Original Article

Gender influence on selection and outcome of deep brain stimulation for Parkinson's disease

Shyambabu Chandran, Syam Krishnan, Ravi Mohan Rao, S. Gangadhara Sarma, P. Sankara Sarma[1], Asha Kishore

Comprehensive Care Centre for Movement Disorders, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, [1]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

Abstract

Background: Gender differences exist in Parkinson's disease (PD), both in clinical manifestations and response to medical treatment. We investigated whether gender differences occur in the clinical characteristics of patients selected for bilateral subthalamic nucleus deep brain stimulation (STN DBS) or in the outcome when resource limits influence treatment choices made by patients. **Materials and Methods:** Fifty-one consecutive patients were evaluated 1 month before, and 12 months after bilateral STN DBS. All patients were rated using Unified Parkinson's Disease Rating Scale, Parkinson's Disease Quality of Life (PDQL) Scale, Addenbrooke's Cognitive Examination and Beck Depression Inventory. **Results:** Pre-operative characteristics did not differ between the genders except for lower doses of drugs ($P = 0.03$), worse emotional scores in PDQL ($P = 0.01$) and worse depression ($P = 0.03$) in women. There was no gender difference in the surgical outcome, except a lesser reduction of dopaminergic drugs in women. Depression and quality of life (QOL) improved equally well in women and men. **Conclusion:** Bilateral STN DBS is equally efficacious in both genders as a treatment for motor complications of PD and for improving QOL. Women are likely to be undertreated because of more severe dyskinesia and may experience less emotional well-being, and could therefore potentially benefit from earlier surgical treatment.

Key Words

Deep brain stimulation, gender differences, Parkinson's disease

For correspondence:
Dr. Asha Kishore, Comprehensive Care Centre for Movement Disorders, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram - 695 011, Kerala, India.
E-mail: ashakishore99@gmail.com

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Introduction

Parkinson's disease (PD) affects 1% of people over the age of 50 years, though unrecognized early symptoms of the disease may be present in as many as 10% of those over 60 years of age.[1,2] Gender difference exists in the incidence and prevalence of PD, being 1.5-2 times[3-8] higher in men than women. The disease also manifests at a later age in women by a mean of 2.2 years.[9] Women with PD have better motor scores in Unified Parkinson's Disease Rating Scale (UPDRS), but higher prevalence of dyskinesia.[10,11] These gender differences are attributed to differences in hormonal and life style factors and differences in exposure to risk factors for PD.[10] Even though the precise nature of the role of estrogen in PD remains unclear, differences in circulating levels of estrogens in men and women could be an important determinant of the differences in clinical manifestations.[10] When such gender differences exist in the risk of developing PD, severity of motor symptoms and treatment related motor complications, it is essential to examine if gender differences influence selection and outcome of surgical treatment for motor complications of PD, particularly in different ethnic populations.

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Deep brain stimulation of the sub thalamic nucleus (STN DBS) has emerged as an effective treatment for the management of motor fluctuations and dyskinesias that are not optimally controlled with medications.[12,13] Hariz *et al.*,[14] in their surgical series of 38 patients who underwent stereotactic neurosurgery concluded that women are probably selected less frequently and later than necessary for surgical treatment. These sort of gender-based differences are more likely to occur in resource-poor countries like India, where the enormous cost of surgical treatment of PD is often met by patients themselves. We undertook this study to address the gender differences in

the pre-operative characteristics and post-operative outcome among 51 consecutive Indian patients who underwent STN DBS at our center.

Materials and Methods

Fifty-one consecutive patients who underwent bilateral STN DBS for advanced PD and completed 1-year follow-up participated in the study.

All subjects were assessed using UPDRS I-IV, 1 month before surgery (baseline evaluation) in the *off*-medication and *on*-medication conditions. All patients underwent bilateral stereotactic implantation of quadripolar DBS electrodes (Medtronic, MN, USA) in one session according to the standard protocol described in our earlier study.[13] All patients were evaluated 1 year after surgery in "*on*-stimulation, *off*-medication" state. UPDRS III was rated (except rigidity) on videos by another blinded movement disorder specialist who was not part of the surgical team. Scores for rigidity were taken from the open-label UPDRS III scores rated as part of yearly follow-up. The levodopa equivalent daily dosage (LEDD) was calculated for all patients.[15] All the patients also underwent mini mental status examination (MMSE), Addenbrooke's cognitive examination (ACE)[16] and quality of life (QOL) assessment using Parkinson's Disease Quality of Life (PDQL)[17] at baseline and 1 year follow-up.

