Gender differences in motor and non-motor symptoms in early Parkinson disease

Kyung Wook Kang, MD[a], Seong-Min Choi, MD[b,c,*] , Byeong C. Kim, MD[b,c]

Abstract

Gender differences in motor and non-motor symptoms in Parkinson disease (PD) are still controversial. This study aimed to investigate gender differences in clinical characteristics in patients with early PD.

This study included 415 PD patients (201 men and 214 women) with modified Hoehn-Yahr stage 1 to 3 and a disease duration of ≤5 years. Demographic information was obtained by interviews, and motor and non-motor PD symptoms were evaluated with appropriate scales.

Women with PD had a shorter duration of formal education than men with PD. No significant differences were found in other demographic variables. Women with PD had significantly lower scores in Unified Parkinson Disease Rating Scale part III and postural tremor compared to men with PD, which was significant after controlling for formal education. No significant gender-related differences were found in scores related to other motor symptoms. Concerning non-motor symptoms, men with PD had higher scores of sexual function on the Non-Motor Symptoms Scale, which means sexual dysfunction was more severe or occurred more frequently in men with PD. Women with PD had significantly higher scores of sleep disturbance in the Pittsburgh Sleep Quality Index, which was not significant after adjustment for multiple comparison.

The present study suggests that women with PD had milder motor symptoms compared to men with PD, and gender differences in sexual function can be observed as non-motor symptoms.

Abbreviations: ANCOVA = analysis of covariance, mHY = modified Hoehn-Yahr, NMSS = Non-Motor Symptoms Scale for Parkinson Disease, PD = Parkinson disease, PSQI = Pittsburgh Sleep Quality Index, UPDRS = Unified Parkinson Disease Rating Scale.

Keywords: gender, motor, non-motor, Parkinson disease

1. Introduction

Gender differences in demographic factors, clinical features, and therapeutic responses have been reported in various neurological disorders, including stroke, epilepsy, and dementia.[1–3] Gender is known as an important determinant of the susceptibility to develop neurodegenerative diseases.[4] Although there have been some reports on gender differences in movement disorders and Parkinson disease (PD),[5–7] gender differences in the field of movement disorders are still an under-recognized topic.

PD is a chronic neurodegenerative disease with various clinical manifestations such as motor and non-motor symptoms.[8] Epidemiologic studies have reported that PD is more prevalent in men than in women.[5,9,10] There are limited reports on gender differences in motor and non-motor symptoms in patients with PD, and the results of these studies are inconsistent.[10–12] Women with PD present as tremor-dominant and more often suffer from depression and sleep disturbances compared to men with PD.[11,12] However, gender differences in other symptoms are not consistent.[12,13] Increased recognition of gender differences in PD could aid the stratification of patients in diagnosis and treatment with respect to a precision medicine approach.[5]

Motor and non-motor symptoms in patients with PD worsen over time. Many factors increase the risk of developing PD and accelerate the progression of PD.[14,15] Gender is one of the important factors that determine PD progression.[9] In patients with mid-to-late stage PD, gender differences in motor and non-motor symptoms are affected by many factors that contribute to the progression of PD. Therefore, this study investigated gender differences in demographic characteristics, and motor and non-motor symptoms only in patients with early PD.

2. Methods

The study included patients with early PD who visited the outpatient clinic of our hospital from 2015 to 2019. PD was diagnosed by movement disorder specialists according to the

[a] Department of Neurology, Chonnam National University Hospital, Gwangju, South Korea, [b] Department of Neurology, Chonnam National University Medical School and Hospital, Gwangju, South Korea, [c] National Research Center for Dementia, Gwangju, South Korea.

* Correspondence: Seong-Min Choi, Department of Neurology, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 58128, South Korea (e-mail: drchoism@gmail.com).

