

Bilateral Subthalamic Nucleus Stimulation for Generalized Dystonia after Bilateral Pallidotomy

Erich Talamoni Fonoff, MD, PhD,^{1*}
 Wuilker Knoner Campos, MD,¹ Maurício Mandel, MD,¹
 Eduardo Joaquim Lopes Alho, MD,^{1,2}
 and Manoel Jacobsen Teixeira, MD, PhD¹

¹Division of Functional Neurosurgery, Department of Neurology of School of Medicine of University of São Paulo, São Paulo SP, Brazil;
²"Julius-Maximilians Universität Würzburg" Labor für Morphologische Hirnforschung (Laboratory for Morphological Brain Research), Würzburg, Germany

ABSTRACT

Background: Thalamotomies and pallidotomies were commonly performed before the deep brain stimulation (DBS) era. Although ablative procedures can lead to significant dystonia improvement, longer periods of analysis reveal disease progression and functional deterioration. Today, the same patients seek additional treatment possibilities.

Methods: Four patients with generalized dystonia who previously had undergone bilateral pallidotomy came to our service seeking additional treatment because of dystonic symptom progression. Bilateral subthalamic nucleus DBS (B-STN-DBS) was the treatment of choice. The patients were evaluated with the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and the Unified Dystonia Rating Scale (UDRS) before and 2 years after surgery.

Results: All patients showed significant functional improvement, averaging 65.3% in BFMDRS ($P = .014$) and 69.2% in UDRS ($P = .025$).

Conclusions: These results suggest that B-STN-DBS may be an interesting treatment option for generalized dystonia, even for patients who have already undergone bilateral pallidotomy. ©2012 *Movement Disorder Society*

Key Words: dystonia; thalamotomy; pallidotomy; deep brain stimulation; subthalamic nucleus

Dystonia is described as abnormal muscle activation in a spectrum ranging from focal to generalized affliction of body segments because of disruption in movement-controlling neural circuits.¹ Although patients are cognitively normal, generalized dystonia often leads to severe physical and social disability, resulting in significant and progressive deterioration of quality of life.^{2–4} Although some patients respond to levodopa treatment, many are disappointed by a lack of results following treatment with available oral pharmacotherapies and botulinum toxin.^{3,5,6}

Hundreds of patients with generalized dystonia have undergone ablative stereotactic neurosurgery. A variety of subcortical structures have been surgically targeted to treat dystonia. Historically, thalamotomy (ventrooralis anterior [Voa] and ventrooralis posterior [Vop]) and pallidotomy (globus pallidus internus [GPi]), often bilateral, have been the major procedures performed in dystonia patients.⁷ Although significant improvement of dystonic symptoms is typically reported at short- and intermediate-term ablative procedure follow-ups,⁸ patients often progress and deteriorate in the long term. Those who previously underwent these procedures are now seeking new treatment possibilities and may be helped by the development of new deep brain stimulation (DBS) targets.

The present report describes the procedures and outcomes of 4 patients who had fewer DBS targets available because of previous bilateral pallidotomy. We attempted to place electrodes in the bilateral subthalamic nucleus (B-STN) and achieved positive and sustained results despite previous pallidotomy.

Patients and Methods

Four patients diagnosed with generalized dystonia who did not respond to conservative medical treatment and had previously undergone bilateral pallidotomy came to our service in order to find surgical alternatives to treat progressive dystonic symptoms. The patients had no prior history of trauma, dementia (Mini–Mental State Examination score > 26), psychiatric illness, or identifiable secondary causes of

*Correspondence to: Dr. Erich Talamoni Fonoff, Division of Functional Neurosurgery, Department of Neurology, University of São Paulo School of Medicine, Rua Dr. Ovídio Pires de Campos, 785, 01060-970, São Paulo, SP, Brasil; fonoffet@usp.br

Funding agencies: This study was supported by grants from the University of São Paulo School of Medicine, São Paulo, Brazil.

