Deep brain stimulation for Tourette syndrome: a single-center series

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OBJECTIVE Tourette syndrome (TS) is a complex neuropsychiatric disorder characterized by multiple motor and phonic tics. While pharmacological and behavioral therapy can be effective in most patients, a subset of patients remains refractory to treatment. Increasing clinical evidence from multiple centers suggests that deep brain stimulation (DBS) of the medial thalamus can be effective in many cases of refractory TS.

METHODS The authors retrospectively reviewed outcomes in 13 patients with refractory TS who underwent medial thalamic DBS performed by their team over a 7-year period. Patients were evaluated by a multidisciplinary team, and preoperative objective assessments were performed using the Yale Global Tic Severity Scale (YGTSS) and Yale-Brown Obsessive Compulsive Scale. YGTSS scores were calculated at visits immediately postoperatively and at the most recent follow-up in patients with a minimum of 6 months of postoperative follow-up. Coordinates of the active DBS contacts were calculated and projected onto each patient's pre- and postoperative images.

RESULTS Patients showed an average decrease of 37% ($p = 0.0063$) in the total tic severity at their first postoperative visit. At their latest visit, their scores achieved significance, decreasing from preoperative scores by an average of 50% ($p = 0.0014$). The average position of the active contact was noted to be at the junction of the posterior ventralis oralis internus/centromedian-parafascicular nuclei. Device-related complications occurred in 2 patients, necessitating additional surgeries. All patients continued to use the system at last follow-up.

CONCLUSIONS The authors' data are consistent with the small but growing body of literature supporting DBS of the ventralis oralis internus/centromedian-parafascicular thalamus as an effective and relatively safe treatment for severe, refractory TS.

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KEY WORDS Tourette syndrome; deep brain stimulation; medial thalamus; Yale Global Tic Severity Scale; YGTSS; Yale-Brown Obsessive Compulsive Scale; YBOCS; functional neurosurgery

GILLES de la Tourette syndrome (TS) is a disorder characterized by involuntary motor and phonic tics, which typically begin in early childhood. While most cases can be managed medically or attenuate in adulthood, a subset of patients has extremely severe and refractory symptoms that result in significant injury and social isolation.^{7,41} For some of these patients who have not responded to a number of pharmacological and cognitive interventions, deep brain stimulation (DBS) has been repeatedly demonstrated to be safe and effective. An increasing number of reports have shown that DBS can dramatically reduce the number of tics in medically refractory TS.^{1–3,8–12,16,18,20,21,23,25,29,35,42} However, debate re-

mains concerning many aspects of the procedure. While recent recommendations for inclusion and exclusion criteria have been put forth,³⁵ the ideal target(s) remain a matter of debate,²⁸ with 9 different regions postulated to provide potential benefit via interruption of a putative TS circuit.^{13,17,22,31} The majority of case reports focus mainly on the subregions of the centromedian thalamus or globus pallidus internus (GPI).^{20,33,40} Our center selected the medial thalamic target (centromedian-parafascicular nucleus/ventralis oralis internus/substantia periventricularis), based on the preponderance of positive case reports supporting its efficacy.^{1,2,32,34,37,38} We report here our surgical and clinical experience with 13 patients over a period of 7

ABBREVIATIONS CM-PF = centromedian-parafascicular; DBS = deep brain stimulation; GPI = globus pallidus internus; OCD = obsessive-compulsive disorder; TS = Tourette syndrome; VOI = ventralis oralis internus; YBOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale.

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years. We further explored the specific regions of stimulation that appear to correlate with symptomatic improvement.

