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Short communication

Gender and non motor fluctuations in Parkinson's disease: A prospective study

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ABSTRACT

Introduction: In Parkinson's disease (PD), non motor symptoms can fluctuate either along or irrespective to motor on/off phenomena. Prospective studies suggest that higher motor scores and levodopa dosage, younger age at onset and female gender represent risk factors for motor fluctuations' development. Yet, the predictors of development of non motor fluctuations (NMF) are less clear.
In this prospective study, we aimed to assess the relationship between NMF and gender along with other potential risk factors.
Methods: Forty-seven (16 women/31 men) de novo, drug-naïve PD patients have been followed for 4 years since diagnosis. Motor and non motor fluctuations were evaluated with the 19-item Wearing off Questionnaire (WOQ-19). The association between gender and NMF was explored with multivariable regression models adjusted for age at onset, motor and non motor symptoms at diagnosis and levodopa intake at follow up.
Results: Female gender was more likely associated with a diagnosis of NMF (adjusted odds ratio, AOR = 5.33,95%CI = 1.21–23.4, p = 0.027), but not with a diagnosis of generic wearing off at follow up (OR = 3.66, 95%CI = 0.8–16.8, p = 0.097). Women had greater likelihood of developing higher WOQ-19 Non motor scores (AOR = 4.58, 95%CI = 1.23–17.03, p = 0.023), but not higher WOQ-19 Total scores (AOR = 2.88, 95%CI = 0.86–9.71, p = 0.087) compared to men. Notwithstanding, no gender differences were detected in medication intake.
Conclusions: We showed that female gender represents a major risk factor for the development of NMF. There were no gender differences in medication intake, thus NMF in women remain mostly underestimated and not properly treated. From a practical standpoint, clinicians should take into account the role of gender in the management of NMF in PD.

1. Introduction

In Parkinson's disease (PD), chronic levodopa treatment is associated with development of motor fluctuations and dyskinesias [1]. In such phase of the disease, non motor symptoms can fluctuate either along or irrespective to motor on/off phenomena. Indeed, non motor fluctuations (NMF) have been recognized in up to 100% of patients with motor fluctuations and represent major determinants of disability and poor quality of life [2]. Prospective studies suggest that higher motor scores and levodopa dosage,

Abbreviations: AOR, adjusted odds ratio; IQR, Interquartile range; LEDD, Levodopa equivalent daily dosage; MDS, Movement Disorders Society; NMF, Non motor fluctuations; NMS Quest, Non Motor Symptoms Questionnaire; PD, Parkinson's disease; SD, standard deviation; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; UPDRS-IV, Unified Parkinson's Disease Rating Scale part IV; WOQ-19, 19-item Wearing Off Questionnaire.

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younger age at onset and female gender are risk factors for motor fluctuations [1]. Yet, the predictors of development of NMF are less clear as only cross-sectional data are available [3,4].

Among several questionnaires available, the 19-item Wearing Off Questionnaire (WOQ-19) is recommended by the Movement Disorders Society (MDS) Task Force on rating scales for PD as an effective and reliable tool to detect both motor and non motor wearing off phenomena in clinical practice [5].

A gender-related pattern of non motor symptoms has been demonstrated in de novo PD patients before [6–8] and after starting dopaminergic treatment [9]; thus, it is conceivable that gender also plays a role in NMF [4]. Yet, no prospective data are available on the relationship between gender and development of NMF in PD.

Herein, we show the results of a prospective study involving de novo, drug-naïve PD patients on the relationship between NMF, assessed with the WOQ-19, and gender along with other potential risk factors.