United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[16] Patients with early PD with modified Hoehn-Yahr (mHY) stage 1 to 3 and a disease duration of ≤5 years were included in this study. Patients with atypical or secondary Parkinsonism, dementia, epilepsy, poor response to dopaminergic drugs, and clinically significant lesion on brain magnetic resonance imaging were excluded. The study was approved by the Institutional Review Board of Chonnam National University Hospital and was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

Demographic information such as age, duration of PD (from the onset of PD symptom to study inclusion), age at symptom onset, and formal education duration, anti-PD drug treatment was obtained via face-to-face interviews. The patients were examined in the "on" or best condition. Motor and non-motor symptoms were evaluated with the mHY stages,[17] the Unified Parkinson Disease Rating Scale (UPDRS) part II (ADL) and part III (motor) subscores,[18] Non-Motor Symptoms Scale for Parkinson Disease (NMSS),[19] Mini-Mental Status Examination,[20] Beck Depression Inventory,[21] and Pittsburgh Sleep Quality Index (PSQI).[22] PSQI global and PSQI individual components score were used for the analysis.[22] All patients with PD were classified into one of the 3 motor subtypes (tremor dominant, mixed, or postural instability-gait disturbance) as described previously.[23] The following subscores of UPDRS part III were calculated in all patients: tremor score (UPDRS 20–21), bradykinesia score (UPDRS 23–26, 31), rigidity score (UPDRS 22), and gait and posture score (UPDRS 27–30).

SPSS version 23.0 for Windows (IBM Corp.; Armonk, NY) was used for statistical analysis. In the test for normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests, no variable showed normal distribution. Therefore, we used non-parametric tests for all statistics. Mann-Whitney test for continuous variables and Fisher exact test for categorical variables were used to investigate significant differences in variables between men and women with PD. Analysis of covariance (ANCOVA) controlling for formal education and UPDRS motor scores, which were significantly different in the Mann-Whitney tests, was used to

compare each variable between the 2 groups. The P values were then Bonferroni-corrected for multiple comparisons. Results with P values below .05 were considered statistically significant.

3. Results

A total of 415 patients with early PD were included in this study of which 214 (51.5%) were female. The duration of formal education was significantly shorter in women than in men with PD. No significant differences were found in other demographic variables such as age, duration of PD, age at symptom onset, and anti-PD drug treatment between the 2 groups. Women with PD had significantly lower scores in mHY stage and UPDRS part III compared to men with PD, even after controlling for formal education using ANCOVA. However, the difference in mHY stage between the 2 groups was not significant after the Bonferroni correction for multiple comparisons. No significant difference was found in UPDRS part II scores between men and women with PD. In non-motor variables, the Mini-Mental Status Examination score of women with PD was lower than that of men with PD, but this was not statistically significant after controlling for formal education and UPDRS part III score using ANCOVA. No significant differences were found in total NMSS, Beck Depression Inventory, and global PSQI scores between the 2 groups (Table 1).

For motor symptoms, the frequency of each motor subtype and the sum of each motor symptom on the UPDRS part III scale were compared between the 2 groups. Tremor dominant subtype was the most common subtype in both groups. There was no statistical difference in the frequency of the 3 subtypes. The scores for tremor, postural tremor, bradykinesia, rigidity, gait and posture were significantly lower in women with PD than in men with PD, after controlling for formal education. However, only the difference in postural tremor score was significant after the Bonferroni correction for multiple comparisons. No significant differences were found in scores related to rest tremor between the 2 groups (Table 2).

For each non-motor symptom on the NMSS, the sexual function score of women with PD was significantly lower than

Table 1

Clinical characteristics of patients with Parkinson disease.

