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ORIGINAL COMMUNICATION

Transient gender-related effects in Parkinson's disease patients with subthalamic stimulation

Luigi Michele Romito · Fiorella Maria Contarino · Alberto Albanese

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Abstract Little is known about the gender-related long-term efficacy and safety after subthalamic nucleus deep brain stimulation (STN DBS) implant for Parkinson's disease (PD), although some differences could be expected as recently stated in a short-term report. We assessed the possible gender-related differences in clinical outcome and disease progression along a 5-year period after STN DBS for PD. A prospective cohort of PD patients who underwent STN DBS and reached the 5-year follow-up (FU) was considered. Clinical outcome, disease progression and side effects were assessed at baseline and 1, 3, and 5 years after surgery. Eleven men and nine women were included in the study. At baseline, no inter-gender difference of age at implant, disease duration and severity or levodopa responsiveness was detected. A higher motor responsiveness in men compared to women was detected only at 1-year FU: this difference was mainly related to worse lower limb akinesia and gait score in women. The difference was not confirmed at 3 and 5 years. Antiparkinsonian drugs reduction, improvement in motor fluctuations and dyskinesias, functional measures and progression of underlying PD, were comparable in both groups. Women had persistent adverse events comparable to men. The present long-term observation confirms the occurrence of slight gender-related differences in PD patients treated with STN DBS, indicating a transient poorer outcome in women. Further observational time and a wider number of patients are needed to better analyze the dimension of long-term gender-related differences.

Keywords Parkinson's disease · Deep brain stimulation · Gender · Subthalamus · Surgery · Movement disorders

Abbreviations

DBS	Deep brain stimulation
IPG	Implantable pulse generator
LEDD	Levodopa-equivalent daily dose
PD	Parkinson's disease
STN	Subthalamic nucleus
TEED	Total electrical energy delivered
UPDRS	Unified Parkinson's Disease Rating Scale

L. M. Romito (✉) · A. Albanese
Università Cattolica del Sacro Cuore, Milan, Italy
e-mail: luigi_romito@yahoo.it; luigiromito@istituto-besta.it

L. M. Romito · A. Albanese
Neurology Department, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Via G. Celoria, 11, 20133 Milan, Italy

F. M. Contarino
Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma, Italy

F. M. Contarino
Department of Neurology, H2-222, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects mainly the motor system. The symptomatic benefits obtained by using the current medications are often associated to troublesome side-effects, like motor fluctuations and on-period dyskinesias, especially in the long-term. Available long-term longitudinal studies document that subthalamic nucleus (STN) stimulation improves motor features in patients with severe PD past 5 years, in particular, rest tremor, rigidity, gait, lower and upper limb akinesia; a deterioration in some symptoms

could be expected [9, 11], regarding especially postural stability and speech.

Some postoperative differences between genders in clinical outcome after STN stimulation could be predictable [1], and this is partly in keeping with the ample documentation addressing the gender-related differences in PD motor phenomenology, progression, drug responses and complications [5, 13, 14].

The aim of our study was to quantify possible long-term gender-related differences in PD patients followed for 5 years after the STN implant. The main objectives were (1) to compare the clinical outcome and disease progression in men and women and (2) to investigate the safety of surgical treatment in these groups.

Subjects and methods

Subjects

We based our data set on the first 20 consecutive PD patients who received a bilateral implant for high frequency STN stimulation and reached the 5-year period of follow-up. All the patients received a diagnosis of PD according to the UK Parkinson's Disease Brain Bank criteria [7]. They all fulfilled recognized inclusion and exclusion criteria and the recommendations of the CAPSIT-PD panel [4], in particular, excellent and sustained response to levodopa, presence of motor complications, such as disabling motor fluctuations with prolonged and at least occasionally unpredictable "off" periods (patients spent at least 25% of the waking day in the off state), Hoehn–Yahr stage $\geq$III in the practically defined off condition. Exclusion criteria were: heart pacemaker bearer, mild parkinsonian features or unstable drug regimen, cognitive impairment, ongoing psychiatric problems, prior brain surgery or inability to comply with the study protocol.

