Ital J Gender-Specific Med 2017; 3(3): 104-108

The role of gender in Parkinson's disease

Marina Picillo[1], Alessandra Nicoletti[2], Vincenza Fetoni[3], Barbara Garavaglia[4], Maria Teresa Pellecchia[1]

1. Center for Neurodegenerative Diseases (CEMAND), Department of Medicine and Surgery, Neuroscience Section, University of Salerno, Italy; 2. Section of Neurosciences, Department GF Ingrassia, University of Catania, Catania, Italy; 3. Neurologia Fatebenefratelli-ASST Fatebenefratelli Sacco, Milan, Italy; 4. Molecular Neurogenetics Unit, IRCCS Foundation Neurological Institute "Carlo Besta", Milan, Italy.
Received 13 September 2017; accepted 23 January 2018.

Summary. Since the official inclusion of sex and gender in biomedical research, gender differences are recognized as important determinants of the risk of developing neurodegenerative diseases in the healthy population. In this review, we collected the available evidence on gender differences in Parkinson's disease regarding motor and non-motor symptoms, with a focus on neuropsychiatric symptoms. Finally, we will briefly discuss the issue of pregnancy for parkinsonian women. Though starting with a more benign phenotype, as the disease progresses, women are at higher risk of developing disabling treatment-related complications, such as motor and non-motor fluctuations as well as dyskinesia, compared with men. Taken together, these findings challenge the definition of a more benign phenotype in women. Improving our understanding in gender differences in Parkinson's disease may result in improving our ability to tailor disease treatment and management.

Key words: Parkinson, gender, motor symptoms, non-motor symptoms, genetics, sex, treatment, surgery, biomarker.

Il ruolo del genere nella malattia di Parkinson

Riassunto. Sin dall'inclusione ufficiale delle variabili sesso e genere nella ricerca biomedica, le differenze di genere sono riconosciute come variabili importanti nel determinare il rischio di sviluppo di malattie neurodegenerative nella popolazione sana. Nel presente manoscritto abbiamo raccolto le evidenze disponibili sulle differenze di genere nella malattia di Parkinson sui sintomi motori e non motori con particolare riguardo ai sintomi neuropsichiatrici. Infine, descriviamo brevemente il capitolo della gravidanza nella donna parkinsoniana. Nonostante numerose evidenze suggeriscano che le donne presentano un fenotipo più benigno all'esordio della malattia, con il progredire dei sintomi le donne hanno maggior rischio di sviluppare complicanze legate al trattamento come fluttuazioni motorie e non motorie e discinesie rispetto agli uomini. Tali riscontri suggeriscono di ridefinire il concetto di fenotipo più benigno di malattia di Parkinson nelle donne. Migliorare le conoscenze sulle differenze di genere nella malattia di Parkinson può migliore la gestione terapeutica di ogni singolo paziente.

Parole chiave: Parkinson, genere, sintomi motori, sintomi non motori, genetica, sesso, trattamento, chirurgia, biomarker.

Introduction

Neurodegenerative diseases, including Parkinson's disease (PD), are deeply influenced by sex differences[1]. Sex determining genes and fetal hormonal programming determinate sex differences in brain structure and function since the beginning of fetal life and have important implications for brain-based disease risk. Then, age-related physical and hormonal changes as well as a variety of external factors, including role expectations and social attitudes, further concur to biological differences in the risk, course and outcome of neurodegenerative diseases[1].

Nonetheless, only 20 years ago the first requirements to include both women and men in clinical trials and analyze results by sex were mandated by a US federal law[2]. Since then, gender differences have gained momentum and are recognized as important determinants for neurodegenerative disease risk and management[3]. Indeed, a variety of lifestyle choices associated with gender differences (e.g., smoking, diet, exercise) are known to be potential modifiers of PD risk throughout life[4].

PD is the second most prevalent neurodegenerative disease after Alzheimer's disease and is classified among the movement disorders. The loss of pigmented dopaminergic neurons in the *substantia nigra* and the deposition of α-synuclein in neurons are the two major neuropathologic findings for a definitive diagnosis of idiopathic PD[5]. Global incidence estimates of PD range from 5 to >35 new cases per 100,000 individuals every year, with a 5-to-10-fold increase from the sixth to the ninth decade of life. Compared with Alzheimer's disease, the most common neurodegenerative disease, PD is more common in men. Corroborating previous data[6,7], a recent French nationwide study reported an overall M:F incidence ratio of 1.49 (95% CI: 1.41-1.57, p<0.001) and an overall M:F prevalence ratio of 1.48 (95% CI: 1.45-1.51, p<0.001)[8]. M:F ratios progressively increase with age[8].

