

## STAGED DEEP BRAIN STIMULATION FOR REFRACTORY CRANIOFACIAL DYSTONIA WITH BLEPHAROSPASM: CASE REPORT AND PHYSIOLOGY

### Kelly D. Foote, M.D.

Departments of Neurosurgery and Neurology, University of Florida McKnight Brain Institute, Movement Disorders Center, Gainesville, Florida

### Justin C. Sanchez, Ph.D.

Departments of Pediatrics, Division of Neurology, University of Florida McKnight Brain Institute, Movement Disorders Center, Gainesville, Florida

### Michael S. Okun, M.D.

Departments of Neurosurgery and Neurology, University of Florida McKnight Brain Institute, Movement Disorders Center, Gainesville, Florida

#### Reprint requests:

Michael S. Okun, M.D., Movement Disorders Center, Departments of Neurology and Neurosurgery, University of Florida, PO Box 100236, Gainesville, FL 32610. Email: okun@neurology.ufl.edu

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**OBJECTIVE AND IMPORTANCE:** We report the intraoperative results, subsequent course, and 1-year follow-up evaluation of a patient with medication-refractory craniofacial dystonia for whom we planned bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) implantation but delayed the left GPi DBS implantation because of robust intraoperative effects of right GPi DBS.

**CLINICAL PRESENTATION:** A 47-year-old patient had a 5-year history of progressively severe, bilateral craniofacial dystonia with blepharospasm (Meige's syndrome) that was refractory to medications and to botulinum toxin (A and B) injections. Blepharospasm interfered with his ability to perform his duties as a Special Forces soldier and ended his military career.

**INTERVENTION:** Under stereotactic guidance (magnetic resonance imaging and computed tomographic image fusion, Cosman-Roberts-Wells frame, and University of Florida surgical navigation software) and with detailed microelectrode mapping (four microelectrode passes), a DBS electrode was implanted in the right posteroventral GPi. Microelectrode recordings were taken to document electrophysiological activity of neurons in the region, and intraoperative macrostimulation was performed. The patient was followed up for 6 months with right unilateral GPi DBS, and later a left GPi DBS electrode was placed.

**CONCLUSION:** Although DBS for primary generalized dystonia is commonly performed by simultaneously implanting bilateral GPi electrodes, it may be reasonable in cases of refractory blepharospasm and/or craniofacial dystonia to use a staged procedure for implantation in selected patients. Additionally, the physiology, especially that encountered in the striatum, may help to elucidate the pathophysiological basis for refractory blepharospasm and Meige's syndrome. More cases will be needed to determine the significance of the results reported in this article.

**KEY WORDS:** Blepharospasm, Craniofacial, Deep brain stimulation, Dystonia, Meige's syndrome

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Medication- and botulinum toxin-refractory blepharospasm and craniofacial dystonia present significant therapeutic challenges to the treating physician. Encouraged by initial positive reports by Capelle et al. (3), Vercueil et al. (11), and Muta et al. (10), we planned bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) implantation but delayed the left GPi DBS implantation because of robust intraoperative effects of right GPi DBS. We report the intraoperative results, subsequent course, and 1-year follow-up evaluation of this patient.

### CASE REPORT

A 47-year-old man had a 5-year history of progressively severe, bilateral craniofacial dystonia with blepharospasm (Meige's syndrome) that was refractory to medications and to botulinum toxin (A and B) injections (*Fig. 1*). Blepharospasm interfered with his ability to perform his duties as a Special Forces soldier and ended his military career. Worsening blepharospasm had since rendered him unable to drive or to read. He was not taking any medications at the time of sur-



**FIGURE 1.** Photographs demonstrating the intraoperative and postoperative effects of right GPi DBS. A, intraoperative photograph obtained before DBS implantation; B, intraoperative photograph during right unilateral DBS with the device on; C, postoperative photograph with the right GPi DBS implanted but off; and D, postoperative photograph, device on.