The study protocol was approved by the hospital internal review board. The eligible patients signed an informed consent before entering the study; they were all evaluated, implanted and followed-up at the same institution.

Study design

After inclusion in the study, a bilateral simultaneous STN implant was performed using a standard stereotactic technique [11], that included an intra-operative test stimulation session and a postoperative neuroimage (MRI and CT scan)-based reconstruction in order to confirm the correct position of the definitive leads. Electronic parameters were checked approximately 1 week later, after the placement of the implantable pulse generators, with the aim of achieving optimal control of motor symptoms and identifying the threshold for side effects.

Dopamine agonists were withdrawn 1 week before surgery and levodopa the evening before. Medication was gradually reintroduced after implant, and was maintained at each follow-up evaluation to the minimum dose necessary to permit optimal motor control in addition to stimulation. For this study, we considered the preoperative and the postoperative evaluations at 1, 3 and 5 years. Preoperative evaluations were performed in the morning, in the practically defined off condition [4] and in the best on condition following the first morning dose of levodopa. Each postoperative test session was performed in the morning and consisted of three consecutive Unified Parkinson's Disease Rating Scale (UPDRS) evaluations: (a) in the practically defined off condition without antiparkinsonian medication and with stimulation turned off; (b) without antiparkinsonian medication, 30 min after switching stimulation on; and (c) with antiparkinsonian medication and stimulation. Condition (a) intended to evaluate the progression of underlying PD motor signs without the influence of treatment; condition (b) was used to measure the efficacy of STN stimulation alone on PD motor signs; and condition (c) served to evaluate the patients' functioning during their best motor condition.

Outcome measures

We examined and compared several motor and functional indices. In particular, upper limb akinesia (sum of 23, 24, and 25 items of the UPDRS), lower limb akinesia (item 26 of the UPDRS), total axial score (encompassing speech, gait and postural stability items, respectively, UPDRS items 18, 29, and 30). Freezing of gait was evaluated using item 14 of the UPDRS part II. The duration of off periods was determined based on item 39 of the UPDRS, part IV. Dyskinesias were calculated by the sum of the dyskinesia duration and disability UPDRS part IV scores (Items 32 and 33) measured preoperatively in the condition with medication and postoperatively in the condition with medication and stimulation turned on. Activities of daily living were evaluated with the UPDRS part II score and the Schwab and England (S&E) functional scale in the patients' best functional state (condition c above). Levodopa-equivalent daily dosage (LEDD, measured in milligrams) was computed for each antiparkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1. The following conversion factors were used: levodopa controlled-release preparations = 0.77, bromocriptine = 10, apomorphine = 15, ropinirole = 20, pramipexole = 60 and pergolide = 100. The total LEDD was then calculated [12]. Total electrical energy delivered (TEED, measured in μJ) were computed by

Table 1 Patients' demographic and clinical characteristics at implant and FU duration (mean ± SD)

	Total	Men	Women
Patients	20	11	9
Age at implant (years)	56.4 ± 6.9	55.9 ± 7.9	57.0 ± 5.8[IGNS]
Age at last FU (years)	61.9 ± 6.9	60.9 ± 7.9	63.0 ± 5.8[IGNS]
Disease duration at implant (years)	14.3 ± 6.2	12.7 ± 4.0	16.2 ± 8.0[IGNS]
UPDRS-motor score (without medication)	59.8 ± 9.7	55.6 ± 10.4	64.9 ± 6.0[IGNS]
UPDRS-motor score (levodopa challenge)	24.9 ± 8.5	21.5 ± 7.7	29.0 ± 7.9[IGNS]
Levodopa challenge responsiveness (%)	58.4	61.3	55.3[IGNS]
Weight (Kgs)	66.6 ± 14.0	74.4 ± 9.0	58.7 ± 14.0[IGNS]
Follow-up (months)	65.4 ± 13.2	60.0 ± 0.0	72.0 ± 18.0[IGNS]

IGNS inter-gender comparison not significant

the formula TEED = (amplitude^2 × pulse width × frequency rate)/impedance [8, 11]. Adverse events were recorded and classified as transient, persistent (if not improved by turning off stimulation for a short time), stimulation-induced (present at optimal stimulation parameters, but improved when stimulation was turned off or stimulation parameters were modified), device-related, or unrelated to the procedure or stimulation [11].