The aim of this paper is to review gender differences in PD in motor and non-motor symptoms (NMS) with a focus on neuropsychiatric symptoms. A final paragraph will be dedicated to pregnancy during PD.

Indeed, enhancing our knowledge in gender differences in PD may have an impact on strategies to identify prodromal PD cases as well as to better tailor treatment and management of parkinsonian patients.

Motor symptoms

PD is clinically defined by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity or rest tremor) with a striking response to levodopa. Onset of motor symptoms is usually unilateral and asymmetry persists throughout the disease. Motor fluctuations variably start after about 5 years since diagnosis and are characterized by levodopa wearing off as well as on/off periods and levodopa-induced involuntary movements termed dyskinesia[5].

Specific gender differences in motor symptoms characterize PD from the earliest phases. By studying a cohort of 253 subjects, Haaxma et al first showed a more benign phenotype in women with PD[9]. The highlights of this study were that: a) at symptom onset, women are 2 years older than men and present more likely with tremor (67% vs 48%); b) tremor dominance is associated with a slower decline on motor scales; c) at symptom onset, women have less involvement of nigro-striatal fibers as shown by neuroimaging data; d) in women, age at onset correlated positively with fertile life span[9]. Indeed, gender differences in PD presentation may be due to biological factors such as estrogenic status[9,10].

Although data suggest a more benign phenotype in women at PD onset, as the disease progresses evidence reports shorter time to develop wearing off and dyskinesia in women than in men[11-13]. A growing body of evidence shows that female gender is one of the most important independent predictors of levodopa-induced dyskinesia, irrespective of body weight dyskinesia (hazard ratio 1.82; 95% CI: 1.14-2.89, p=0.011 with a median time to dyskinesia of 4 years in women and 6 years in men)[14]. A "brittle response" to levodopa has recently been described, defined as the presence of highly disabling dyskinesia after small doses (i.e., 100 mg or less per dose)[15]. Those extremely sensitive patients are mainly women (58%) with lower body weight and body mass index (63.5 vs 79.6 kg, p<0.001 and 22.3 vs 26.5, p<0.001, respectively), compared with patients without a "brittle response"[15]. Although this study suggests new insights into the phenomenology of the response to levodopa, the genetic background of patients with "brittle response" is not mentioned[15].

However, lower body weight cannot entirely account for the gender discrepancy in the development of levodopa-related dyskinesia. The profound alteration in central networks and control of energy metabolism characterizing PD as well as genetic polymorphisms certainly play a role in modulating the risk of dyskinesia[16,17]. There is a need for prospective ad-hoc studies to clarify why women with PD have higher rates of levodopa-related complications and are at risk for presenting a "brittle response" to levodopa.

Non-motor symptoms

Although PD is classically considered a movement disorder, NMS represent very common features of the disease[18]. NMS involve different domains, such as psychiatric and behavioral problems, cognitive dysfunction, sleep disorders, gastrointestinal problems, sexual dysfunction and cardiovascular symptoms. Indeed, NMS are very common also in the elderly population occurring in about 50% of healthy people of the same age[19]. Nonetheless, studies taking into account the so-called "background risk" attributable to normal aging have demonstrated a significantly higher prevalence of NMS among PD patients[20].

In recent decades, several studies have evaluated the occurrence of NMS in large cohorts of PD patients suggesting the existence of gender-related differences in NMS. Several studies have shown that specific neuropsychiatric symptoms, such as feelings of nervousness, sadness and pain, are more common in women, while reduced interest in sex and problems having sex are more prevalent in men[21-25]. When analyzing the different aspects featuring depression, melancholy characterizes prominently women, while the more classical factors associated with depression in PD, such as apathy and loss of libido, feature more prominently in men[26]. However, as regards major limitations, these studies used different scales to evaluate NMS and only included patients on dopaminergic treatment. Since it is known that dopaminergic treatment may affect the severity and the spectrum of NMS[27], data from drug-naïve patients are needed before drawing conclusions. A recent study conducted on 200 early, drug-naïve PD patients and 93 age and sex-matched healthy controls was able to show disease-specific gender differences in NMS, regardless of dopaminergic treatment and disease progression[28]. Men with PD had more frequently dribbling, sadness/blues, loss of interest, anxiety, acting-out during dreams, and taste/smelling difficulties compared with healthy control men, while women with PD reported more frequently loss of interest and anxiety compared with healthy control women[28]. As opposed to previous data on treated parkinsonian patients[21,22,26], despite female parkinsonian patients presented with more neuropsychiatric symptoms when compared with their healthy counterparts, they did not report higher prevalence of mood symptoms when compared to male parkinsonian patients. Comparison with healthy controls showed that several

NMS described in healthy subjects with subsequent development of PD in large population studies (i.e., sadness/blues, acting out during dreams, taste/smelling difficulties)[29-32], are more frequent in men than in women with PD. In keeping with these findings, Liu et al. recently described a set of NMS that can best differentiate PD from controls[33]. Poor olfaction was the most powerful NMS predicting PD diagnosis in both men and women, followed by a cognitive screening score. However, the presence of dysautonomia was a predictor of PD diagnosis only in men, while REM sleep behavior disorder (i.e., a sleep disorder highly specific for PD) only in women[33].