gery, but botulinum toxin serotypes A and B as well as maximal doses (titrated to side effect) of trihexyphenidyl, baclofen, lorazepam, diazepam, olanzapine, and quetiapine had previously failed. He had no family history of dystonia and no significant exposures to toxins. He did not drink or smoke, and his vital signs and general physical examination results were unremarkable. His neurological examination results were normal with the exception of blepharospasm (with associated photophobia) so severe that it rendered him functionally blind. He also had mild contractions of the platysma with facial grimacing (craniofacial dystonia). He did not have an associated cervical dystonia, tremor, writer's cramp, or geste antagoniste.

Under stereotactic guidance (magnetic resonance imaging and computed tomographic image fusion, Cosman-Roberts-Wells frame, and University of Florida surgical navigation software) and with detailed microelectrode mapping (Axon microelectrode recording system; Axon Instruments, Foster City, CA; four microelectrode passes), a DBS electrode was implanted in the right posteroventral GPi. Microelectrode recordings were taken to localize the sensorimotor region of the pallidum electrophysiologically, and intraoperative macrostimulation was performed. The patient was followed up for 6 months with right unilateral GPi DBS. He was then given a left GPi DBS implant (same procedure as above), and the clinical results of stimulation were recorded on videotape and assessed by administration of the Unified Dystonia Rating Scale (4).

Intraoperative patient-blinded macrostimulation of the right GPi resulted in complete, reproducible resolution of bilateral blepharospasm and craniofacial dystonia (bipolar; 1– or 2– cathodal; 3+ anodal; pulse width, 90; rate, 135–185 Hz; 4–8 V). With the patient blinded to the state of the device,

stimulation resulted in complete resolution of symptoms, and the symptoms returned each time the device was turned off.

Because right-sided GPi stimulation had resulted in complete resolution of symptoms, the planned left GPi DBS implantation was canceled. Although the 100% symptom resolution observed intraoperatively was not reproduced with chronic stimulation, the patient did experience a 40 to 50% reduction of symptoms during the 6 months of follow-up with unilateral right GPi DBS (Table 1). This was a stable reduction in symptomatology, and it matched the global impression of the patient, who subjectively felt “40 to 50% better” and reported that he had regained the ability to read and had returned to school.

After a 6-month follow-up visit, he was offered and opted to proceed with implantation of a left GPi DBS. There was complete resolution of symptoms with left GPi DBS during surgery; however, it should be noted that at baseline for that procedure (after chronic right GPi DBS), the patient had some lasting benefit noted in the “off” condition. Six months later (1 year from the initial right GPi DBS implantation), he reported a “75% improvement” in all symptoms. He reported only a slight increase in blink rate and occasional jaw pulling, especially during times of stress. Clinical examination revealed only a minimally notable increase in blinking rate and no visible craniofacial dystonia (Table 1).

Postoperative imaging confirmed implantation of both electrodes within the posteroventral GPi (right lead: 20 mm lateral, 1.3 mm anterior to the midcommissural point, and 5 mm below the anterior commissure-posterior commissure plane; left lead: 21 mm lateral, 0.6 mm anterior to the midcommissural point, and 6.8 mm below the anterior commissure-posterior commissure plane). The DBS electrodes were confirmed not to have moved from their intended targets by postoperative computed tomographic-magnetic resonance imaging fusion and comparison with detailed microelectrode recording maps. Chronic DBS parameters remained unchanged for the last 3 months of follow-up (right DBS monopolar 1– (cathodal), case positive (anodal), 2.5 V, 450 ms, 185 Hz; left DBS bipolar 1– (cathodal), 3+ (anodal), 3.3 V, 450 ms, 185 Hz). The contacts used for chronic DBS were located in the GPi region (confirmed by microelectrode recording).

