The effectiveness of deep brain stimulation in dystonia: a patient-centered approach

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HIGHLIGHTS

- Functional priorities in life of dystonia patients and their caregivers vary greatly
- The effect of DBS on functional priorities did not correlate with motor outcome
- Half of the motor 'non-responder' patients reported important changes in their priorities
- The effect of DBS in dystonia should not be measured by motor outcome alone

ABSTRACT

Background: To systematically evaluate the effectiveness of deep brain stimulation of the globus pallidus internus (GPi-DBS) in dystonia on pre-operatively set functional priorities in daily living.

Methods: Fifteen pediatric and adult dystonia patients (8 male; median age 32y, range 8-65) receiving GPi-DBS were recruited. All patients underwent a multidisciplinary evaluation before and 1-year post DBS implantation. The Canadian Occupational Performance Measure (COPM) first identified and then measured changes in functional priorities. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was used to evaluate dystonia severity.

Results: Priorities in daily functioning substantially varied between patients but showed significant improvements on performance and satisfaction after DBS. Clinically significant COPM-score improvements were present in 7/8 motor responders, but also in 4/7 motor non-responders.

Discussion: The use of a patient-oriented approach to measure GPi-DBS effectiveness in dystonia provides an unique insight in patients' priorities and demonstrates that tangible improvements can be achieved irrespective of motor response.

INTRODUCTION

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, abnormal posturing, or both. Dystonia comprises a heterogeneous patient population due to a broad spectrum of underlying acquired and inherited etiologies.[1]

Over the past decades, deep brain stimulation of the globus pallidus internus (GPi-DBS) has emerged as a safe treatment option with a good response in non-lesional, mostly isolated forms of dystonia and a more variable response in combined forms of dystonia that are due to a static lesion or neurodegenerative process.[2] The application of this elective neurosurgical procedure therefore frequently gives rise to discussion, especially in secondary dystonia patients.

The effect of GPi-DBS has been predominantly measured with objective standardized dystonia rating scales.[2] However, the variability of dystonic symptoms within days, or even hours or minutes, makes it difficult to reliably capture overall dystonia severity in just one evaluation. Furthermore, it is unclear how dystonia severity reflects disease burden and there is only weak evidence that a reduction in symptoms in isolated forms of dystonia may correlate with meaningful improvements in functioning.[3,4]

In line with the World Health Organization guidelines advocating patient-centered outcome measures,[5] we aimed to systematically evaluate the effect of DBS in terms of individualized functional priorities set by the patient and/or their caregivers.

METHODS

Patients

We prospectively included fifteen consecutive dystonia patients that received GPi-DBS between January 2013 and July 2016. All patients were evaluated pre and 1-year post-

operatively screened by a multidisciplinary team. The local ethical committee classified the study as care as usual.

Outcome measures

Priorities were identified by the Canadian Occupational Performance Measure (COPM). The COPM is an individualized outcome measure to capture everyday problems that impact daily functioning. Together with a trained occupational therapist, patients and/or caregivers imaginary walked through a typical day in the patient's life to identify priorities that they would like to see improved by GPi-DBS. For the three most important priorities performance (1-10) and satisfaction (1-10) were rated. Change between pre- and postoperative ratings was used for further analyses. At the 1-year follow-up, patients and/or their caregivers were blinded for their pre-operative ratings. A difference of two or more points was considered clinically significant.[6]

Dystonia severity was assessed with the motor subscale of the Burke-Fahn-Marsden dystonia rating scale (BFMDRS). Videos were blinded for operative status and rated by experienced clinicians (ALB, RB, KJP, MFC) who were blinded to treatment state. Mean total scores were calculated. In order to be able to compare the results in all patients (generalized and focal/segmental) the relative change in BFMDRS (% of improvement) was used for further analyses. In addition, patients were subdivided into motor 'responders' (>20% change in BFMDRS score) and 'non-responders' (<20% change in BFMDRS score).[7] For absolute scores, see supplementary table 1.

Data-analysis

Data-analysis was performed using Statistical Package for the Social Sciences (SPSS, version 23.0). Due to the heterogeneity of the sample, medians and interquartile ranges (IQR) were used. Differences between pre- and postoperative scores were compared with the Wilcoxon

Signed Ranked Test for total group and the responders and non-responder subgroups. Correlations between the outcome measures were calculated with the Spearman's ρ.

