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Tremor and Other Hyperkinetic Movements

Articles

Brittle Dyskinesia Following STN but not GPi Deep Brain Stimulation

Ashok Sriram[1], Kelly D. Foote[1], Genko Oyama[1], Joshua Kwak[1], Pam R. Zeilman[1] & Michael S. Okun[1]*

[1] Departments of Neurology and Neurosurgery, Center for Movement Disorders and Neurorestoration, Gainesville, Florida, USA

Abstract

Background: The aim was to describe the prevalence and characteristics of difficult to manage dyskinesia associated with subthalamic nucleus (STN) deep brain stimulation (DBS). A small subset of STN DBS patients experience troublesome dyskinesia despite optimal programming and medication adjustments. This group of patients has been referred to by some practitioners as brittle STN DBS-induced dyskinesia, drawing on comparisons with brittle diabetics experiencing severe blood sugar regulation issues and on a single description by McLellan in 1982. We sought to describe, and also to investigate how often the "brittle" phenomenon occurs in a relatively large DBS practice.

Methods: An Institutional Review Board-approved patient database was reviewed, and all STN and globus pallidus internus (GPi) DBS patients who had surgery at the University of Florida from July 2002 to July 2012 were extracted for analysis.

Results: There were 179 total STN DBS patients and, of those, four STN DBS (2.2%) cases were identified as having dyskinesia that could not be managed without the induction of an "off state," or by the precipitation of a severe dyskinesia despite vigorous stimulation and medication adjustments. Of 75 GPi DBS cases reviewed, none (0%) was identified as having brittle dyskinesia. One STN DBS patient was successfully rescued by bilateral GPi DBS.

Discussion: Understanding the potential risk factors for postoperative troublesome and brittle dyskinesia may have an impact on the initial surgical target selection (STN vs. GPI) in DBS therapy. Rescue GPi DBS therapy may be a viable treatment option, though more cases will be required to verify this observation.

Keywords: Subthalamic, induced, globus pallidus, adverse event, complication, fluctuation

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*To whom correspondence should be addressed. E-mail: okun@neurology.ufl.edu

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Introduction

Dopamine-induced dyskinesia (DID) is a common complication of Parkinson's disease (PD) and also of pharmacological replacement therapy.[1–3] Typical management of DID includes changing dosages and dosage intervals.[4] The treatment may also involve alterations in multiple different dopaminergic medications.[5,6] Refractory on–off fluctuations and dyskinesia despite multiple medication adjustments commonly results in referral for consideration of deep brain stimulation (DBS).[5] Subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS have both been recently documented to be reasonable treatment approaches for addressing on–off fluctuations and for addressing treatment of intractable dyskinesia.[6,7] There are, however, a small subset of patients in whom we have observed that management utilizing STN DBS has resulted in either troublesome

dyskinesia or, alternatively, when changing the DBS setting, unacceptable "off time periods." We refer to this group of patients as "brittle" STN DBS-associated dyskinesia, drawing an analogy to a brittle diabetic whose blood sugars cannot be managed despite aggressive medical and behavioral therapy. In 1982 McLellan and Dean[8] also employed the term brittle Parkinsonism to describe a patient who alternated between severe bradykinesia and violent chorea as a result of her medication regimen. Striking the balance between medications and stimulation in this patient group may not satisfactorily address an individual brittle PD patient's disabling symptoms. We will review and discuss four such cases. One case was rescued using bilateral GPi DBS.

Methods

The IRB-approved UF-INFORM patient database was reviewed and all STN DBS patients operated at the University of Florida from July 2002 to July 2012 were included. Of 197 total cases, four patients (2%) were identified with severe and difficult to manage stimulation-induced dyskinesia. These cases could not be managed without the induction of an "off state", or alternatively by precipitating a severe dyskinetic state despite vigorous stimulation and also medication adjustments. The patients were all evaluated in person at the University of Florida site and medication and stimulation settings were aggressively optimized monthly for at least 6 months following each DBS lead implantation operation.

