Dystonic tics induced by deep brain stimulation of the posterior subthalamic area for essential tremor

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OBJECTIVE The posterior subthalamic area (PSA) is a promising target of deep brain stimulation (DBS) for medication-refractory essential tremor (ET). This case series describes a novel adverse effect manifesting as dystonic tics in patients with ET undergoing DBS of the PSA.

METHODS Six patients with ET received electrode implants for DBS of the dorsal and caudal zona incerta subregions of the PSA.

RESULTS Five of the 6 patients developed dystonic tics soon after clinical programming. These tics were of varying severity and required reduction of the electrical stimulation amplitude. This reduction resolved tic occurrence without significantly affecting ET control. Dystonic tics were not observed in 39 additional patients who underwent DBS of the same brain regions for controlling non-ET movement disorders.

CONCLUSIONS The pathophysiology of tic disorders is poorly understood and may involve the basal ganglia and related cortico-striato-thalamo-cortical circuits. This series is the first report of DBS-induced tics after stimulation of any brain target. Although the PSA has not previously been implicated in tic pathophysiology, it may be a candidate region for future studies.

Clinical trial registration no.: NCT01945567 (clinicaltrials.gov)

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THE posterior subthalamic area (PSA) is a promising alternative target in the thalamus for neurosurgeons performing deep brain stimulation (DBS) for both Parkinson's disease and essential tremor (ET).^{6,12,16,18} The structures composing the PSA include the zona incerta, posterodorsal part of the subthalamic nucleus, and pallidothalamic (fields of Forel) and cerebellothalamic (prelemniscal) fiber tracts.^{5,27}

Targeting the PSA in treatments for movement disorders has been advocated largely because of positive results of subthalamotomy performed in the early 1960s for a wide range of these disorders, including ET.⁵ Subthalamotomy provided good initial ET control; however, this good outcome was associated with poor long-term efficacy, with some studies suggesting up to a 20% ET recurrence and high morbidity and mortality rates.¹⁵ Mod-

ern surgical techniques and DBS have reduced these rates and have also improved ET control. Posterior subthalamic DBS in particular may make adverse effects such as dysarthria less problematic, improve proximal tremor control, and avoid tachyphylaxis observed with thalamic stimulation.^{4,12,16}

Targeting the PSA for DBS has been shown to be generally very safe, but several stimulation-dependent, reversible adverse effects have also been reported.^{9,10} In general, these negative effects can be categorized as affecting motor, sensory, or cerebellar function. The motor adverse effects include tonic muscle contractions of the contralateral arm and face with increased tone and have been attributed to modulation of the adjacent axons in the internal capsule. Sensory adverse effects most commonly consist of short-lived contralateral paresthesias due to modulation of

ABBREVIATIONS cZI = caudal zona incerta; DBS = deep brain stimulation; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; dZI = dorsal zona incerta; ET = essential tremor; PSA = posterior subthalamic area.

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the medial lemniscus system. Stimulation of the cerebellothalamic tracts may also cause postural instability, gait ataxia, and dysarthria, but the latter may also be ascribed to involvement of the internal capsule.

Tics have never been reported to be an adverse effect of DBS. The definition of a tic in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), is a “sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.”¹¹ Motor tics can be clonic (fast and brief), dystonic (slow and sustained with limb movement), or tonic (slow and sustained without limb movement).¹³ Tics may be preceded by a premonitory urge and can be suppressed for varying lengths of time, often associated with a rising inner tension, which is relieved by performing the tic.³ Primary tic disorders as classified in the DSM-5 (except for Diagnosis 307.20: Other Specified Tic Disorder) are those that start before the age of 18 years, last for at least 1 year, and have no secondary causes. The pathophysiology of tic disorders, including Gilles de la Tourette syndrome, remains unknown, but the prevailing model of their pathophysiology encompasses an abundance of structural and functional changes in extended brain areas involving motor and nonmotor cortico-striato-thalamo-cortical loops.¹¹

We present 5 cases in which patients with ET developed transient stimulation amplitude-dependent dystonic tics of the upper limbs and face after DBS of the PSA. The induction of tics after DBS is a new finding and may have implications for the future understanding of tic disorder etiology.

Methods

Clinical Setting

Patients with ET were part of a single-center, double-blind, randomized crossover, randomized controlled trial that had reached interim analysis. The clinical findings reported here were identified during clinical programming sessions to adjust DBS settings and not at clinical trial end points. These observations were not confined to any single stimulation setting and were not deemed to bias the ongoing trial, which is predicted to continue recruiting patients for an additional 5 years (NCT01945567, <http://clinicaltrials.gov>).

