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Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk?

A. Nicoletti [a], R. Vasta [a], G. Mostile [a], G. Nicoletti [b], G. Arabia [c], G. Iliceto [d], P. Lamberti [d], R. Marconi [e], L. Morgante [f], P. Barone [g], A. Quattrone [b, c], M. Zappia [a, *]

[a] Dipartimento G.F. Ingrassia, Sezione di Neuroscienze, Università Degli Studi di Catania, Italy
[b] Istituto di Bioimmagini e Fisiologia Molecolare – Consiglio Nazionale delle Ricerche, Catanzaro, Italy
[c] Clinica Neurologica, Università "Magna Græcia" di Catanzaro, Italy
[d] Dipartimento di Scienze Mediche di Base, Neuroscienze e Organi di Senso, Università di Bari, Italy
[e] Divisione di Neurologia, Ospedale Misericordia, Grosseto, Italy
[f] Dipartimento di Neuroscienze, Università di Messina, Italy
[g] Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Italy

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ABSTRACT

Introduction: Several gender differences have been reported in Parkinson's Disease (PD). We evaluated the burden of non-motor symptoms (NMS) in PD and the possible gender differences in their occurrence.
Methods: The FRAGAMP study is a large multicenter case-control study. PD patients and controls underwent a face-to-face interview and a neurological examination performed by trained neurologists. Presence of NMS was investigated using a standardized questionnaire; cognitive impairment and depression were assessed using the Mini Mental State Examination and the Hamilton Depression Rating Scale respectively.
Results: 585 PD patients (59.5% men) and 481 controls (34.9% men) were enrolled in the study. All NMS were significantly more frequent among PD patients than controls. PD women showed a significantly higher frequency of depression and urinary disturbances than parkinsonian men; a close frequency among PD women and men was recorded for hallucination, cognitive impairment and sleep disorders. Nonetheless, with respect to the control population, according to logistic regression stratified by sex and adjusted by age, PD men showed a stronger positive significant association with almost all NMS compared to women, excepting for urinary disturbances. The strongest association among PD men was recorded for cognitive impairment (adjusted OR 5.44 for men and 2.82 for women) and depression (adjusted OR 30.88 for men and 12.72 for women).
Conclusions: With respect to the general population, presence of NMS was stronger associated with male gender. Our data suggest that the presence of NMS among PD men is more strictly due to the neurodegenerative processes related to PD.

1. Introduction

Despite the classic clinical characteristics which are peculiar for the diagnosis [1], Parkinson's Disease (PD) symptomatology goes beyond the merely motor aspects, encompassing several non-motor symptoms (NMS) which involve different domains, such as psychiatric and behavioural problems, cognitive dysfunction, sleep disturbance, gastrointestinal problems, sexual dysfunction and cardiovascular symptoms. NMS, quite common also among the normal aging population, can appear at any time during the disease course [2], even being the first sign of PD. They may lead to increased disability and poor quality of life for both patients and caregivers [3].

Differences between genders have been thoroughly studied for several neurodegenerative diseases, included PD [4]. In particular, a higher incidence of PD among men has been reported, suggesting a possible protective effect of female hormones [4,5]. Furthermore, several observations have described developmental and functional

* Corresponding author. Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy.
E-mail address: m.zappia@unict.it (M. Zappia).

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modifications of the nigrostriatal system related to sex hormones which might influence the PD pathogenesis [6], suggesting that gender may play a key role in the development and progression of PD. In agreement with this observation, different clinical characteristics have been reported by gender. In particular a more severe progression and greater rigidity have been described among men, while a more frequent tremor-dominant phenotype and a major risk of developing dyskinesia were reported among women [7–11].

Nonetheless limited data are available regarding the possible role of gender on NMS in patients affected by PD. During the last decades, in fact, several studies have evaluated the occurrence of NMS in large cohorts of PD patients, but only a few have compared the occurrence of NMS in PD and in the general population in order to take into account the risk attributable to normal aging and, at the same time, to evaluate the possible gender effect.

The FRAGAMP study *(Fattori di Rischio Ambientali e Genetici Associati alla Malattia di Parkinson, that is Environmental and Genetic Factors in Parkinson's Disease)* is a large multicenter case-control study carried out in Central-Southern Italy to evaluate the possible role of environmental and genetic factors in PD [12]. Aim of the present study was to estimate the real burden of NMS among PD patients with respect to the general population and to evaluate the possible gender differences in their occurrence.