Of 75 total GPi cases, none was identified with the brittle dyskinesia phenomenon.

Case 1

A 48 year-old right-handed male with an 8-year history of PD presented with progressive difficulty walking. He complained of bradykinesia and this symptom was followed by an intermittent right hand resting tremor. He was initially treated with ropinirole, and then with pramipexole, but these therapies were discontinued due to medication intolerance. He was successfully initiated on a titration of carbidopa/levodopa, and he reported cessation of all disabling PD symptoms for 3 years. As his disease duration lengthened, and his dosages were increased, his dosage intervals decreased, and his medical management increased in complexity. He developed motor fluctuations, peak dose dyskinesia, and problems sleeping. His optimal medication regimen was 1–1.5 tablets of 25/100 carbidopa/levodopa administered every 3 h, along with amantadine 100 mg twice a day, and rasagiline 1 mg once a day. One 25/100 carbidopa/levodopa tablet resulted in a short-lasting benefit for less than 1 h, and 1.5 tablets of carbidopa/levodopa resulted in troublesome and disabling dyskinesia. He reported that his peak dose dyskinesia was more disabling than his off-medication state symptoms. He underwent interdisciplinary screening for consideration of DBS.

He underwent bilateral staged STN DBS with a 6-month time lapse between the implantation of each hemisphere (left then right). Following left-sided STN DBS, he experienced right upper extremity and right lower extremity dyskinesia at both the 1 and the 2 contacts on the DBS lead (Medtronic 3387, Minneapolis, MN). The 1 and 2 DBS lead contacts corresponded to his best therapeutic benefit during programming sessions. Multiple programming strategies were employed, including attempts at slow stimulation titrations, and the use of a more dorsal DBS contact site. The dyskinesia only abated when the DBS was turned off. Attempts were made to commensurately decrease carbidopa/levodopa dosage in combination with stimulation changes, but this worsened his off state, though at low medication dosages dyskinesia abated (preoperative levodopa equivalent dose was 1,000, postoperative was 720, and post-rescue GPi was 1,220). He experienced a similar clinical scenario when the right STN DBS was added. At settings that improved his freezing of gait, he had bothersome left lower extremity dyskinesia. Many other attempted settings failed to capture his gait freezing and his off symptoms.

He underwent rescue bilateral staged GPi DBS in a single operative sitting, and following programming, the dyskinesia completely abated, and he was able to maintain a smooth on medication state. His preoperative medications before rescue bilateral GPi placement were carbidopa/levodopa 25/100, half to one tablet every 3.5–4 h, and ropinirole XL 8 mg twice a day. At 4 months postoperatively, he had been completely weaned off the ropinirole XL, and he was taking carbidopa/levodopa one tablet every 3.5 h. The lead locations for the active DBS contacts are summarized in Table 1. The Unified Parkinson's Disease Rating Scale (UPDRS) pre- and postoperative scores are summarized in Table 2.

Case 2

A 73-year-old man with a 14-year history of idiopathic PD reported that his initial symptom was a right hand resting tremor. He developed bradykinesia, rigidity, and a shuffling gait. Over the course of 5 years he developed on–off fluctuations and dyskinesia. He responded to carbidopa/levodopa; however the development of motor fluctuations, dose failures, and disabling peak dose dyskinesia led to a referral for DBS therapy. Eleven years following his diagnosis he received a right STN DBS.

