SHORT REPORT

Pallidal stimulation in dystonia: effects on cognition, mood, and quality of life

T D Hälbig, D Gruber, U A Kopp, G-H Schneider, T Trottenberg, A Kupsch

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Bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi) alleviates symptoms in patients with dystonia but its effects on cognition, neuropsychiatric status, and quality of life have not been examined. This is a case series report of 15 consecutive patients with different forms of dystonia who underwent bilateral implantation of DBS electrodes in the GPi. The patients were evaluated preoperatively and after 3–12 months of DBS with tests of cognition (Mattis Dementia Rating Scale, Stroop Test, Trail Making Test, Phonemic and Category Word Fluency, Digit Span, Rey Auditory Verbal Learning Test, Tonic and Phasic Alertness), neuropsychiatric status (Beck Depression and Anxiety Inventories, Montgomery Asberg Depression Rating Scale, Snaith–Hamilton Pleasure Scale, Brief Psychiatric Rating Scale), quality of life, and motor functions. GPi DBS significantly improved dystonic symptoms, functional abilities, and quality of life allowing for a significant reduction of antidystonic medications. No deterioration was observed in cognitive scores and neuropsychiatric measures. The present case series report thus provides preliminary evidence for the safety of GPi DBS regarding cognitive and neuropsychiatric functions in patients with dystonia.

Dystonia is a clinically heterogeneous motor syndrome characterised by sustained and often painful muscle contractions, frequently causing twisting, repetitive movements or abnormal postures.¹ With the exception of dopa-responsive dystonia, pharmacological treatment is mostly unsatisfactory in generalised or multifocal dystonia.

Recently, several publications have reported beneficial effects of deep brain stimulation (DBS) of the internal globus pallidus (GPi) in primary and tardive dystonia.^{2–5} DBS is a reversible “non-lesioning” surgical treatment and is continuously applied via stereotactically implanted macroelectrodes.⁶ Interestingly, the neuropsychological effects of DBS of the GPi in dystonia are not known.

DBS of the GPi has been used for the treatment of Parkinson's disease (PD). Even if GPi DBS in PD in general seems to be safe regarding cognition,⁷ some studies have reported postoperative impairments of executive functions, verbal fluency, and memory (delayed free and cued recall).^{8–9} Furthermore, a recent study reported higher prevalence of suicide in patients treated with DBS for various movement disorders.¹⁰ Finally, total energy of GPi DBS used in dystonia, mainly pulse-width and voltage, are usually much higher than in PD, suggesting the possibility of neuropsychological side effects.¹¹ The aim of the present case series report was therefore to assess the influence of bilateral GPi stimulation on cognition, neuropsychiatric status, and quality of life in dystonia.

METHODS

Patients

We included 15 (six male, nine female) consecutive patients with dystonia who were treated with bilateral GPi DBS. Of these, 13 patients had primary dystonia (three positive for torsion dystonia gene (*DYT1*)) and two patients had tardive dystonia according to the criteria recently published by Adityanjee and colleagues.¹² Mean (SD) age of disease onset was 37.5 (20) years (range 6–62). At surgery, patients had a mean disease duration of 12.6 (9.6) years (range 2.5–40) and a mean age of 45.5 (17.7) years (range 13–68). Before surgery, all patients had marked disability due to segmental, multifocal, or generalised dystonia and had not achieved sufficient benefit from medical treatment including anticholinergics, tetrabenazine, pimozide, primidone, tetrazepam, lorazepam, clobazam, lithium, baclofen, and zolpidem. For additional patient characteristics see table 2 (available online at <http://www.jnnp.com/supplemental/>). Patients were considered for DBS when their medical status was stable and neuropsychiatric functioning allowed cooperation during the surgical procedure and postsurgical management of DBS devices. However, none of the patients who were screened during the enrolment period was rejected for DBS because of neuropsychological dysfunctions. All patients older than 18 years of age or the legal representatives of those patients younger than 18 years gave written informed consent before surgery.

Target localisation

We chose the primary stereotactic target point in the posteroventral medial globus pallidus at 20 mm lateral to the midline of the third ventricle, 4 mm below the intercommissural line (ICL), and 3 mm anterior to the mid-commissural point similar to that used in patients with PD.¹³ Adjustments of the intended coordinates were made in accordance to the individual stereotactic MRI. Intraoperative electrode positions were adjusted according to clinical effects of macrostimulation in all patients and with reference to teleradiography by using the intraoperatively performed contrast ventriculography and a long distance biorthogonal x ray system. If no optic or capsular responses were evoked during macrostimulation below a threshold of 2 mA (0.1 ms pulse duration, 130 Hz), a permanent quadripolar electrode was inserted (model 3387; Medtronic, Minneapolis, MN). Furthermore, postoperative MRI was done to verify correct electrode placement and control for subclinical complications.