Methods

We conducted a retrospective review of all patients with TS who underwent thalamic DBS performed by our team (Table 1). Of 15 patients who underwent surgery between January 2009 and May 2016, 13 consecutive patients with at least 6 months of follow-up were included. Before undergoing surgery, all patients were screened by an experienced movement disorders neurologist and stereotactic neurosurgeon familiar with DBS and the management of TS. Patients were assessed using the Yale Global Tic Severity Scale (YGTSS), the Yale-Brown Obsessive Compulsive Scale (YBOCS), and formal neuropsychological evaluation.^{14,23} A complete assessment of treatment modalities was reviewed. Patients were required to have tried a course of cognitive behavioral therapy, 1 alpha adrenergic agonist, and at least 3 dopamine receptor-blocking medications with either adequate dosages or limiting side effects. Significant psychiatric comorbidities, including debilitating obsessive-compulsive disorder (OCD) and/or depression, were considered relative contraindications pending further psychiatric evaluation. A minimum age of 16 years in cases of self-injury or 18 years in the absence of self-injury was used. All cases were subsequently reviewed by a multidisciplinary committee comprising 2 psychiatrists (1 pediatric psychiatrist in patients < 18 years old), a neuropsychologist, 2 neurosurgeons, and 2 movement disorder neurologists familiar with the diagnosis and management of TS. All operations were performed by the same neurosurgeon (A.Y.M.), and the deep brain stimulator was programmed by the same neurologist (M.P.); some patients underwent additional follow-up programming at outside medical centers. Institutional review board approval was obtained for the retrospective chart review as well as for subsequent administration of a brief questionnaire.

Surgical Technique

The DBS implantation was performed as a multistage procedure.⁴ A few weeks prior to surgery, stereotactic MRI was performed under general anesthesia in order to minimize head movement. Preliminary target and trajectory planning was then performed using the Brainlab stereotactic system (Brainlab AB). The indirect coordinates for the electrode tip were chosen at 5 mm lateral to the midline, 4 mm posterior, and 0 mm superior to the mid-commissural plane,¹ corresponding to the substantia periventricularis. Entry angles ranged from 45° to 65° in the sagittal plane and from 25° to 38° lateral in the coronal plane.

The MR images were fused the day of surgery with thin-cut (0.6 or 1 mm) CT-scan images obtained after placement of the stereotactic frame (Leksell, Elekta AB). Surgery was performed with the patient under conscious sedation (6 patients) or general anesthesia (7 patients). Microelectrode recordings were obtained intraoperatively, starting at 15 mm above the stereotactic target (Alpha-

Omega Engineering). Test stimulation, either macrostimulation through the microelectrode sheath (3 mm above the tip) or direct stimulation through the DBS electrode, was performed to assess for side effects. In no cases did test stimulation lead to repositioning of the lead. All patients underwent bilateral implantation with DBS leads (model 3387, Medtronic). The pulse generators (bilateral single channel in 11 patients, dual channel in 2 patients) were placed under general anesthesia either the same day (2 patients), or within 14 days following lead placement. A high-resolution CT scan was obtained immediately postoperatively in all patients. In addition, 2 patients underwent postoperative high-resolution MRI. The postoperative images were then fused with the preoperative data set to identify the actual stereotactic coordinates of the lead contacts.

Postoperative Care

Initial programming typically began approximately 2 weeks after the DBS implantation at the first postoperative visit. Each electrode was evaluated using a pulse width of 90 μ sec, a frequency of 130 Hz, and steadily increasing voltages up to 4 V or less, depending on tolerability. The initially selected active electrode was either the one associated with subjective improvement or, in the absence of immediate benefit (as was more commonly the case), the most ventral, best tolerated electrode. During follow-up visits, the settings were adjusted according to perceived benefit or side effects, typically with increasing voltages followed by addition of adjacent electrodes or higher pulse width in patients who were not robustly responding. Patients usually received voltage in the range of 1–2 V, which they could adjust on their own between visits. The patients were closely monitored for side effects and serious adverse events, usually monthly initially and then every 3–6 months after the 3rd month depending on proximity and need. At each visit, the patient's YGTSS score was usually calculated and, where appropriate, the YBOCS score was calculated as well. All patients also participated in 2-question telephone surveys administered from 6 to 74 months after the procedure. The first question was to rate their current symptoms on the Clinical Global Impression scale,¹⁵ and the second question was to answer the query, "Knowing what you know now, would you have the surgery again?" The preoperative and postoperative YGTSS and YBOCS scores were compared and, along with the answers to the survey questions, served as measures of efficacy.

The preoperative scores were compared with postoperative scores using a Wilcoxon signed-rank test. Patients served as their own controls, with preoperative YGTSS scores being compared with those obtained at the initial and the most recent follow-up visits. A Pearson correlation coefficient was calculated for the individual subscores compared with the overall improvement in YGTSS score. Preoperative YBOCS scores were compared only to the latest follow-up visit and were not performed in 1 patient who denied OCD symptoms. Given the sample size and the multiple tests involved, a $p < 0.01$ was considered significant. All calculations were performed using the SPSS statistical software package (IBM).