Statistical analysis

We analyzed the gender based differences for the pre-operative disease-related characteristics and the outcomes of STN DBS. The post-operative outcome was measured from the assessment in "*on*-stimulation, *off*-medication" state. The outcome of DBS was assessed as the change of each score from the baseline to the post-operative state in both genders. To compare data before and after surgery and between genders, a repeated measures analysis of variance (ANOVA) was done with factors gender (independent measure) and 'DBS outcome' (repeated measures). Mann-Whitney test was used to compare percentage reductions for each item between the two genders. A probability value of $P < 0.05$ was considered significant.

Results

Baseline characteristics

There were 32 men and 19 women. Baseline evaluation [Table 1] revealed no gender differences in the age at onset, duration of disease and severity of the motor symptoms of the disease assessed by Hoehn and Yahr staging. The activities of daily living (ADL) scores (UPDRS II), were similar in OFF, though there was a trend for it to be worse in women in ON ($P = 0.05$). No significant differences were noted in the UPDRS III motor scores, even though women showed a trend towards having worse bradykinesia ($P = 0.05$) and axial motor ($P = 0.07$) scores compared to men during ON. Women were on lesser LEDD than men ($P = 0.03$). The dyskinesia and fluctuations scores (UPDRS IV) were also similar between the genders. PDQL showed significantly worse emotional sub scores in women ($P = 0.03$). Baseline neuropsychological evaluation showed no difference in ACE and MMSE scores. Depression at baseline was worse in women ($P = 0.03$).

Table 1: Characteristics of the study population at baseline

Variable	Men (*n*=32) Mean (SD)	Women (*n*=19) Mean (SD)	*P* value
Age at onset (years)	44.3 (11.5)	42.7 (11.4)	0.733
Age at DBS (years)	55.8 (10.7)	54.5 (10.7)	0.711
Duration of disease (years)	11.1 (5.8)	10.1 (4.6)	0.837
Hoehn-Yahr			
OFF	3.73 (1.00)	3.79 (0.98)	0.770
ON	2.69 (0.74)	2.47 (0.51)	0.252
UPDRS[1] I			
OFF	1.69 (1.51)	2.47 (2.41)	0.319
ON	1.16 (1.59)	1.42 (2.34)	0.832
UPDRS II			
OFF	24.66 (7.77)	26.47 (5.71)	0.344
ON	7.91 (8.15)	10.79 (6.82)	0.05
UPDRS III			
OFF	47.72 (13.21)	52.05 (14.97)	0.453
ON	16.19 (10.60)	18.11 (9.94)	0.401
UPDRS 1VA	4.28 (2.41)	4.74 (2.10)	0.432
UPDRS IV B	3.81 (1.23)	3.89 (1.32)	0.759
Bradykinesia[2]			
OFF	16.00 (5.86)	18.16 (5.57)	0.384
ON	5.03 (4.06)	8.11 (5.46)	0.05
Tremor			
OFF	4.81 (3.81)	4.95 (4.5)	0.891
ON	0.50 (1.14)	0.26 (0.73)	0.545
Rigidity			
OFF	10.00 (4.16)	9.95 (4.58)	0.876
ON	3.59 (3.36)	3.47 (3.06)	0.992
Axial score[3]			
OFF	4.72 (2.35)	5.26 (1.76)	0.448
ON	1.03 (1.40)	1.53 (1.22)	0.073
Gait			
OFF	2.50 (1.02)	2.53 (0.96)	0.960
ON	0.94 (0.95)	0.95 (0.97)	0.950
Stability			
OFF	2.19 (1.06)	2.37 (1.21)	0.536
ON	1.31 (0.82)	1.32 (0.75)	0.906
LEDD[4]	808.41 (448.50)	551.89 (256.21)	0.039
PDQL[5] (Total)	98.25 (22.94)	89.74 (20.28)	0.141
Parkinsonism	34.47 (9.06)	33.89 (8.04)	0.725
Systemic	19.06 (5.12)	18.37 (5.58)	0.632
Emotional	28.25 (7.74)	22.68 (5.29)	0.014
Social	16.47 (5.30)	14.79 (4.58)	0.278
BDI[6]	12.87 (10.93)	17.78 (8.67)	0.039
MMSE[7]	26.94 (3.15)	26.29 (3.58)	0.517
ACE[8]	77.04 (14.52)	75.25 (16.46)	0.903

[1]UPDRS=Unified Parkinson's disease rating scale, [2]Bradykinesia=Sum of items 23, 24, 25 and 26 of UPDRS III, [3]Axial Score=Items 27 and 31 of UPDRS III, [4]LEDD=Levodopa equivalent daily dosage, [5]PDQL=Parkinson disease quality of life, [6]BDI=Becks depression inventory, [7]MMSE=Mini mental status examination, [8]ACE=Addenbrooke's cognitive examination, DBS=Deep brain stimulation

Table 2: Comparison of the outcome of STN DBS among men and women 1 year after surgery