The role of gender in the response of NMS to dopamine replacement therapy was subsequently studied in a 2-year prospective assessment of gender-related differences in the burden of NMS before and after starting dopaminergic therapy.[34] While sadness/blues presented a significant percentage reduction compared to baseline in both sexes, other NMS, such as urgency, daytime sleepiness, weight gain and increase in sex drive presented an increase only in men possibly in connection with disease progression as well as dopaminergic treatment[34]. As for the impulse control disorders spectrum, compulsive sexual behavior is known to be more frequent in men with Parkinson's disease, while impulsive shopping and binge eating occur more frequently in women[35].

With the progression of disease, NMS occur as non-motor fluctuations more frequently in women than in men[36]. Mood-related non-motor fluctuations (i.e., anxiety, mood changes and pain) are more prevalent in women, possibly accounting for the higher prevalence of neuropsychiatric symptoms in women than in men in the treated cohort of PD patients with variable disease duration[23-26]. Despite this difference, women with PD do not receive different treatments compared with men, suggesting that non-motor fluctuations in women remain mostly undertreated[36].

Regarding cognition, the literature is not consistent. As opposed to the prevalence in women of dementia (e.g., Alzheimer's disease), male gender has been shown to act as a risk factor for the development of dementia in PD patients[37], but this association has not been confirmed by other studies that have reported a close prevalence between genders[38]. However, due to the different methodology and neuropsychological assessment results across the studies are difficult to compare. In a recent case-control study including only drug-naïve patients, Liu et al. demonstrated that women outperformed men in global cognition assessments and memory domain, but underperformed in the visuo-spatial domain[33].

Pregnancy in Parkinson's disease

The impact of pregnancy on PD symptoms is highly variable with reports indicating either a worsening or improvement during or shortly after pregnancy[39]. Reduction or withdrawal of dopaminergic treatment may have a role in the worsening of parkinsonian symptoms[40]. However, other factors, such as alteration in medication absorption and metabolism as well as physical and psychological distress, should be taken into account[41]. Systematic analysis of data indicates that PD *per se* does not increase the risk of spontaneous abortion or birth complications. As for the anti-parkinsonian treatment, there are no specific guidelines[41]. Levodopa is the most accepted option during pregnancy[42]. Although levodopa crosses the placenta and is metabolized by the fetus, carbidopa, the dopamine decarboxylase inhibitor given with levodopa to reduce peripheral metabolism, does not access fetal circulation[43]. Overall, levodopa has not been associated with birth complications or specific teratogenicity. Therefore, it is considered the first-line treatment in pregnant women with PD. As for breastfeeding, data are very limited, and it is typically suggested not to breastfeed while on antiparkinsonian medications.

Due to its efficacy on psychomotor status and medication sparing, deep brain stimulation is a safe option in the management of young parkinsonian women who wish to become pregnant[44]. However, there is the need to define strategies to prevent and control any worsening of clinical conditions during pregnancy and to consider device-related options (i.e., rechargeable battery to avoid battery replacement and subclavicular placement instead of abdominal) in women who plan to become pregnant[44].

The role of estrogens

Estrogens are a likely contributor to gender differences in PD[45]. Evidence seems to suggest a link between decreased PD risk and milder features at onset in women and longer estrogen exposure during lifetime. Accordingly, animal models with estrogen deprivation show dopaminergic neuron loss, altered dopaminergic metabolism and transporter uptake, which can be partially reversed by the administration of exogenous estrogens, thus suggesting that estrogens are protective against dopaminergic damage[46,47].

A large body of evidence shows that estradiol and related compounds exert neuromodulatory and neuroprotective activities in the *striatum* and *substantia nigra* through several intracellular mechanisms that ultimately decrease apoptosis of neurons. In addition, estrogens might also prevent Lewy body deposition through spe-

cific α-synuclein anti-aggregation and fibril destabilization properties[46,47].

Nonetheless, a handful of studies have tested estrogens as a treatment with a potential to slow disease progression in PD[45].