Procedures and tests

We assessed the patients before and a mean of 6.5 months (range 3–12) after surgery. Postsurgical testing was

Abbreviations: BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; DBS, deep brain stimulation; GPi, globus pallidus internus; PD, Parkinson's disease; TMT, Trail Making Test

Table 1 Presurgical and postsurgical scores for motor functions, quality of life, neuropsychiatric status, and cognition (n = 15) and number of patients demonstrating changes >1 and >2 SD

Tests (n)		Mean scores		p value*	No of patients demonstrating changes					
		Presurgical	Postsurgical with GPI DBS		Improved			Declined		
		Mean (SD)	Mean (SD)		>2 SD	>1 SD	<1 SD	>1 SD	>2 SD	
Motor functions										
BFMDRS—motor score (15)†		33.8 (16.7)	13.7 (10.7)	<0.001	0	11	4	0	0	
BFMDRS—disability score (15)†		9.9 (3.8)	3.5 (2.5)	<0.001	6	7	2	0	0	
Quality of life										
PDQ 39 (13)†		66.3 (27.1)	41.6 (26.7)	0.002	2	4	7	0	0	
Neuropsychiatric status										
Beck Depression Inventory (15)†		13.6 (9.5)	9.4 (11.3)	0.06	0	3	11	1	0	
Montgomery Asberg Depression Rating Scale (15)†		13.1 (9.6)	7.7 (7.7)	0.01	1	2	12	0	0	
Beck Anxiety Inventory (10)†		15.0 (12.8)	10.9 (12.3)	0.20	0	2	8	0	0	
Snaith–Hamilton Pleasure Scale (10)†		1.6 (1.1)	0.5 (0.7)	0.04†	1	3	6	0	0	
Brief Psychiatric Rating Scale (9)†		27.7 (11.4)	19.4 (8.5)	0.09	2	1	6	0	0	
Bech–Rafaelson Mania Rating Scale (9)†		1.2 (1.6)	0.4 (1.3)	0.02†	0	2	7	0	0	
Cognition										
Global cognition										
Mattis Dementia Rating Scale Total (of 144) (15)		136.9 (8.3)	140.3 (4.7)	0.11	1	2	11	1	0	
Attention (15)		36.3 (1.1)	36.6 (0.9)	0.10	2	0	13	0	0	
Initiation (15)		32.9 (6.1)	35.1 (3.8)	0.17	1	2	11	1	0	
Construction (15)		6.0 (0.0)	6.0 (0.0)	–	0	0	15	0	0	
Conceptualisation (15)		38.7 (0.7)	38.5 (1.1)	0.38	0	1	12	1	1	
Memory (15)		23.7 (1.7)	24.3 (0.9)	0.19	0	4	10	1	0	
Alertness										
Tonic alertness	Simple reaction times (ms) (13)†	303.4 (75.6)	323.6 (91.7)	0.43	0	2	9	1	1	
Phasic alertness	Precued reaction time (ms) (13)†	299.3 (74.3)	301.4 (107.5)	0.95	0	2	10	0	1	
	Gain of time (ms) (13)†	4.1 (37.6)	22.2 (49.4)	0.18	2	1	9	0	1	
Attention and executive functions										
Stroop Test										
Words	Time (s) (10)†	39.1 (11.0)	35.2 (6.8)	0.09	0	2	8	0	0	
	False responses (10)†	0 (0.0)	0 (0.0)	–	0	0	10	0	0	
Color	Time (s) (10)†	58.0 (17.4)	55.1 (12.6)	0.26	0	0	10	0	0	
	False responses (10)†	0 (0.0)	0.1 (0.3)	0.34	0	0	9	1	0	
Interference	Time (s) (10)†	123.4 (84.6)	155.9 (201.7)	0.46	0	0	9	0	1	
	False responses (10)†	2.4 (5.3)	1.5 (3.4)	0.22	0	1	9	0	0	
Phonemic Verbal Fluency (F,A,S) (14)		30.4 (14.2)	30.9 (11.6)	0.81	0	0	13	1	0	
Category Verbal Fluency (animals, supermarket, furniture) (14)		45.8 (15.1)	48.5 (12.7)	0.33	0	2	12	0	0	
Trail Making Test										
Part A	Time (s) (15)†	47.8 (18.0)	38.5 (14.7)	0.04	0	5	9	1	0	
	Errors (15)†	0 (0.0)	0 (0.0)	–	0	0	15	0	0	
Part B	Time (s) (15)†	101.5 (37.1)	83.7 (46.6)	0.22	2	2	9	1	1	
	Errors (15)†	0.7 (1.4)	1.1 (1.8)	0.31	0	0	13	1	1	
B–A		Time (s) (15)	55.7 (30.4)	45.2 (40.5)	0.48	2	2	9	1	1
Learning and memory										
Rey Auditory Verbal Learning Test										
Recall A list, 1. trial (no. of words of 15) (15)		5.2 (2.5)	5.6 (1.5)	0.56	0	3	10	2	0	
Recall A list, 1.–5. trial (no. of words of 75) (15)		44.3 (11.5)	46.7 (10.6)	0.23	0	3	12	0	0	
Recall B list (of 15) (15)		5.3 (2.1)	6.0 (2.2)	0.25	1	2	10	2	0	
2. Recall A list, (of 15) (12)		9.2 (3.8)	9.6 (3.5)	0.62	0	1	10	1	0	
Delayed recall A list (of 15) (11)		8.2 (4.1)	9.0 (3.2)	0.46	0	2	8	1	0	
Delayed recognition A list (of 15) (13)		14.4 (1.0)	14.2 (1.2)	0.61	1	1	9	1	1	
Digit span										
Total score (15)		11.9 (2.6)	12.1 (3.3)	0.74	0	1	14	0	0	
Forward (15)		6.6 (1.6)	6.7 (1.9)	0.74	1	1	11	2	0	
Backward (15)		5.3 (1.4)	5.3 (1.9)	1.00	0	1	14	0	0	