	All patients (n=415)	Male (n=201)	Female (n=214)	P value	ANCOVA P value	Corrected P value**
Age (yrs)	65.6±9.5	65.4±10.2	65.9±8.9	.936		
Duration of disease (mos)	17.1±14.4	16.8±14.5	17.3±14.3	.698		
Age at onset (yrs)	64.3±9.5	64.0±10.1	64.5±8.8	.883		
Formal education (yrs)	9.5±4.0	10.7±4.0	8.5±3.7	**<.001**		
PD treatment - YES (%)	90 (21.6)	44 (21.8)	46 (21.4)	.508		
mHY stage	1.78±0.69	1.86±0.68	1.71±0.70	**.019**	**.009**[*]	.063
UPDRS part III score	19.4±9.2	20.6±9.3	18.3±9.1	**.008**	**.001**[*]	**.007**
UPDRS part II score	6.2±5.1	6.3±5.2	6.1±5.0	.783	.304[*]	1.000
NMSS total score	42.7±32.0	42.6±32.4	42.9±31.6	.807	.946[†]	1.000
MMSE score	26.9±2.4	27.3±2.2	26.6±2.5	**.003**	.112[†]	1.000
BDI score	10.9±9.4	10.1±9.0	11.7±9.7	.071	.150[†]	1.000
PSQI global score	6.4±3.6	6.1±3.7	6.7±3.5	.051	.323[†]	1.000

Data are presented as mean ± standard deviation.
Covariates of ANCOVA were [*] formal education or [†] formal education and UPDRS part III score.
The corrected P values** were Bonferroni corrected for multiple comparisons.
ANCOVA = analysis of covariance, BDI = Beck Depression Inventory, mHY = modified Hoehn-Yahr scale, MMSE = Mini-Mental State Examination, NMSS = Non-Motor Symptoms Scale for Parkinson Disease, PD = Parkinson disease, PSQI = Pittsburgh Sleep Quality Index, UPDRS = Unified Parkinson Disease Rating Scale.
The bold values mean statistically significant p-values (p-value < 0.05).

Table 2

Motor subtype and individual motor symptoms of patients with Parkinson disease.

	Male (n=201)	Female (n=214)	P value	ANCOVA P value	Corrected P value**
Motor subtype					
Tremor dominant	145	153	.885		
Mixed	13	13			
PIGD	48	48			
Tremor	2.66±2.38	2.34±2.06	.280	.024*	.144
Rest tremor	1.57±1.79	1.55±1.60	.739	.425*	1.000
Postural tremor	1.09±1.27	0.79±1.10	**.014**	.002*	**.012**
Bradykinesia	9.89±4.73	9.15±4.95	.084	.039*	.234
Rigidity	5.00±2.79	4.53±2.75	.076	.040*	.240
Gait and posture	1.08±1.55	0.97±1.68	.130	.043*	.258

Data are presented as number of patients and mean ± standard deviation.
Covariates of ANCOVA were * formal education.
The corrected P values** were Bonferroni corrected for multiple comparisons.
ANCOVA = analysis of covariance, PIGD = postural instability and gait disturbance.

that of men with PD, after controlling for formal education and UPDRS part III score. Since the NMSS domain score is multiplied by the severity and frequency of each non-motor symptom, a high score in sexual function means that sexual dysfunction is severe or occurs frequently. No significant differences were found in other non-motor symptom scores between men and women with PD (Table 3).

Finally, PSQI component scores were compared to identify differences in sleep components between the 2 groups. Women with PD had a significantly higher score in the sleep disturbances component than men with PD, after controlling for formal education and UPDRS part III score. However, these difference was not significant after the Bonferroni correction for multiple comparison. No significant differences were found in other PSQI component scores between the 2 groups (Table 4).

4. Discussion

In this retrospective study on gender differences in motor and non-motor symptoms in patients with early PD, we observed that the duration of formal education was significantly shorter in women with PD than in men with PD; women with PD had lower scores in UPDRS part III and postural tremor than men with PD; and men with PD had a higher score of sexual function in NMSS.