2. Materials and methods

2.1. Study population

The FRAGAMP study is a large multicenter case-control study involving five Movement Disorder centers located in Central-Southern Italy. Patients affected by PD diagnosed according to the Gelb's diagnostic criteria [1], were consecutively enrolled in the study. Control population consists of healthy individuals recruited from subjects who accompanied non-parkinsonian patients for hospital check-ups. These subjects were frequency matched by age (±5 years) and area of residence.

All subjects underwent a face-to-face interview and a neurological examination performed by trained neurologists. Several demographical, epidemiological and clinical data were collected. Severity of disease was investigated through both the Unified Parkinson Disease Rating Scale – Motor Evaluation (UPDRS-ME) and the Hoehn-Yahr (HY) scale. For dopaminergic therapy, the Levodopa Equivalent Dose (LED) was calculated for those patients taking dopamine agonists [13].

2.2. NMS assessment

Presence of NMS was face-to-face investigated by trained neurologists in both cases and controls using a standardized questionnaire and validated scales to explore the following domains: sleep, mood and cognition, gastrointestinal, urinary and sexual dysfunctions. In particular, in order to evaluate the presence of cognitive impairment and depression, the Mini Mental State Examination (MMSE) and the Hamilton Depression Rating Scale (HDRS) were administered to all the enrolled subjects. For cognitive impairment we adopted the Italian version of the MMSE using the suggested cut-off point of $\leq$24, applied to the score adjusted by age and education while, according to the recommendations of the Movement Disorder Society (MDS), for the HDRS we adopted a cut-off score > 9 to screen depression in PD patients (mild depression) and a cut-off >13 for major depressive disorders [14]. Presence of hallucinations was evaluated using the Scale for the Assessment of Positive Symptoms (SAPS) while data on sleep, gastrointestinal, urinary and sexual disturbances were collected using a standardized questionnaire.

Background and clinical characteristics of PD patients have been extensively reported elsewhere [12].

2.3. Standard protocol approvals and patient consents

The study was approved by the local ethical committee and both patients and controls were enrolled only after have signed the informed consent.

2.4. Statistical analysis

Data were analyzed using STATA 12.0 software packages (Stata corp. STATA statistical software: release 12.1. College Station, TX USA: STATA corporation). Data were double entered into the database. Data cleaning was also performed before the data analysis considering both range and consistence checks. Quantitative variables were described using mean and standard deviation. The difference between means and the difference between proportions was evaluated by the *t*-test and the Chi-square test respectively. In case of not normally distribution, appropriate non-parametric tests were performed.

Unconditional logistic regression analysis was performed to evaluate the possible association between the different non-motor domains investigated and PD; Odds Ratio (OR), 95% Confidence Interval (CI), and p-value (two-tailed test, $\alpha = 0.05$) were computed. Parameters associated with the outcome at the univariate analysis with a threshold of $p = 0.10$ were included in the model. The model was manually constructed using the likelihood ratio test (LRT) to compare the log-likelihood of the model with and without a specific variable.

Multivariate analysis, unconditional logistic regression was also performed considering both age and sex as *a priori* confounders. Whenever variables were dichotomized or polychotomized, the cut-offs were derived from the pooled distribution of cases and control subjects (e.g., using the median value). In order to evaluate the possible gender effect, multivariate analysis has been also stratified by sex.

3. Results

At the end of the study 585 PD patients (59.5% men; mean age of 66.8 ± 9.8 years) and 481 controls (34.9% men; mean age of 63.4 ± 10.1 years) were enrolled. Most of PD patients were taking levodopa alone or in combination with dopamine-agonists and only 5% of patients did not have any treatment. Demographic and clinical characteristics are shown in Table 1. No significant difference in LED between PD men and women was observed (626.3 ± 368.8 *versus* 575 ± 345.1; *p-value* = 0.1).

The presence of at least one NMS was significantly more frequent in PD patients than in controls (87.2% *versus* 59.5%; *p-value* <0.0001). All non-motor domains were more frequent among PD patients, even if a similar distribution was recorded in both cases and controls. In particular, sleep, gastrointestinal and sexual dysfunctions were the most frequent NMS in both groups (60.7%, 57.8% and 55.3% respectively in cases; 37%, 26.2% and 23.7% respectively in controls) as shown in Table 2.

All the NMS investigated were more frequent among PD patients than controls with ORs, adjusted by age and sex, ranging from 2.71 (95% CI 2.09–3.53) for sleep disturbances to 19.6 (95% CI 8.47–45.27) for major depression. Presence of hallucinations was recorded in 79 PD patients (13.5%) and in none of the control population (Table 2).

In both cases and controls presence of NMS was significantly associated with age. In particular among PD patients we found a stronger positive association with the population aged 70 years and