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Chronic Deep Brain Stimulation in Patients with Tardive Dystonia Without a History of Major Psychosis

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Video 

Abstract: Tardive dystonia usually occurs with a delay after neuroleptic exposure in patients with major psychosis. A subgroup of patients, however, is given such medication for "mild depression" or "neurasthenia." Tardive dystonia, in general, may respond favorably to pallidal deep brain stimulation (DBS). Nevertheless, it remains unclear thus far whether or not similar beneficial outcome is achieved with pallidal DBS in different subgroups of patients with tardive dystonia. Four women (mean age 59 years at surgery) underwent stereotactic pallidal DBS in the frame of an observational study. Tardive dystonia occurred secondary to medication with fluspirilene and haloperidol, and injection of long-acting depot neuroleptics prescribed for mild depression or "nervousness." Assessment included the Burke-Fahn-Marsden (BFM) scale preoperatively and at 12 months follow-up. Extended follow-up was available at a mean of 27.3 months postoperatively (range 16–36 months). There were no surgically related complications. All 4 patients experienced sustained statistically significant benefit from pallidal DBS. Mean improvement at 12 months was 77% for the BFM motor score (range, 45–91%; $P = 0.043$), and 84% at the last available follow-up (range, 70–91%; $P = 0.03$). This was paralleled by improvement of the BFM disability score. Chronic pallidal DBS in patients with tardive dystonia without a history of major psychosis provides sustained improvement which is similar to that in other subgroups of patients with tardive dystonia. This effect is stable on extended follow-up for up to 3 years. © 2010 Movement Disorder Society

Key words: tardive dystonia; deep brain stimulation; major psychosis

INTRODUCTION

Tardive dystonia is a complication of chronic neuroleptic medication which most frequently manifests as focal or segmental dystonia.[1,2] The severity of dystonia does not correlate with the time of exposure to the medication, and also short periods of medication intake may cause tardive dystonia.[3,4]

Deep brain stimulation (DBS) was introduced about a decade ago as a treatment option for dystonia.[5] Over the years, DBS of the globus pallidus internus (GPi) has been shown to improve various types of dystonia.[6–9] DBS in secondary dystonia, in general, was reported to be less beneficial than in primary dystonia.[10] Tardive dystonia, however, was demonstrated to respond favorably to pallidal and subthalamic nulceus stimulation but not to thalamic stimulation.[10–17] Usually, drugs which may induce tardive dystonia are being prescribed for patients with major psychosis, although a subgroup of patients may have such medication for "mild depression" or "neurasthenia." As both the pathophysiological mechanisms of tardive

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TABLE 1. *Summary of clinical characteristics of 4 patients with tardive dystonia without a history of major psychosis*

	Age/Sex	Neuroleptic drugs	Indications for neuroleptic medication	Age tardive dystonia occurred	Interval between neuroleptic exposure and occurrence of tardive dystonia
Patient 1	45/F	fluspirilene	mild depression	41	6 yr
Patient 2	76/F	haloperidol	"nervousness"	65	5 yr
Patient 3	65/F	fluspirilene and pimozide	mild depression + "neurasthenia"	58	3 yr
Patient 4	48/F	fluspirilene	mild depression	43	1 yr

dystonia and the response to electrical modulation of the basal ganglia circuitry might differ in the later instance, evaluation of outcome after pallidal DBS is of particular interest.

Here, we present a series of 4 patients with tardive dystonia without a history of major psychosis who underwent bilateral pallidal DBS.

PATIENTS AND METHODS

Four women (mean age 59 years at surgery) were included in this observational study. Inclusion criteria were tardive dystonia secondary to neuroleptic medication, a lack of history of major psychosis, and insufficient improvement of tardive dystonia to medication in appropriate dosages (including tetrabenazine, tiapride, trihexyphenidyl, and biperiden). The term major psychosis in this context was used to cover schizophrenia, bipolar disorders, and major depression. Exclusion criteria were unclarities about the psychiatric history and the medication, or lack of overall disability or suffering. All patients had preoperative MR scans.

Clinical characteristics are summarized in Table 1. Patient 1 received fluspirilene for treatment of mild reactive depression. Six years later, she presented with blepharospasm together with jerky involuntary movements of the right arm. While walking, severe retrocollis and retrotruncus occurred (Video Segment). There were also dystonic storm-like episodes. Patient 2 developed cervical dystonia at the age of 59. She complained of being nervous and was treated with benzodiazepine and haloperidol. One year later a selective ramisectomy on the left side from C1 to C6 was performed. There was marked improvement of cervical dystonia after surgery, and medication was tapered off. Five years later, she presented with severe blepharospasm and oromandibular dyskinesias including the tongue. Patient 3 was treated with depot injections of fluspirilene and pimozide for mild depression and "neurasthenia." She developed orofacial dyskinesias with clonic blepharospasm. In the following years, dysphonia and mild cervical dystonia became apparent. Patient 4 had fluspirilene for treatment of mild depression. Six months follow-up after unilateral stimulation was reported elsewhere.[18] The electrode on the other side was not activated as it had been misplaced. As unilateral stimulation did not result in sustained improvement over the years, the patient was scheduled for revision of the misplaced electrode. The patient then was enrolled in this study. In all four patients, tardive dystonia occurred with a delay of more than 6 months after the exposure to neuroleptic medication (range 12–72 months, mean 45 months). No patient was on neuroleptic medication at the time of DBS surgery. Drugs for treatment of dystonia at the time of surgery included trihexyphenidyl in 1 patient.

