

Clinical Characteristics of Patients with Parkinson's Disease and Essential Tremor Undergoing Deep Brain Stimulation Surgery at Columbia University Medical Center, 2009–2014

Meir Kestenbaum MD¹, Daphne Robakis MD¹, Blair Ford MD¹, Roy N. Alcalay MD MSc¹ and Elan D. Louis MD MSc^{2,3,4}

¹Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

²Department of Neurology and ³Center for Neuroepidemiology and Clinical Neurological Research, Yale School of Medicine, and ⁴Center for Neuroepidemiology and Clinical Neurological Research, Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, CT, USA

ABSTRACT: **Background:** Only a minority of patients with essential tremor (ET) and Parkinson's disease (PD) undergo deep brain stimulation (DBS) surgery. Data on patient selection factors are useful.

Objectives: To compare the clinical characteristics of ET and PD patients who underwent DBS surgery with those of patients who had not undergone surgery.

Methods: We abstracted data from the electronic medical records of 121 PD and 34 ET patients who underwent DBS surgery at Columbia University Medical Center during the period 2009–2014. We compared this group with 100 randomly selected PD and 100 randomly selected ET patients at the Center who had not undergone DBS surgery.

Results: Among other differences, age of onset in PD patients who had undergone surgery was younger than in those who did not: 14.9% vs. 3.0% with onset before age 40 ($P = 0.003$). They had also tried nearly double the number of medications (3.9 ± 1.7 vs. 2.3 ± 1.5 , $P < 0.001$). Interestingly, there was no difference in the proportion of patients with tremor (81.0% vs. 88.0%, $P = 0.16$). Medical co-morbidities (heart and lungs) were less common in the PD patients who underwent DBS surgery. In the ET group, tremor causing impairment in activities of daily living occurred in all surgical patients compared to 73.0% of non-surgical patients ($P < 0.001$). The former had tried nearly double the number of medications compared to the latter (3.2 ± 1.7 vs. 1.3 ± 1.3 , $P < 0.001$).

Conclusions: These data add to our understanding of the numerous clinical factors associated with patient referral to DBS surgery.

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For Editorial see page 424

Over the last two decades, deep brain stimulation (DBS) surgery has become an important treatment for patients with essential tremor (ET) and Parkinson's disease (PD) [1,2]. The proportion of patients with these disorders who undergo DBS surgery is low (1.4% of PD and 2.9% of ET patients in one recent estimate) [3]; hence, surgical patients are highly selected. In this study we focused on the clinical features that distinguished patients who underwent DBS surgery from those who did not.

Proper selection of patients who will benefit from DBS surgery is critical to its success. The most suitable PD candidates are those with motor fluctuations, dyskinesias, or medication-refractory tremor that are not adequately controlled with optimized medical therapy, and who have an excellent response to levodopa, with a normal or minimally affected cognitive status and no serious co-morbidities [4–6].

Previous studies have described the clinical features of patients undergoing DBS surgery [7–9]. Data from these studies have shown that most PD patients who undergo DBS surgery range in age from 40 to 60 years, have a mean disease duration of 10–15 years, and have symptoms and signs that are generally responsive to DBS surgery, including akinesia, rigidity, tremor, dystonia and dyskinesias [10]. Yet most published studies focus on the effects of DBS surgery by comparing the pre- and postoperative states.

To the best of our knowledge, the design of this study differs from other published studies. We focused on the preoperative clinical characteristics of PD and ET patients, comparing patients undergoing DBS surgery with a group of randomly selected patients treated more conservatively. To that end, the primary aims of the current study were: (i) to compare the clinical characteristics of PD patients who underwent DBS surgery with those of PD patients who had not undergone surgery, and (ii) to compare the clinical characteristics of ET patients who underwent DBS surgery with those of ET patients who

had not undergone surgery. Two additional aims were (i) to compare the two surgical groups with one another (i.e., ET with PD), and (ii) to examine the clinical characteristics in patients who had not had surgery. These data are likely to increase our understanding of the factors affecting patient referral to DBS.

