

Bilateral Deep Brain Stimulation of the Pallidum for Myoclonus-Dystonia Due to ϵ -Sarcoglycan Mutations

A Pilot Study

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Objective: To assess the efficacy of bilateral deep brain stimulation of the internal pallidum in patients with myoclonus-dystonia due to genetically proved ϵ -sarcoglycan (SGCE-M-D) deficiency.

Design: Patients with documented SGCE-M-D undergoing bilateral deep brain stimulation of the internal pallidum were recruited. Standardized assessments of M-D were videorecorded before surgery and 6 to 9 months and 15 to 18 months after surgery, using the movement and disability subscales of the Burke-Fahn-Marsden Dystonia Rating Scale and the Unified Myoclonus Rating Scale. The analysis was based on blinded evaluation of the recordings.

Setting: Movement disorder unit in a university hospital in Paris.

Patients: Five consecutive patients with documented SGCE-M-D.

Main Outcome Measures: Myoclonus and dystonia scores at follow-up.

Results: The median myoclonus score decreased from 76 before surgery (range, 38-116) to 10 at 6 to 9 months after surgery (range, 6-31). The median dystonia score decreased from 30.0 before surgery (range, 18.5-53.0) to 4.5 after surgery (range, 3.5-16.0). Disability was also improved and symptoms remained stable between the postoperative evaluations. No adverse effects occurred.

Conclusions: Bilateral deep brain stimulation of the internal pallidum is safe and highly effective in this homogeneous population of patients with SGCE-M-D. This therapeutic option should therefore be considered for patients with severe, drug-resistant forms of the disorder.

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INHERITED MYOCLONUS-DYSTONIA (M-D) is a rare movement disorder of variable severity. Myoclonus is usually the main and most disabling feature. Although genetically heterogeneous, most inherited forms of the disease are caused by mutation of the ϵ -sarcoglycan (SGCE) gene



Video available online at www.archneurolog.com

(OMIM #159900).^{1,2} In a subset of patients with M-D, severe, disabling, abnormal movements are poorly responsive to drugs and have a major effect on social interaction and daily life activities.² Deep brain stimulation (DBS) of the internal pallidum (GPi) can be beneficial in medically intractable primary torsion dystonia,^{3,4} and this procedure has also been tried in isolated cases of M-D, as reviewed in 2

recent reports.^{5,6} Six patients with genetically proved SGCE-M-D received bilateral DBS, targeting the GPi in 5 cases⁵⁻⁸ and the ventral intermediate median nucleus of the thalamus in 1 case⁹ according to previous reports. Overall, myoclonus and dystonia improved by 60% to 90%. Four other patients with genetically undocumented M-D also experienced a fair improvement after thalamic (n=2) or pallidal (n=2) neurostimulation. However, the clinical evaluation was blinded in only 2 of these patients.^{5,9} A recent report of concomitant thalamic and pallidal DBS in a patient with SGCE-M-D suggested that the GPi might be the optimal target.¹⁰ Based on the improvement of myoclonus, tremor, and dystonia in patients with severe primary torsion dystonia included in a previous study by our team,⁴ we conducted a pilot study of the effect of bilateral GPi DBS on motor impairment and functional disability

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Table 1. Characteristics of the Patients

Patient No./ Sex ^a	Age at Onset/ Surgery, y	SGCE Gene Abnormality	Pharmacological Treatments	
			Preoperative	12-mo Postoperative
1/F	6/71	c304C>T p.Arg102X	None	None
2/M ^b	17/36	mUDP7	Zonisamide, 150 mg/d	Botulinum toxin (neck)
3/M	12/30	c734-737delAATT p.Gln245ArgfsX10	Zonisamide, dosage unknown	None
4/F	19/44	c856C>T p.Gln286X	Clonazepam, 2 mg/d; piracetam, 2400 mg/d	Clonazepam, 2 mg/d
5/F	19/42	c856C>T p.Gln286X	Levetiracetam, 1000 mg/d; valproate sodium, 1500 mg/d; piracetam, 2400 mg/d; clonazepam 2 mg/d	Clonazepam, 2 mg/d; levetiracetam, 500 mg/d

Abbreviation: SGCE, ε-sarcoglycan.

^aAlcohol improved myoclonus in all patients.