Statistical analysis

Means and standard deviations of every item were computed separately for men and women. The mean values of the clinical scales (considered to have a non-normal distribution of values) were analyzed by means of the Wilcoxon signed-rank test, while LEDD and TEED values (considered to have a normal distribution of values) were analyzed by means of the Student's *t* test (unpaired and paired data).

Any p values <0.05 were considered statistically significant. To compare data before STN implant and along the 5-year follow-up, and between the genders, an analysis of variance was applied (ANOVA): the first main factor was "gender" (independent measures); the second main factor was "condition" (repeated measures). The non-parametric Mann–Whitney test was used to compare percentage reductions for each clinical item between the two genders. Chi squared test was used to compare the frequency of the STN surgery adverse events in both groups.

Statistical analysis was performed with SPSS software (http://www.spss.com/spss/, release 12.0).

Results

Eleven men and nine women were considered for the study. Table 1 reports patients' demographic and clinical characteristics: there was no gender difference in age, disease duration and body weight at implant, and in FU duration. At implant, the disease severity and levodopa responsiveness were comparable (Table 1).

Compared with preimplant, at 5 years and in both groups, UPDRS-motor score had improved significantly and levodopa equivalent dose was reduced (Table 2). Rest tremor, rigidity, gait, lower and upper limb akinesia, and total axial score were improved in decreasing order. Postural stability and speech improved transiently, whereas on-period motor fluctuations and dyskinesias recovered durably. Dopaminergic medication remained stable during the observation period, but delivered energy was progressively increased over time.

Gender-based comparison of outcome after STN implant revealed more sustained UPDRS-motor score improvement in men compared to women (58.3 and 41.8%, respectively, $p < 0.05$) at 1-year follow-up but this was not confirmed 3 and 5 years after the implant. The difference was mainly related to worse lower limbs akinesia and gait score in women (Table 2). LEDD reduction, TEED trend, motor fluctuations, and dyskinesias improvement were comparable in both groups. Additionally, we did not find gender-related variations in functional measures (UPDRS ADL, Schwab & England Scale) and in the progression of underlying PD (Table 2).

Women had a number of *persistent* adverse events comparable to men (Table 3), who conversely were the only to show some transient adverse events.

Discussion

The long-term effect of STN stimulation on male and female PD patients consisted in a comparable sustained and marked improvement of the UPDRS-motor score, with reduction of severity and duration of dyskinesias and of off-periods compared with the pre-implant state. Both groups showed no changes of the motor condition without medication and stimulation, thus underlying the lack of natural disease progression 5 years after implant compared with baseline values.

Our long-term study, however, evidenced the occurrence of *transient* gender-related differences after STN

Table 2 Efficacy of STN stimulation and progression of motor signs in all 20 patients, evaluated at different times after the implant (±SD)