PATIENTS AND METHODS

M.K. searched the computerized billing database at the Center for Parkinson's Disease and Other Movement Disorders, Columbia University Medical Center (CUMC) for all ET and PD patients who underwent DBS surgery at the Center during the 5 year period 1 January 2009 to 8 May 2014. All electronic medical records of the patients during the above-mentioned dates were reviewed (M.K.), and data were abstracted. In addition, M.K. reviewed the electronic medical records of 100 randomly selected PD and 100 randomly selected ET patients who were followed at our center during the same time period but did not undergo DBS surgery. This study was approved by the Columbia University Internal Review Board.

DATA ABSTRACTION

Using data abstraction forms designed at the start of the study, demographic data (e.g., gender, age) as well as data on clinical symptoms and their effect on activities of daily living, cognitive function, family history of PD and ET, and medications tried throughout the clinical course were abstracted and coded in a study-specific computerized database. In addition, data on the indications for referral for DBS, reasons for not referring for DBS surgery, and the target of DBS were abstracted. Age of symptom onset was determined according to the history provided by the patient. Duration of symptoms prior to DBS surgery was calculated by subtracting the age of symptom onset from the patient's age at the time of DBS surgery. Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) test, when available [11]. Presence of symptoms and signs, including wearing off, dyskinesia, tremor (in the limbs, head and voice), freezing of gait, and history of falls were abstracted from the history and neurological examinations. The presence of medical co-morbidities, especially heart and lung diseases, were abstracted from the patient's history. Family history (first-degree) of PD, ET, or tremor without a definite diagnosis was abstracted from the history. Information on physician-patient discussions about DBS surgery were similarly abstracted from the history.

The number of movement disorder medications that the patient had taken throughout the course of disease was obtained from the patient history and the medication list provided by the patient at each medical encounter. For PD patients, any levodopa-containing preparations, dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors, anticholinergic for-

mulations, botulinum toxin and amantadine were recorded. For ET patients, beta-blockers, primidone, gabapentin, topiramate, sodium oxybate and benzodiazepines were recorded.

In ET patients, the effect of tremor on performance of daily activities was assessed according to the patient's history of ability to eat, drink, dress or write and according to the findings on examination. If the patient reported any tremor-related difficulty performing these activities, or if a moderate or severe tremor was seen during the daily activities performed during the neurological examination (e.g., writing, drinking), the patient was coded as having impairment in activities of daily living.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS software (Version 21.0). We compared ET and PD patients who had undergone DBS surgery to those with the same diagnoses who did not undergo DBS surgery. In addition, we compared ET patients who had undergone DBS surgery with PD patients who had undergone DBS surgery. We used chi-square tests for categorical variables and Student *t*-tests for continuous variables.

RESULTS

During the 5 year time interval, 186 patients underwent DBS surgery (121 PD, 34 ET, 15 ET and PD, and 16 others). In the PD group (N=121) the most common indications for DBS surgery were wearing off and motor fluctuations, dyskinesia and tremor [Table 1]. The most common targets were the subthalamic nucleus (N=110, 90.8%) followed by the globus pallidum interna (N=9, 7.4%) and the ventral intermediate (VIM) nucleus of the thalamus (N=2, 1.7%). The majority of patients underwent bilateral DBS surgery (N=99, 81.8%); 22 (18.2%) underwent unilateral surgery. Compared with 100 PD patients who had not undergone DBS surgery, the PD patients who had undergone surgery had a younger mean age of symptom onset [Table 1]. In this cohort, 18/121 PD patients (14.9%) who underwent DBS surgery had onset of symptoms before the age of 40 years compared to 3/100 (3.0%) who did not undergo DBS surgery (chi-square 8.98, *P* = 0.003). A larger proportion of PD patients who underwent DBS surgery had wearing off, dyskinesias, dystonia, and freezing of gait compared with PD patients who had not undergone surgery. They had also tried nearly double the number of medications compared to those who had not had surgery (3.9 ± 1.7 vs. 2.3 ± 1.5 , *P* < 0.001) [Table 1]. There was no difference in the MoCA score or proportion of patients with a history of falls. Interestingly, there was no difference in the proportion with tremor (81.0% vs. 88.0%, *P* = 0.16). Medical co-morbidities (heart and lungs) were less common in the PD patients who underwent DBS surgery compared to patients who did not.