TABLE 1. Characteristics of the 13 patients with TS

Case No.	Age at Onset of TS (yrs)*	Age at Op	Initial YGTSS Score†	OCD	ADD	Depression	Anxiety	Self-Injurious Behavior
1	6	16	39	No	No	No	No	No
2	7	17	100	Yes	No	Yes	Yes	Yes
3	6	21	67	No	Yes	No	No	No
4	3	16	88	Yes	Yes	Yes	Yes	Yes
5	6	19	95	Yes	Yes	Past	No	Past
6	11	17	94	Yes	Yes	Yes	No	Yes
7	3	18	91	No	No	Past	Yes	Past
8	4	24	85	Yes	Yes	No	Yes	Past
9	7	19	92	Yes	No	Yes	Yes	No
10	3	19	95	Yes	Yes	No	Yes	Past
11	16	33	74	Yes	Yes	Yes	Yes	No
12	7	24	88	Yes	No	Yes	Yes	Yes
13	9	16	95	Yes	Yes	No	No	Yes

ADD = attention deficit disorder.

* When symptoms were first noticed by the parent or patient.

† Preoperative TS-related symptom severity.

Results

Patients had a mean follow-up time of 23 months (range 6–58 months). The mean improvement in the YGTSS score was 50% compared with preoperative testing ($p = 0.0014$). All patients demonstrated improvement in their symptoms due to DBS therapy, although degrees of improvement ranged from 16% to 100% based on change in YGTSS score (Fig. 1 upper). Improvement of greater than 30% was seen in 84% of patients, and improvement greater than 50% was noted in 55% of patients. One patient, who had the the mildest tic severity at baseline, remained virtually tic free at the last follow-up, and 3 additional patients with more marked baseline severity reported minimal tic activity at the last follow-up. No patient reported an increase in tic severity at the latest follow-up post-DBS, although intervisit tic severity varied considerably in some patients (Fig. 1 lower). The YGTSS data also showed a significant difference between the preoperative scores and the first follow-up visit ($p = 0.0063$). However, the difference between the first follow-up visit and the latest follow-up visit was not statistically significant ($p = 0.42$). At their first follow-up visit, 54% of patients had a greater than 30% reduction in score, and 46% had a greater than 50% reduction in score. While most patients continued to have tics, an overall 50% improvement in terms of subjective impairment, motor, and vocal subscores of the YGTSS was observed in all patients, demonstrating significant correlations with overall improvement. The strongest correlation was with subjective impairment ($R = 0.9044$), followed by motor tics ($R = 0.8654$) and then vocal tics ($R = 0.8575$) (Fig. 2A–C).

The YBOCS scores were not calculated for all patients since some patients reported no or minimal OCD behaviors. However, when captured, the scores were compared preoperatively and postoperatively ($n = 12$). The difference between the scores was not significant between the preoperative and most recent postoperative YBOCS scores ($p = 0.033$) at our alpha level of 0.01. Though individual results

varied, 63% of patients had a greater than 50% reduction in their YBOCS scores, while 1 patient experienced an increase in OCD behaviors (Fig. 2D).

In response to the 2-question survey, 100% of patients reported that they would rate their symptoms as either much improved or very much improved on the Clinical Global Impression scale. In addition, 100% of patients reported that knowing what they know about the procedure now, they would elect to have the surgery again.

Stimulation Parameters and Lead Locations

Stimulation parameters for each patient are listed in Table 2. The majority (9/13) of patients had programming in simple monopolar mode, while the others had programming in bipolar mode (Cases 1, 5, and 11) or double monopolar mode (Case 9). The coordinates of the lead tips and active contacts, as determined by postoperative image fusion, are displayed in Table 3. The average active contact location localized to the junction of the posterior ventralis oralis internus (VOI)/anterior centromedian-parafascicular (CM-PF) complex (Fig. 3). There were no significant differences between the left and right side for either the lead tip or the active contact location. No significant correlations were observed between active contact coordinates and the degree of symptomatic improvement among patients (1-way ANOVA).