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 20 February 2012; **Revised:** 21 June 2012; **Accepted:** 13 July 2012

Published online in Wiley Online Library (wileyonlinelibrary.com).
 DOI: 10.1002/mds.25127

Table 1. Patient baseline characteristics and outcomes after bilateral subthalamic stimulation

Case No.	Sex	Dystonia type	Family history	Age (y)							STN DBS						
				Age (y)			Bilateral Pdt				Clinical Outcome						
				At onset	At Op Pdt	At Op DBS	Time from Pdt (y)	Result	Adverse effects	Scale	Preop	6 months	12 months	Last FU ^a	Stimulation parameters	Adverse effects	
1	F	Idiopathic generalized dystonia	None	2	14	23	9	able to sit upright for 2 y after Pdt	Severe hypophonia	BFM UDRS CGI	108 116 7	78 72 —	72 76 —	65 57 2	3.2/2.8 V 130 Hz 210 μs bilat. 1–/c+	Hypophonia	
2	M	Idiopathic generalized dystonia	None	11	17	41	24	Modest upper limb improvement	—	BFM UDRS CGI	88 96 5	76 68 —	28 32 —	20 18 1	1.7/1.9 V 130 Hz 210 μs bilat. 1–/c+	—	
3	F	Secondary generalized dystonia	None	40	42	58	18	Limb improvement, able to stand for 2.5 y	Speech impairment	BFM UDRS CGI	78 69 6	32 37 —	22 28 —	18 22 1	2.2/2.8 V 130 Hz 210 μs bilat. 1–/c+	Hypophonia induced by stimulation	
4	M	Idiopathic generalized dystonia	None	10	15	20	5	Limb improvement Able to hold objects for 4.5 y	—	BFM UDRS CGI	98 104 6	54 72 —	42 48 —	32 24 1	3.4/3.0 V 130 Hz 210 μs bilat. 1–/c+	—	
Average										BFM (% ^b) UDRS (% ^b)	— —	37.2% 37%	57.5% 53.5%	65.3% 69.2%			

Outcome from prior pallidotomy was approached by retrospective analysis based on medical records and family interview. Outcome after STN-DBS was evaluated according to Burke–Fahn–Marsden (BFM), Unified Dystonia Rating Scale (UDRS), and Clinical Global Impression (CGI; Spearing et al, 1997²⁵) scales. Item 1 measures preoperative status—severity of illness: 1, normal not ill at all; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, among the most extremely ill patients). Item 2 measures outcome at the last follow-up—global improvement: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse.

^aFU (last follow-up) was at 36, 36, 24, and 28 months for patients 1, 2, 3, and 4, respectively.

^bAverage improvement related to preoperative status. Op, operation; Pdt, pallidotomy; STN, subthalamic nucleus; DBS, deep brain stimulation; bilat., bilateral; 1–/c+, negative pole in contact one and positive pole in the stimulator case.

dystonia, except for 1 patient with a history of neuroleptic and antidepressant use (case 3). Genetic marker analysis for dystonia was not available in our center. Patient 1 had early-onset dystonic symptoms (at 2 years of age) with progression to very severe generalized dystonia. She underwent bilateral pallidotomy at age 14 and showed some improvement and was able to sit upright. Patient 2 had severe dystonic symptoms, predominantly in the limbs, and marked hypophonia prior to pallidotomy. Patients 3 and 4 reported generalized dystonic symptoms, including retrocollis and trunk dysfunction; their limb dystonia had moderately improved after pallidotomy. The patients were evaluated with the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and the Unified Dystonia Rating Scale (UDRS) before DBS implantation, 6 and 12 months after the operation, and at the last follow-up (Table 1 and Fig. 1). Clinical global impression (CGI scale) was also evaluated in these patients. All postoperative assessments were made in the stimulator-on state.

Surgical Procedure

Permanent quadripolar DBS electrodes (model 3387; Medtronic, Inc., Minneapolis, MN) were implanted in the STN bilaterally in all 4 patients using stereotactic image guidance (computed tomography/magnetic resonance imaging [MRI] fusion), intraoperative impedance measurements, and macrostimulation. Electrode

orientation was calculated in order to permit additional stimulation of the zona incerta based on the conformation atlas/MRI electronic fusion (MSA software; Micromar, São Paulo, Brazil). To illustrate electrode trajectory and the proposed target region (STN), a scaled 3-dimensional model of the quadripolar electrode was created using modeling software (Autodesk® 3ds Max® 7, Autodesk Inc, San Rafael, CA, USA) and fused into a postoperative MRI and 3-D histological representations of the STN and thalamus (Amira 5.4.1; Visage Imaging Inc., GmbH, Berlin, Germany; Fig. 1B). Surgical implantation of intracranial electrodes was initially performed under local anesthesia. Intraoperative threshold current testing for side effects was performed using high-frequency macrostimulation in order to avoid motor, sensory, and ocular side effects. The pulse generators (Kinetra/Soletra; Medtronic Inc.) were implanted under general anesthesia.