2. Methods

2.1. Study design

All the patients included in this study have been prospectically enrolled in an ongoing research project on de novo, drug-naïve PD patients at the Movement Disorders Center of the University "Federico II", Naples, Italy, between January 1, 2008 and June 30, 2009. Inclusion and exclusion criteria have been extensively described elsewhere [10]. In brief, inclusion criteria were: 1) the presence of Parkinson's disease according to United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (bradykinesia associated to tremor or rigidity or postural instability) [11]; 2) disease duration since onset of PD motor symptoms less than 2 years; 3) no history of present or past therapy with antiparkinsonian agents. Additional criteria for inclusion were lack of significant cerebral lesions on neuroimaging or severe concomitant disease that might explain the presence of neurological or psychiatric disturbances.

Enrolled patients were assessed three times: at diagnosis (T0), after 2 (T2) and 4 years (T4). Parkinsonism was diagnosed by movement disorder specialists and during follow up examinations patients who developed features implicating an alternative clinical diagnosis were excluded [11]. Owing to the observational nature of our ongoing project, after enrollment and baseline evaluation, dopaminergic therapy was started according to the discretion of each supervising physician.

The study was approved by the local ethics committee and all patients provided written informed consent according to the Declaration of Helsinki.

2.2. Data collection

Detailed clinical information was obtained from the patient's history and neurological examination. During all the three assessments, motor disability was evaluated according to the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) and patients completed the Non Motor Symptoms Questionnaire (NMS Quest), a validated and recommended tool for detection of non motor symptoms [12]. Dopaminergic treatment (type of drug, daily dose and duration) was recorded at T2 and T4. Levodopa equivalent daily dosage (LEDD) was calculated for each drug and total LEDD reported. Intake of antidepressants or benzodiazepines was also recorded.

At both T2 and T4, clinicians used a semi-structured interview investigating the periodic reappearance of symptoms during the day, the temporal relationship with the intake of at least one scheduled dose of medication in a consistent and predictable modality, and the improvement after intake of the drug. In addition, motor fluctuations were evaluated with the UPDRS part IV (UPDRS-IV).

At T4, the patients were also asked to fill the Italian version of the WOQ-19 [5]. The questionnaire includes 9 items assessing motor fluctuations including tremor, difficulty in speech, weakness, problems with balance, slowness, reduced dexterity, general stiffness, muscle cramps, difficulty getting out of the chair (WOQ-19 Motor score); and 10 items evaluating non motor fluctuations including anxiety, sweating, mood changes, numbness, panic attacks, cloudy mind, abdominal discomfort, experience hot and cold, pain, aching (WOQ-19 Non motor score) [5]. For each item, patients were asked to tick whether symptoms were present and whether they improved after the following dose of dopaminergic treatment: a cut off of $\geq$2 for the WOQ-19 Total score indicated a diagnosis of generic wearing off [5], while a cut off of $\geq$1 for either the WOQ-19 Motor or Non motor score specifically disclosed a diagnosis of motor or non motor fluctuations, respectively [4].

2.3. Statistical analysis

After checking the normal distribution of the variables by using both graphical and statistical methods, comparisons were performed either by t-test or Mann-Whitney for continuous variables and Chi-square or Fisher exact test for categorical data, as appropriate. Accordingly, descriptive analyses are shown in mean and standard deviation (SD), or median and interquartile range (IQR). Only fully completed scales were considered for the statistical analysis.

The association between gender and wearing off and NMF was explored by using multivariable logistic regression models for binary outcomes (considering WOQ-19 Total score $\geq$ 2 and WOQ-19 Non motor score $\geq$ 1 as dependent variables) and multivariable ordered logistic regression models for ordinal outcomes (considering WOQ-19 Total score and WOQ-19 Non motor score as dependent variables). All models were adjusted for age at onset, NMS Quest and UPDRS-III at T0 and treatment with levodopa at T4. Results were considered statistically significant if $p \leq 0.05$.

