Movement Disorders
CLINICAL PRACTICE

Deep Brain Stimulation in Patients with Isolated Generalized Dystonia Caused by *PRKRA* Mutation

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Dystonia is defined by sustained or intermittent involuntary contractions leading to abnormal movements and postures, with a heterogeneous etiology and a complex pathophysiology. Advances in genetics have allowed the identification of several monogenic forms of dystonia.[1] Recently, a novel form of recessively inherited dystonia characterized by early-onset generalized dystonia-parkinsonism (DYT16) has been described caused by a mutation in the *PRKRA* gene,[2] responsible for 4.5% of the idiopathic dystonia cases in a Brazilian cohort.[3] The management of DYT16 is challenging.

Deep brain stimulation (DBS) of globus pallidus internus (GPi) is an established treatment for dystonia, but the outcomes vary regarding the underlying cause and genetic subtype.[4] Here we describe the effect of GPi-DBS in 2 DYT16 patients.

Case 1: A 35-year-old man developed phonation difficulties and hand dystonia at age 6. Over time, the movements spread to his neck and trunk, leading to extreme side-bending, without parkinsonism. Treatment attempts with anticholinergics, levodopa, and botulinum toxin showed poor responses. At 4 years before the current presentation, a unilateral palidotomy was performed with mild improvement.

Case 2: A 16-year-old woman presented at age 7 with dystonia in her right leg followed by her trunk, neck, and speech. No parkinsonism was observed. Conventional oral medications and botulinum toxin injections have been tried with mild response.

As a result of refractory symptoms, bilateral GPi-DBS was proposed after both patients signed the written informed consents. This study was approved by the local ethics committee. A neuropsychological assessment was made showing significant improvement in anxiety and depression symptoms. The patients were assessed by the Burke–Fahn–Marsden Dystonia Rating Scale before and 6 months after surgery and by the Patient's Global Impression of Change Scale postoperatively. Wireless accelerometers and a rigid surface were used to assess gait and balance control, respectively.

The Burke–Fahn–Marsden Dystonia Rating Scale motor/disability scores improved 42%/50% in case 2 and 49%/57% in case 2, respectively (Video S1). In the gait analysis, time to complete the walk decreased after DBS in both patients. Case 1 showed smaller values of wrist and head acceleration during walking after DBS, showing improved gait stability. Analysis of the quiet stance indicated improved balance in both patients as registered by the center of pressure. Speech was not affected by stimulation. No adverse effects were reported (detailed in Fig. 1).

To date, only a single case of DYT16 with DBS performed as treatment was described superficially without prospective assessment.[5] Several factors are thought to be good predictors of DBS response, including age of onset, characteristics such as phasic dystonia, leads location, and stimulator settings.[4] The current evidence suggests that genetic screening may provide useful information regarding the selection of potential DBS candidates.[4] Some studies have suggested that patients with *TOR1A* mutations respond to GPi-DBS more consistently, whereas patients with DYT-*THAP1* have more variable outcomes.

In the era of individualized DBS for movement disorders, a deeper understanding of the outcomes regarding the genetic status in dystonia is crucial, as preoperative screening could provide valuable prognostic information. Moreover, considering the possibility of higher *PRKRA* mutation prevalence than is currently known,[3] it seems reasonable to study new therapies to optimize the results for refractory cases.

Our series is the first prospective study of GPi-DBS response in patients with a *PRKRA* mutation. Although robust conclusions are limited because of the small number of cases, our observation supports GPi-DBS as a treatment option for DYT16.