	Baseline		1 year		3 years		5 years	
	Men	Women	Men	Women	Men	Women	Men	Women
Efficacy on motor features[a]								
UPDRS-motor score	55.6 ± 10.4$^{\#}$	64.9 ± 6.0	23.2 ± 11.0**$^{\#}$	37.8 ± 12.0**	25.4 ± 11.7**	37.3 ± 10.0**	21.2 ± 10.7**	34.3 ± 11.4**
Rest tremor	7.2 ± 7.2	6.2 ± 5.5	1.3 ± 3.6*	0.8 ± 1.7*	0.7 ± 1.1*	1.1 ± 2.2*	0.4 ± 0.8*	0.3 ± 1.0*
Rigidity	10.5 ± 3.6	12.0 ± 3.6	5.8 ± 3.2*	7.0 ± 4.3*	5.5 ± 2.8**	7.7 ± 5.4*	3.4 ± 2.6**	6.7 ± 4.3*
Upper limb akinesia	12.4 ± 4.5	15.7 ± 3.5	5.9 ± 4.1	13.4 ± 4.4	7.5 ± 4.8*	11.9 ± 3.5*	6.4 ± 4.9**	10.7 ± 4.9*
Lower limb akinesia	4.3 ± 2.1$^{\#}$	6.6 ± 1.5	1.4 ± 1.5**$^{\#}$	5.0 ± 2.5	1.9 ± 1.6*	4.4 ± 1.7*	1.8 ± 1.5**	4.4 ± 1.8*
Total axial score	5.5 ± 1.7$^{\#}$	7.6 ± 1.8	2.4 ± 1.4**	4.0 ± 2.1**	3.4 ± 1.7*	4.7 ± 1.6**	3.6 ± 1.8*	4.6 ± 1.6**
Speech	2.1 ± 0.2	2.4 ± 0.9	1.7 ± 0.7	1.8 ± 1.2	1.8 ± 0.8	1.8 ± 1.0	1.9 ± 1.0	2.0 ± 1.0
Postural stability	1.4 ± 1.0	2.3 ± 1.1	0.6 ± 0.8	0.9 ± 0.8*	0.7 ± 0.8	1.2 ± 0.7*	0.8 ± 0.8	1.2 ± 0.8*
Gait	2.0 ± 0.8	2.8 ± 1.1	0.3 ± 0.5**$^{\#\#}$	1.3 ± 0.9*	0.8 ± 0.9**	1.7 ± 0.7*	0.9 ± 0.7**	1.3 ± 0.9*
Dyskinesia score	4.2 ± 1.8	4.4 ± 0.9	0.5 ± 1.0**	0.6 ± 0.7**	0.7 ± 1.1**	0.7 ± 1.1**	0.5 ± 1.0**	1.0 ± 2.0*
Off period duration	2.0 ± 0.8	2.1 ± 0.8	0.2 ± 0.4**	0.0 ± 0.1**	0.0 ± 0.1**	0.2 ± 0.4**	0.1 ± 0.3**	0.1 ± 0.1**
Efficacy on functional measures[b]								
UPDRS ADL	8.4 ± 6.0	12.8 ± 10.1	5.2 ± 3.0*	10.0 ± 6.3*	5.8 ± 3.3	11.4 ± 8.3	7.0 ± 5.9	9.3 ± 6.1
Schwab & England Scale	81.8 ± 8.7	72.2 ± 20.5	94.0 ± 5.2*	89.4 ± 8.1*	91.0 ± 8.8*	80.0 ± 12.2*	90.0 ± 12.5	82.2 ± 13.0
LEDD	1,561.1 ± 814.9	1,331.1 ± 776.4	484.2 ± 428.2**	492.7 ± 223.2**	563.7 ± 458.9*	732.0 ± 497.1*	607.1 ± 500.1**	721.0 ± 627.3*
TEED (μJ)	87.6 ± 28.9	127.3 ± 55.7	118.9 ± 40.3**	121.7 ± 26.8	122.0 ± 36.4**	130.3 ± 60.4	153.0 ± 63.8*	170.2 ± 70.9
Evaluation of underlying PD[c]								
UPDRS-motor score	55.6 ± 10.4	64.9 ± 6.0	53.0 ± 17.8	63.0 ± 12.7	53.1 ± 16.7	56.4 ± 15.8	53.0 ± 18.4	59.1 ± 17.6
Speech	2.1 ± 0.3	2.4 ± 0.9	1.8 ± 0.8	2.0 ± 1.0	2.2 ± 1.2	2.3 ± 1.4	2.3 ± 1.0*	2.1 ± 1.3
Rigidity	10.8 ± 3.6	12.0 ± 3.6	11.1 ± 3.9	11.4 ± 4.6	10.8 ± 3.0	12.1 ± 5.3	10.7 ± 4.6	12.6 ± 4.3
Postural stability	1.4 ± 1.0	2.3 ± 1.1	0.8 ± 0.8	1.4 ± 0.5*	1.3 ± 1.2	2.0 ± 1.0	1.2 ± 1.3	1.9 ± 1.1
Gait	2.0 ± 0.8	2.8 ± 1.1	1.7 ± 0.9	2.0 ± 1.1	1.7 ± 1.3	2.2 ± 1.1	1.7 ± 1.2**	2.3 ± 1.1