Postoperatively, he had dyskinesia in his left upper extremity and left lower extremity when he was stimulated at contacts 1, 2, and 3 on his DBS lead (Medtronic 3387), and with medications off. All of these DBS contact locations provided therapeutic benefits. He had the greatest benefits at contacts 1 and 2, but, as the voltages were slowly increased, he developed severe dyskinesia. Following multiple DBS programming sessions, he reported persistent and bothersome dyskinesia. Seven months after his initial left STN DBS surgery, he received a right STN DBS. Again, stimulation at contacts 1 and 2 resulted in good tremor control, but he had intolerable stimulation-induced dyskinesia in the left upper and lower extremity even with medications off. He had persistent dyskinesia even after multiple programming sessions. Attempts to decrease medication, to slowly increase his voltage, and to use more dorsal DBS contacts failed to suppress the dyskinesia. His preoperative levodopa equivalent dose was 475 and postoperative was 400. His postoperative course was complicated by dopamine dysregulation syndrome (DDS). His

Table 1. DBS Lead Locations for Active Contacts

Patient	DBS Lead	y	x	z
Case 1	Left STN	−1.30	−12.6	−4.35
	Right STN	−0.40	11.16	−0.30
	Left GPi	4.28	−20.7	−1.40
	Right GPi	7.45	23.07	−1.23
Case 2	Left STN	0.81	−12.3	−1.48
	Right STN	−0.23	13.8	−0.92
Case 3	Left STN	−1.69	−11.9	2.83
	Right STN	−0.20	11.58	1.91
Case 4	Left STN	−2.98	−12.3	−1.27
	Right STN	0.13	9.69	−3.45

DBS, Deep Brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus.
A summary of the location of the active STN DBS contact(s) with respect to mid-commissural point in antero-posterior (*y*), lateral (*x*), and axial (z) plane measured in millimeters from a postoperative computed tomography–magnetic resonance imaging fusion.

caregiver reported worsened cravings for levodopa postoperatively; however, DDS was thought to be possibly present preoperatively. He was started on valproic acid extended release 250 mg at bedtime, and he reported resolution of DDS.[10]

His optimized preoperative medications included carbidopa/levodopa/entacapone 100 mg every 3 h. His optimized postoperative medications were carbidopa/levodopa immediate release 25/250, 0.5 of a tablet every 2 h for a total of seven to eight doses, and amantadine 100 mg twice daily. His dyskinesia persisted even off medication, and when at optimized DBS settings.

Case 3

A 50-year-old right-handed Hispanic man with a 9-year history of PD was referred to our center for a DBS candidacy evaluation. Right upper extremity stiffness and slowness were the initial symptoms, and he was diagnosed with PD. Carbidopa/levodopa was the first medication attempted, and this medication resulted in significant clinical improvement in PD symptoms. Two years after his initial diagnosis, he noticed difficulty with walking, but this improved with adjustment in his carbidopa/levodopa dosage. Four years after the diagnosis, he reported having troublesome right upper and lower extremity resting tremor. Eight years into his disease, he reported a left upper extremity resting tremor. The dosage of carbidopa/levodopa was increased numerous times over many years in order to address symptom worsening, and the emergence of new PD-related symptoms. Pramipexole was tried and was discontinued due to excessive daytime somnolence, and due to sleep attacks when driving. He also reported a 5-year history of depression, and he was put on venlafaxine 75 mg XR. The dose was increased to a total of 225 mg per day. His depression resolved. He reported motor fluctuations, sudden unpredictable offs, and peak dose dyskinesia that progressively worsened over 4 years. Amantadine, 100 mg twice a day, was mildly helpful in controlling dyskinesia.

He received staged bilateral STN DBS (second implant at 6 months) starting with a left-sided implantation (Medtronic 3387). Tremor and motor fluctuations improved, but he experienced persistent dyskinesia that was unrelated to the carbidopa/levodopa dosages (occurred in the off-medication condition), and the dyskinesia abated when the DBS was switched off. Preoperative levodopa equivalent dose was 800, and postoperatively it was 1,050. The optimal stimulation settings where he derived good tremor control, also evoked severe dyskinesia. Despite discontinuation of selegiline, and also carbidopa/levodopa dose reductions, the bothersome dyskinesia persisted. Multiple programming sessions and gradual increases in programming parameters, and also the use of more dorsal DBS contacts, all resulted in bothersome dyskinesia.

