Deep brain stimulation lead removal in Tourette syndrome

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Deep brain stimulation lead removal in Tourette syndrome

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ABSTRACT

Introduction: Tourette syndrome (TS) is a complex neuropsychiatric disorder. A small percentage of individuals with TS can experience persistent severe, refractory, and impairing tics. Deep brain stimulation (DBS) has been increasingly used for symptom management, especially in these settings. In this article, we aim to evaluate the rate and the reasons for removal of DBS hardware in TS patients.

Methods: Data was analyzed from patients enrolled in the Tourette Association of America's International Tourette Syndrome Registry and Database.

Results: Fifteen of 269 (5.6%) patients required removal of their DBS systems. The mean age at explantation was 33.8 years. In these cases we observed a rate of 1.9 explantations per year of follow up from implantation. None of the removals took place in the immediate post-operative period. Infection was the most common cause (46.7%). Only one patient received explantation for tic resolution. There were no significant associations between explantation and the presence of specific psychiatric comorbidities, including OCD, depression, anxiety, or ADHD.

Discussion: The rate of removal of 5.6% was lower than the previously reported rate in the TS DBS literature. Infections accounted for nearly half of the TS DBS explantations in this cohort. There was no relationship to psychiatric comorbidities.

1. Introduction

Tourette syndrome (TS) is a complex neuropsychiatric disorder characterized by the presence of multiple motor and vocal tics. These tics, when disabling, are frequently managed with a combination of behavioral and pharmacological approaches. It is estimated that approximately 5% of all individuals with TS are refractory to current therapies. In these cases, the tics can persist and manifest in disabling and severe tic symptoms [1]. Expert consensus defines refractory cases as those with severe disabling tics with documentation on clinical scales, those who have failed at least three classes of pharmacologic agents, and those whose psychiatric symptoms are at least stable for six months [2,3]. For these patients, deep brain stimulation (DBS) has been utilized as an experimental treatment. Multiple brain targets have been employed, including thalamic regions such as the centromedian parafascicular nucleus region (CM-Pf), the globus pallidus internus (both anteromedial amGPi and posteroventral pvGPi), and the anterior limb

of the internal capsule inclusive of the nucleus accumbens (ALIC-NA). The literature has collectively revealed a positive outcome from TS DBS with an average reduction of motor and vocal tic scores in the 30–50% range, regardless of target [4].

There has been a concern in the literature that TS DBS may be associated with a higher incidence of hardware complications and with infections. In a recent comprehensive review, Jitkriksadikul et al. reported that hardware complications occurred in 24.8% of patients with TS as compared to 14.4% of patients with PD. The difference was more pronounced when considering hardware infections and skin erosions: 11.7% in TS versus 5.8% in PD [5]. These results have, however, been limited by small sample size (from each study site) in the dataset (largest TS DBS study with $n = 39$). The results were also limited by variability in study design, methodology, and duration of follow-up. The systematic review did not include some case series (as these cases did not fulfill inclusion criteria). Additionally, and importantly, there is a paucity of data on DBS explantation when utilizing a large TS cohort.

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Indeed, a significant limitation for the more widespread use of DBS will be the small number of reported cases and the variability in reporting of adverse effects. To address these limitations, the Tourette Association of America (TAA) created an International Tourette Syndrome Registry and Database [6]. Our aim in this project was to report on the extent and reasons underpinning DBS explantations in TS patients through the utilization of data from a large multi-country cohort.

2. Methods

The International Tourette Syndrome Registry and Database collects clinician-submitted data from the multiple participating subspecialty centers. Individual participating sites are not compensated for participation. The University of Florida received funds as the coordinating site through the Tourette Association of America (listed in funding sources).

On 11/25/2019, the registry and database was queried for data on DBS lead explantation. Explantation was defined as a DBS lead removed from the brain regardless of the reason for removal. Information on sex, age of TS onset, age at surgery, age at explantation, reason for explantation, re-implantation information, lead type, unilateral or bilateral lead(s), target, presence or absence of common comorbidities such as obsessive-compulsive disorder (OCD), and body distribution of motor tics were all included in the analysis. The outcome of this analysis was descriptive in nature. Pearson's Chi-Square analysis using SPSS was performed to assess if there was a difference between the presence of psychiatric comorbidity between patients who were explanted and those who were not.