Conclusions

Here, we collected evidence regarding gender differences in PD motor and non-motor symptoms, as well as pregnancy in PD. Several data demonstrate that PD in women starts with a more benign phenotype, probably due to the effect of estrogens. However, as the disease progresses, women are at higher risk of developing highly disabling treatment-related complications, such as motor and non-motor fluctuations as well as dyskinesia, compared with men[45].

Improving our understanding in this field may result in the implementation of strategies to identify prodromal PD cases and expedite efforts to discern new directions for PD-tailored treatment and management.

Key messages

- Data demonstrate that PD in women starts with a more benign phenotype, probably due to the effect of estrogens.
- As the disease progresses, women have higher risk of developing motor and non-motor fluctuations as well as dyskinesia compared with men.
- Women have lower chances of receiving effective treatment for PD, such as deep brain stimulation.
- As a whole, these findings challenge the definition of a more benign phenotype in women.
- Improving our understanding in this field may expedite efforts to discern new directions for disease tailored treatment and management.

References

1. Institute of Medicine Board on Health Sciences Policy, Committee on Understanding the Biology of Sex and Gender Differences (eds). Exploring the biological contributions to human health: does sex matter? Washington (DC): National Academies Press (US), 2001.
2. Mazure CM, Jones DP. Twenty years and still counting: including women as participants and studying sex and gender in biomedical research. BMC Womens Health 2015; 15: 94.
3. Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. Lancet Neurol 2016; 15: 451-2.
4. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord 2016; 23: 1-9.
5. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. Nat Rev Dis Primers 2017; 3: 17013.
6. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004; 75: 637-9.
7. Taylor KSM, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry 2007; 78: 905-12.
8. Moisan F, Kab S, Mohamed F, et al. Parkinson disease male-to-female ratios increase with age: French nationwide study and meta-analysis. J Neurol Neurosurg Psychiatry 2015; 87: 952-7.
9. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007; 78: 819-24.
10. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G. Reproductive factors and clinical features of Parkinson's disease. Parkinsonism Relat Disord 2013; 19: 1094-9.
11. Sato K, Hatano T, Yamashiro K, et al. Prognosis of Parkinson's disease: time to stage III, IV, V, and to motor fluctuations. Mov Disord 2006; 21: 1384-95.
12. Bjornestad A, Forsaa EB, Pedersen KF, Tysnes OB, Larsen JP, Alves G. Risk and course of motor complications in a population-based incident Parkinson's disease cohort. Parkinsonism Relat Disord 2016; 22: 48-53.
13. Colombo D, Abbruzzese G, Antonini A, et al. The "gender factor" in wearing-off among patients with Parkinson's disease: a post hoc analysis of DEEP Study. Scientific World Journal 2015; 2015: 787451.
14. Hassin-Baer S, Molchadski I, Cohen OS, et al. Gender effect on time to levodopa-induced dyskinesias. J Neurol 2011; 258: 2048-53.
15. Martinez-Ramirez D, Giugni J, Vedam-Mai V, et al. The "brittle response" to Parkinson's disease medications: characterization and response to deep brain stimulation. PLoS One 2014; 9: e94856.
16. Zappia M, Annesi G, Nicoletti G, et al. Sex differences in clinical and genetic determinants of levodopa peak-dose dyskinesias in Parkinson disease: an exploratory study. Arch Neurol 2005; 62: 601-5.
17. Montaurier C, Morio B, Bannier S, et al. Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation. Brain 2007; 130: 1808-18.