Case 4

A 75-year-old Caucasian woman with a 12-year history of PD presented to our center for an evaluation. Right hand resting tremor was the initial symptom, and she later developed slowness of movements, stiffness, and decreased dexterity of her right side. Symptoms were insidious onset and progressive. Over the next few

Table 2. Preoperative and Postoperative UPDRS Motor Scores. GPi represents the UPDRS scores with the added bilateral GPi DBS leads (all four activated)

	Preoperative off-medication	Preoperative on-medication	Postoperative off-medication and on DBS	Postoperative on-medication and on DBS
Patient 1	45 (43 GPi)	31 (35 GPi)	39 (34 GPi)	25 (29 GPi)
Patient 2	52	40	44	34
Patient 3	46	15	25	14
Patient 4	40	20	N/A	N/A

DBS, Deep Brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus; UPDRS, Universal Parkinson's Disease Rating Scale.

years, she developed difficulty walking, and noticed tremor in her left hand. Pramipexole was the first medication tried, but was discontinued due to hallucinations and dyskinesia. When evaluated at our center, she was on carbidopa/levodopa 25/100 1.5 tablets every 4 h and ropinirole 1 mg three times a day. Tremors were not fully captured, and an attempt to increase the dose of carbidopa/levodopa was met with bothersome peak dose dyskinesia, orthostatic hypotension, and syncope. She was placed on fludrocortisone 0.1 mg three times a day and midodrine 10 mg three times a day for orthostatic hypotension, and her syncope resolved. She was placed on escitalopram 10 mg once a day for depression and on methylphenidate 10 mg once a day for daytime sleepiness and fatigue.

She received bilateral STN DBS (Medtronic 3387) starting with a left-sided implantation (implants staged over 6 months). Her tremors improved, but she developed bilateral stimulation-induced dyskinesia (even when off medications). DBS settings that revealed tremor benefit resulted in troublesome dyskinesia. At DBS settings where she was not experiencing stimulation dyskinesia, she could not achieve tremor control. Despite multiple device programming sessions and the use of dorsal DBS contacts, the stimulation-induced dyskinesia persisted. There were multiple unsuccessful attempts made to adjust medications. The preoperative levodopa equivalent dose was 1,200 and the postoperative dose was 1,000. The lead locations for the active DBS contacts are summarized in Table 1. The UPDRS pre- and postoperative scores are summarized in Table 2.

Discussion

An infrequent but nonetheless potential complication of STN DBS has been difficult to control stimulation-induced dyskinesia. Some DBS practitioners have clinically dubbed the phenomenon as "brittle dyskinesia," drawing a comparison to brittle diabetics. [1] The emergence of troublesome dyskinesia post-STN DBS has been challenging; however, rescue GPi DBS has proven effective in one of our cases, but was not attempted in the other three. There are several important issues worthy of discussion about the occurrence and treatment of this phenomenon.

The predictors and risk factors for the occurrence of troublesome "brittle" dyskinesia post bilateral STN DBS remain unknown. It will be important to draw on larger pooled datasets from multiple expert DBS centers to ascertain better predictor and more accurate risk factor information. Young-onset PD (without DBS) has been associated with the occurrence of "more" dyskinesia in some published studies, though this issue must be more carefully examined.[7,9] Two of the four cases in this series were below the age of 50 when they developed PD. This observation raises the possibility that young-onset of PD may play a role in the genesis of this post-STN DBS brittle dyskinesia; however, we must consider that our other two cases were elderly.[10,11] Interestingly, no cases of brittle dyskinesia were observed in our patients initially implanted with GPi DBS. Recently there was a paper from our group that examined a definition for brittle dyskinesia and risk factors.[27] In this report, the brittle response occurred more commonly in patients with a longer disease duration, longer duration of levodopa therapy, and in female patients with a low body weight. Whether these risk factors will be the same as in DBS-induced brittle dyskinesia remains unknown, and a large multicenter study would be required to answer this question.