In the ET group [Table 2], the most common indication for DBS surgery was tremor causing impairment in activities of

Table 1. Demographic and clinical characteristics of PD patients who underwent DBS surgery vs. those who did not

	PD patients who underwent DBS surgery	PD who did not undergo DBS surgery	P value
No. of patients	121	100	
Gender (male)	76 (62.8)	68 (68.0)	0.25*
Age at onset of symptoms (years)	51.4 ± 9.5	61.4 ± 11.5	< 0.001 [†]
Age at DBS surgery (years)	63.2 ± 8.6	NA	NA
Current age (years)	66.7 ± 8.7	68.0 ± 13.3	0.42 [†]
Duration of symptoms prior to DBS surgery (years)	11.7 ± 4.9	NA	NA
MoCA score	25.2 ± 3.6	24.2 ± 4.2	0.36 [†]
Wearing off	112 (92.6)	29 (29.0)	< 0.001*
Dyskinesias	110 (90.9)	23 (23.0)	< 0.001*
Tremor	98 (81.0)	88 (88.0)	0.16*
Dystonia	46 (38.0)	15 (15.0)	< 0.001*
Freezing of gait	48 (39.7)	14 (14.0)	< 0.001*
History of falls	29 (24.0)	20 (20.0)	0.48*
Family history of PD	21 (18.6)	15 (16.1)	0.24*
Medical co-morbidities (heart and lung)	11 (9.3)	22 (22.0)	0.04*
No. of movement disorder medications tried	3.9 ± 1.7	2.3 ± 1.5	< 0.001 [†]

All values represent mean ± standard deviation or number (percentage)

*Chi-square test, [†]Student t-test

DBS = deep brain stimulation, MoCA = Montreal Cognitive Assessment, NA = not applicable, PD = Parkinson's disease

Table 2. Demographic and clinical characteristics of ET patients who underwent DBS surgery vs. those who did not

	ET undergoing DBS surgery	ET not undergoing DBS surgery	P value
No. of patients	34	100	
Gender (male)	14 (41.2)	57 (57.0)	0.11*
Age at onset of symptoms (years)	40.6 ± 18.7	47.4 ± 23.2	0.13 [†]
Age at DBS surgery (years)	66.3 ± 12.3	NA	NA
Current age (years)	70.6 ± 12.5	65.8 ± 16.7	0.13 [†]
Duration of symptoms prior to DBS surgery (years)	25.6 ± 14.8	NA	NA
MoCA score	23.7 ± 4.9	27.2 ± 2.1	0.08 [†]
Hand tremor	100 (100)	100 (100)	1.00
Head tremor	20 (58.8)	49 (49.0)	0.32*
Voice tremor	12 (35.3)	28 (28.0)	0.42*
Family history of ET/tremor	19 (59.4)	56 (56.0)	0.74*
Medical co-morbidities (heart and lung)	15 (45.5)	17 (17.0)	0.02*
Impairment in ADL	100 (100)	73 (73.0)	0.001*
No. of movement disorder medications tried	3.2 ± 1.7	1.3 ± 1.3	< 0.001 [†]

All values represent mean ± standard deviation or number (percentage)

*Chi-square test, [†]Student t-test

ADL = activities of daily living, DBS = deep brain stimulation, ET = essential tremor, MoCA = Montreal Cognitive Assessment, NA = not applicable

Table 3. Demographic and clinical characteristics of ET vs. PD patients who underwent DBS surgery

	PD undergoing DBS surgery	ET undergoing DBS surgery	P value
No. of patients	121	34	
Gender (male)	76 (62.8)	14 (41.2)	0.02*
Age of onset of symptoms (years)	51.4 ± 9.5	40.6 ± 18.7	<0.001 [†]
Age at DBS surgery (years)	63.2 ± 8.6	66.3 ± 12.3	0.09 [†]
Current age (years)	66.7 ± 8.7	70.6 ± 12.5	0.04 [†]
Duration of symptoms prior to DBS surgery (years)	11.7 ± 4.8	25.6 ± 14.7	<0.001 [†]
MoCA score	25.2 ± 3.6	23.7 ± 4.9	0.36 [†]
First affected body region by motor symptoms = hand	77 (77.0)	100 (100.0)	0.02*
Tremor	98 (81.0)	100 (100.0)	0.01*