Postoperative Stimulation Parameters

The patients were discharged from the hospital 3–5 days after surgery, and postoperative stimulation programming was performed in an outpatient setting. Medication regimens were not changed. The stimulation parameters were adjusted at monthly intervals for the first 3 months and at 3- to 6-month intervals during the follow-up period according to the patient’s clinical status. Statistical analysis was performed using paired *t* tests.

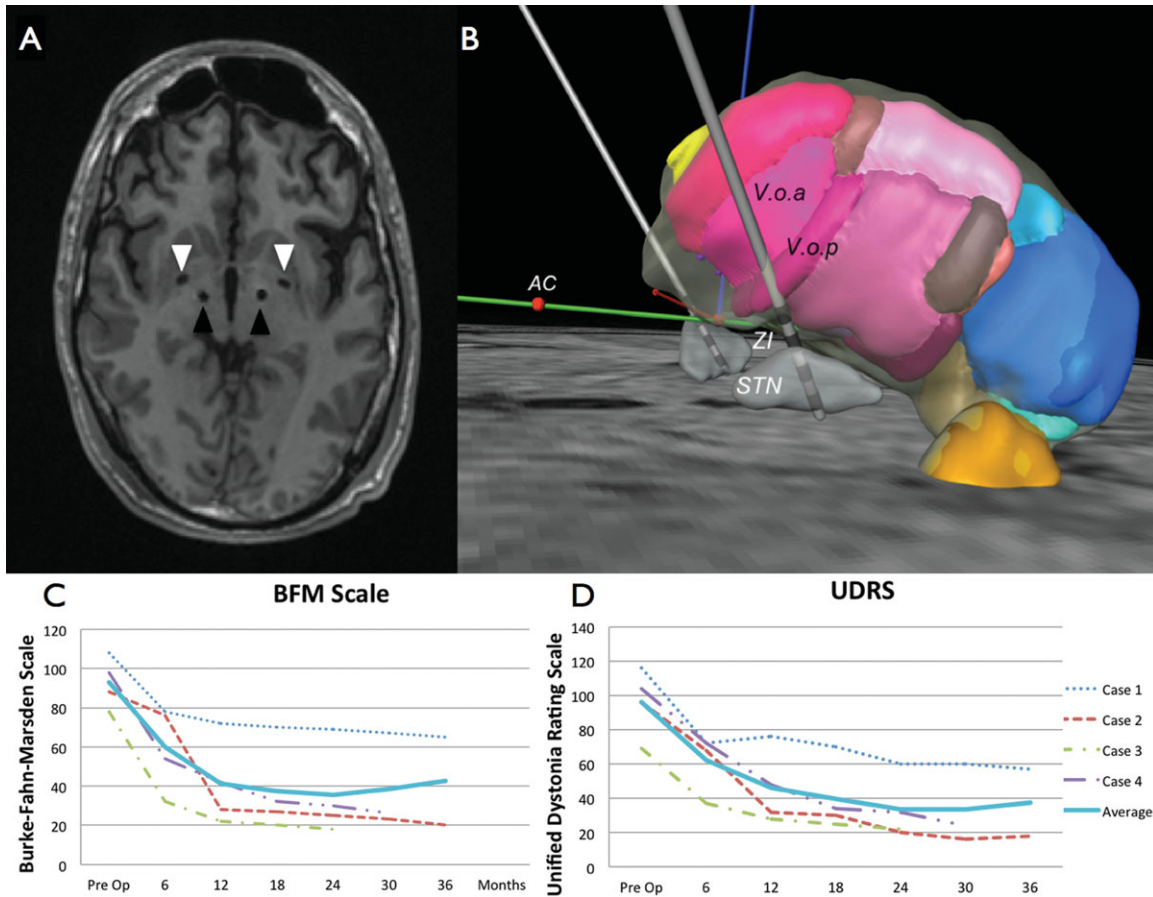


FIG. 1. A: Postoperative T1-weighted magnetic resonance image (MRI) in the transverse plane showing electrode artifacts in the B-STN (black arrowheads) and ablated tissue in the GPi from previous bilateral pallidotomy (white arrowheads) in case 2. **B:** Oblique view of the 3-dimensional reconstruction of the same patient: MRI fused with the histological STN reconstruction of the STN (almond-shaped silver structure), the thalamus (Voa and Vop), and a scaled model of the Medtronic DBS electrode (model 3387). The 3-dimensional representations of the STN and thalamus were based on 400- μ m histological sections of the São Paulo–Würzburg Electronic Atlas of the Human Brain Project merged into the same stereotactic space.²⁶ Results on rating scales from baseline to the last follow-up and imaging showing surgical procedures. **C:** BFMDRS. **D:** UDRS.

Results

Overall, significant functional scale score improvements were observed over time, averaging 65.3% for the BFMDRS ($P = .014$) and 69.2% for the UDRS ($P = .025$), with respective improvement in the CGI scale (Table 1 and Fig. 1C,D). Table 1 displays the clinical results following surgery. Follow-up assessments were made in the ON-stimulation state because no substantial differences were acutely observed between the ON and OFF states (data not shown).

Discussion

Ablative procedures, in which the motor thalamus or GPi is permanently lesioned, were previously used to treat dystonia. Over time, DBS has evolved from ablative procedures and has emerged as a powerful, reversible therapeutic strategy for movement disorders.^{9–12} GPi DBS has replaced pallidotomy as the surgical treatment of choice, and according to current guidelines and previously published results, the patients in this series would have been good candi-

dates for bilateral GPi DBS.^{11,12} However, recent studies have also shown that STN-DBS can improve movement disorders, including dystonia.^{13–17} Patients who have previously undergone pallidotomy often seek new treatment possibilities when their symptoms return and progress. STN-DBS is a possible option for these patients because the STN extends numerous projections to the GPi, and areas not lesioned by pallidotomy could still be influenced by STN stimulation, resulting in improved dystonic symptoms.