*Student's *t* tests for paired samples. A *p* value < 0.05 was considered significant.

†A lower score means better performance.

‡Parameters, although statistically significantly improved, were preoperatively and postoperatively in the normal reference range.

BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; DBS, deep brain stimulation; GPi, globus pallidus internus.

conducted while patients were on stimulation with DBS parameters that were individually optimised for each patient. Patients were evaluated on their medications. To test the clinical efficacy of DBS, we evaluated the dystonic symptoms with the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS),¹⁴ which assesses symptom severity and disability in functional activities. For a global cognitive evaluation we used the Mattis Dementia Rating Scale (DRS),¹⁵ and to evaluate alertness, patients performed simple and precued visual reaction tasks.¹⁶ As tests of attention and executive functions, patients had to perform the Stroop Test,¹⁷ Phonemic and Category Verbal Fluency tasks,¹⁷ and the

Trail Making Test (TMT).¹⁷ Memory functions were evaluated using parallel versions of the Rey Auditory Verbal Learning Test (RAVLT)¹⁷ and the Digit span test.¹⁷ Mood and neuropsychiatric state were assessed using the Montgomery Asberg Depression Rating Scale (MADRS),¹⁸ the Beck Depression Inventory (BDI),¹⁹ the Beck Anxiety Inventory (BAI),²⁰ the Snaith–Hamilton Pleasure Scale (SHAPS),²¹ the Brief Psychiatric Rating Scale (BPRS),²² and the Bech–Rafaelsen Mania Rating Scale (BMRS).²³ Since no specific scale for the assessment of quality of life in patients with dystonia was available, the PDQ-39,²⁴ a questionnaire originally designed for PD was administered.

Data analysis

Student's *t* tests for paired samples were calculated for comparison of presurgical and postsurgical test scores. Because we aimed to assess the safety of a clinical intervention, a magnified type 1 error was appropriate and no correction for multiple comparisons was made.

RESULTS

There were no lasting adverse events associated with electrode implantation. At the time of the postoperative evaluation, stimulator settings using an anodal case and one or two adjacent cathodal contacts were as follows:

- Mean (SD) voltage:
  - right GPi—3.1 (1.2) V (range: 1.5–5.0)
  - left GPi—3.1 (1.1) V (range 1.5–5.0)
- Mean pulse width:
  - both sides—106.0 (55.4) μ s (range: 60.0–210.0)
- Mean frequency:
  - both sides—142.3 (32.2) Hz (range: 130.0–250.0).

In 10 patients the antidystonic medications could be decreased or tapered off (see table 2B online at <http://www.jnnp.com/supplemental/>).

Motor functions as assessed by the BFMDRS motor score improved in all patients (range 26–93%; table 2B). Accordingly, group analysis showed a significant mean improvement of dystonic symptoms by approximately 60% (table 1), whereas BFMDRS disability scores improved post surgically by about 65%.