Complications

There were no postoperative hemorrhages or any other immediate postoperative surgical complications. Two patients experienced device-related complications, necessitating additional surgical intervention (Table 2). One patient experienced wound erosion and infection (methicillin-sensitive *Staphylococcus aureus*) at the connector site in the left parietal scalp 8 months postoperatively, necessitating removal of the left lead and generator, which was replaced 5 months later without adverse sequelae. In another patient, excessive manual manipulation of the right pulse genera-

FIG. 1. Upper: Bar graph showing YGTSS scores preoperatively, immediately postoperatively, and at the latest follow-up compared using the Wilcoxon signed-rank test. The average difference from preoperatively to the first postoperative visit was 37% and was significant ($n = 13$, $p = 0.0063$). The average difference from the preoperative to the latest score was 50% and was significant ($n = 13$, $p = 0.0015$). By the first postoperative visit, 54% had a greater than 30% reduction and 46% had a greater than 50% reduction in their initial scores. By the latest follow-up, 84% had greater than 30% reduction and 55% had greater than 50% reduction of their initial scores. *YGTSS score of 0. **Lower:** Line graph showing YGTSS score versus time for all patients ($n = 13$). Time point zero represents the preoperative scores. The 2 following time points represent follow-up appointments throughout the patient's treatment. The red line represents the average response. *Statistically significantly different from preoperative scores based on the Wilcoxon signed-rank test. Figure is available in color online only.

tor ("twiddler's syndrome") resulted in an extension lead fracture 10 months after system implantation as previously reported. The extension lead was replaced, but a postoperative infection developed 3 weeks later (organism: *Pseudomonas aeruginosa*), and the entire right-sided system

was removed. It was reimplanted 4 months later, but the same right-sided system needed to be removed when an aseptic cyst developed at the lead tip 13 months later, resulting in headaches and mental status changes secondary to obstructive hydrocephalus.¹⁹ Upon removal of the entire

FIG. 2. A: Bar graph showing preoperative YGTSS impairment subscore versus the latest follow-up YGTSS impairment subscore. The average difference was 53% ($p = 0.0015$). Sixty-two percent of patients had a greater than 50% reduction in their subjective impairment score by their latest follow-up visit. This showed a positive correlation with the overall YGTSS score ($R = 0.9044$, $p = 0.000022$). **B:** Bar graph showing the preoperative YGTSS motor subscore versus the latest follow-up subscore. The average difference was 50% ($p = 0.0018$). Sixty-three percent of patients had greater than 50% reduction in their motor tic symptoms by their latest follow-up visit. This showed a positive correlation with the overall YGTSS score ($R = 0.8654$, $p = 0.00013$). **C:** Bar graph showing preoperative YGTSS vocal subscore versus the latest follow-up vocal subscore. The average difference was 47% ($p = 0.0022$). Forty-six percent of patients had greater than 50% reduction in their symptoms by their latest follow-up visit. This showed a positive correlation with the overall YGTSS score ($R = 0.8575$, $p = 0.00018$). **D:** Bar graph showing preoperative YBOCS score versus the latest follow-up YBOCS score. The average difference was 57% ($p = 0.033$, $n = 12$). Sixty-three percent of patients had greater than 50% reduction in their symptoms by their latest follow-up visit. One patient (Case 1) had no recorded YBOCS data and was not included in analysis, indicated by the lack of a bar. All comparisons were performed using the Wilcoxon signed-rank test. *A subscore/score of 0. Figure is available in color online only.

system, the cyst regressed and the patient returned to her baseline condition, albeit with hemi-tics on the nonstimulated side.³⁰

Discussion

Our findings further support that the CM-PF region is a consistently if not uniformly effective target for the treatment of TS. All patients demonstrated a response to the treatment with a reduction in symptoms, and on average they showed a significant 50% decrease in their YGTSS scores. These results are similar to other case series and observational studies, adding further support for the selective use of DBS to treat TS.^{10,11,18,20,25,29,35} To our knowledge, only the case series published by Servello et al.³⁷ and Porta et al.²⁹ involved a similar number of CM-PF DBS patients with long-term follow-up. These reports demonstrated a 47% and 73% mean reduction in the YGTSS, respectively.