RESULTS

Baseline characteristics, etiology and pharmacological treatment of all 15 patients (8 male; median age 32y range 8-65; median disease duration 8y range 3-47) are shown in table 1.

Individual priorities

The 45 priorities (3 per patient) were categorized in self-care/activities of daily living (ADL) (n=10); comfort in sitting and sleep (n=9); communication (n=7); social/leisure activities (n=7); and mobility (n=12). Communication priorities involved the ability to use an electric communication device, sign language or normal social interaction without interference of dystonic posturing. Social activities included sports, interactive games or going out for dinner. Mobility comprised walking, cycling, driving a car or the use of public transport.

For each patient, priorities comprised at least two categories. There was a very strong correlation between performance and satisfaction scores (ρ = 0.86, p<0.0001) and both scores significantly improved after the application of DBS (Table 2). At patient level, a clinically significant change in satisfaction in two or three individual priorities was reported in 73% (11) of the patients. In 47% all three priorities were improved, in 27% two priorities were improved, in 13% one priority was improved and in 13% none of the priorities was improved.

Dystonia severity

BFMDRS scores improved with a median change of 30% (pre 46.8 IQR 17.0-66.0 vs post 35.4 IQR 11.3-53.0; p=0.027). Eight patients (53%) were classified as responders with a decrease in their BFMDRS of more than 20% and seven (47%) as non-responders.

131 The non-responders were two patients with cerebral palsy (case 8 and 14), one patient with a
132 mitochondrial disorder (case 1), one patient with DYT-THAP1 (case 6) and three patients
133 with segmental dystonia (case 3, 12 and 15).
134
135 **Priorities versus dystonia severity**
136 Change in dystonia severity did neither correlate with change in performance (ρ = -0.15,
137 p=0.601) nor satisfaction score (ρ = 0.17, p=0.557).
138 Seven of the eight responders reported a clinically significant improvement in performance
139 and satisfaction on at least two or three individual functional priorities. In the group of non-
140 responders, despite the lower motor response, clinical significant improvement in at least two
141 priorities was achieved in four of these patients for performance and three for satisfaction,
142 with a statistically significant change in COPM score (Case 6, 12, 14 and 15, p=0.017).
143
144 **DISCUSSION**
145 This prospective case series aimed to systematically evaluate the effectiveness of GPi-DBS
146 as measured with change in preoperatively set functional priorities. The priorities of the
147 patients and their caregivers lay within the domains of ADL, seating and sleep,
148 communication, social/leisure activities and mobility. A clinically significant motor response
149 coincided with improvements in functional priorities in 7/8 patients. Interestingly, half of the
150 motor 'non-responder' patients also showed a clinically significant change in two or three
151 priorities. Our findings are in line with a previous study in childhood dystonia showing that
152 DBS may lead to improvement of functional goals also in patients with only moderate to
153 'insignificant' motor response.[8]
154 In contrast to the vast majority of efficacy studies primarily focusing on motor response, we
155 evaluated effect of GPi-DBS by looking at functional priorities. These priorities provide an

unique insight in what patients and their caregivers identify as most important aspects in daily living. Given the heterogeneous nature of dystonia, it is not surprising that needs varied greatly between patients. An additional advantage is that this method may facilitate recognition of patients that might be unsuitable for the procedure due to goals that are unrealistic or not likely to be achieved by GPi-DBS. One might argue that with a goal-oriented approach changes are subjective to the patients' perception of improvement rather than objective symptom reduction. In addition, a potential placebo effect cannot be excluded in the absence of a control group. However, we agree with Kubu and colleagues that the main goal of DBS is to improve quality of life as perceived by the patient more than by the clinician, and that the effect of an elective neurosurgical option as DBS should be measured accordingly.[9] In the future, it would be useful to objectify the patient centered outcome. This can be done by transforming the patients' priorities into a treatment goal and pre-operatively decide with the patient and caregivers when the goal is met, for instance by using the goal attainment scale.

The heterogeneous patient sample may be seen as a limitation, both in terms of age as well as etiology. On the other hand, it can be seen as an advantage for the generalizability of the study. We did not correct for changes in medication, which could account for some of the perceived improvements. We realize that our conclusions are bases on a small case series with a possibly limited power, but hope these results serve as a pilot study to trigger future studies focusing on the effectiveness of GPi-DBS in dystonia. First to assess to what extent a good motor outcome corresponds with the perceived outcome on the patient's priorities. This may not always be the case, as 1/8 motor responders did not reach a significant improvement on his priorities, and might provide clarity in the repeatedly reported discrepancy between motor outcome and patient reported outcome. A systematical use of patient centered

outcomes might shine a new light on the current opinion that GPi-DBS is more effective in isolated than in combined forms of dystonia.