All values represent mean ± standard deviation or number (percentage)

*Chi-square test, [†]Student t-test

DBS = deep brain stimulation, ET = essential tremor, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease

daily living (eating, drinking, writing, etc.), which occurred in all patients who underwent surgery (N=34) compared to 73.0% (N=73) of the patients who did not ($P < 0.001$). In all ET patients, the VIM nucleus of the thalamus was the target for DBS surgery. The majority of patients (N=23, 67.6%) underwent bilateral rather than unilateral DBS surgery. They had also tried nearly double the number of medications compared to those who had not had surgery (3.2 ± 1.7 vs. 1.3 ± 1.3 , $P < 0.001$) [Table 2]. The two groups did not differ by age of symptom onset, body regions affected by tremor, or MoCA score.

We also compared PD and ET patients who underwent DBS surgery [Table 3]. More of the PD patients were males. The ET patients had an earlier age of symptom onset, more prolonged duration of symptoms prior to DBS surgery, and the first affected region was more often the hands, compared to PD patients. There were no differences in the MoCA score.

The charts of 100 PD and 100 ET patients who did not undergo DBS surgery were reviewed. In 35% of ET patients (N=35) and in 16% of PD patients (N=16) the possibility of undergoing DBS surgery was discussed during the clinical encounter while in the remaining patients it was not. Among patients with whom DBS surgery was discussed, the reasons for not proceeding with DBS surgery were as follows: disease severity not causing severe impairment in activities of daily living; preference of both physician and patient to further adjust medical treatment prior to surgery (N=9, 56.3% in the PD and N=31, 88.6% in the ET group); medical contraindication to surgery, mainly significant cognitive symptoms (N=5, 31.3% in the PD and N=1, 2.9% in the ET group); and refusal by the patient to undergo DBS surgery despite the recommendation

of the treating physician (N=2, 12.5% in the PD group, and N=3, 8.6% in the ET group).

A subgroup of 28 of the 100 PD patients who were not treated with DBS surgery had wearing off and motor fluctuations, and the majority of them experienced dyskinesia as well (N=19 patients, 67.8%). The option of undergoing DBS surgery was discussed with 11 of the 28 (39.3%). In six of them, further medication adjustments were recommended. Although discussed with the patients, DBS surgery was contraindicated in 3 of 11 patients due to cognitive decline, and 2 of 11 patients refused to undergo DBS surgery despite the recommendation of their physicians.

DISCUSSION

As expected, PD patients undergoing surgery had more wearing off and dyskinesias compared to those not referred for surgery, as these symptoms respond well to DBS surgery. Dystonia and freezing of gait were also more common in the surgically treated group. Interestingly, however, the two groups did not differ with respect to the proportion of patients affected with tremor. This result is surprising especially due to the excellent response of tremor to DBS surgery in PD patients [12,13] and the debilitating effect that tremor has on several domains of quality of life in PD patients [14]. This finding could suggest that in PD patients the presence of tremor is less of an indicator for referral for DBS surgery compared to other motor symptoms such as wearing off, dyskinesia, dystonia and freezing of gait. On the other hand, this finding could be explained by the fact that tremor, whether at rest, postural or kinetic, occurs in the large majority of PD patients at some point during their illness [14,15], both in patients undergoing DBS surgery and in patients treated more conservatively. Moreover, tremor has commonly been seen early in the course of PD and in many cases it is the presenting symptom of PD [16]. In contrast, dyskinesias, wearing off and freezing of gait more commonly occur in advanced PD patients with more prolonged duration of symptoms [17,18], which explains their preponderance in the PD patients undergoing DBS surgery compared to those not undergoing DBS surgery. In addition, tremor severity was not specifically assessed in this study. It is possible that a higher proportion of patients with severe tremor are referred for DBS surgery compared to those treated only with medications.

Compared with 100 PD patients who had not undergone DBS surgery, PD patients undergoing DBS surgery had a younger mean age of symptom onset and a greater proportion of them had young-onset PD. Indeed, age of onset was 10 years younger among the surgical patients. Interestingly, however, the groups did not differ with respect to current age. These data likely reflect a longer duration of disease in the surgical group, with an attendant greater severity of symptoms and a willingness to try additional (i.e., surgical) options.