DBS of the PSA

Dorsal and caudal zona incerta (dZI and cZI) subregions of the PSA were targeted with an MRI-directed, implantable guide-tube technique under general anesthesia.²⁵ Intraoperative MRI scans of carbothane stylets facilitated accurate mapping of the DBS active electrode contacts by plotting these contacts on atlas slices according to the electrode positions relative to the surface of the subthalamic nucleus. Stimulation of either the cZI or the dZI was achieved by activating the different electrode contacts on the same leads, planned with a single constrained trajectory.

During the randomized crossover phase, the prescribed DBS consisted of monopolar stimulation with a pulse width of 60 μ sec, frequency of 130 Hz, and an amplitude of up to 3 mA or until any acute adverse effects occurred (whichever occurred first). If a patient experienced

adverse neurological effects, the stimulation amplitude was reduced, and if this reduction did not diminish the adverse effects, the patient underwent formal assessment and early crossover to the other stimulation location (i.e., cZI or dZI). During the following 6 months of unblinded empirical programming, any combination of electrodes and stimulation parameters could be used. Standardized neurological assessments were part of several tests performed at 3, 6, and 12 months after electrode implantation.

Clinical Assessments

Of 6 patients undergoing treatment for ET, 5 were noted to exhibit dystonic tics during the regular clinical programming intervals of the randomized trial phase, necessitating stimulator adjustments. The patients' medical history and examination findings and the electrode settings associated with the tics were recorded. The location of active electrode contacts contralateral to any tics were plotted on atlas slices (Fig. 1).²² Intraoperative MRI series of the electrode contacts were also analyzed (Fig. 2).

Results

Patient Demographics

The mean age of the cohort was 66.3 ± 7.8 years (range 55–79 years), and the mean length of the period of symptomatic ET before surgery was 23.1 ± 9.5 years (range 14–40 years) (Table 1). The patients were in relatively good health, with only 1 patient having more than 2 comorbid conditions. None of the patients had a personal or family history of tics, viral encephalitis, substance abuse, head trauma, obsessive-compulsive disorder, or attention deficit hyperactivity disorder.

Adverse Effects and Stimulation Settings

All 6 patients experienced DBS-related adverse effects during the clinical programming phase. Five patients developed upper-limb dystonic tics of varying severity within days of the programming (Table 2). Two of these 5 patients also exhibited cervical tics, and 2 developed orofacial tics, both ipsilateral to upper-limb symptoms. Symptom onset was delayed for hours to several days after the programming and resolved only after subsequent reduction of the stimulation amplitude.

In all of these 5 patients, the involuntary movements occurred at the maximum prescribed amplitude setting of 3 mA. In all but 1 patient, these movements resolved after the stimulation amplitude was reduced without any loss of optimal ET control. In the 1 patient, to resolve the DBS-induced tics, some sacrifice of optimal tremor control was required at that particular electrode contact.

All 5 patients reported that they could control their movements by force of will but that they felt an increasing urge to move the longer they suppressed them. All of these patients also reported a premonitory urge to move and that performance of the various movements was accompanied by transient cessation of this urge and a feeling of pleasure. Movements were stereotypical in all cases.

As mentioned in the foregoing, the patients' tics were easily controlled by a reduction in stimulation amplitude, and this reduction did not result in loss of ET control in all

FIG. 1. Active DBS electrode contacts contralateral to the side of dystonic tics on axial T2-weighted MRI scans plotted relative to an atlas depiction of the surface of the subthalamic nucleus. **Left:** Horizontal-ventral 0.5-mm slice with dZI contacts (red circle, Patient 3; white circle, Patient 2; and blue circle, Patient 5). **Right:** Horizontal-ventral 0.5-mm slice with cZI contacts (green circle, Patient 4; yellow circle, Patient 1; and red circle, Patient 3). Modified with permission from Schaltenbrand G, Hassler RG, Wahren W: *Atlas for Stereotaxy of the Human Brain*, ed 2. Stuttgart: Thieme, 1977. Courtesy of Thieme.

cases, except for Patient 3. This patient’s tics were associated with stimulation of both the cZI and dZI. Stimulation reduction in this patient resolved the tics, but residual ET remained. The patient expressed some disappointment in the loss of the tics after the reduction in amplitude. In the minutes after the reduction, he could mimic the tics but derived fading pleasure from doing so. Weeks after the reprogramming, he recalled the pleasure of the tics, but could no longer mimic them convincingly.