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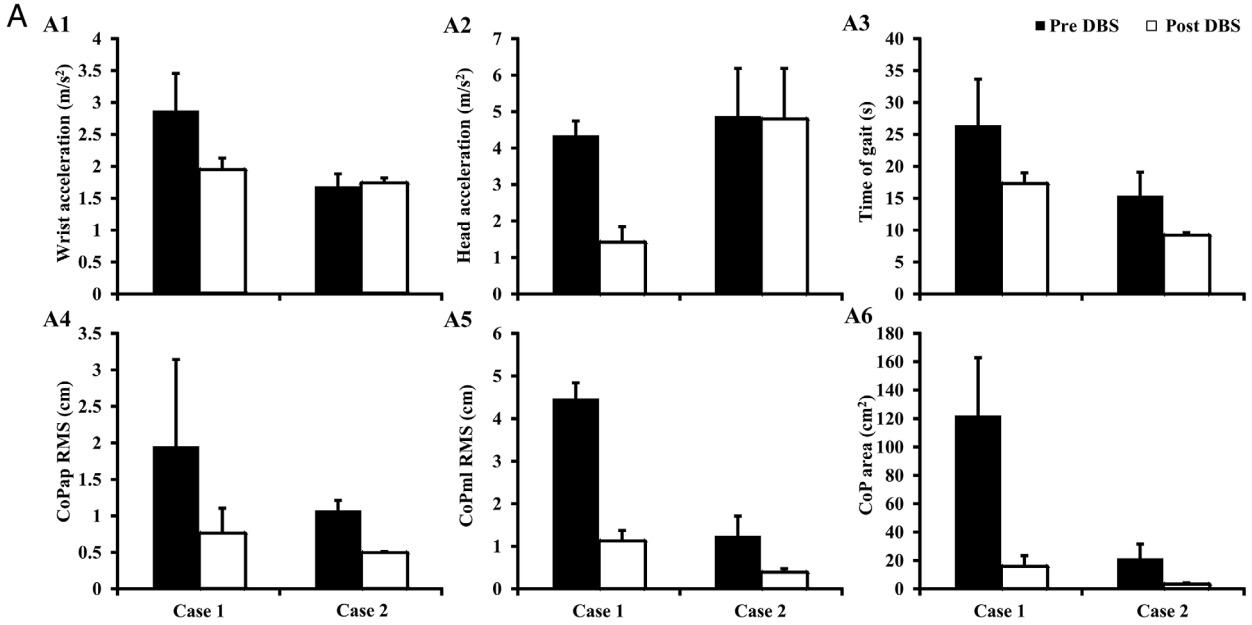
A



B

	Baseline	Post-op (6mo)	Improvement %
BFMDRS motor/ disability score (Case 1)	102/24	58.5/12	42/50
BFMDRS motor/ disability score (Case 2)	63/7	32/3	49/57
Patient's Global Impression of Change scale (Case 1)	-	6 (better)	-
Patient's Global Impression of Change scale (Case 2)	-	7 (a great deal better)	-

C

	Lead	Contact	Electrical Settings Current Pulse width Frequency
Stimulation Parameters (Case 1)	Left	Ventral contact cathode (-), Case anode (+)	4.2 mA 117µs 160 Hz
	Right	Ventral contact cathode (-), Case anode (+)	4.6 mA 117µs 160 Hz
Stimulation Parameters (Case 2)	Left	Most ventral contact cathode (-), Case anode (+)	2.5 mA 120 µs 130 Hz
	Right	Ventral contact cathode (-), Case anode (+)	2.5 mA 120 µs 130 Hz

FIG. 1. **A:** Comparison of the effects of deep brain stimulation (DBS) with averages (standard deviation in vertical bars) for gait (wrist [A1] and head [A2] acceleration, time [A3]) and quiet stance (center of pressure [CoP] root mean square [RMS] for the anteroposterior [A4] and mediolateral [A5] directions, CoP area [A6]). **B:** BFMDRS motor and disability scores and Patient's Global Impression of Change Scale preoperative and postoperative. **C:** The optimal stimulation parameters after 6 months. BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale.

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Author Roles

1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

S.C.B.C.: 1A, 1B, 1C, 2A, 2B, 3A, 3B
C.L.: 1B, 1C, 2A, 3B
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Disclosures

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. In the first part, the video shows both patients (cases 1 and 2) with generalized dystonia walking before the surgery. Note the severe and disabling axial dystonia of case 1, most of the time needing support to keep standing. The second part shows the effects after 6 months of globus pallidus internus deep brain stimulation. Note the important improvement of dystonia and posture in case 1 and dystonia and velocity of gait in case 2.