Variables	Gender	Baseline (off medication) Mean (SD)	At 1 year (on-stimulation, off-medication) Mean (SD)	*P* value*	Difference from baseline to 1 year Mean (SD)	*P* value**
UPDRS[1] I	Men	1.69 (1.51)	1.75 (1.95)		0.06 (1.87)	
	Women	2.47 (2.41)	2.00 (2.26)	0.557	0.47 (3.12)	0.504
UPDRS II	Men	24.66 (7.77)	14.09 (7.89)		10.56 (9.85)	
	Women	26.47 (5.71)	11.63 (4.91)	<0.001	14.84 (7.01)	0.141
UPDRS III	Men	47.72 (13.21)	20.34 (14.72)		27.38 (16.51)	
	Women	26.47 (5.71)	18.95 (10.80)	<0.001	33.11 (13.16)	0.188
UPDRS IVA	Men	4.28 (2.41)	1.34 (1.70)		2.94 (2.65)	
	Women	4.74 (2.10)	1.11 (1.10)	<0.001	3.63 (2.09)	0.297
UPDRS IVB	Men	3.81 (1.23)	2.28 (1.63)		1.53 (2.00)	
	Women	3.89 (1.33)	2.53 (0.96)	<0.001	1.37 (1.95)	0.743
Tremor	Men	4.81 (3.81)	1.22 (1.77)		3.59 (3.86)	
	Women	4.95 (4.50)	1.00 (1.60)	<0.001	3.95 (4.06)	0.953
Rigidity	Men	10.00 (4.16)	3.97 (3.67)		6.03 (4.82)	
	Women	9.95 (4.58)	3.26 (3.41)	<0.001	6.68 (5.48)	0.488
Bradykinesia[2]	Men	16.00 (5.86)	7.31 (5.84)		8.69 (6.70)	
	Women	18.16 (5.57)	7.58 (5.04)	<0.001	10.58 (5.77)	0.211
Axial scores[3]	Men	4.72 (2.35)	1.75 (1.95)		2.75 (2.46)	
	Women	5.26 (1.75)	2.32 (1.73)	<0.001	2.95 (1.55)	0.686
Gait	Men	2.50 (1.02)	1.25 (1.02)		1.25 (1.24)	
	Women	2.53 (0.96)	1.21 (0.787)	<0.001	1.32 (0.75)	0.628
Stability	Men	2.19 (1.06)	1.50 (0.95)		0.69 (1.03)	
	Women	2.37 (1.21)	1.32 (0.89)	<0.001	1.05 (1.35)	0.323
LEDD[4]	Men	808.41 (448.5)	428.48 (400.99)		379.92 (315.08)	
	Women	551.89 (256.21)	349.32 (242.01)	<0.001	202.58 (202.11)	0.022
MMSE[5]	Men	26.94 (3.15)	27.69 (2.21)		0.63 (5.80)	
	Women	26.29 (3.59)	26.47 (5.51)	0.539	0.18 (3.45)	0.360
ACE[6]	Men	77.04 (14.52)	81.64 (12.41)		0.04 (21.65)	
	Women	75.25 (16.46)	75.25 (22.88)	0.267	0.00 (10.41)	0.678
BDI[7]	Men	12.87 (10.93)	7.87 (6.10)		4.42 (11.69)	
	Women	17.78 (8.67)	14.28 (9.75)	0.016	3.50 (8.57)	0.693
PDQL[8] (Total)	Men	98.25 (22.94)	124.56 (22.19)		26.31 (28.04)	
	Women	89.74 (20.28)	123.32 (21.66)	<0.001	33.58 (28.25)	0.533
Parkinsonism	Men	34.47 (9.06)	46.31 (9.60)		11.84 (12.25)	
	Women	33.89 (8.04)	47.53 (8.42)	<0.001	13.63 (11.19)	0.792
Systemic	Men	19.06 (5.12)	23.31 (4.12)		4.25 (5.78)	
	Women	18.37 (5.58)	24.00 (5.27)	<0.001	5.63 (5.68)	0.646
Emotional	Men	28.25 (7.74)	33.47 (5.93)		5.22 (7.21)	
	Women	22.68 (5.30)	30.58 (6.92)	<0.001	7.89 (9.11)	0.391
Social	Men	16.47 (5.30)	21.47 (5.36)		5.00 (6.80)	
	Women	14.79 (4.58)	21.21 (4.28)	<0.001	6.42 (6.13)	0.369

*Repeated measures ANOVA, **Mann Whitney test, [1]UPDRS=Unified Parkinson's disease Rating scale, [2]Bradykinesia=Items 23, 24, 25 and 26 of UPDRS III, [3]Axial score=Items 27 and 31 of UPDRS III, [4]LEDD=Levodopa equivalent daily dosage, [5]MMSE=Mini mental status examination, [6]ACE=Addenbrooke's cognitive examination, [7]BDI=Becks depression inventory, [8]PDQL=Parkinson's disease quality of life, SD=Standard deviation

