

Brief Reports

Comparison of Parkinson's Disease Patients' Characteristics by Indication for Deep Brain Stimulation: Men Are More Likely to Have DBS for Tremor

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Abstract

Background: We investigated whether the characteristics of Parkinson's disease (PD) patients differ based on the primary indication for deep brain stimulation (DBS).

Methods: We reviewed data for 149 consecutive PD patients who underwent DBS at the University of Virginia. Patients were categorized based on primary surgical indication, and clinical characteristics were compared between groups.

Results: Twenty-nine (93.5%) of 31 PD patients who underwent DBS for medication refractory tremor were men, and 66 (62.3%) of 106 PD patients who underwent DBS for motor fluctuations were men ($p = 0.001$). Other primary indications for DBS were tremor and fluctuations ($n = 5$), medication intolerance ($n = 5$), and dystonia ($n = 2$).

Discussion: Patients who underwent DBS for medication refractory tremor were predominantly men, while patients who had DBS for motor fluctuations approximated the gender distribution of PD. Possible explanations are that men with PD are more likely to develop medication refractory tremor or undergo surgery for medication refractory tremor in PD compared to women.

Keywords: Deep brain stimulation, Parkinson's disease, gender, tremor, motor fluctuations

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Ethics Statement: This study was reviewed by the authors' institutional ethics committee and was considered exempted from further review.

Introduction

Deep brain stimulation (DBS) can be an effective treatment for certain motor symptoms of Parkinson's disease (PD) that become refractory to oral medications.¹ The two primary indications for DBS surgery in PD are motor fluctuations and medication refractory tremor.² Motor fluctuations describe the vacillation between "on" periods when motor symptoms are improved by medication and "off" periods when medication response wanes or is absent. Motor fluctuations may or may not be accompanied by troublesome dyskinesias. In PD, DBS is also indicated for a disabling tremor that persists despite adequate trials of dopaminergic medications or when patients are unable to reach adequate doses of dopaminergic medications due to dose-limiting side effects. There has been much research about patient outcomes based on surgical indication and other patient characteristics.² No studies have explicitly investigated whether patient characteristics differ depending on the primary indication for surgery, although prior studies suggest that there may be a greater proportion of men who undergo DBS for medication refractory tremor.³⁻⁵ The objective of this study was to determine whether the characteristics of PD patients, including sex, disease characteristics, Unified PD Rating Scale scores, and cognitive scores, differ depending on their primary indication for DBS surgery.

Methods

Participants

We analyzed data for 149 consecutive PD patients who underwent their first deep brain stimulation procedure between January 1, 2010, and August 31, 2017, at the University of Virginia. The diagnosis of PD was confirmed by a movement disorders neurologist as part of the pre-surgical evaluation. The institutional review board at the University of Virginia approved this study.

Clinical data

We obtained patient characteristics from a clinical database and chart review. Primary surgical indication was determined based on an independent evaluation by a movement disorders neurologist experienced with DBS, in conjunction with patient-reported symptoms. Procedure notes were used to corroborate the surgical indication when available. Patients were assigned to the following groups: medication refractory tremor, motor fluctuations (with or without dyskinesias), motor fluctuations and tremor (when neither could be determined to be the primary indication), adverse effects of medications (mainly intolerable side effects such as nausea), and dystonia. Within the medication refractory tremor group, the maximal levodopa equivalent daily dose was determined for each patient.⁶

Patients completed Unified Parkinson's Disease Rating Scale (UPDRS) parts 1, 2, and 3 and comprehensive neuropsychological testing as part of their pre-surgical evaluation. As the evaluations were conducted for clinical purposes, not all patients completed the same neuropsychological tests. Most patients were administered the Montreal Cognitive Assessment (MoCA) as a global measure of cognition. Other tests included in this study that were completed by a majority of patients included the Trail

Making Test A&B, Controlled Oral Word Association (COWA), Semantic Fluency Test (animals), Beck Depression Inventory-II (BDI-II), and Parkinson's Disease Questionnaire-39 (PDQ-39).