^bMyoclonus-dystonia was caused by maternal uniparental disomy of chromosome 7 (mUPD7), leading to SGCE deficiency due to maternal imprinting.¹

in patients with M-D due to mutations in the SGCE gene starting in 2003. Herein we report results in 5 consecutive patients with SGCE-M-D who were treated in our center with bilateral GPi DBS and underwent evaluation using blinded and standardized assessments.

METHODS

PATIENTS

With their written informed consent, 5 consecutive patients with severe and refractory SGCE-M-D (**Table 1**) were treated with bilateral GPi DBS between January 1, 2003, and December 31, 2008. Their median age at the time of surgery was 42 (range, 30-71) years. Pharmacological treatments, including the highest-tolerated doses of anticholinergics, antiepileptic drugs (such as levetiracetam and valproate sodium), clonazepam, and levodopa, had been poorly effective. Cognitive function and findings on magnetic resonance imaging of the brain were normal.

STUDY DESIGN AND EVALUATIONS

Dystonia severity was assessed by the movement subscore (range, 0-120) of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS).¹¹ Myoclonus was assessed using the sum of the rest and action subscores (range, 0-288) of the Unified Myoclonus Rating Scale (UMRS).¹² We evaluated the functional impairment using the disability subscore of the BFMRS. The patients were videotaped during a standardized protocol¹³ preoperatively and 6 to 9 months postoperatively during continuous neurostimulation and while receiving their usual medication. Patient identities were removed from the videotapes that were scored off-line in random order by a single neurologist (J.A.-Z.) blinded to the stimulation conditions. The second evaluation was performed 15 to 18 months postoperatively, during routine follow-up. The primary end point was the improvement in the motor scores after 6 to 9 months of continuous GPi DBS. Secondary end points were the improvement at 15 to 18 months and the effect on disability. We systematically checked for adverse events related to the surgical procedure or to stimulation.

SURGERY AND STIMULATION SETTINGS ADJUSTMENT

The target of DBS was the posteroventral part of the GPi. Surgery was performed as previously described.¹³ Briefly, the pro-

cedure was based on frame stereotaxy and magnetic resonance imaging-guided targeting. The posteroventrolateral portion of the GPi was identified using visible anatomical landmarks on the stereotaxic preoperative magnetic resonance image. The targeting was refined using intraoperative microelectrode recordings that allowed precise mapping of the GPi. At the end of the surgical procedure, an electrode with 4 contacts (DBS-3389; Medtronic, Inc, Minneapolis, Minnesota) was implanted at the chosen target. Pulse generators (a single Kinetra or 2 Soletra generators; Medtronic, Inc) were implanted in the subclavicular region 3 days later with the patient under general anesthesia.

In the immediate postoperative period, the threshold for unwanted effects (eg, flashes of light, muscle contractions, or dysarthria) was determined for each electrode contact in monopolar mode by using a frequency of 130 Hz and a pulse width of 60 microseconds. The long-term therapeutic contact was selected as the most ventral with the highest threshold for unwanted effects. The improvement of myoclonus sometimes observed during short-term testing was also used as a clue to select the best contact. The amplitude was initially set at 25% to 30% below the threshold for adverse effects and progressively increased during the first 3 months to achieve optimal efficacy without adverse effects.

The anatomical location of the leads and contacts was determined with the researcher blinded to the results of neurostimulation by using a 3-dimensional atlas of the basal ganglia.¹³

STATISTICAL ANALYSIS

Given the small number of patients, the results were analyzed using nonparametric statistics (Friedman test followed by the Wilcoxon signed rank test for matched pairs for post hoc comparisons). We compared the preoperative BFMRS movement subscore and the preoperative UMRS rest and action subscores with values obtained 6 to 9 months after surgery. The analysis also included the comparison between the preoperative BFMRS movement subscores and the preoperative UMRS rest and action subscore with values obtained 15 to 18 months after surgery. Finally, we compared the preoperative BFMRS disability subscores with the values obtained after 6 to 9 months and 15 to 18 months of continuous stimulation. $P < .05$ was considered to indicate statistical significance.