3. Results

There were 269 patients enrolled in the International Tourette Syndrome Registry and Database from 31 international centers. The largest subject contribution was by Istituto Galeazzi in Italy with 21.9% of all cases. The full details of subject distribution per center are provided in [Supplemental Table 1](#). Fifteen patients required explantation of their DBS devices (14 were bilateral) (5.6%). None of the devices were re-implanted. The mean age of TS onset in the cohort was 7.6 years $\pm$ 5.1 (range 1–20). Twelve subjects were male and three female. Only one subject in the explantation cohort had a unilateral DBS system, and one subject in the series was implanted with more than one brain target. The most common target was the CM/Pf thalamic region ($n = 10$) followed by the pvGPi target ($n = 3$), ALIC-NA ($n = 1$), and CM/Pf + ALIC-NA targets ($n = 1$) ([Table 1](#)). The target distribution for the remainder of the patients was CM/Pf thalamus ($n = 130$), amGPi ($n = 77$), pvGPi ($n = 39$), unspecified GPi ($n = 4$), ALIC-NA ($n = 3$), and Ce-Spv-Voi thalamus ($n = 1$).

Table 1
Demographics and baseline data.

Patient	Sex	Age of Onset of TS	Age at Surgery	Lead	Target	Laterality	Age at explantation
1	Male	10	37	Medtronic 3387	CM/Pf	Bilateral	39
2	Female	1	28	Medtronic 3387	CM/Pf	Bilateral	32
3	Male	11	48	Medtronic 3387	CM/Pf	Unilateral (Right)	49
4	Male	9	19	Medtronic 3387	pvGPi	Bilateral	24
5	Female	20	21	Medtronic 3387	pvGPi	Bilateral	25
6	Male	10	28	Medtronic 3387	pvGPi	Bilateral	33
7	Female	3	16	Medtronic 3387	CM/Pf	Bilateral	19
8	Male	8	17	Medtronic 3389	CM/Pf	Bilateral	25
9	Male	7	27	Medtronic 3389	CM/Pf	Bilateral	34
10	Male	4	36	Medtronic 3389	CM/Pf + ALIC-NA	Bilateral	44
11	Male	12	48	Medtronic 3387	ALIC-NA	Bilateral	55
12	Male	1	19	Medtronic 3387	CM/Pf	Bilateral	22
13	Male	1	18	Medtronic 3387	CM/Pf	Bilateral	24
14	Male	10	39	Medtronic 3387	CM/Pf	Bilateral	41
15	Male	7	35	Medtronic 3387	CM/Pf	Bilateral	41

Age is reported in years. Abbreviations: CM/Pf – centromedian parafascicular nucleus of the thalamus, pvGPi – posteroventral portion of the globus pallidus internus, ALIC-NA – anterior limb of the internal capsule and nucleus accumbens.

Table 2
Reasons for explantation.

Patient	Reason for explantation
7	Cyst with associated obstructive hydrocephalus
4	Discomfort from the hardware
5	Discomfort from the hardware
6	Discomfort from the hardware
10	Infection (dermal erosion)
14	Infection (dermal erosion)
9	Infection (IPG pocket)
11	Infection (IPG pocket)
13	Infection (IPG pocket)
3	Infection (unspecified site)
15	Infection (unspecified site)
1	Lack of perceived benefit
2	Poor compliance with therapy
12	Poor compliance with therapy
8	Tic resolution

The patients are clustered by reason group.

3.1. Explantation

The mean age at surgery was 29.1 years $\pm$ 10.9 (range 16–48). The mean age at explantation was 33.8 years $\pm$ 10.8 (range 19–55). For a duration of 8 years, there were two explantations per year from the time of implantation to the time of explantation except for the first year with only one explantation. The average explantation per year of follow-up was 1.9. None of the explantations took place in the immediate post-operative period.

3.2. Reasons for explantation

The reasons for the explantations were variable and are summarized in [Table 2](#). Infection was the most common cause, with a total of 7/15 cases. The sites of infection included: implantable programmable generator (IPG) pocket ($n = 3$), dermal erosion with lead infection ($n = 2$), and unspecified site ($n = 2$). Other reported causes for explantation included discomfort from the hardware ($n = 3$), poor compliance with therapy ($n = 2$), lack of perceived benefit ($n = 1$), the formation of a cyst with associated obstructive hydrocephalus ($n = 1$), and tic resolution ($n = 1$).

Table 3

Distribution of tics in different body parts as reported in the total study sample ($n = 269$), those who received lead explantation, and those who did not. Pearson Chi-Square test was done to compare the distribution of tics in different parts between those with explanted leads and those who did not have leads explanted.