Microelectrode recording revealed useful although limited qualitative and quantitative information. During the first procedure, it was observed that the firing rates particularly of the striatum were abnormally fast. Because the procedure was performed for clinical and not research purposes, limited numbers of cells could be recorded; however, spike sorting using the Spike 2 software package (Cambridge Electronic Design, Ltd., Cambridge, England) was performed. Recordings in the right striatum showed elevated mean firing rates of 41, 74, and 94 spikes/s on three cells. Qualitatively, the striatal and GPi cells were markedly abnormal compared with previous dystonia cases performed by the same surgical team and by other researchers (7, 13). Recordings in the globus pallidus externus revealed firing rates of 49 and 74 spikes/s on two cells, and the GPi recording showed a rate of 94 spikes/s on a

TABLE 1. Results of deep brain stimulation according to Unified Dystonia Rating Scale<sup>a</sup>

Time of recording	DBS condition		UDRS score						
	Left DBS	Right DBS	Eyes, severity	Eyes, duration	Lower face, severity	Lower face, duration	Eyes, total	Lower face, total	Total
Baseline	Baseline	Baseline	3	4	3	3	7	6	13
Preoperative	Preop	Preop	2	3	2	3	5	5	10
Operating room	NA	On	0	0	0	0	0	0	0
1 mo (right)	Off	On	3	3	2	3	6	5	11
3 mo (right)	Off	On	2	3	1	3	5	4	9
5 mo (right)	Off	On	2	3	1	3	5	4	9
6 mo (right)	Off	On	2	1	2	1	3	3	6
1 mo (left)	On	Off	2	1	2	1	3	3	6
1 mo (left)	On	On	1	1	0	0	2	0	2
6 mo (left)	On	On	1	1	0	0	0	0	2
15 mo (last)	On	On	2	1	1	0	3	1	4
15 mo (last)	Off	On	3	3	2	2	6	4	10
15 mo (last)	On	Off	3	3	2	2	6	4	10

<sup>a</sup> DBS, deep brain stimulation; UDRS, Unified Dystonia Rating Scale; Preop, preoperative; NA, not applicable; Baseline, UDRS score at the first clinic visit; Preoperative, UDRS score just before the right globus pallidus internus DBS; Operating room, UDRS with the right globus pallidus internus DBS “on”; month number, follow-up time; last, last clinical follow-up with bilateral globus pallidus internus DBS.

single cell. Recording in the left striatum revealed a firing rate of 5 spikes/s in one cell. The globus pallidus externus recording showed 42 spikes/s and 38 spikes/s on two cells, and the GPi recording showed 109 spikes/s on a single cell (Fig. 2).

In Figure 3, normal and abnormal neuronal activity (as shown by the raw waveforms in Fig. 2) was assessed quantitatively and qualitatively using distributions of interspike intervals. The left striatal cell in Figure 2 had a highly irregular interspike firing distribution, with a mean and standard deviation of  $220 \pm 275$  milliseconds. Comparatively, the right striatal cell displayed a tonic firing pattern. Finally, both the left and right GPi produced burst-like skewed firing patterns. One theory for elucidating the abnormal firing patterns and elevated firing rates is that the striatum is overactive in dystonia and this overactivity leads to abnormalities in downstream basal ganglia structures. The striatum has been proposed to be overactive in dystonia in several models (12). Additional case studies and more recordings of craniofacial dystonia are needed to confirm these data.

DISCUSSION

Although bilateral GPi DBS has been demonstrated to be an effective treatment for primary generalized dystonia (1, 2, 9, 14), the role of DBS in the treatment of refractory blepharo-