Many reports in the literature have described stimulation of a previously lesioned structure.^{14–16,18,19} Some authors have reported postpallidotomy Parkinson's disease patients with good outcomes after STN-DBS.^{1,13,20} The biological justification for these targets is based on a pathophysiological model of information processing in basal ganglia–thalamomotor cortical circuits.^{21,22} Abnormal patterns of synchronous bursting in pallidal neurons are transmitted through this network in dystonic patients, causing reduced motor specificity and loss of inhibitory control of motor cortical areas and leading to abnormal motor output.²³

A prior pallidal lesion does not seem to limit the effects of B-STN-DBS, and this brings into question the mechanism of action of STN-DBS in basal ganglia circuitry in dystonic patients, as reported by Novak et al.¹⁵ Moreover, as reported by Kim et al,¹⁹ prior bilateral thalamotomy and pallidotomy did not rule out good GPi DBS outcomes. DBS activates neuronal structures and alters pathological neuronal activity responsible for movement disorders by providing a high-frequency “jamming” signal.²⁴ The major excitatory STN projections are to the GPi and to the substantia nigra pars reticulata. High-frequency STN stimulation may disrupt local pathological activity, preventing STN excitatory signals to residual GPi that was not destroyed by posterovenral pallidotomy. In addition, the STN is directly connected to a wide range of structures, including the cerebral cortex, the globus pallidus externus, the centromedian nucleus of the thalamus, and brain stem structures like the peduncle–pontine and raphe nuclei. Therefore, STN stimulation likely affects a number of circuits in addition to the GPi, and these may also be important in the development of dystonia.

In the present series of adults with refractory, severe idiopathic dystonia who had previously undergone bilateral pallidotomy, B-STN-DBS led to dystonia symptom improvement and reduced disability in 4–8 months. The initial results were more pronounced, but patients continued to improve over time, and these outcomes were maintained for at least 32 months following surgery (Fig. 1). These patients were also able to markedly reduce their medication doses for dystonia treatment. The literature defines success in dystonia surgery as a 25% reduction of dystonic symptoms, as gauged by a rating scale. Nearly all our patients demonstrated such improvement (37%–65%).