We wondered whether patients with severe dyskinesia preoperatively, even at relatively low dopaminergic dosages, could be at risk for this phenomenon; however, our sample size was too small to ascertain this information. Prior to DBS, all of our cases were observed to tolerate carbidopa/levodopa 25/100, and all were taking medications every few hours during wakefulness. One patient had a possible preoperative dopamine dysregulation syndrome, and none had Impulse Control Disorders (ICDs). Therefore, the role of medication and of pre-morbid behavior syndromes remains unknown, but should also be investigated.

Stimulation-induced dyskinesia has been commonly reported as a side effect of STN DBS.[12] In most cases when this phenomenon occurs, it has been interpreted as a good prognostic sign, indicating that the optimal lead location has been achieved.[13] Further, the occurrence of stimulation-induced dyskinesia in the operating room setting has been referenced as a positive predictive sign by DBS practitioners, though this has never been validated.[14,15] No cases of brittle dyskinesia were reported in the available randomized DBS studies, though multiple authors from large DBS centers have communicated verbally to us that they have observed this phenomenon.[16–19] We suspect the small number of reports may be due to both a low prevalence, and also under-reporting, though it should be noted that simple uncomplicated and non-troublesome stimulation-induced dyskinesia occurs frequently with DBS therapy.[12,15]

Another possible predictor of stimulation-induced dyskinesia may be location of the DBS lead's actively utilized contact. Though stimulation of the dorsal STN and zona incerta has been reported to improve parkinsonism, stimulation within the STN itself may provoke the dyskinesia.[20,21] These observations have not been confirmed in a larger series, and may be subject to great bias. It is however possible that the current spread into the dorsally adjacent lenticularis fasciculus and zona incerta exerts an effect similar to that of pallidal stimulation, and ultimately suppresses dyskinesia.[22] This issue remains unresolved.

Fifteen percent of the PD patients who underwent unilateral subthalamotomy in the large Cuban series developed hemichorea and hemiballism postoperatively, and more than half required a subsequent pallidotomy to effectively control their symptoms.[23] All of these patients were reported to have achieved adequate motor benefits on long-term follow-up. This observation may at least partially explain why the GPi target for DBS was successful as a rescue procedure for dyskinesia suppression in our single case.

Boulet et al.[24] reported that in a hemi-parkinsonian rat model high-frequency STN DBS induced forelimb dyskinesia. These authors also reported that dyskinesia was aborted by injection of a glutamate receptor antagonist into the substantia nigra. The experiment suggests that glutamate neurotransmitter release may underpin stimulation-induced dyskinesia; however, the exact mechanisms remain unknown.

Though this paper was limited by a small sample size, the implications of this phenomenon are important as they may potentially

impact the initial surgical target site selection (STN vs. GPI) for DBS therapy. It is important to consider that every preoperative PD patient likely possesses a different dyskinesia threshold, and this threshold can be difficult to account for especially in small studies. Additionally, occasionally small strokes and hemorrhages can lead to similar findings as reported in this series; however, these phenomena were not present in our cases. Nutt and colleagues[25,26] also observed that frequently the threshold to improve PD symptoms with medications is the same or close to the threshold for dyskinesia. Our correspondence with multiple large DBS centers supports the data from our center, suggesting that this phenomenon occurs in a small handful of DBS patients, and that it seems to occur with the STN target. GPi DBS proved effective in one of our patients for suppressing dyskinesia, and therefore rescue GPi DBS maybe a viable treatment option in cases where the dyskinesia is bothersome and disabling, though more cases will be required to verify the observation. A large multicenter effort will likely be needed to better understand the brittle phenomenon and to define the most appropriate brain target for treatment. Rescue GPi DBS was only attempted on case 1 in our series. Case 2 preferred programming and medication adjustments vs. another operation. Case 3 was a poor reoperation candidate (age and frailty) and passed away from an unrelated cause. Case 4 was lost to follow-up. It remains unknown if GPi DBS should be preoperatively chosen as the target for patients with very severe and disabling dyskinesia, and when rescue GPi lead(s) should be offered.

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