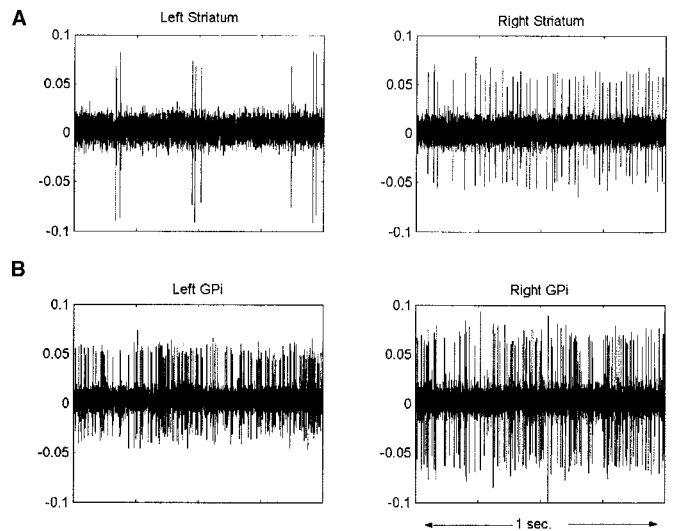
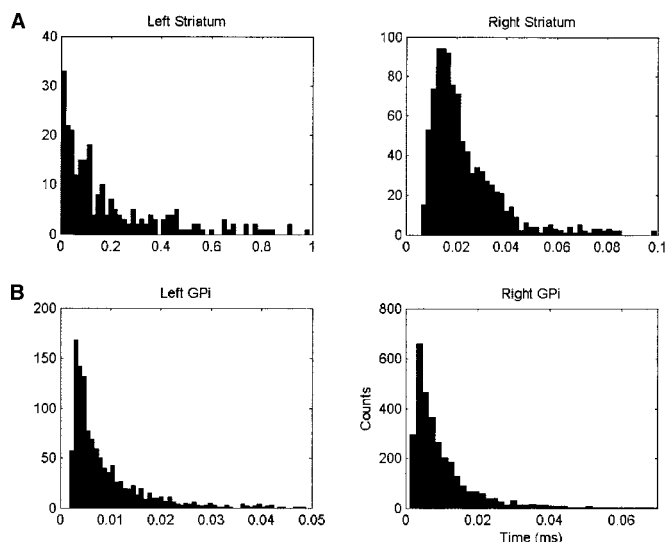


FIGURE 2. Recordings demonstrating striatal and GPi intraoperative neurophysiology. A, 1-second samples of recordings from the striatum show an increased firing rate of the right striatum. B, 1-second samples of recordings from the GPi on both the left and right also show an increased firing rate.



**FIGURE 3.** Striatal and GPi interspike interval histograms. Three cellular firing patterns were observed from interspike interval histograms: irregular bursting (A, left striatum); tonic (A, right striatum); and burst-like skewed (B, left and right GPi).

spasm and/or craniofacial dystonia is less well established. This case illustrates a successful application of DBS for such a patient.

Although DBS for primary generalized dystonia is commonly performed by simultaneously implanting bilateral GPi electrodes (1, 2, 4, 6), it may be reasonable in cases of refractory blepharospasm and/or craniofacial dystonia to implant selected patients in a staged procedure. Although we anticipate that most patients will require bilateral DBS, if patients experience a satisfactory clinical benefit with unilateral implantation, then a second procedure may not be necessary. Although our patient experienced complete resolution of symptoms during surgery, at the 6-month follow-up, the dramatic and complete benefit had waned significantly. After implantation of the second DBS device, there was sustained improvement in blepharospasm and resolution of the other features of craniofacial dystonia. The reasons for the decline remain unknown, but we suspect that long-term improvement of midline and axial symptoms will require bilateral intervention, although in this case, unilateral implantation positively influenced the dystonia. It should be noted that the left lead was placed 1 mm more lateral than the right lead, making lead location a potentially important difference that could have been a factor in the outcome. Additionally, physiological studies have associated blepharospasm with disinhibition of the R2 trigeminal component of the blink reflex. On the basis of these findings, abnormalities of sensory gating in dystonia have been proposed to play a role in blepharospasm, which may provide some explanation for the effects of unilateral and then bilateral DBS seen in this case (5, 6). More study will be needed to replicate these findings, to determine the significance of the laterality of the placement of the DBS electrodes

(right versus left), and to determine whether unilateral implantation may have beneficial physiological effects on bilateral basal ganglia systems.