RESULTS

Bilateral GPi DBS improved M-D. With blinded assessment on standardized videotapes, the median BFMRS movement subscore decreased from 30.0 (range, 18.5-53.0) preoperatively to 4.5 (range, 3.5-16.0) 6 to 9 months

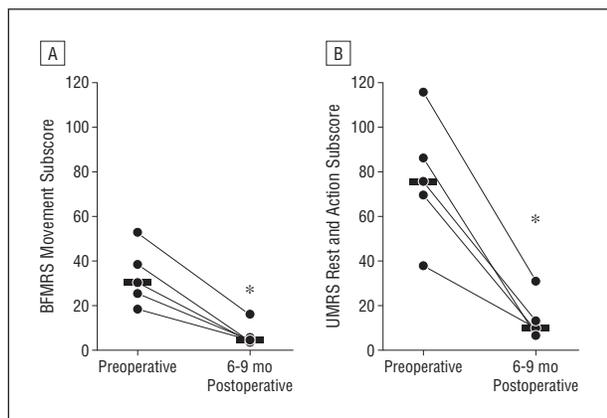


Figure 1. Individual dystonia and myoclonus scores preoperatively and 6 to 9 months (blinded assessment) postoperatively. Overview of changes in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS) movement subscore (A) and in the rest and action subscores of the Unified Myoclonus Rating Scale (UMRS) (B) between baseline and 6 to 9 months after surgery in each patient. Median values are indicated by the horizontal black bars. * $P < .05$.

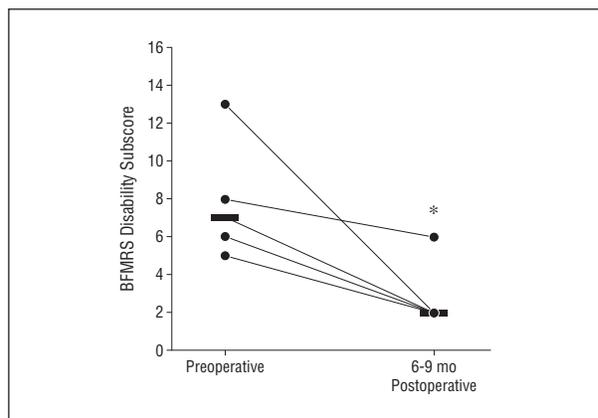


Figure 2. Individual disability scores preoperatively and 6 to 9 months (blinded assessment) postoperatively. Overview of changes in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS) disability subscore between baseline and 6 to 9 months after surgery in each patient. Median values are indicated by the horizontal black bars. * $P < .05$.

Table 2. Effect of Bilateral GPI Stimulation on Dystonia, Myoclonus, and Disability

Patient No.	BFMRS Movement Subscore ^a				UMRS, Rest and Action Subscore ^b				BFMRS, Disability Subscore ^c		
	Preop	Postop			Preop	Postop			Preop	Postop	
		6-9 mo	12-15 mo	Improvement at 6-9 mo, %		6-9 mo	15-18 mo	Improvement at 6-9 mo, %		6-9 mo	15-18 mo
1	53.0	16.0	16.5	70	116	31	36	73	8	6	4
2	18.5	5.5	6.0	70	76	13	20	83	6	2	2
3	30.0	4.5	5.0	85	38	10	8	74	5	2	2
4	25.5	3.5	2.5	86	70	8	6	89	6	2	2
5	38.5	3.5	2.5	91	86	6	8	93	13	2	2

Abbreviations: BFMRS, Burke-Fahn-Marsden Dystonia Rating Scale; GPI, internal globus pallidus; postop, postoperative; preop, preoperative; UMRS, Unified Myoclonus Rating Scale.

^aIndicates the sum of individual scores for each body region and represents the severity of motor disability related to dystonia (range, 0-120; a higher score indicates more severe dystonia).

^bIndicates the sum of individual scores for each body region that reflect the frequency and amplitude of myoclonus at rest and during specific actions (range, 0-288; a higher score indicates more severe myoclonus).