One striking feature of the response is the variable latency of effect. Half of the patients demonstrated an immediate and marked improvement. While this could

represent a placebo effect, the enduring benefit, maintained in some cases for years, suggests that the benefit is at least in part related to a “microlesion” effect. Similar immediate postoperative improvement has been reported in lesion-based surgical approaches for TS.⁵ The remaining patients required several months before experiencing a meaningful improvement, sometimes even without great changes in parameters. In this respect, the programming effect can be likened to that of dystonia, where improvement may be seen immediately or only after months. As in the double-blind GPI study reported by Kefalopoulou et al.,²⁰ improvement in the YGTSS score was most pronounced in the impairment subscore. Although this could be an artifact of the nature of the rating scale, which is more heavily weighted toward impairment, it suggests that improvement in social stress is not solely correlated with the raw change in motor or vocal tic scores. This may explain why even patients without a robust improvement in the overall YGTSS scores reported feeling either “improved” or “very much improved” on the Clinical Global Impression scale.

The overall benefit is also supported by answers to

TABLE 2. Surgical details and medications for all 13 patients

Case No.	Active Contact	Current Amplitude (V)	Current Width (μsec)	Current Frequency (Hz)	Complications	Medications Tried & Stopped Prior to DBS (max doses if possible)*	Current Medications
1	Lt: 3+ 2-; rt: 3+ 1- 2-	Lt: 3.2; rt: 3.0	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Aripiprazole, lamotrigine, methylphenidate, risperidone, sertraline, Topamax, ziprasidone	None
2	Lt: C+ 1-; rt: C+ 1-	Lt: 3.5; rt: 3.5	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Clonazepam, clonidine, fluphenazine, haloperidol, levetiracetam, olanzapine, pimozide, tetrabenazine, ziprasidone	None
3	Lt: C+ 1-; rt: C+ 9-	Lt: 3.5; rt: 3.5	Lt: 90; rt: 90	Lt: 185; rt: 185	None	Atomoxetine, botulinum toxin, clonazepam, clonidine, guanfacine, haloperidol, olanzapine, pimozide, risperidone	Pimozide
4	Lt: C+ 2-	Lt: 4	Lt: 90	Lt: 130	1) Lead fracture on rt, replacement; 2) lead tip cyst on rt, removal	Aripiprazole, botulinum toxin, clonazepam, clonidine, haloperidol, risperidone	Gabapentin, pimozide, clomipramine, lamotrigine
5	Lt: 3+ 1- 2-; rt: 3+ 1- 2-	Lt: 3.0; rt: 3.0	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Aripiprazole, clonazepam, guanfacine, haloperidol, risperidone, tetrabenazine, Topamax	Diazepam, benzotropine
6	Lt: C+ 2-; rt: C+ 2-	Lt: 4.6; rt: 4.6	Lt: 210; rt: 210	Lt: 130; rt: 130	None	Clonazepam, clonidine, guanfacine, haloperidol, pimozide, risperidone, ziprasidone	Aripiprazole
7	Lt: C+ 0-; rt: C+ 0-	Lt: 2.2; rt: 2.0	Lt: 120; rt: 120	Lt: 135; rt: 135	None	Aripiprazole, clonidine, pimozide, risperidone	Carisoprodol, marijuana, sertraline, tetrabenazine
8	Lt: C+ 1-; rt: C+ 1-	Lt: 0.6; rt: 0.26	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Clonidine, desipramine, fluphenazine, haloperidol, pimozide	Ativan, clonazepam, sertraline
9	Lt: C+ 1- 2-; rt: C+ 1- 2-	Lt: 4.5; rt: 4.5	Lt: 90; rt: 90	Lt: 185; rt: 185	None	Aripiprazole, guanfacine, haloperidol, olanzapine, paliperidone, pimozide, risperidone, ziprasidone	Clomipramine, clonazepam, clonidine, perphenazine, venlafaxine
10	Lt: C+ 1-; rt: C+ 1-	Lt: 3.7; rt: 3.5	Lt: 90; rt: 90	Lt: 145; rt: 145	None	Aripiprazole, atomoxetine, clonidine, fluphenazine, guanfacine, haloperidol, risperidone	None
11	Lt: 0+ 1- 2-; rt: 3+ 1- 2-	Lt: 3.5; rt: 3.5	Lt: 120; rt: 90	Lt: 130; rt: 130	Wound infection on lt, removal	Aripiprazole, clonazepam, guanfacine, haloperidol, perphenazine, pimozide, quetiapine, risperidone, tetrabenazine, trazodone	Clonazepam, clonidine, escitalopram, quetiapine, risperidone
12	Lt: C+ 1-; rt: C+ 1-	Lt: 3.2; rt: 3.2	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Citalopram, clonidine, clorazepate, donepezil, fluoxetine, fluphenazine, risperidone, tetrabenazine, Topamax, ziprasidone	Benzotropine, clonazepam, fluoxetine, guanfacine, lorazepam, pimozide
13	Lt: C+ 1-; rt: C+ 1-	Lt: 1.0; rt: 1.0	Lt: 90; rt: 90	Lt: 130; rt: 130	None	Clonazepam, clonidine, methylphenidate, pimozide, risperidone, sertraline, Topamax	Diazepam