Assessment 1 year after surgery

The 1-year post-operative assessment [Table 2] showed significant improvement in UPDRS I-IV in both genders. The analysis of UPDRS III scores did not show any difference in the degree of improvement of any of the cardinal motor manifestations of PD [Table 2]. Even though both genders achieved significant reduction of the LEDD at the end of 1 year ($P < 0.001$), women achieved lesser reduction of LEDD ($P = 0.022$). All domains of PDQL improved with surgery without any gender differences in the degree of improvement [Table 2]. MMSE and ACE scores also showed no gender differences. Depression improved in both genders ($P = 0.016$) and equally. The electrical stimulation parameters also did not differ significantly between men and women (data not shown).

Discussion

In our surgical cohort of 51 patients who underwent bilateral STN DBS for advanced PD, we found no gender differences in the age of onset, duration, and severity of motor symptoms or levodopa-induced dyskinesia before surgery. Nevertheless, women were on lower doses of dopaminergic medications

and showed a trend toward worse control of bradykinesia and poorer functioning in activities of daily living. They were more depressed compared to men. Despite these differences, motor symptoms, ADL, depression, and QOL improved equally well in women as in men following STN DBS. The only post-operative gender difference was that women achieved lesser reduction of dopaminergic medications.

Contrary to the observation by Hariz *et al*.,[14] we found that women undergoing STN DBS for advanced PD are selected for the procedure at similar severity and duration of motor symptoms as men, indicating that women in our study received an equal opportunity for STN DBS. The surgical cohort in that study was heterogeneous, consisting of patients undergoing not only DBS, but ablative procedures like pallidotomy and thalamotomy also. A more recent study by Accolla *et al*.,[18] on patients undergoing DBS found no such differences; their results were similar to our findings. Our results suggest that only financial limitations and not gender based discrimination act as constraints for women with PD to undergo DBS. In the pre-operative assessments, we did not find worse dyskinesias in our female patients, probably due to the lower dose of dopaminergic medications taken by them. This difference in dosage of dopaminergic medications prescribed to women was the result of an intentional reduction in the dosage of medications aimed at the control of troublesome dyskinesia in women. This could explain the equal severity of dyskinesias between the genders, even though women are reported to have more dyskinesia.[10,11] This dose restriction may also explain the poorer control of bradykinesia and axial signs in ON and the impairment of ADL in women. The reduction in LEDD after surgery was also lesser in women probably because women were already receiving a lower dose prior to surgery. The policy of drug reduction after STN DBS followed at our center aims only to reduce dyskinesias.

The women subjects in our cohort at baseline evaluation were more depressed and had worse emotional score for QOL. Biological factors contribute to worse depression in women, and depression is more common in women with PD,[19,20] though this has not been a consistent observation.[21] The prevalence of depression in the general population is also higher in women.[19] The poorer functioning in activities of daily living even in ON could also have contributed to the poorer emotional state of women in QOL scores. Nevertheless, gender difference in depression disappeared at 1 year of follow-up.

We found that STN DBS resulted in excellent improvement in UPDRS motor scores, fluctuations, dyskinesias, activities of daily living and all domains of quality life irrespective of gender. Romito *et al*.[22] found slightly worse lower limb akinesia and gait scores in women at 1 year follow-up, but the difference was not seen on subsequent yearly follow-up evaluations. Accolla *et al*.[18] found that bradykinesia responded poorly in women at baseline as in our study, though a trend for better improvement in ADL was also found after DBS. However, in the present study, the ADL improved to a similar degree in both genders.

The relatively short duration of follow-up (1 year) is a limitation of our study. Moreover, the group of patients that are ultimately candidates for DBS for PD is highly selected, and may not be the ideal one to study the gender differences and to answer the question whether women get an equal opportunity as men to undergo DBS in resource poor countries. Ideally, a prospective study on a cohort of patients with PD being referred for consideration of DBS may be required to address these issues. However, to the best of our knowledge, this is the first attempt to analyze gender differences in patient selection and outcome of STN DBS from a resource-limited country like India. Apart from those used by earlier investigators,[14,18] we included additional outcome measures for depression and QOL. In conclusion, we found that women with advanced PD are likely to be maintained on lower doses of dopaminergic medications compared to men with similar duration and severity of motor symptoms, probably as an adjustment for the propensity of women to have more dyskinesia. This may also contribute to more functional impairment and reduced emotional well-being in them. Women respond equally well to STN DBS, with similar improvement of ADL, QOL, and depression and would therefore benefit from early surgical interventions when dyskinesias becomes dose-limiting.

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