However, patients define success in a more subjective way. All patients reported a positive global impression of the treatment and described themselves as “satisfied” (1 patient) or “very satisfied” (3 patients) with the results achieved. One limitation of the present study is the lack of a blinded OFF-state, which could be employed to improve data quality in future studies. However, as the effects of B-STN-DBS are observed during long-term follow-up, the probable cumulative effect could be an enormous bias for data interpretation.

To summarize, our results suggest that B-STN-DBS in patients with dystonia seems to be effective, even if they have already undergone bilateral pallidotomy. However, further studies with larger numbers of patients are necessary to support the present results.

References

- Bressman SB. Dystonia update. *Clin Neuropharmacol.* 2000;23:239–251.
- Blahak C, Wöhrle JC, Capelle HH, et al. Health-related quality of life in segmental dystonia is improved by bilateral pallidal stimulation. *J Neurol.* 2008;255:178–182.
- Giron LT, Jr., Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Saf.* 1996;14:365–374.
- Lagrange E, Krack P, Moro E, et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology.* 2002;59:1976–1978.
- Fahn S, Bressman SB, Marsden CD. Classification of dystonia. *Adv Neurol.* 1998;78:1–10.
- Jankovic M, Reciputo A, Haupt R, et al. ELTEC: ten years of activity (1990–2000)—a report of the International BFM Study Group. *Med Pediatr Oncol.* 2002;38:124.
- Krack P, Vercueil L. Review of the functional surgical treatment of dystonia. *Eur J Neurol.* 2001;8:389–399.
- Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia. *Mov Disord.* 1997;12:865–870.
- Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet.* 2000;355:2220–2221.
- Tronnier VM, Fogel W. Pallidal stimulation for generalized dystonia. Report of three cases. *J Neurosurg.* 2000;92:453–456.
- Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med.* 2005;352:459–467.
- Kupsch A, Benecke R, Müller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med.* 2006;355:1978–1990.
- Chou KL, Hurtig HI, Jaggi JL, Baltuch GH. Bilateral subthalamic nucleus deep brain stimulation in a patient with cervical dystonia and essential tremor. *Mov Disord.* 2005;20:377–380.
- Kleiner-Fisman G, Liang GS, Moberg PJ, et al. Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg.* 2007;107:29–36.
- Novak KE, Nenonene EK, Bernstein LP, Vergenz S, Cozzens JW, Rezak M. Successful bilateral subthalamic nucleus stimulation for segmental dystonia after unilateral pallidotomy. *Stereotact Funct Neurosurg.* 2008;86:80–86.
- Pastor-Gomez J, Hernando-Requejo V, Luengo-Dos Santos A, Pedrosa-Sanchez M, Sola RG. [Treatment of a case of generalised dystonia using subthalamic stimulation]. *Rev Neurol.* 2003;37:529–531.
- Sun B, Chen S, Zhan S, Le W, Krahl SE. Subthalamic nucleus stimulation for primary dystonia and tardive dystonia. *Acta Neurochir Suppl.* 2007;97:207–214.
- Mogilner AY, Sterio D, Rezai AR, Zonenshayn M, Kelly PJ, Beric A. Subthalamic nucleus stimulation in patients with a prior pallidotomy. *J Neurosurg.* 2002;96:660–665.
- Kim JP, Chang WS, Park YS, Chang JW. Bilateral globus pallidus internus deep brain stimulation for DYT1+ generalized dystonia with previously received bilateral thalamotomy and unilateral pallidotomy. *Stereotact Funct Neurosurg.* 2011;89:205–209.
- Benabid AL, Koudsie A, Benazzouz A, et al. Deep brain stimulation of the corpus luyisi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. *J Neurol.* 2001;248(Suppl 3):III37–III47.
- Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 1989;12:366–375.
- DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 1990;13:281–285.
- Vitek JL. Pathophysiology of dystonia: a neuronal model. *Mov Disord.* 2002;17(Suppl 3):S49–S62.
- McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol.* 2004;115:1239–1248.
- Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res.* 1997;73:159–171.
- Alho E J L, Grinberg L, Heinsen H, Fonoff ET. Review of printed and electronic stereotactic atlases of the human brain. In: Peres JFP, eds. *Neuroimaging for Clinicians - Combining Research and Practice.* 1st ed. Rijeka, Croatia: InTech; 2011:145–172.