* Each patient was screened for a number of psychiatric comorbidities. Careful documentation was kept regarding the failed therapies for each patient.

the 2-question survey, which was administered at least 6 months after the procedure. All patients reported either much improved or very much improved symptoms on the Clinical Global Impression scale. In addition, all patients would be willing to have the surgery again, knowing what they know now, even those patients who had complications or experienced relatively less robust responses. Both patients who required hardware removal for infections experienced a significant increase in tics and were eager to have the DBS device reimplanted as soon as possible.

Approximately two-thirds of patients (63%) experienced some improvement in OCD symptoms as corroborated by YBOCS scores, with the overall group experienc-

ing an average reduction of 57% over their preoperative scores. This did not achieve significance with our alpha cutoff of 0.01, but did trend toward significance. This is also consistent with the currently available literature on DBS for TS using the CM-PF as the target, although Bajwa et al. and Servello et al. reported more robust improvement in OCD scores.^{6,36}

As mentioned above, the most ventral, best tolerated contact was selected for therapy. In most patients, stimulation of the most ventral/deepest contact (0 left, 4 right) resulted in untoward side effects, and thus Contact 1 left/5 right was most commonly used. Thus, the average stimulation zone maps to the VOI/CM-PF junction, consistent

TABLE 3. The stereotactic coordinates for distal contacts (center of Contact 0) and active contacts in all patients

Case No.	Lt Contact	Rt Contact	Lt Lead*						Rt Lead*					
			Lead Tip			Active Contact†			Lead Tip			Active Contact†		
			x	y	z	x	y	z	x	y	z	x	y	z
1	2	1,2	3.4	-8.0	-2.0	6.0	-4.4	2.2	2.7	-7.5	-1.0	5.3	-5.2	2.0
2	1	1	5.0	-4.6	-1.1	6.2	-2.8	0.6	4.2	-4.4	-1.4	5.2	-2.7	1.0
3	1	1	4.7	-4.7	0.4	6.0	-3.2	2.6	5.7	-3.7	1.0	7.1	-2.7	3.5
4	2	NA	5.0	-4.1	-2.0	7.7	-1.0	2.6	5.3	-4.1	-1.2	NA	NA	NA
5	2	2	5.3	-3.7	-0.2	7.8	-0.2	4.5	4.7	-3.6	-1.2	7.3	-0.3	3.7
6	2	2	5.2	-3.0	-0.1	8.4	-0.6	4.5	4.8	-3.5	-0.2	7.4	-0.7	4.8
7	1	1	5.3	-3.2	-0.4	7.0	-1.9	2.1	4.2	-3.9	0.0	5.4	-2.6	2.5
8	1	1	5.8	-3.6	-0.8	7.4	-1.9	1.5	4.2	-3.9	0.2	5.6	-2.1	2.1
9	1,2	1,2	5.3	-4.0	0.1	7.5	-1.4	3.6	4.5	-3.5	0.1	7.5	-1.4	3.6
10	1	1	4.2	-4.1	1.0	5.8	-2.2	3.5	5.0	-4.3	0.2	5.8	-2.2	3.5
11	1,2	1,2	4.4	-4.2	0.6	6.5	-2.4	4.4	4.3	-4.1	-0.9	6.5	-2.4	4.4
12	1	1	4.9	-3.6	-0.4	6.5	-2.2	2.1	4.8	-3.0	-0.1	6.5	-2.2	2.1
13	1	1	4.0	-3.4	-0.1	5.7	-2.0	2.3	4.9	-3.4	0.3	5.7	-2.0	2.3
Mean			4.8	-4.2	-0.4	6.8	-2.0	2.8	4.6	-4.1	-0.3	6.3	-2.2	3.0