3. Results

One-hundred and forty-three patients were enrolled in the study at T0. During follow up, 9 patients were excluded because of a diagnosis other than PD (namely, 3 multiple system atrophy, 1 progressive supranuclear palsy, 1 corticobasal syndrome and 1 Lewy body dementia) and 4 because withdrew their consent [10]. One hundred patients completed the assessments at T2 and 75 at T4. Fully completed WOQ-19 scales were available for 47 out of 75 patients (16 women and 31 men), who, therefore, represent the cohort considered in the present study. Demographic and clinical features of the study population as a whole and divided according to gender are shown in Table 1. Patients not included in the analysis (28, of whom 6 reported wearing off symptoms with the semi-structured interview, but only 2 had UPDRS-IV > 0) did not display significant differences compared to those included with regard to baseline demographic and clinical features.

At T0 women presented worse UPDRS-III compared with men ($p = 0.001$), while other clinical features were comparable (Table 1).

By means of the semi-structured interview, clinicians identified 7 patients at T2 [14.89%; 3 women (18.75%) and 4 men (12.9%), $p = 0.23$] and 18 at T4 [38.29%; 8 women (50%) and 10 men (32.25%), $p = 0.01$] presenting wearing off symptoms.

At T4 according to the WOQ-19 Total score cut-off, wearing off

Table 1
Demographic and clinical features of the study population as a whole and divided by gender.

	All patients (47)	Women (16)	Men (31)	p
T0				
Age, years	60.77 (8.48)	61 (9.3)	60.65 (8.19)	0.89
Age at onset, years	59.51 (8.51)	59.56 (9.39)	59.48 (8.19)	0.97
Disease duration, months	14.02 (5.66)	13.5 (4.6)	14.29 (6.18)	0.65
UPDRS-III	13.87 (6.83)	18.38 (6.51)	11.47 (5.77)	**0.001**
NMS Quest	4.61 (3.05)	4.73 (3.26)	4.55 (3)	0.85
T2				
UPDRS-III	11.64 (4.98)	13.47 (5.64)	10.69 (4.42)	0.08
UPDRS-IV	0 (0)	0 (0)	0 (0)	NA
NMS Quest	4.8 (2.87)	4.88 (3.64)	4.76 (2.41)	0.89
LEDD	307.68 (154.05)	348.44 (135.11)	286.65 (160.99)	0.19
Dopamine agonist, n (%)	33 (70.2)	11 (34.8)	22 (65.2)	0.5
Dopamine agonist duration, months	12.74 (10.86)	12.55 (11.52)	12.83 (10.79)	0.94
Levodopa, n (%)	20 (42.6)	8 (50)	12 (38.7)	0.33
Levodopa duration, months	7.66 (10.38)	8.88 (10.11)	7.03 (10.62)	0.57
Antidepressants, n (%)	3 (6.38)	1 (6.25)	2 (6.45)	0.97
Benzodiazepines, n (%)	3 (6.38)	1 (6.25)	2 (6.45)	0.97
T4				
UPDRS-III	13.59 (4.46)	14.20 (5.73)	13.28 (3.72)	0.56
UPDRS-IV	0.44 (1.34)	0.6 (1.45)	0.35 (1.29)	0.52
NMS Quest	8.98 (4)	9.88 (4.6)	8.52 (3.65)	0.27
LEDD	457.35 (199.79)	488.13 (281.03)	441.96 (147.31)	0.47
Dopamine agonist, n (%)	31 (66)	10 (62.5)	21 (70)	0.42
Dopamine agonist duration, months	23.81 (21.32)	23.71 (20.65)	23.86 (22)	0.98
Levodopa, n (%)	37 (78.6)	12 (75)	25 (83.3)	0.37
Levodopa duration, months	25.57 (19.72)	24.44 (22)	26.17 (18.76)	0.78
Antidepressants, n (%)	5 (10.63)	3 (18.75)	2 (6.45)	0.76
Benzodiazepines, n (%)	2 (4.25)	1 (6.25)	1 (3.22)	0.62
WOQ-19 Total[#]	2 (5)	4 (6)	1 (5)	0.06
WOQ-19 Motor score[#]	2 (3)	2.5 (3.5)	1 (3)	0.16
WOQ-19 Non motor score[#]	0.5 (1)	1.5 (3)	0 (1)	**0.01**