^cBased on activities of daily living. The total score (range, 0-30; a higher score indicates poorer autonomy in activities of daily living) is the sum of individual scores for 7 activities, namely, speech, handwriting, degree of dependency for hygiene, dressing, feeding, swallowing, and walking.

postoperatively ($P = .04$, Friedman test; $P = .03$, Wilcoxon signed rank test for matched pairs). The median UMRS rest and action subscores also decreased significantly from 76 (range, 38-116) to 10 (range, 6-31) ($P = .04$, Friedman test; $P = .03$, Wilcoxon signed rank test for matched pairs). Overall, the median improvement was 85% (range, 70%-91%) for dystonia and 83% (range, 73%-93%) for myoclonus (**Figure 1**, **Table 2**, and the Video [available at <http://www.archneuro.com>]). The median BFMRS disability subscore also improved significantly from 6 (range, 5-13) at baseline to 2 (range, 2-6) after 6 to 9 months of continuous stimulation ($P = .02$, Friedman test; $P = .03$, Wilcoxon signed rank test for matched pairs) (**Figure 2** and **Table 2**). Compared with the assessment at 6 to 9 months, the BFMRS dystonia and disability subscores and the UMRS rest and action subscores remained stable at 15 to 18 months in an open evaluation ($P = .97$ for dystonia and $P > .99$ for disability, Wilcoxon signed rank test for matched pairs) (**Table 2**). Monopolar settings with a frequency of 130 Hz and pulse width of 60 microseconds were used for

all patients. Voltage ranged from 2.0 to 4.7 V for the right GPI and from 1.6 to 3.7 V for the left GPI (**Table 3**). Except for patient 2, who required additional current intensity adjustments, the stimulation settings did not need to be modified after the first month. After 15 to 18 months, 3 patients were free of drug therapy, 2 were receiving low doses of benzodiazepines, and 1 was receiving botulinum toxin injections for mild cervical dystonia (**Table 1**).

No hardware- or stimulation-related adverse events occurred during surgery or during the 15 to 18 months of follow-up.

Seven of the 10 therapeutic contacts were located within the sensory-motor GPI, whereas 3 contacts (2 in the right and 1 in the left GPI) were located tangentially to the GPI in the internal medullar lamina (**Table 3** and **Figure 3**).

COMMENT

Bilateral GPI DBS was successful in all 5 consecutive patients with SGCE-M-D enrolled in this pilot study. Over-

Table 3. Stimulation Settings and Localization of Therapeutic Contacts

Patient No.	Pulse Width, μ s/Frequency, Hz/Amplitude, V/Active Contact ^a		Therapeutic Contact	
	Right Hemisphere	Left Hemisphere	Right	Left
1	60/130/4.7/1	60/130/3.7/1	IML	GPI
2	60/130/3.3/1	60/130/3.2/1	GPI	GPI
3	60/130/2.0/2	60/130/1.6/2	GPI	GPI
4	60/130/3.3/1	60/130/2.9/1	IML	GPI
5	60/130/3.4/1	60/130/3.5/1	GPI	IML

Abbreviations: GPI, internal globus pallidus; IML, internal medullar lamina.

^aIndicates the active contact among the 4 possible contacts for each lead (by convention, contact 0 is the ventral-most and contact 3 is the dorsal-most contact).

all, the median improvement was similar for myoclonus and dystonia (83% and 85%, respectively) and always exceeded 70%. This motor benefit was associated with a marked functional improvement because the BFMRS disability subscore fell by a median of 67%. To our knowledge, this is the largest published report of bilateral GPI DBS in a homogeneous population of patients with *SGCE*-M-D. All patients with *SGCE*-M-D eligible for DBS from 2003 to 2008 were enrolled in the study and underwent prospective assessment by means of blinded video-based evaluation.

The benefits were similar in the 5 patients. Even patient 1, who was 71 years old at the time of surgery and had been ill for 65 years, experienced a 73% improvement for myoclonus and 70% improvement for dystonia, indicating that GPI DBS can remain highly effective in elderly patients with a long history of disease. This does not appear to be the case in patients with primary torsion dystonia, possibly because they are more prone to musculoskeletal abnormalities than are patients with M-D, in whom the dystonia is often less pronounced than the myoclonus. This large time window for surgery is important. Indeed, patients with *SGCE*-M-D should not undergo the operation too early in adulthood owing to the possibility of waxing and waning symptoms or spontaneous improvement during the first 2 decades of life.²