Statistical analysis

For the purposes of this study, PD patients whose primary surgical indication was both tremor and motor fluctuations ($n = 5$), medication intolerance ($n = 5$), or dystonia ($n = 2$) were excluded from the primary analysis. Clinical characteristics and assessments were compared between groups based on surgical indication (motor fluctuations or tremor) and gender. Univariate comparisons were performed using Student's *t*-test and chi-squared test of association or non-parametric equivalents when appropriate. A *p*-value < 0.05 was considered statistically significant. All hypothesis tests were two-sided. Analyses were performed using Stata 14 (Statacorp. 2015. College Station, TX: StataCorp LP).

Results

The clinical characteristics and assessments for the 137 patients who underwent DBS for motor fluctuations ($n = 106$) or medication refractory tremor ($n = 31$) are reported in Table 1. There were 4 men and 1 woman who had DBS for treatment of tremor and motor fluctuations, 3 men and 2 women who had surgery for medication intolerance, and 2 men who had surgery for dystonia. Of the 137 patients who had DBS for either motor fluctuations or medication refractory tremor, 95 were men (69.3%) and 42 were women (30.7%). Of the patients who had DBS for medication refractory tremor, the target was subthalamic nucleus (STN) for 23 (74.2%), globus pallidus interna (GPI) for 5 (16.1%), and ventral intermediate nucleus of the thalamus (Vim) for 3 (9.7%). Of the patients who had DBS for motor fluctuations, the target was STN for 47 (46.2%) and GPI for 59 (55.7%).

A greater proportion of men had DBS for medication refractory tremor compared to motor fluctuations (93.5% vs. 62.3%, $p = 0.001$). The mean maximal LEDD within the medication refractory tremor group was 851 mg (SD = 330 mg). PD patients who pursued DBS for medication refractory tremor had a significantly shorter duration of disease (8.3 years vs. 10.7 years, $p = 0.01$) compared to those who had surgery for motor fluctuations. Patients who had DBS for medication refractory tremor also had significantly later age of symptom onset compared to those with motor fluctuations (56.7 years vs. 52.2 years, $p = 0.007$). In bivariate comparisons, there were no significant differences in UPDRS part 1, 2, or 3 score, any of the cognitive measures, PDQ-39 score, or BDI-II score between patients who had DBS for motor fluctuations compared to patients who had DBS for medication refractory tremor ($p > 0.05$; Table 1).

When men and women who underwent DBS for medication refractory tremor or motor fluctuations were compared, there was no difference in either disease duration (9.8 vs. 10.7 years, $p = 0.31$) or age at onset (53.5 vs. 52.5, $p = 0.55$). Women had a significantly worse quality of life compared to men as measured by the PDQ-39 (61.2 vs. 49.2, $p = 0.008$). There were otherwise no significant differences in UPDRS part 1, 2, or 3 score, any of the cognitive measures, or BDI-II between men

Table 1. Characteristics of Parkinson's Disease Subjects with Motor Fluctuations and Medication Refractory Tremor

Baseline Variables	PD Subjects (n = 137)	Motor Fluctuations (n = 106)	Medication Refractory Tremor (n = 31)	p
Men, n (%)	95 (69.3)	66 (62.3)	29 (93.5)	0.001
Years of education, median (IQ range)	14 (12–18) (n = 135)	16 (13–18) (n = 105)	14 (12–16) (n = 30)	0.09
Age of onset, years (SD)	53.2 (8.4)	52.2 (8.0)	56.7 (8.9)	0.007
Age at evaluation, years (SD)	63.1 (7.8)	62.8 (7.4)	65.0 (8.4)	0.17
Duration of disease, years (SD)	10.1 (4.6)	10.7 (4.8)	8.3 (3.6)	0.01
UPDRS Part 1 score, median (I.Q. range)	2 (1.4) (n = 137)	2 (1.4) (n = 106)	2 (1.3) (n = 31)	0.53
UPDRS Part 2 score, mean (SD)	14.6 (6.5) (n = 137)	15.0 (6.6) (n = 106)	13.3 (6.0) (n = 31)	0.19
UPDRS Part 3 score (off), mean (SD)	36.0 (11.2) (n = 122)	36.6 (10.8) (n = 94)	34.0 (12.4) (n = 28)	0.28
MoCA score, median (IQ range)	25 (23–27) (n = 95)	26 (23–27) (n = 72)	25 (23–26) (n = 23)	0.68
BDI-II, median (IQ range)	9 (5–14) (n = 101)	9 (6–15) (n = 77)	6.5 (3.5–12) (n = 24)	0.07
PDQ-39, mean (SD)	52.7 (22.0) (n = 111)	53.8 (22.2) (n = 88)	48.6 (20.9) (n = 23)	0.31
Trail making Test A, mean (SD)	42.5 (10.3) (n = 127)	42.4 (10.4) (n = 99)	42.7 (9.9) (n = 28)	0.90
Trail making Test B, mean (SD)	42.8 (11.3) (n = 125)	42.4 (11.7) (n = 98)	44.1 (9.6) (n = 27)	0.48
COWA, mean (SD)	44.9 (11.2) (n = 84)	46.2 (11.1) (n = 65)	40.5 (10.6) (n = 19)	0.052
Semantic fluency, mean (SD)	46.5 (10.1) (n = 92)	47.0 (10.0) (n = 68)	44.9 (10.6) (n = 24)	0.38