[a] Evaluated without antiparkinsonian medication and with stimulation turned on

[b] Evaluated in the patients' best functional state, with current antiparkinsonian medication and with stimulation turned on

[c] Evaluated with stimulation turned off and without antiparkinsonian medication

* $p < 0.05$, ** $p < 0.005$ compared with baseline values

$^{\#}$ $p < 0.05$, $^{\#\#}p < 0.005$ for variation in the same value between men versus women subgroup. All the other comparisons were not significant

Table 3 Adverse events and side effects observed in the patients

	Men	Women
Number of patients	11	9
Transient		
Increased sexuality	2 (18%)	–
Manic psychosis	3 (27%)	–
Apathy	2 (18%)	–
Seizure (responsive to antiepileptic drug)	1 (9%)	–
Persistent		
Hypophonia	1 (9%)	2 (22%)
Hypophonia and dysarthria	2 (18%)	1 (11%)
Hypophonia, dysarthria, oral district dystonia, dysphagia	–	1 (11%)
Eyelid opening apraxia	–	2 (22%)
Apathy	2 (18%)	2 (22%)
Limb dystonia	2 (18%)	2 (22%)
Buccinators spasm	–	1 (11%)
Troublesome weight gain	2 (18%)	2 (22%)
Stimulation-induced		
Hypophonia	1 (9%)	–
Limb dystonia	1 (9%)	1 (11%)
Unilateral blepharospasm	1 (9%)	–
Monolateral buccinators spasm	1 (9%)	1 (11%)
Device-related		
Unexplained switching off	1 (9%)	1 (11%)
Cable dehiscence due to infection	1 (9%)	
Unrelated to procedure or stimulation		
Severe spinal arthrosis	2 (18%)	1 (11%)
Transitory ischemic attack	1 (9%)	1 (11%)
Cardiac arrhythmia	1 (9%)	–
Cardiac ischemia	1 (9%)	–
Cardiac decompensation	1 (9%)	–
Persistent glottal oedema	1 (9%)	–

stimulation, in particular a poorer motor outcome in women, mainly related to worse lower limb akinesia and gait score. The individual baseline values for UPDRS, age, disease duration at implant, levodopa-responsiveness and body weight, were comparable among men and women, and should not be considered at the base of these slight differences. Nevertheless, women have persistent adverse events comparable to men, in particular hypophonia and eyelid opening apraxia. In contrast, men are more prone to develop *transient* mood and behavioral disorders, like hypersexuality, hypomania and apathy, but this difference could be related to the little patients' sample analyzed.

Although this is not the first study to investigate the interaction between gender and efficacy and safety of STN stimulation in PD, ours involved a longer observational follow-up time encompassing the first 5 years after the implant and involving consecutive and strictly selected patients. The only comparable previous study [1] considering gender effects in STN stimulation outcome, investigated a wider PD population (38 patients) followed up to 1 year after the implant, and provided similar results on bradykinesia and ADL score. Another study [6] is subject to many uncertainties, due to the lack of homogeneity of the studied PD patients and the applied surgical (ablative or stimulation, GPi or STN) procedures.

In recent years, worldwide studies have focused on an increased understanding of the potential gender effects on drug and surgical outcome in PD treatments. Sex influences on brain anatomy, chemistry and function [2], hormonal modulation on dopaminergic receptors and gene expression in human dopaminergic nigral neurons [3] are the main contributors to gender differences in PD: their biological effects are, however, poorly understood and probably do not act when the cortico-basal ganglia–thalamo-cortical circuitry is chronically modulated by STN stimulation. However, the existence of gender-related neurophysiologic differences in the activity of the human subthalamic area has recently investigated [10] and may be important for understanding possible dopaminergic and subthalamic stimulation gender-specific outcome profile.

Overall, these data indicate that chronic STN stimulation is an efficacious method to control levodopa-responsive parkinsonian symptoms and allows maintaining a long-lasting reduction of dopaminergic treatment for 5 years in both genders. Further longer-term data and a wider number of patients are, however, needed to better analyze the nature and magnitude of gender-specificity in surgical PD treatment.

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