Electrode Location

Active contacts contralateral to the patient’s side of dystonic tic were located in both cZI and dZI subregions of the PSA with a maximal vector separation of 4 mm (Fig. 1). Two patients exhibited dystonic tics with active electrodes in the cZI, 2 in the dZI, and 1 in both locations.

Discussion

Adverse effects on motor function after DBS in the subthalamic area are common at a median stimulation amplitude of 4.8 V; these effects often consist of contralateral tonic contraction of the face and arm due to electrical current spreading into the adjacent internal capsule.²⁶ Stimulation-induced dystonia is less common, and motor tics have not been previously reported. Stimulation-induced dystonia has been noted by Fytagoridis et al.⁹ These authors have reported that muscle contractions of the face, upper limb, and, less commonly, lower limb were observed after stimulation with 19 electrode contacts widely distributed throughout the PSA and with a median amplitude of 2.9 V. Given the low stimulation amplitude and the predominance of upper-limb rather than facial symp-

FIG. 2. Intraoperative MRI scans showing the location of the implanted carbothane stylets within the PSA and indicating the position of the electrode contacts contralateral to the side of the dystonic tics. The pink lines delineate the subthalamic nucleus and the red lines the carbothane stylet. Image view is stereotactic. **A:** Left cZI of Patient 1. **B:** Left dZI of Patient 2. **C:** Left dZI of Patient 3. **D:** Left cZI of Patient 3. **E:** Left cZI of Patient 4. **F:** Right dZI of Patient 5.

TABLE 1. Patient demographics*

Pt No.	Age (yrs)	Yrs w/ ET	Comorbidities
1	60	14	None
2	64	15	Hypercholesterolemia
3	72	40	Hypertension & hypercholesterolemia
4	55	30	Hypertension
5	79	25	Type 2 diabetes mellitus, abdominal aortic aneurysm w/ stent, hypertension, hypercholesterolemia, & emphysema
6	68	15	Bipolar disorder w/ last manic episode >15 yrs earlier & hypercholesterolemia

Pt = patient.
* All patients were men.

TABLE 2. Summary of the dystonic tics and the DBS settings that generated them*

Pt No.	Pt's Description of Sx	Movements Controlled by Voltage Reduction	Stimulated PSA	Dystonic Tic Location	Stimulation Amp at Time of Sx (mA)	Other Adverse Effects
1	Rolling shoulder movements; unusual facial expressions	Yes	cZI	Orofacial, rt upper limb	3 & 2.2	Dysarthria & gait imbalance
2	Rt shoulder & hand movements; worse w/ action	Yes	dZI	Rt upper limb	3	None
3†	Jerking movements of shoulders & constant lt arm movements	Yes	dZI	Orofacial & lt upper limb	3	None
	Abnormal neck posture	Yes, but some loss of tremor control at <1.9 mA	cZI	Neck (arm Sx absent at this electrode location)	3 & 1.9	None
4	Rt arm muscle cramps & rolling hand movements	Yes	cZI	Neck & rt upper limb	3 & 2.1	Transient paresthesia & dysarthria
5	Lt arm fidgeting & urge to grab things	Yes	dZI	Orofacial & lt upper limb	3 & 2.5	Postural instability & visual Sx

Amp = amplitude; Sx = symptoms.

* All patients experienced an urge to perform the typical movements and a sense of relief after performing them.

† Stimulating the cZI or dZI in this patient resulted in dystonic tic symptoms.

toms, Fytagoridis et al. argued that this was a previously unreported dystonic phenomenon rather than a capsular adverse effect. They did not discuss whether the dystonic movements they observed had any features of tics.

Here, we report that 5 of 6 patients with ET undergoing DBS of the PSA showed stimulation-induced dystonic tics after anatomically directed stimulation in 2 specific locations (the dZI and cZI). All 5 patients showed typical, anticipated, and suppressible dystonic movements of the upper limbs, and 2 also experienced involuntary movements of the cervical and orofacial muscles. All had urge–release phenomena entirely consistent with tics. All patients exhibited symptoms at the maximum voltage of 3 mA to the PSA, with only 1 patient having tics overlapping part of the monopolar stimulation therapeutic window for ET.