All patients underwent bilateral DBS of the posteroventral lateral GPi under local anesthesia. The preliminary target was defined by CT-stereotactic imaging: 20–22 mm lateral to and 4 mm below the intercommissural line, and 2–3 mm anterior to the intercommissural midpoint. The detailed surgical procedure has been reported elsewhere.[19] Microelectrode recordings were used to define the target in the posteroventral lateral GPi. Moreover, to locate the electrodes within the sensorimotor part of the GPi passive movements of the contralateral limbs were performed intraoperatively and were linked to the response in the microelectrode recordings. Based on the mapping of neurons and the response to passive movements, the quadripolar DBS electrode was then implanted in a way that contact 1 and 2 (model 3387, Medtronic, Minneapolis, MN) were placed within the sensorimotor part of the GPi. Microelectrode recordings were useful in all 4 patients. After insertion of the DBS electrodes, macrostimulation was used to assess thresholds for visual phosphenes and capsular responses.

We routinely choose a bipolar configuration (cathode contact 1 and anode contact 2). Usually, in the beginning of stimulation frequency is set at 130 Hz and pulse width at 210 μsec. Impedances of all electrode contacts are checked. We stepwise increase the amplitude in the first 6 to 8 weeks up to 3.6 Volts in case there are no stimulation-induced side effects. If satisfactory clinical improvement occurs, the amplitude is

TABLE 2. *Preoperative and postoperative scores after bilateral GPi DBS*

	BFM preoperative motor disability	BFM postoperative motor disability 12 months FU	Postoperative improvement BFM (%) motor disability at 12 months FU	BFM postoperative motor disability at last available FU	Postoperative improvement BFM (%) motor disability at last available FU
Patient 1	65	5,5	91 %	5,5	91 %
	8	1	87.5 %	1	87,5 %
				27 mo	
Patient 2	55	30	45 %	16	70 %
	6	4	33 %	3	50 %
				30 mo	
Patient 3	18	2	88 %	2	88 %
	1	0	100 %	0	100 %
				16 mo	
Patient 4	33	5,5	83 %	4,5	86.5 %
	8	4	50 %	4	50 %
				36 mo	

FU, follow-up; BFM, Burke-Fahn-Marsden Scale.

not further increased. Otherwise, we further increase the amplitude up to 5.0 V or more. At this stage, also monopolar stimulation via single contacts is used when there are side effects or insufficient improvement.

Assessments pre- and postoperatively included amongst others the Burke-Fahn-Marsden (BFM) scale and standard videotaping.

Statistical analysis was performed using the Wilcoxon rank sum test.

RESULTS

There were no surgically related complications. The electrode localization was controlled with postoperative stereotactic CT scans. Two single channel pacemakers were used in 3 patients (Soletra, Medtronic) and a dual channel pacemaker in 1 patient (Kinetra, Medtronic). Phasic dystonic movements improved within several days, whereas more pronounced improvement of the tonic postures usually took several weeks to months.

All four patients experienced statistically significant benefit from pallidal DBS when the 12-month follow-up and the last available follow-up at 16 to 36 months were compared to preoperatively. Table 2 gives an overview about the patients' individual BFM subscores pre- and postoperatively at 12 months and at the last available follow-up. At 12 months follow-up with bilateral pallidal stimulation, there was a mean improvement of 77% of the BFM motor score (range 45–91%; $P = 0.043$; mean preoperative score 43, mean 12-month follow-up score 11), respectively, of 68% of the BFM disability score (range 33–100%; $P = 0.077$). At the last available follow-up (mean, 27.3 months), there was a mean improvement of 84% of the BFM motor score (range 70–91%, $P = 0.03$; mean score 7), respectively, of 72% of the BFM disability score (range 50–100%, $P = 0.058$).

The attached Video Segment shows patient 1, preoperatively and at 27 months of follow-up. Patient 2 had a more unstable benefit initially. The BFM motor score was improved by 45% and the BFM disability score by 33% at 12 months follow-up. After adjustment of stimulation settings, however, the motor score was improved by 70% and the disability score by 50% at the last available follow-up at 30 months. Presumably, because of the small number of patients the Wilcoxon test did not yield statistical significance for the BFM disability score but showed a trend towards beneficial improvement after DBS.

Unilateral stimulation before revision of the misplaced contralateral electrode in Patient 4 had yielded a 63% improvement in the AIMS score.[18] The episodes of dystonic storm in Patient 1 reoccurred a few times in the first weeks after initiation of bilateral stimulation but disappeared completely in the further course. Patient 2 needed several adjustments of stimulation settings also beyond 2 years follow-up.