Both PD and ET patients undergoing DBS surgery had taken a larger number of medications to treat their movement disorder compared to patients not undergoing surgery. This result is not surprising since one of the indications for referral to DBS surgery is the presence of symptoms that are resistant to medical therapy. To the best of our knowledge, prior studies in PD patients reported the daily levodopa dose that patients were taking prior to the DBS surgery [12,19], but they did not report the number of medications that were tried throughout the course of the disease. Similarly, prior studies in ET patients did not report the number of medications that were tried to treat the movement disorder.

In our cohort, ET patients had on average longer disease duration prior to DBS surgery compared with PD patients. This is consistent with prior studies reporting an average duration of symptoms in PD patients of 10–15 years at the time of DBS surgery [20,21] and more than 30 years in the ET patients at the time of DBS surgery [22]. This finding suggests a slower rate of progression of symptoms and disability in ET patients compared to PD patients. It should be mentioned that most of the patients in this study underwent DBS surgery prior to the publication of the EARLYSTIM study, which suggested that earlier referral of PD patients to DBS surgery could improve quality of life. It is possible that in the future the duration of disease prior to DBS surgery would decrease.

The surgical and non-surgical groups did not differ by gender. While previous studies in other fields of medicine have reported that women are less likely to undergo aggressive treatments compared to men [23,24], we did not find such a difference. In fact, in the ET group there was a non-significant trend towards more women undergoing DBS surgery.

In cases where DBS surgery was discussed but the patient did not undergo surgery, it was not recommended as an immediate course of action because the disease was not causing severe impairment in activities of daily living and there was a preference on the part of the physician and patient to further adjust medical treatment prior to surgery. In a small number of cases, medical contraindications to DBS surgery and patient refusal were the reason for not proceeding with DBS surgery. A previous study looking at the quality of referral for DBS consideration found that movement disorder specialists were more likely to refer good DBS candidates for DBS consideration than were general neurologists and primary care physicians [25]. As far as we know, there are no prior published data on the likelihood of introducing the option of DBS surgery to PD patients. Our data show that 2–3% of patients in both the ET and PD group were referred for DBS surgery by their physicians but refused to undergo surgery. Understanding the reasons for their refusal and possibly better addressing the patients' concerns regarding the procedure and outcomes of the surgery could increase the number of patients undergoing DBS surgery.

Our study has limitations. Firstly, it is retrospective in design and based on chart review. If documentation of patient encounters was not complete, the data obtained might not be complete. Second, our study looked at a 5 year time period, 2009 to 2014, and it is likely that extension of this period would have increased the number of patients with whom DBS surgery was discussed, possibly increasing the number of patients referred for DBS surgery. It is possible that with time, as disability from symptoms increases, some of the patients in the non-surgical group would have been referred for DBS surgery. Moreover, it is likely that the refusal rate of patients to undergo DBS surgery would decline if disabling symptoms persist to a point of affecting quality of life. In addition, it is possible that a small number of our non-surgical patients decided to undergo DBS surgery at another medical center.

In conclusion, our data, retrieved by retrospective chart review of a 5 year period of DBS surgery experience in a large tertiary center, provide additional empirical information on the clinical characteristics of PD and ET patients undergoing DBS surgery compared to those treated with medications only. These data are likely to be useful for assessing the likelihood of patient referral to DBS surgery and thus help estimate the number of patients who are potential surgical candidates.

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Correspondence

Dr. M. Kestenbaum

Dept. of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

Tel: (1-347) 324-1702

Fax: (1-212) 305-1304

email: meirkes@gmail.com

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“There is always something to do. There are hungry people to feed, naked people to clothe, sick people to comfort and make well. And while I don't expect you to save the world, I do think it's not asking too much for you to love those with whom you sleep, share the happiness of those whom you call friend, engage those among you who are visionary, and remove from your life those who offer you depression, despair, and disrespect”

Nikki Giovanni (b. 1943), American poet, writer, commentator, activist, and educator, known as the “Poet of the Black Revolution”