18. Munhoz RP, Moro A, Silveira-Moriyama L, Teive HA. Nonmotor signs in Parkinson's disease: a review. Arq Neuropsiquiatr 2015; 73: 454-62.
19. Krishnan S, Sarma G, Sarma S, Kishore A. Do nonmotor symptoms in Parkinson's disease differ from normal aging? Mov Disord 2011; 26: 2110-13.
20. Nicoletti A, Vasta R, Mostile G, et al. Gender effect on nonmotor symptoms in Parkinson's disease: are men more at risk? Parkinsonism Relat Disord 2017; 35: 69-74.
21. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. Mov Disord 2011; 26: 484-92.
22. Leentjens AF, Moonen AJ, Dujardin K. Modeling depression in Parkinson disease: disease-specific and nonspecific risk factors. Neurology 2013; 81: 1036-43.
23. Szewczyk-Krolikowski K, Tomlinson P, Nithi K. The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. Parkinsonism Relat Disord 2014; 20: 99-105.
24. Solla P, Cannas A, Ibba FC. Gender differences in motor and non-motor symptoms among Sardinian patients with Parkinson's disease. J Neurol Sci 2012; 323: 33-9.
25. Martinez-Martin P, Falup Pecurariu C . Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. J Neurol 2012; 259: 1639-47.
26. Perrin AJ, Nosova E, Co K, etal Gender differences in Parkinson's disease depression. Parkinsonism Relat Disord 2017; 36: 93-7.
27. Erro R, Picillo M, Vitale C, et al. Non-motor symptoms in early Parkinson's disease: a 2-years follow-up study on previously untreated patients, J Neurol Neurosurg Psychiatry 2013; 84: 14-7.
28. Picillo M, Amboni M, Erro R, et al. Gender differences in non-motor symptoms in early, drug naïve Parkinson's disease. J Neurol 2013; 260: 2849-55.
29. Song Y, Gu Z, An J, Chan P; Chinese Parkinson Study Group. Gender differences on motor and non-motor symptoms of de novo patients with early Parkinson's disease. Neurol Sci 2014; 35: 1991-6.
30. Shen CC, Tsai SJ, Perng CL, Kuo BI, Yang AC. Risk of Parkinson disease after depression: a nationwide population-based study. Neurology 2013; 81: 1538-44.
31. Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015; 84: 1104-13.
32. Picillo M, Pellecchia MT, Erro R, et al. The use of University of Pennsylvania Smell Identification Test in the diagnosis of Parkinson's disease in Italy. Neurol Sci 2014; 35: 379-83.
33. Liu R, Umbach DM, Peddada SD, Xu Z, Tröster AI, Huang X, Chen H. Potential sex differences in non motor symptoms in early drug-naive Parkinson disease. Neurology 2015; 84: 2107-15.
34. Picillo M, Erro R, Amboni M, et al. Gender differences in non-motor symptoms in early Parkinson's disease: a 2-years follow-up study on previously untreated patients. Parkinsonism Relat Disord 2014; 20: 850-4.
35. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010; 67: 589-95.
36. Picillo M, Palladino R, Moccia M, et al. Gender and non motor fluctuations in Parkinson's disease: a prospective study. Parkinsonism Relat Disord 2016; 27: 89-92.
37. Cereda E, Cilia R, Klersy C, et al. Dementia in Parkinson's disease: is male gender a risk factor? Parkinsonism Relat Disord 2016; 26: 67-72.
38. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. Lancet Neurol 2017; 16: 66-75.
39. Lamichhane D, Narayanan NS, Gonzalez-Alegre P. Two cases of pregnancy in Parkinson's disease. Parkinsonism Relat Disord 2014; 20: 239-40.
40. Hagell P, Odin P, Vinge E. Pregnancy in Parkinson's disease: a review of the literature and a case report. Mov Disord 1998; 13: 34-8.
41. Seier M, Hiller A. Parkinson's disease and pregnancy: An updated review. Parkinsonism Relat Disord 2017; 40: 11-7.
42. Nageshwaran S, Smith M, Bordelon YM. Movement disorders and pregnancy. In: Klein A, O'Neil MA, Scifres C, Waters JF, Waters JH (eds). Neurological illness in pregnancy: principles and practice. Oxford: John Wiley & Sons, 2016:179-90.
43. Merchant C, Cohen G, Mytilineou C, et al. Human transplacental transfer of carbidopa/levodopa. J Neural Tranmission 1995; 9: 239-42.
44. Scelzo E, Mehrkens JH, Bötzel K, Krack P, et al. Deep brain stimulation during pregnancy and delivery: experience from a series of "DBS babies". Front Neurol 2015; 6: 191.
45. Picillo M, Nicoletti A, Fetoni V, Garavaglia B, Pellecchia MT. The relevance of gender in Parkinson's disease: a review. J Neurol 2017; 264: 1583-607.
46. Jurado-Coronel JC, Cabezas R, Ávila Rodríguez MF, Echeverria V, García-Segura LM, Barreto GE. Sex differences in Parkinson's disease: features on clinical symptoms, treatment outcome, sexual hormones and genetics. Front Neuroendocrinol 2017 Sept 30 [Epub ahead of print].
47. Smith KM, Dahodwala N. Sex differences in Parkinson's disease and other movement disorders. Exp Neurol 2014; 259: 44-56.

Conflict of interest statement: The authors declare no financial disclosures related to the content of this article.

Acknowledgments: This review is the product of the Study Group on Gender differences in Movement Disorders within the Italian LIMPE-DISMOV for Parkinson's disease and Movement Disorders.

Correspondence to:
Marina Picillo
Center for Neurodegenerative Diseases (CEMAND)
Department of Medicine and Surgery
University of Salerno
Via Allende, Baronissi (SA), Italy
email picillo.marina@gmail.com