Data are shown in mean (standard deviation), unless otherwise specified. Significant differences are highlighted in bold. Abbreviations: #: data in median and interquartile range; LEDD: L-dopa equivalent daily dosage; NMS Quest: Non Motor Symptoms Questionnaire; T0: diagnosis; T2: 2-year follow up; T4: 4-year follow up; UPDRS-III: Unified Parkinson's Disease Rating Scale part III; UPDRS-IV: Unified Parkinson's Disease Rating Scale part IV; WOQ-19: 19-items wearing off questionnaire.

symptoms were present in 26 patients (55.3%), more frequently in women [12 (75%) versus 14 men (45.2%), p = 0.04] (Table 2). Accordingly, there was a trend towards significance for higher WOQ-19 Total scores in women compared to men [median (IQR)] [4 (6) versus 1 (5), p = 0.06] (Table 1). NMF were more frequently reported by women compared with men [10 (62.5%) versus 8 (25.8%), p = 0.01), with particular regard to anxiety, mood changes and pain (p = 0.05, 0.03 and 0.01 respectively) (Table 2). Correspondingly, the WOQ-19 Non motor score was higher in women compared with men [1.5 (3) versus 0 (1), p = 0.01] (Table 1). No gender differences were detected in motor fluctuations neither with the WOQ-19 Motor score nor with the UPDRS-IV (Tables 1 and 2).

Table 2
Frequency of motor and non motor wearing off symptoms as reported by the WOQ-19 at 4-year follow up for the whole population and according to gender.

WO symptoms, n (%)	Patients			
	All (47)	Women (16)	Men (31)	p
Motor				
Tremor	12 (25.5)	4 (25)	8 (25.8)	0.62
Difficulty in speech	6 (12.8)	3 (18.8)	3 (9.7)	0.32
Weakness	8 (17)	4 (25)	4 (12.9)	0.25
Problems with balance	5 (10.6)	3 (18.8)	2 (6.5)	0.2
Slowness of movements	19 (40.4)	7 (43.8)	12 (38.7)	0.48
Reduced dexterity	16 (34)	6 (37.5)	10 (32.3)	0.48
General stiffness	8 (17)	4 (25)	4 (12.9)	0.25
Muscle cramps	2 (4.3)	1 (6.3)	1 (3.2)	0.57
Getting out of chair	2 (4.3)	0 (0)	2 (6.5)	0.43
Non Motor				
Anxiety	10 (21.3)	6 (37.5)	4 (12.9)	**0.05**
Sweating	0 (0)	0 (0)	0 (0)	1
Mood changes	9 (19.1)	6 (37.5)	3 (9.7)	**0.03**
Numbness	5 (10.6)	3 (18.8)	2 (6.5)	0.20
Panic attacks	1 (2.1)	1 (6.3)	0 (0)	0.34
Cloudy mind	4 (8.5)	1 (6.3)	3 (9.7)	0.58
Abdominal discomfort	0 (0)	0 (0)	0 (0)	1
Feelings of hot/cold	2 (4.3)	1 (6.2)	1 (3.2)	0.57
Pain	6 (12.8)	5 (31.3)	1 (3.2)	**0.01**
Aching	2 (4.3)	2 (12.5)	0 (0)	0.11
WOQ-19 Total score ≥ 2	26 (55.3)	12 (75)	14 (45.2)	**0.04**
WOQ-19 Motor score ≥ 1	28 (59.6)	12 (75)	16 (51.6)	0.1
WOQ-19 Non motor score ≥ 1	18 (38.3)	10 (62.5)	8 (25.8)	**0.01**

Significant differences are highlighted in bold. Abbreviations: WO: wearing off; WOQ-19: 19-items wearing off questionnaire.