Abbreviations: BDI-II, Beck Depression Inventory-II; COWA, Controlled Oral Word Association Test; I.Q., Interquartile Range; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson's Disease Questionnaire-39; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale. Bold values indicate statistical significance ($p < 0.05$).

and women who underwent DBS for motor fluctuations or medication refractory tremor ($p > 0.05$; Table 2).

Discussion

In this single institution series, PD patients who underwent DBS for medication refractory tremor were predominantly men (93.5%), while the percentage of men who had DBS for motor fluctuations (62.3%) more closely approximated the commonly reported gender distribution of PD (3 men:2 women).⁷ A review of prior studies also shows that men appear more likely to have surgical intervention for tremor in PD. A retrospective case series of 15 patients who underwent DBS for “benign tremulous parkinsonism” was 80% men,⁴ and another study comparing Vim and STN DBS in PD patients with medication refractory tremor included 15 men (83%) and 3 women.⁵ In a clinical trial of focused ultrasound thalamotomy for treatment of medication refractory tremor

in PD, 25 of 27 participants were men (93%).³ In comparison, in a clinical trial of DBS for PD patients with “parkinsonian motor symptoms or dyskinesias,” and not specifically tremor, 64% were men.¹

We show that in a large, consecutive clinical population of PD patients who underwent DBS surgery at a high-volume DBS center, men are more likely to have DBS for medication refractory tremor compared to women. Potential explanations for the discrepancy are that men are more likely to have refractory tremor, they are more likely to be referred for and offered surgical treatment for medication refractory tremor (clinician bias), and/or they are more likely to pursue surgical intervention for medication refractory tremor (patient preference).

Prior studies consistently show that the proportion of men who have DBS surgery exceeds the expected gender distribution of PD.⁸ One potential explanation offered for this finding is that women are more likely to be risk-averse and therefore less likely to undergo a surgical procedure than men.⁹ Our finding that men had lower

Table 2. Characteristics of Parkinson's Disease Subjects by Gender

Baseline Variables	PD Subjects (n = 137)	Men (n = 95)	Women (n = 42)	p
Years of education, median (IQ range)	14 (12–18) (n = 135)	16 (13–18) (n = 105)	14 (12–16) (n = 30)	0.09
Age of onset, years (SD)	53.2 (8.3)	53.5 (8.8)	52.5 (7.3)	0.55
Age at evaluation, years (SD)	63.3 (7.6)	63.3 (7.5)	63.3 (7.9)	0.97
Duration of disease, years (SD)	10.1 (4.6)	9.8 (5.0)	10.7 (3.8)	0.31
UPDRS Part 1 score, median (I.Q. range)	2 (1.4) (n = 137)	2 (1.4) (n = 95)	2 (1.4) (n = 42)	0.61
UPDRS Part 2 score, mean (SD)	14.6 (6.5) (n = 137)	15.1 (6.4) (n = 95)	13.6 (6.6) (n = 31)	0.24
UPDRS Part 3 score (off), mean (SD)	36.0 (11.2) (n = 122)	36.1 (10.6) (n = 85)	35.9 (12.5) (n = 37)	0.94
MoCA score, median (IQ range)	25 (23–27) (n = 95)	25 (23–27) (n = 69)	25.5 (23–27) (n = 26)	0.73
BDI-II, median (IQ range)	9 (5–14) (n = 101)	9 (4–13) (n = 69)	9.5 (7–18.5) (n = 32)	0.09
PDQ-39, mean (SD)	52.7 (22.0) (n = 111)	49.2 (22.4) (N = 78)	61.2 (18.5) (n = 33)	0.008
Trail making Test A, mean (SD)	42.5 (10.3) (n = 127)	42.3 (10.3) (n = 87)	43.0 (10.4) (n = 40)	0.74
Trail making Test B, mean (SD)	42.8 (11.3) (n = 125)	43.2 (10.7) (n = 86)	41.7 (12.5) (n = 39)	0.49
COWA, mean (SD)	44.9 (11.2) (n = 84)	44.1 (11.1) (n = 60)	46.9 (11.3) (n = 24)	0.30
Semantic fluency, mean (SD)	46.5 (10.1) (n = 92)	46.4 (10.4) (n = 68)	46.5 (9.7) (n = 24)	0.98