Many studies have reported that men have a higher prevalence and incidence of PD and tend to develop PD at an earlier age than

women.[5,9,10] However, the gender difference in PD incidence is reported to be low in Asia or Easterners.[24] Similarly, there were no differences in age, duration of PD, age at onset, and anti-PD treatment between men with PD and women with PD in our study. However, the duration of formal education was significantly lower in women with PD than in men with PD. These results seem to be related to the past culture of South Korea.[25] Therefore, the formal education level was adjusted in the statistical analyses to investigate the gender differences in motor and non-motor symptoms of PD.

Previous studies have identified differences in motor symptoms between women and men with PD, for example, women with PD tend to have tremor-dominant phenotype,[10,11] slower disease progression,[10] earlier onset of wearing-off,[26] and a greater likelihood of developing dyskinesia[27] compared to men with PD. Our study showed that UPDRS motor scores of women with PD were lower than that of men with PD. Therefore, women with PD had milder motor symptoms compared to men with PD. These results are supported by previous reports showing higher baseline dopaminergic activity and a possible protective effect of estrogens in women with PD.[10,28] Women with PD are more likely to present with tremor as an initial symptom and have higher rates of tremor than men with PD.[10,11] In contrast, postural tremor scores in women with PD were lower than in men with PD in our study. These differences in postural tremor were statistically significant after adjusting for formal education and

Table 3

Non-motor symptoms of patients with Parkinson disease.

	Male (n=201)	Female (n=214)	P value	ANCOVA P value	Corrected P value**
Cardiovascular including falls	2.0±3.3	1.9±3.3	.903	.890†	1.000
Sleep/fatigue	7.5±7.6	8.3±8.0	.376	.465†	1.000
Mood/cognition	7.3±9.8	8.5±10.4	.148	.108†	1.000
Perceptual problems/hallucination	0.2±0.8	0.1±0.8	.551	.519†	1.000
Attention/memory	3.3±4.5	2.9±3.5	.975	.221†	1.000
Gastrointestinal tract	4.7±5.6	4.7±5.7	.766	.919†	1.000
Urinary	13.0±12.3	12.6±12.0	.842	.476†	1.000
Sexual function	0.5±1.7	0.1±0.9	**.003**	**.005†**	**.045**
Miscellaneous	3.6±5.4	3.3±4.3	.851	.752†	1.000

Data are presented as mean ± standard deviation.
† Covariates of ANCOVA were formal education and UPDRS part III score.
The corrected P values** were Bonferroni corrected for multiple comparisons.
ANCOVA = analysis of covariance, UPDRS = Unified Parkinson Disease Rating Scale.

Table 4

Pittsburgh Sleep Quality Index scores of patients with Parkinson disease.

	Male (n=201)	Female (n=214)	P value	ANCOVA P value	Corrected P value**
Subjective sleep quality	1.1 ± 0.7	1.2 ± 0.7	.229	.345[†]	1.000
Sleep latency	1.1 ± 0.9	1.3 ± 1.0	.087	.074[†]	.518
Sleep duration	1.0 ± 0.9	1.1 ± 1.0	.164	.376[†]	1.000
Habitual sleep efficiency	0.5 ± 0.9	0.5 ± 0.9	.430	.624[†]	1.000
Sleep disturbances	1.1 ± 0.4	1.3 ± 0.5	**.003**	**.047**[†]	.329
Use of sleep medication	0.3 ± 0.8	0.1 ± 0.6	.122	.061[†]	.427
Daytime dysfunction	0.8 ± 1.0	0.9 ± 1.0	.630	.812[†]	1.000

Data are presented as mean ± standard deviation.
[†] Covariates of ANCOVA were formal education and UPDRS part III score.
The corrected P values** were Bonferroni corrected for multiple comparisons.
ANCOVA = analysis of covariance, UPDRS = Unified Parkinson Disease Rating Scale.

correction for multiple comparisons. Low motor scores in women with PD seemed to influence the gender difference of postural tremor.