	Total	Subjects with explanted leads	Subjects without explanted leads	Pearson Chi-Square	p-value	Phi
Eyes	37.9%	33.3%	38.2%	0.142	0.706	-0.023
Nose	24.2%	20.0%	24.4%	0.150	0.698	-0.024
Mouth	32.3%	40.0%	31.9%	0.426	0.514	0.040
Neck	39.0%	40.0%	39.0%	0.006	0.937	0.005
Shoulders	39.8%	46.7%	39.4%	0.315	0.575	0.034
Arms	36.8%	46.7%	36.2%	0.665	0.415	0.050
Hands	32.3%	40.0%	31.9%	0.426	0.514	0.040
Trunk	26.8%	40.0%	26.0%	1.419	0.233	0.073
Pelvis	15.6%	13.3%	15.7%	0.063	0.802	-0.015
Legs	26.0%	26.7%	26.0%	0.003	0.953	0.004
Feet	16.4%	20.0%	16.1%	0.154	0.695	0.024
Number	269	15	254			

3.3. Tics and comorbidities

The frequency of body area involved in tics was the neck (46.7%), arms (46.7%), mouth (40%), shoulders (40%), hands (40%), trunk (40%), eyes (26.7%), feet (20%), legs (20%), pelvis (13.3%), and nose (13.3%). The distribution of motor tics did not differ between those who underwent hardware removal and those who did not (Table 3).

Despite incomplete data for some patients implanted in the registry, the Yale Global Tic Severity Scale (YGTSS) at six months, 12 months, and 24 months were reviewed and summarized (Table 4). All of the patients except patient 5 manifested improvement in the total YGTSS score.

At the time of data analysis, the information regarding comorbidities was limited due to their coding as present or absent. Validated scales, which can assess the severity and impairment of the symptoms, were available for a minority of subjects, and thus were not used in this

analysis. Furthermore, a description of the symptoms associated with these comorbid disorders was not available. For instance, the nature of obsessions and compulsions in subjects with OCD was not collected. Nevertheless, the most common comorbidity associated with explantation was OCD (66.7%). The other comorbidities included depression (46.7%), anxiety (46.7%), and attention-deficit hyperactivity disorder (ADHD) (20%). The frequencies of the comorbidities in subjects drawn from the international registry who did not undergo lead explantation ($n = 254$) were 53.9%, 36.6%, 30.7%, and 27.6%, respectively.

There was no statistically significant difference in the frequency of OCD, depression, anxiety, or ADHD between explanted patients and those not explanted (for OCD, $X^2 (1, n = 257) = 1.62, p = 0.2$; for depression, $X^2 (1, n = 254) = 1.23, p = 0.27$; for anxiety, $X^2 (1, n = 254) = 2.7, p = 0.1$; and for ADHD, $X^2 (1, n = 258) = 0.54, p = 0.46$). Moreover, there were no statistically significant different odds for lead removal in the cases of specific psychiatric comorbidities – for OCD 2.11 (95% CI = 0.65–6.81), for depression 1.79 (95% CI = 0.63–5.11), for anxiety 2.36 (95% CI = 0.83–6.74), and for ADHD 0.62 (95% CI = 0.17–2.26). Similarly, when psychiatric comorbidities were pooled, there was no statistically significant difference in the frequency of having any psychiatric comorbidity when comparing explanted patients to those not explanted ($X^2 (1, n = 269) = 2.37, p = 0.12$).

4. Discussion

The rate of DBS lead explantation in patients enrolled in the International Tourette Syndrome Registry and Database ($n = 269$) was 5.6%, which was lower than reported in the literature. Although there was a variability in the number of subjects contributed by different centers (to the database), none of the centers contributed the majority. Indeed, 11 centers contributed ten or more subjects each (Supplemental Table 1). Servello et al. reported a rate of 22.9% for hardware removal in a cohort ($n = 11/48$) of TS DBS patients drawn from a single center in Italy [7]. A systematic review also reported an increased risk of DBS surgical complications leading to hardware removal (explantation) in more recent DBS indications inclusive of TS [5]. The reason for the difference in hardware explantation between this report and Servello

Table 4

Change in the Yale Global Tic Severity Scale (YGTSS) scores.

Patient	Motor subscore change at 6 months	Phonic subscore change at 6 months	Total score change at 6 months	Motor subscore change at 12 months	Phonic subscore change at 12 months	Total score change at 12 months	Motor subscore change at 24 months	Phonic subscore change at 12 months	Total score change at 24 months
1			-69			-53			-77
2			2			-14			
3			-39			-49			
4			-34			-54			-54
5						42			
6	-3	-3	-6	-6	-11	-17	-11	-11	-32
7	-1	0	-1	-1	-2	-13	-2	-4	-16
8	-4		-4	-6		-6	-9		-19
9				-6	-10	-16			
10			-30			-47			-21
11			-39			-37			-24
12			-29			-30			-43
13			-16			-35			-30
14			-10			-34			
15	-12	-10	-52	-5	-3	-18	-8	-11	-29

et al. is not clear. Servello et al. report a possible role for poor compliance of patient and caregivers, which might have improved with better education. The role of education and its impact on DBS outcomes and expectations, as well as the issue of anticipation and management of emerging concerns, have been possibly associated with improved outcomes [8]. A more systematic evaluation for potential educational interventions is needed.