We are aware that our design did not include a sham stimulation period and that the patients were not blinded to the stimulation condition. We therefore adopted blinded evaluation of standardized videotapes, in random order, by an independent neurologist who was unaware of the patients' stimulation status. This approach has previously been used in only 2 recent cases.^{5,9} It is unlikely that the benefit experienced by our patients was related to the placebo effect because the improvement was major and long-lasting. In addition, the placebo effect was minor in controlled studies of GPI stimulation for primary dystonia.³ Another limitation was the lack of specific measurement of the quality of life. However, our results suggest that the spectacular reduction of myoclonus and dystonia in all the patients was translated in terms of disability (as assessed by the disability subscore of the BFMRS). Because the motor benefit of GPI DBS was not hampered by adverse effects, it is probable that the quality of life was improved as subjectively reported by all the patients. Overall, our results in this homogeneous group of patients with *SGCE*-M-D are consistent with those obtained in the few

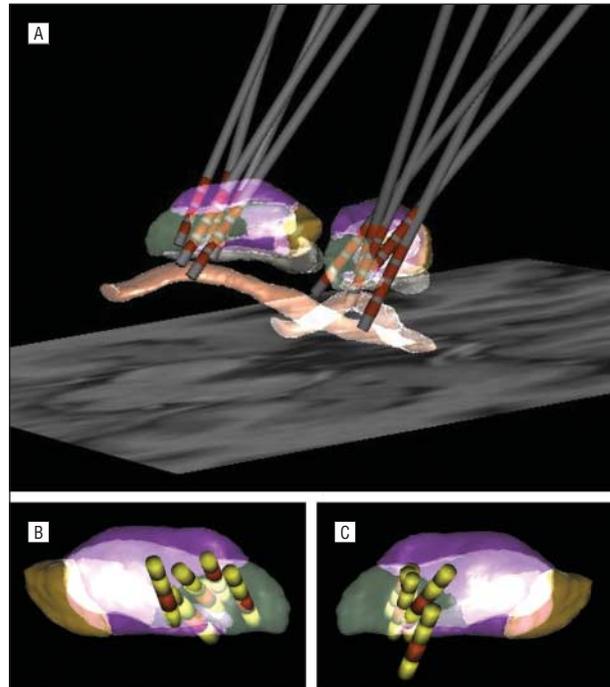


Figure 3. Location of therapeutic contacts. Right posterolateral 3-dimensional view of the right and left internal pallidum (GPI) superimposed on a transversal magnetic resonance imaging section at the level of the mesencephalon (A), illustrating the location of all stimulation leads (DBS 3389; Medtronic, Inc, Minneapolis, Minnesota) in the 5 patients. The contact locations were reconstructed using a 3-dimensional atlas of the basal ganglia.¹³ The optic tract is represented in brown. Lateral 3-dimensional view of the right (B) and left (C) GPI displaying the 4 contacts for each lead. Active contacts are represented in red. Sensory-motor, associative, and limbic territories of the GPI are shown in green, pink, and yellow, respectively.

similar patients described in the literature, some of whom did not have documented mutations of the *SGCE* gene. In these latter reports,³⁻⁸ the myoclonus score (assessed with the UMRS) fell by 78% to 94% and the BFMRS movement subscore fell by 59% to 90% after GPI DBS; these improvements were associated with a marked functional benefit. Other case reports^{6,9,10} describe stimulation of the ventral intermediate median nucleus of the thalamus, but this approach mainly improved the myoclonus rather than the dystonia.

None of our patients experienced any adverse effects directly related to the surgery or to stimulation, such as dysarthria. This may be explained primarily by the absence of baseline speech dystonia in M-D. In addition,

because of the strong efficacy of GPi DBS in all the patients with pulse widths as low as 60 microseconds, we did not need to use higher values as reported in previous studies,^{3,4} leading to less spread of the current to structures adjacent to the GPi, such as the corticospinal tract.

In contrast to the more variable and unpredictable outcomes reported in primary dystonia,^{3,13} our findings support the safety of GPi DBS for SGCE–M-D and the consistency of the motor improvement. Together with previous reports,^{5–8} these findings suggest that GPi DBS should be offered to patients whose condition is refractory to medical treatment.¹⁰ Further studies including sham stimulation are required to confirm these results and to address specific questions, such as the outcomes on quality of life and psychiatric comorbidity of SGCE–M-D. The place of GPi DBS in patients with M-D who do not have genetic disorders also remains to be determined.

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