At T4 according to multivariable logistic regression models, female gender was more likely associated with a diagnosis of NMF as assessed with WOQ-19 Non motor part (adjusted odds ratio, AOR = 5.33, 95%CI = 1.21–23.4, p = 0.027), but not with a diagnosis of generic wearing off as assessed with WOQ-19 Total score (AOR = 3.66, 95%CI = 0.8–16.8, p = 0.095). Results were confirmed when using WOQ-19 Non motor score ≥ 2 as dependent variable (AOR = 7.31, 95%CI = 1.48–36.1, p = 0.015). According to multivariable ordered logistic regression models, at T4 women had greater likelihood of developing higher WOQ-19 Non motor scores (AOR = 4.58, 95%CI = 1.23–17.03, p = 0.023), but not higher WOQ-19 Total scores (AOR = 2.88, 95%CI = 0.86–9.71, p = 0.087) compared to men.

4. Discussion

Along with young age at onset and levodopa intake, female gender has traditionally been considered a risk factor for the development of motor fluctuations in PD [1]. Yet, no prospectical studies investigated the relationship between gender and NMF [2–4]. In the present study, we showed that female gender represents the most important risk factor for the development of NMF

after 4 years since PD diagnosis, irrespective of age at onset, levodopa intake, motor and non motor symptoms at diagnosis.

We previously reported a specific gender pattern of NMS prevalence in PD before and after starting dopaminergic treatment [6,9], suggesting that therapy may have a greater effect in reducing the burden of NMS in women compared to men in the earliest phase of the disease [9]. Subsequently, as the disease progresses, NMS appear in the form of NMF more frequently in women than in men. Confirming previous data [4], the analysis of the individual items of WOQ-19 showed that mood-related NMF (i.e., anxiety, mood changes and pain) were more prevalent in women (Table 2). These findings possibly account for the higher prevalence of mood-related NMS reported by women in studies including PD patients on dopaminergic treatment and with different stages of disease [8]. Strikingly, in our cohort no gender differences were detected in neither dopaminergic or antidepressants/benzodiazepines intake, despite the higher frequency of wearing off and NMF in women pointed by the WOQ-19. Several explanations may account for such discrepancy. First, men and women may present different response to medications (e.g., due to disparities in bioavailability, pharmacokinetics, tolerability, etc), thus making a direct comparison between genders not straightforward [1,4]. Second, and more likely, despite in recent years clinicians gained increasing awareness regarding non motor symptoms, NMF may still remain underestimated and undertreated. Lastly, non motor symptoms as anxiety, mood changes and pain are common complaints in healthy women of the same age and, as such, specific treatment may be considered unnecessary by both the patient and the clinician [6].

We acknowledge our study has limitations. First, the WOQ-19 is available only for T4 and for a subgroup of all the patients reassessed at follow up (47 out of 75 patients). However, at the time our study was planned this tool was not yet available and was therefore added later to the set of assessments. Second, the generalizability of our findings is limited by the small sample size, which also accounts for the wide confidence intervals. Lastly, although the WOQ-19 is a validated tool recommended by the MDS, it reports only the presence/absence of fluctuating symptoms, without gathering any information on their severity. Notwithstanding, our cohort of de novo, drug-naïve PD patients followed prospectically represents the ideal setting to study the factors associated with the development of NMF.

In conclusion, we conducted a prospective study on early, drug-naïve PD patients followed for 4 years since diagnosis and showed that female gender represents a major risk factor for the development of NMF. No gender differences in medication intake were noticed, supporting the hypothesis that NMF in women remain mostly underestimated and undertreated. From a practical standpoint, our findings prompt the clinician to consider the role of gender in the management of NMF in PD.

Contributorship

1. Research project: A. Conception, B. Organization, C. Execution;
2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

MP: 1A, 1B, 1C, 2A.
RP, MM, RE,MA,CV:1C, 2B.
PB, MTP: 2B.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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