Quality of life improved in all patients and resulted in a significant overall improvement of 37% (PDQ-39; table 1). Apart from a slight improvement on part A of the TMT (TMT-A; table 1), there was no significant effect on any of the cognitive tests. However, descriptive analysis revealed that individual patients showed improvement or decline on single or several test measures (see table 3 online at <http://www.jnnp.com/supplemental/>). For example, patient 8 remained stable on 26 cognitive measures and consistently worsened on five measures whereas patient 11 was stable on 19 measures and consistently improved on 11 measures. On neuropsychiatric tests, the only significant effect of GPi DBS was a mild improvement in depression. Remaining neuropsychiatric scores were unchanged or improved within the normal reference range (tables 1 and 3; for table 3 see online at <http://www.jnnp.com/supplemental/>).

DISCUSSION

Dystonic symptoms in our patients were reduced postsurgically by almost 60%. This confirms efficient pallidal electrode placement and complies with previous reports on beneficial effects of GPi DBS on motor symptoms in dystonia.^{2–5} Furthermore, stimulation parameters in our patients were similar to parameters reported by other studies.^{2–4}

Overall, we found cognitive measures stable or mildly improved. The only significant effect of stimulation was an improvement on TMT-A. The TMT-A is thought as baseline for the cognitively rather complex part B of the TMT. Since the TMT-A heavily relies on motor processes, the decrease in performance time on stimulation is likely to be attributable to the overall improvement of motor function. However, cognitive changes with deteriorations and improvements were found in individual patients. These changes could not be related to preoperative patient characteristics. Therefore,

our data does not allow identification of predictors for postsurgical cognitive outcome.

The marked improvement of motor symptoms allowed a postsurgical reduction or cessation of antidystonic medication in 10/15 patients. Since most antidystonic drugs are known to potentially impair cognition, we cannot entirely rule out that postsurgical medication changes masked neuropsychological deterioration induced by GPi DBS. Indeed non-parametrical post hoc comparisons of performance in those patients with unchanged medication regimen and patients with reduced antidystonic medication showed that simple reaction times after surgery increased in patients with stable medication. However, all remaining cognitive and neuropsychiatric parameters were unchanged. More importantly, non-parametrical post hoc analysis revealed that the five patients who were tested before and after surgery under identical pharmacological treatment conditions did not change on any of the cognitive measures.

Subjects were repeatedly tested and for many established cognitive tests, no parallel versions are available. In some instances, therefore, the same tests had to be applied twice. Thus, test-retest effects may have offset DBS induced cognitive deterioration. However, there are no test-retest effects described for both the tonic and phasic alertness tests.¹⁶ Furthermore, for the RAVLT, parallel versions were used. Although reliability measures of the remaining cognitive tests are considered reasonably good,¹⁷ practise effects have been described for the DRS, TMT, Stroop, and Fluency tasks. We therefore cannot rule out the possibility that test-retest effects may have masked mild cognitive decline on some of the cognitive measures.

With the exception of mild improvement on depression scales, neuropsychiatric status including anxiety, anhedonia, and mania did not change. The finding of mildly improved mood is most likely secondary to marked alleviation of disabling dystonic symptoms and improvement of functional abilities.

Although after surgery our patients were not assessed without DBS and our study does not allow differentiation between effects of surgery (micropallidotomy) and DBS, the present study provides preliminary support for the safety of GPi DBS in dystonia with regard to cognition, mood, and neuropsychiatric status. This result is compatible with recent neuroanatomical research suggesting a neuroanatomical and functional subdivision of the GPi with posteroventrolateral parts mediating motor functions and mediodorsal parts cognitive functions.²⁵ Since DBS of the GPi targets posteroventral parts of the GPi, our observation of improved motor function and unaffected neuropsychological status is consistent with the dissociation of motor and non-motor parts of the GPi.²⁵

In summary, the present case series report supports the efficacy of bilateral pallidal stimulation in the treatment of dystonia. More importantly, it is the first report providing preliminary support for the cognitive and neuropsychiatric safety of GPi DBS. Finally, it has been demonstrated that GPi DBS leads to an overall improvement of functional abilities and quality of life in a condition which can be most disabling. Our preliminary results will have to be confirmed by long term studies involving larger and more homogeneous patient samples differentiating between different age groups, retesting of dystonic control patients who do not undergo surgery, and using even more comprehensive neuropsychological test batteries.

An appendix to this paper has been posted online at <http://www.jnnp.com/supplemental/>

Authors' affiliations

T D Hälbig, D Gruber, U A Kopp, T Trottenberg, A Kupsch, Department of Neurology, Charité—University Medicine Berlin, Berlin, Germany
G-H Schneider, Department of Neurosurgery, Charité—University Medicine Berlin, Berlin, Germany

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Correspondence to: Dr T D Hälbig, Department of Neurology, Mount Sinai School of Medicine, One Gustave L Levy Place, Box 1137, New York, NY 10029, USA; thomas.haelbig@mssm.edu

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