Stimulation settings at the last follow-up were as follows: mean amplitude 4.5 V (range 3.0–6.5), pulse width 210 μsec in 3 patients, and 90 μsec in 1 patient. The frequency was at 130 Hz in 3 patients and at 160 Hz in 1 patient. Three patients were on bipolar stimulation, whereas one patient was on monopolar stimulation.

Patient 2 underwent replacement of the pulse generator after 16 months of chronic stimulation due to battery depletion. Stimulation-induced side effects included mild dysarthria in Patient 2 which diminished after adjustment of settings. Medication with trihexyphenidyl was tapered off after a few weeks.

DISCUSSION

Tardive dystonia most frequently is secondary to chronic exposure to neuroleptic medication acting via D2-receptor antagonism such as haloperidol. However, atypical neuroleptics and antiemetics with an effect on central dopamine receptors may also cause tardive dystonia.[4] As tardive dystonia in adults usually is focal or segmental, it is important to exclude primary adult-onset dystonia, necessitating a careful patient medication history.[3] Tardive dystonia initially involves often muscles of the face or neck and, typically, may display oromandibular and orolingual dystonia.[3] As exemplified by the medical history of Patient 2 in our study, patients with focal idiopathic dystonia may also develop tardive dystonia after neuroleptic medication with a delay. In particular, the temporal relationship with the exposure of the neuroleptic medication and the delayed appearance of oromandibular dyskinesias without reoccurrence of cervical dystonia supports this concurrence. All patients included in this study had oromandibular dyskinesias and/or blepharospasm typical for tardive dystonia. The pathophysiology of tardive dystonia has not been clarified fully thus far.[20] Neuroleptic medication certainly interacts both with the hyperactive mesostriatal dopaminergic pathway in psychosis and the nigrostriatal pathway at different target sites including the ventral striatum, the associative striatum and the sensorimotor striatum. It has been shown recently that dopamine release within the various functional territories of the striatum is contingent upon the release in other striatal subterritories.[21–23]

After pallidal DBS had been introduced as a symptomatic treatment option for primary idiopathic generalized[24] and cervical dystonia,[5] the spectrum of indications was widened gradually over the past few years. Initially, the indication "tardive dystonia" was met with considerable skepticism. The reasons for this were twofold. First, it soon became clear that patients with secondary dystonia fare less well after surgery then those with primary dystonia;[10] and second, psychiatric comorbidity was and still is considered a contraindication for DBS by many investigators.

Although a beneficial response to pallidal DBS was reported in single instances with tardive dystonia, case-series and multicenter studies were published only recently.[10–12,14,16,17] A series of 5 patients was reported to achieve a mean improvement of 87% in the BFM motor subscore which was sustained at 6 months, and in 2 patients up to 39 months postoperatively.[12] Also, DBS of the subthalamic area has been reported to provide benefit in tardive dystonia.[15] Publication of the results of the French Stimulation for Tardive Dyskinesia (STARDYS) Study Group marked a major breakthrough. Damier et al. reported[16] the results of a double-blind videotape based evaluation in 10 patients. Symptoms improved by more than 40% (mean improvement 61%; range, 44%-75%) in the first enrolled 10 patients 6 months after bilateral GPi DBS. The psychiatric status of all patients remained stable. Among the patients included in that study, four had been treated with neuroleptics for major depression. In 5 patients, Thobois et al. evaluated the changes of regional cerebral blood flow (rCBF).[25] GPi stimulation initiated a reduction of rCBF in the primary motor and prefrontal cortex and the cerebellum while the patients were performing motor exercises. In contrast, rCBF at rest increased in the primary motor and anterior cingulate cortex as well as in the supplementary motor area. In a recent study of Gruber et al. on 8 patients with tardive dystonia, pallidal DBS yielded an 83% improvement at a mean follow-up of 41 months after pallidal DBS.[26] This study compromised also instances of patients with tardive dystonia without psychosis.

The main point of our report was the selective investigation of patients with tardive dystonia without a history of major psychosis. Our results, overall, are in line with the findings of those series reported previously which evaluated the efficacy of DBS in patients with a diagnosis of tardive dystonia and major psychosis. Chronic pallidal DBS in patients with tardive dystonia without a history of psychosis provides sustained improvement. It underlines also the role of DBS in some forms of secondary dystonia. As this was an observational study, there are inherent limitations. Randomized controlled studies with blinded outcome assessment, which have been conducted for primary generalized and segmental dystonia, are currently being performed also for tardive dystonia. In the future also patients with tardive dystonia without a medical history of major psychosis should be considered as good candidates for bilateral GPi DBS.

Legends to the Video

Segment 1. Videotaping of patient 1 prior to implantation of DBS electrodes in the posteroventral lateral GPi.

Segment 2. This segment shows patient 1 benefitting from marked and sustained improvement after 27 months of chronic bilateral pallidal DBS.

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