia should be evaluated for DBS regardless of their baseline BFMDRS scores.

Patients carrying the DYT-1 gene mutation were significantly younger at surgery and showed higher percentage improvement than those with sporadic primary dystonia at both the 3 and 12 month follow-ups. The faster improvement seems clinically most relevant, with DYT1-positive improving an average 53 percentage points more than DYT1-negative patients at 3 months, but only 13 percentage points more at 12 months. Nevertheless, this apparent difference in response was lost when the groups were stratified by disease duration. Therefore, it appears that the younger age and shorter disease duration of DYT1-positive patients at the time of surgery may have contributed to the widely held impression that DYT1-positive subjects respond best to pallidal DBS (Coubes *et al.*, 2000; Yianni *et al.*, 2003; Tagliati *et al.*, 2004).

There were no significant differences in clinical outcome between patients with predominantly tonic (or sustained) versus phasic dystonia, another clinical feature previously suggested as a possible outcome predictor for pallidal DBS (Vercueil *et al.*, 2001, Volkmann and Benecke, 2002; Kupsch *et al.*, 2003, 2006; Tagliati *et al.*, 2004; Vidailhet *et al.*, 2005;Wang *et al.*, 2006). The discrepancy of our results with those reported in the literature may stem from two factors. First, patients with phasic movements have been noted to improve faster (in the order of minutes or hours) than patients with tonic symptoms (Volkmann and Benecke, 2002; Krauss *et al.*, 2004; Vidailhet *et al.*, 2005; Hung *et al.*, 2007), a difference that would not have been captured at 3 months follow-up. Second, our exclusion from analysis of patients with FSD may have eliminated patients who would otherwise have been classified as predominantly tonic and would have probably resulted in our confirming these previous findings. Consequently, we propose that no particular long-term predictive value should be associated with phasic or tonic dystonia, unless fixed contractures or skeletal deformities are present. Of course, such secondary orthopaedic changes are more likely with longer disease duration. While patients with FSD showed poorer outcomes 12 months after surgery than those without, they still may benefit significantly from pallidal DBS. Indeed, some of these patients showed further improvement when skeletal deformities were surgically corrected.

In conclusion, we confirm that patients with primary, medically refractory dystonia are generally outstanding candidates for pallidal DBS. Our results suggest that DBS for primary dystonia should be entertained before the occurrence of fixed contractures or axial deformities. Patients with disease duration shorter than 15 years may expect to improve faster and achieve a better general outcome than those with longer disease duration. We find no particular predictive value of age at onset of dystonia, severity of disease at baseline, DYT1 status or phasic/tonic predominance of dystonic symptoms.

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