There have been only sporadic case reports of the beneficial effects of DBS for blepharospasm and craniofacial dystonia (1, 3, 10). Our findings are similar to those reported by Capelle et al. (3). However, it is difficult to compare our observations because the procedure was not performed in a staged fashion in the study by Capelle et al. More cases of refractory blepharospasm and craniofacial dystonia need to be studied carefully to validate this application of DBS and to determine how generalizable these results may be. Additionally, staging of DBS implantation may provide insight into potential differential effects of right- versus left-sided GPi stimulation.

The neurophysiology seen in this case, although limited, may provide some insights into the pathophysiology of dystonia and specifically blepharospasm. The marked overactivity of the striatum, particularly on the right (initial) side was striking. This striatal hyperactivity may fit with proposed models of dystonia. The reason that this finding was not seen on the subsequent left side, although unknown, may be related to bilateral effects of chronic stimulation. Similarly, the reasons for the overactivity of the GPi remain unknown. Definitive conclusions should not be drawn from these data because too few cells were recorded during the procedure. It will be important for future groups implanting GPi DBS for refractory blepharospasm to document neurophysiological findings, which will help to confirm or refute the findings seen in our patient. Confirmation of these findings may enlighten us on disease mechanisms.

In this patient, right unilateral DBS had robust intraoperative effects on bilateral blepharospasm and craniofacial dystonia and durable, although diminished, effects at the 6-month follow-up. The staged addition of a left GPi DBS further improved the blepharospasm and resulted in resolution of the other features of craniofacial dystonia. It is unknown why the improvement in dystonia occurred immediately and was not delayed, as has been seen in other reports (1, 3, 8–11, 14). We conclude that GPi DBS for craniofacial dystonia may be beneficial and that staged implantation may be a reasonable approach in these cases.

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## COMMENTS

**D**eep brain stimulation (DBS) of the globus pallidus internus (GPi) is gaining favor for treatment of severe dystonia, with generalized dystonia patients having the best benefit. The favorable results in this population have led to trials of pallidal DBS for treatment of focal dystonia. Although usually less disabling and less medically refractory than generalized dystonia, focal dystonia can sometimes be both.

Idiopathic, adult-onset, focal dystonia, usually affecting cranial or cervical myotomes, may be classed as, for example, blepharospasm, Meige's syndrome, torticollis, or any one of a variety of task-specific focal dystonias, such as writer's cramp or musician's dystonia, depending on the muscle groups involved and the activities with which it interferes. These disorders affect a large number of patients, and the role of GPi DBS in helping these patients is of growing interest.

The authors add to the growing body of reports demonstrating benefits of GPi DBS for focal dystonia. They describe successful treatment of a patient with disabling and medically and botulinum toxin A and B-intractable blepharospasm as part of a more generalized cranial dystonia. The authors found that unilateral (right-sided) GPi stimulation abolished bilateral symptoms intraoperatively and offered 40 to 50% symptom reduction with chronic stimulation. Addition of left GPi chronic stimulation improved this further to 75%. Previous clinical studies have not addressed the effectiveness of unilateral pallidal stimulation for cranial dystonia; however, physiological studies have associated blepharospasm with disinhibition of the R2 (bilateral) trigemino-facial component of the blink reflex (3), which perhaps provides an explanation for this observation.

The authors also report an immediate benefit of blinded stimulation intraoperatively, which was more dramatic than with chronic stimulation. This is in contrast to the usual time

course (days to months) with which pallidal stimulation improves dystonia and suggests that cranial dystonia (or perhaps specifically blepharospasm) differs from other kinds of dystonia in this respect. However, Bereznai et al. (1) reported a delayed (3 mo) benefit in their Patient 3 with Meige's syndrome, blepharospasm, and torticollis, whereas Capelle et al. (2) reported improvement "within days." These differences remain to be explained. What seems clear, however, is that even if unilateral pallidal stimulation is 100% effective intraoperatively for cranial dystonia, bilateral stimulation may ultimately be required.