In the TAA database, infections accounted for nearly half of the explantations. These infections occurred either at the level of the IPG pocket or involved dermal erosion. There are several potential reasons for an increased rate of infection in TS DBS. Picking, poking, scratching, and touching behaviors have been reported as more common in TS patients, especially those with OCD symptoms [9]. OCD was the most commonly reported TS comorbidity in the International Tourette Syndrome Registry and Database. The rates of these behaviors in our cohort were consistent with the general population of TS patients [10,11]. In addition to direct picking behaviors, an alteration in the immune response in TS has been proposed, but has not been proven [12,13].

Following the resolution of the infection, it is not clear why the explanted patients were not reimplanted, as this information was not systematically collected. Notable was patient 3 who developed recurrent infections of the DBS system leading to a final decision of explantation without reimplantation.

Three patients developed discomfort from the DBS hardware requiring explantation, and this accounted for 1.1% of the total patient population in the cohort, which was the same rate reported in other indications such as Parkinson's disease and hyperkinetic disorders [14]. Furthermore, of a total of 48 patients who received surgery at the age of 18 years or younger, only three patients were explanted (6.3%). One was explanted for tic resolution, another for IPG pocket infection, and the third for the formation of a cyst at the tip of the lead. The patient who developed tic resolution was implanted at the age of 17 years and explanted at the age of 25 years. A meta-analysis reported on the use of DBS in 58 children and adolescents with TS and identified six cases of hardware explantation (10.3%) [15]. Three patients reported the resolution of tic symptoms, which was higher than our observed rate.

Another reason for explantation of DBS hardware has been a lack of perceived benefit, and this was the case for one patient in the registry. Contrary to expectations, he had a clear improvement in the total YGTSS score at 6 months, 12 months, or 24 months (Table 4). A retrospective study assessed 13 patients with TS who received DBS at the Beijing Tiantan Hospital. Three patients had their hardware removed, between four to five years post-implantation, due to a lack of perceived benefit despite having a notable decrease in their total YGTSS scores (54.2%, 60%, and 83.6%) [16]. The authors proposed several potential explanations, including Chinese cultural expectations and the psychosocial difficulties relating to altered post-DBS self-perception [17]. Future studies are needed to evaluate post-DBS self-perception [18]. This dissociation between tic improvement and perceived benefit highlights the importance of evaluating drivers of impairment in TS. Tics, despite their frequency and severity, might not be the drivers of disability, rather psychiatric comorbidities, social difficulties, or academic limitations may all be important considerations. This point emphasizes the importance of the published consensus guidelines which focus on the significance of a thorough multidisciplinary approach for evaluating patients with TS for possible DBS [3].

This study had both advantages and limitations. An advantage was the large cohort with patients drawn from a range of countries. The sample was thus more representative and the analysis less sensitive for the bias of single clinic studies (since the registry was not dependent on the authors publishing their findings). Furthermore, systematic reviews and meta-analyses may have biased in favor of studies where complications were highlighted and used as key words [5]. At the same time, the underreporting of cases in the registry and database is possible as, despite following specific templates and scales, it is voluntary and can sometimes be delayed. Participating centers might not report all their

cases, such as those lost to follow-up or with incomplete data sets. Patient selection, evaluation schedule, symptom/disorder scales used, and the report of complications can vary in detail in registries and databases. The registry and database has employed mechanisms to attempt to decrease these biases as much as possible [6]. The registry and database does not have statistical data on whether the participating centers have submitted data on all their subjects with TS who received DBS and whether some subjects refused to be included. Moreover, a limitation was that the small number of explantations in our total cohort reduced the power to identify and to clarify potential risk factors. Further, the information available regarding psychiatric comorbidities was not detailed and was categorical (e.g. presence versus the absence of the condition). Finally, detailed information on the rationale for explantation, and the decision for not reimplanting was not available.

In summary, the International Tourette Syndrome Registry and Database cohort revealed a low rate of explantation in TS (5.6%). Almost half of the cases of explantation were associated with infection, and only one case was associated with tic resolution. There were no associations of the risk of explantation with the presence of specific psychiatric comorbidities. The presence or absence of specific psychiatric comorbidities might not have altered the risk of explantation, though this was not based on the severity of scales. Further work on elucidating the role of these comorbidities in TS DBS explantation is needed. The presence of psychiatric symptoms should not be considered as a contraindication for DBS, however properly addressing and considering psychiatric comorbidities should be included in an integrated DBS multidisciplinary risk-benefit evaluation.

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Author roles

WD: conception, organization, execution, design, execution, and writing of the first draft; AFGL, AYM, DS, FM, JZ, and TFG: critical review and critique of drafts; MSO: conception, design, and review and critique.

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Domenico Servello and Tommaso Francesco Galbiati report no financial interests.

Appendix A. Supplementary data

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