In conclusion, the effect of GPi-DBS should be measured not by motor symptom reduction alone, as clinically significant improvements on individual predefined priorities can be achieved irrespective of motor response. In addition, a goal- or patient-oriented approach provides unique insights in the priorities in daily living of dystonia patients and their caregivers. This may not only be of added value for DBS candidates, but also for patients across the entire dystonia population.

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Pt	Gender / age (yr)	Body distribution	Isolated or combined	Etiology	Pre-operative medical treatment	Post-operative medical treatment
1	M/8	Generalized	Combined (spasticity)	Mitochondrial disorder	Gabapentin 100mg; intrathecal baclofen 3ug/hr	Unchanged
2	M/8	Generalized	Isolated	Idiopathic	THP 20mg	No
3	M/18	Segmental	Isolated	Idiopathic	THP 24mg; BTX	THP 24mg
4	F/22	Generalized	Isolated	ACTB mutation	THP 16mg; tramadol 50mg	THP 12mg; clonazepam 1.5mg; clozapine 18.75; BTX
5	F/32	Segmental	Isolated	Idiopathic	Ibuprofen; BTX	No
6	M/9	Generalized	Isolated	DYT-THAP1	THP 21mg; baclofen 12.5mg	THP 11mg
7	M/22	Segmental	Isolated	TTPA	Vitamin E	Unchanged
8	M/47	Generalized	Combined (spasticity)	Cerebral palsy	Antidepressants	Unchanged
9	M/53	Segmental	Isolated	Idiopathic	Clonazepam 0.5mg; BTX	BTX
10	F/65	Segmental	Combined (parkinsonism)	Idiopathic	Pramipexole; L-dopa; Diazepam 5mg; BTX	Pramipexole; L-Dopa
11	F/48	Generalized	Isolated	ACTB mutation	THP 12mg; clozapine 12.5mg; oxazepam 10mg; diclofenac; BTX antidepressant	THP 12mg; clozapine 12.5mg; antidepressant
12	F/63	Segmental	Isolated	Idiopathic	Clonazepam 2.5mg	Clonazepam 0.5mg
13	M/62	Segmental	Isolated	Idiopathic	BTX	Clonazepam 1.0mg; BTX
14	F/8	Generalized	Combined (spasticity)	Cerebral palsy	THP 1.5mg; baclofen 12mg; gabapentin 600mg; clonazepam 0.5mg	Unchanged
15	F/63	Segmental	Isolated	Idiopathic	No	No

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235 ACTB: beta-actin gene; BTX: botulinum toxin injections; THP: trihexiphenidyl; TTPA α-

236 tocopherol transfer protein – vitamin E.

237

Table 2: Pre- and postoperative COPM scores for all functional priorities and per subcategory

	COPM-Performance			COPM-Satisfaction		
	Baseline	1 year	Improved priorities†	Baseline	1 year	Improved priorities†
All priorities	3.0 (1.0-4.0)	7.0 (5.0-8.0)	32/45*	2.0 (1.0-3.5)	7.0 (4.0-8.5)	31/45*
- itting and sleep	3.0 (2.0-4.0)	7.0 (5.5-8.0)	8/9	2.0 (1.5-3.5)	7.0 (3.5-9.0)	5/9
- elf-care/ADL	1.5 (1.0-4.3)	6.0 (2.5-7.3)	6/10	1.5 (1.0-3.0)	6.5 (2.5-7.3)	7/10
- ommunication	4.0 (3.0-4.0)	8.0 (6.0-10.0)	5/7	3.0 (1.0-4.0)	9.0 (7.0-9.0)	6/7
- ocial/leisure	3.0 (1.0-4.0)	7.0 (3.0-7.0)	4/7	3.0 (1.0-4.0)	6.0 (1.0-7.0)	4/7
- ransfer	2.5 (1.3-4.8)	6.5 (5.3-7.0)	9/12	2.0 (1.0-3.8)	6.5 (5.3-8.8)	9/12

ADL activities of daily living; †Change or 2 point or more between baseline and 1-year post-operative score *p<0.0001