NA = not applicable.
* Values represent stereotactic coordinates.
† The active contact was calculated as the average of the 2 cathodes in patients undergoing dual cathodic stimulation (Cases 1, 5, 9, and 11).

with the published literature. No apparent differences in the region of stimulation were observed between those with greater and lesser degrees of improvement. The results of this observational study, like most of the DBS TS literature at this time, are limited by virtue of the small size and lack of randomization, blinding, or control group. Moreover, the variable nature of tics over time, compared with the progressive nature of Parkinson's

disease, further clouds the impact of DBS in TS. We cannot exclude the possibility that some patients may have experienced an improvement in tic severity over time even without DBS. The worsening and subsequent improvement in tics following device malfunction and revision, as previously reported in 1 patient, provides at least anecdotal evidence that stimulation plays a continuing role in long term-symptom control.³⁰ These limitations continue to

FIG. 3. Image from the Schaltenbrand and Wahren stereotactic atlas, axial slice at 2.0 mm above the anterior commissure–posterior commissure plane. The yellow dot represents the average area of stimulation as calculated using the postoperative imaging studies. Figure is available in color online only.

prove to be a vexing challenge in establishing consensus and approval for DBS. Until such time when a multicenter study proves feasible, however, case series demonstrating efficacy and safety over long periods of time provide added support for DBS in severe, refractory cases of TS. The small size is partially compensated for by the large effect size demonstrated in this and other studies of DBS for TS. Of particular note with this cohort is the relatively young age of several patients (mean 20 years, range 16–33 years) compared with other publications and with the mean age of 29 years in the multicenter Tourette's DBS database.²⁷ The appropriate minimum age to pursue DBS in TS, which may attenuate with time, remains an area of debate, as reflected in changing recommendations by consensus committees. Suggested guidelines published in 2006 recommended a minimum age of 25 years,²⁶ whereas more recently proposed guidelines did not provide a cutoff but rather recommend "local ethics committee involvement" for patients younger than 18 years.³⁵ Our medical rationale for inclusion of patients as young as 16 years old was one of benefit versus risk, where tics were so violent as to result in numerous hospitalizations as well as resultant social isolation, including an inability to drive or attend school. Establishing the appropriate minimum age for DBS in TS will likely remain an area of debate. Another important and unresolved question involves the optimal target for TS literature, demonstrating variable efficacy for a number of targets, predominantly focusing on the medial thalamus and globus pallidus.

The most recent large case series reported by Servello et al.³⁷ was notable for a high rate of device removal (11 of the original 48 device implants) due to "inflammatory complications or poor compliance." As mentioned, device-related complications, including infection and extension lead fracture, occurred in 2 of our patients, with 1 patient requiring 3 revisions over a 5-year period for extension lead fracture secondary to "twiddler's syndrome." This phenomenon (extension lead fracture) occurred despite the generator being replaced in a subpectoral pocket as described by Servello and colleagues.³⁹ Our experience reinforces the perception that DBS for TS may be associated with a higher incidence of such complications when compared with other traditional indications for DBS. That the complication rate in a recent GPI TS cohort was 13%²⁰ suggests that complication rates are not target specific but more of an inherent challenge within this patient population.

Conclusions

This study adds to the growing, but still small, body of literature regarding DBS for TS. It is also notable for the younger age of the cohort, which remains an area of debate regarding inclusion/exclusion criteria. This series, which follows patients for as long as 7 years after DBS, supports the potential for CM-PF DBS to improve severe, refractory TS symptoms with relatively few significant side effects. This retrospective, observational study, like many other DBS TS reports, is limited by its nonrandomized, nonblinded nature and by the relatively small sample size. Clearly, a large, multicenter trial would be preferable,

but innumerable challenges make such an eventuality unlikely. Until such time, larger case series provide support that DBS of the CM-PF is an effective and safe treatment for TS.

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Dr. Pourfar reports that he is a consultant for and has received teaching honoraria from Medtronic Neurological. Dr. Mogilner reports that he is a consultant for and has received honoraria and grant support from Medtronic Neurological and is a consultant for Alpha Omega Engineering.

Author Contributions

Conception and design: all authors. Acquisition of data: Dowd. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Dowd. Administrative/technical/material support: Dowd. Study supervision: Mogilner, Dowd.

Supplemental Information

Previous Presentations

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