Abbreviations: BDI-II, Beck Depression Inventory-II; COWA, Controlled Oral Word Association Test; I.Q., Interquartile Range; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson's Disease Questionnaire-39; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale. Bold values indicate statistical significance ($p < 0.05$).

PDQ-39 scores, and therefore better quality of life compared to women at the time of surgery, suggests that for women the risk of surgery was offset by the potential benefit only when their disease-related quality of life was comparatively worse. Importantly, the differences in quality of life did not seem to be related to the indication for surgery, as there was no difference in PDQ-39 score between the motor fluctuations and medication refractory tremor groups. Although there was no difference in UPDRS part 2 scores between the two subgroups, we cannot exclude the possibility that medication refractory tremor may impair job- or hobby-related activities not surveyed in UPDRS part 2 that favor a gender difference in surgical decision-making. Higher PDQ-39 scores among women may also indicate that there is a referral bias, as clinicians may wait to refer women for DBS until their quality of life is worse; however, this specific possibility has not been studied.

Our study provides evidence that the lower utilization of DBS in women may arise from differences in disease manifestations between men and women, that is, men may be more likely to experience a disabling, medication refractory tremor than women. At least at the time of

diagnosis, one study found no difference in tremor scores between men and women.¹⁰ It is unknown if gender differences regarding tremor arise as the disease progresses. Given our finding that patients with medication refractory tremor also had shorter duration of disease at time of surgery, there may be an underlying biological difference in men that predisposes a subset to have medication refractory tremor. Studies have shown that there is higher bioavailability of levodopa in women¹¹ and that women tend to have a better response to levodopa than men.¹² Comparison of local field potentials in the STN showed significant physiological differences in response to levodopa in men and women.¹³ Combined with our findings, these data suggest that men may be more likely to have tremor that is incompletely responsive to dopaminergic medications.

This study is limited by being a retrospective cohort study of patients accumulated from a single center. Regional variation in clinician referral patterns and patient preference may have influenced our findings. Specifically, our center was a site for a clinical trial evaluating focused ultrasound for medication refractory tremor in PD at the same time this patient cohort was collected. This may have affected the number and

characteristics of patients undergoing deep brain stimulation for medication refractory tremor in PD at our center.

In summary, patients who had DBS for medication refractory tremor were predominantly men, while patients who had DBS for motor fluctuations approximated the gender distribution of PD. Understanding the biological or social determinants of this gender difference may influence future treatment approaches.

Authors' Roles

1. Research Project
 - a. Conception: WAD, MJB, AP
 - b. Organization: WAD, MJB, AP
 - c. Execution: WAD, MJB, AP, SAS, DSH, MBH, WJE, BBS
2. Statistical Analysis
 - a. Design: WAD, MJB, AP, JLF
 - b. Execution: WAD, MJB, AP, JLF
 - c. Review and critique: WAD, MJB, AP, JLF
3. Manuscript
 - a. Writing of the first draft: WAD
 - b. Review and critique: WAD, MJB, AP, SAS, DSH, MBH, BBS, WJE, JLF

Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This study was approved by the IRB-HSR at the University of Virginia as IRB-HSR #19377. Informed consent was not obtained.

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