The authors used the most commonly applied therapeutic use of high-frequency stimulation at 185 Hz. This differs from Muta et al. (4), who saw maximal benefit at 60 Hz in a patient undergoing bilateral GPi DBS for cranial dystonia; this difference may be of significance, but no comparison of the effects of varying frequencies was reported.

Overall, this article provides further support for the expanding role of GPi DBS for treatment of focal dystonia. However, it should be noted that dystonia involves a heterogeneous group of patients and clinical manifestations. There is a need for further studies focusing on a larger number of patients with specific dystonias. In addition, the use of unilateral versus bilateral DBS and the variability of the time course for clinical improvements warrant further investigation.

**Scott Cooper**  
**Ali R. Rezaei**  
*Cleveland, Ohio*

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**E**ntirely too little is known about craniofacial dystonia with or without blepharospasm. Foote et al. present an interesting case report of treatment of Meige's syndrome. There are only a few reports about bilateral DBS treatment for this condition. The authors present information on a staged GPi DBS implantation in which the initial effectiveness of the first GPi DBS intraoperatively delayed the second-side implantation. However, it is clear that the second side was essential. Although a number of interesting aspects are learned by staging the procedure, I think that inevitably, with this type of central axial symptomatology, bilateral stimulation is necessary.

Our anecdotal experience is quite limited, but we have had positive experiences with either pallidotomy or DBS (RAE

Bakay and JL Vitek, unpublished data; RAE Bakay and L Verhagen, unpublished data). In general, hemidystonia or regional dystonia that involves craniofacial dystonia as a component improves acutely with a single DBS lead contralateral to the hemidystonia or regional dystonia. Almost invariably, there is some return of blepharospasm and craniofacial dystonia symptomatology within a few months. Control of these symptoms seems to be difficult at best. Improvement has been good enough that we have not needed to place a second lead in this particular circumstance.

In generalized dystonia, bilateral placement is invariably needed. We have seen good response to a unilateral staged GPi DBS placement with very good contralateral effect and modestly good ipsilateral effect. Again, the effect on blepharospasm and craniofacial dystonia tends to fade on the ipsilateral side rather quickly after a few months. Thus, for generalized dystonia, a bilateral procedure is always needed, but staged procedures may provide interesting data that may go toward better understanding of the mechanism of the disorder. As we begin to understand the mechanism of the DBS and the positive effect of stimulation in the globus pallidus externus, this also may become an important target (1).

We have found little intraoperatively that is reliably correlated with the ultimate outcome. In some cases, good responses are observed intraoperatively, and this usually translates into very good responses postoperatively. However, in most cases, we see very little intraoperative effect, and yet very good effects are observed later with chronic DBS stimulation.

Entirely too little known is about most dystonic processes, and the most advantageous course would be for a concerted research effort to be made with a multicenter consortium-type approach funded either by the National Institutes of Health or

by private agencies. A systematic study is certainly in order, and as long as an institutional review board–approved protocol is required under the current Food and Drug Administration approval for DBS in dystonia, it would seem that this would be a logical approach. The need is there. Whether or not appropriate efforts will be made will depend on what type of support neurosurgery transitional research receives.

**Roy A.E. Bakay**  
*Chicago, Illinois*

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**T**his article reports a patient with Meige’s syndrome treated with pallidal stimulation. The authors have shown the results of a few cells recorded with microelectrodes.

The most interesting aspect of the article was the fact that in the operating room, unilateral stimulation was sufficient to reduce the patient’s symptoms. However, this has been demonstrated previously, to a certain extent. Capelle et al. (1) have shown that unilateral stimulation in Meige’s syndrome has bilateral effects, even though it predominantly improved contralateral symptoms.

**Andres M. Lozano**  
*Toronto, Ontario, Canada*

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