Unlike in the aforementioned report of dystonic phenomena with PSA stimulation,⁹ the active DBS contact electrodes causing dystonic tics in our study could be localized to 2 specifically studied PSA subregions, the cZI and dZI. Electrode contacts were plotted within a sphere of a 2-mm radius within the planned target location. Both loci were within 5 mm of the internal capsule, but the dystonic movements we noted were quite unlike those usually associated with stimulation of this structure. In particular, the patients did not display slurring of speech or increased limb tone suggestive of capsular stimulation.

Our patients' involuntary movements had features of both dystonia and tics (i.e., dystonic tics): they experienced sustained muscle contractions that caused twisting and repetitive movements or abnormal postures (typical of dystonia),¹⁴ as well as a premonitory urge and ability to suppress this urge (typical of tics).⁷ While recognizing the significant overlap between dystonia and dystonic tics,⁸ we believe that the cognitive/affective components of the tics provided compelling evidence for the latter diagnosis. These DBS-induced tics, if left untreated, would be consistent with the DSM-5 category Other Specified Tic Disorder (code 307.20).¹

To our knowledge, tics have never been reported as an adverse effect of DBS or with any lesioning target within the brain. Secondary tics may occur after traumatic brain injury.^{21,23} Imaging studies in patients with such injuries have indicated hemorrhages in the lentiform nucleus and diffuse axonal injury, although the limited availability of high-quality MRI scans at the time when these studies were conducted limited localizing the exact anatomical location in these reports.

Findings of functional neuroimaging studies suggest that the pathophysiology of tics in patients with Tourette's syndrome appears to involve the basal ganglia and cortico-striato-thalamo-cortical circuits.²⁰ The co-occurrence of primary dystonias and tics has led to the hypothesis that the pathophysiological mechanisms of these symptoms may be shared.^{7,17,19,24} The PSA has never before been implicated in tic pathophysiology. According to the observations reported in the present study, the PSA may be a candidate region for future investigations of tic disorders, including Tourette's syndrome.

It is interesting to note that in this cohort, 4 of 5 patients developed dystonic tics with stimulation of the cZI or dZI, but did not develop them when treatment crossed over to the other location (i.e., the cZI or dZI). One patient exhibited dystonic tics after sequential stimulation in both locations. Furthermore, we have used the same DBS targets in 36 patients with Parkinson's disease, in 3 patients with non-ET movement disorders, and also in Patient 6 (Table 1) without inducing dystonic tics in any of these patients. Therefore, the presence of ET may induce susceptibility to PSA-induced tics.

Lesioning of the zona incerta was previously used to treat patients with medically intractable Tourette's syndrome. In one study covering a 28-year period (from 1970 to 1998), 4 patients underwent zona incerta lesioning alone, and 13 others underwent concurrent thalamic lesioning.² The zona incerta region targeted was identified on ventriculography images and was located 12 mm be-

hind the ventral border of the foramen of Monro, 3–5 mm below the foramen of Monro posterior commissural line, and 8–9 mm lateral to the border of the third ventricle.

While recognizing the limitations of older imaging modalities for locating anatomical features, we infer that this target appeared to be medial and anterior to the cZI target used in our study. We also note that the lesion volumes were not ascertained postoperatively. It is difficult to reconcile our findings that DBS of the PSA induces tics with the significant improvement in tics reported after zona incerta and thalamic lesioning by Babel et al.² We note that the surgical protocols used in their study leave significant room for doubt about the brain structures targeted.²

Conclusions

Five of 6 patients with ET undergoing DBS centered on the cZI and dZI of the PSA exhibited subacute dystonic tics during systematic, anatomically prescribed stimulation. Reducing the stimulation amplitude resolved these tics without significant loss of tremor control in most cases.

Dystonic tics were not observed in 39 additional patients with non-ET movement disorders after stimulation of the same PSA targets. Therefore, ET may be a precondition of dystonic tics triggered by DBS of the PSA. This is the first report of tics induced by DBS. The PSA could be a candidate region for future studies of tic pathophysiology.

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Disclosures

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Author Contributions

Conception and design: Lind, Chandran, Joshi. Acquisition of data: Lind, Chandran, Stell. Analysis and interpretation of data: Lind, Chandran, Stell. Drafting the article: Chandran, Joshi. Critically revising the article: Lind, Joshi, Thorburn, Stell. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lind. Study supervision: Lind.

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