Several studies have reported differences in non-motor symptoms between men and women with PD, with very diverse results.[13,29] Some studies showed higher prevalence or severity of sleep disturbance,[11,12,29] depression,[11–13] pain[12,30] in women with PD, whereas a higher prevalence of sexual dysfunction was found in men with PD.[11,30,31] The prevalence of urinary disturbance differed. One study found it to be more common in women with PD[13] while another study found it to be more common in men with PD.[12] PD-related non-motor fluctuations seem to be more frequent in women than in men with PD.[32] Our study showed a higher prevalence of sexual dysfunction in men with PD, which is consistent with the results of previous studies. These results were statistically significant after adjusting for formal education and UPDRS part III scores. Therefore, it is thought that the low motor score in women with PD did not affect the difference. Since there was no difference in the PSQI total score between men and women with PD and the differences of PSQI component scores in sleep disturbances were not significant after adjustment for multiple comparison, the association between women with PD and sleep disturbance seems to be weak. Our findings indicate that the frequency and severity of non-motor symptoms show different gender distributions in patients with early PD, which suggests a possible gender-related effect.

This study had several limitations. First, this study did not include a control group, so it was not possible to compare the clinical variables between patients with PD and healthy controls. Second, this study was a retrospective study conducted in a single tertiary referral center. Thus, there is a possibility that gender differences may be influenced by biases such as the effects of treatment and recruitment. Third, an influence of dopaminergic drugs on motor and non-motor symptoms cannot be excluded, although we targeted patients with early PD. Forth, although PSQI is a generic scale, it is useful in assessing sleep disturbances in patients with PD.[33] However, other scales such as PD sleep scale and Scales for Outcomes in PD-Sleep might be more specific in detecting PD-related sleep disturbances.

5. Conclusion

To exclude the influence of disease progression, this study investigated gender differences in clinical variables for patients with early PD. The study showed that women with PD had a shorter duration of formal education, lower UPDRS part III scale score, lower postural tremor score, and lower scores in sexual dysfunction compared to men with PD. Our findings suggest milder motor symptoms in women with PD and different gender distributions of non-motor symptoms in early PD. Gender differences should be considered in the management of early PD.

Author contributions

Conceptualization: Seong-Min Choi.
Data curation: Seong-Min Choi, Byeong C Kim.
Formal analysis: Kyung Wook Kang.
Funding acquisition: Kyung Wook Kang, Seong-Min Choi.
Investigation: Kyung Wook Kang, Byeong C Kim.
Methodology: Kyung Wook Kang, Seong-Min Choi.
Project administration: Seong-Min Choi, Byeong C Kim.
Resources: Kyung Wook Kang, Seong-Min Choi.
Software: Kyung Wook Kang, Seong-Min Choi.
Supervision: Seong-Min Choi, Byeong C Kim.
Validation: Seong-Min Choi.
Visualization: Kyung Wook Kang.
Writing – original draft: Kyung Wook Kang, Seong-Min Choi.
Writing – review & editing: Seong-Min Choi, Byeong C Kim.

References

[1] Bushnell CD, Chaturvedi S, Gage KR, et al. Sex differences in stroke: challenges and opportunities. J Cereb Blood Flow Metab 2018;38:2179–91.
[2] Savic I. Sex differences in human epilepsy. Exp Neurol 2014;259:38–43.
[3] Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. Dialogues Clin Neurosci 2016;18:437–46.
[4] Picillo M, Nicoletti A, Fetoni V, Garavaglia B, Barone P, Pellecchia MT. The relevance of gender in Parkinson's disease: a review. J Neurol 2017;264:1583–607.
[5] Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. Nat Rev Neurol 2020;16:84–96.
[6] Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: what's the difference? J Parkinsons Dis 2019;9:501–15.
[7] Smith KM, Dahodwala N. Sex differences in Parkinson's disease and other movement disorders. Exp Neurol 2014;259:44–56.
[8] Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386:896–912.
[9] Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 2016;46:292–300.
[10] Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:819–24.
[11] Solla P, Cannas A, Ibba FC, et al. Gender differences in motor and non-motor symptoms among Sardinian patients with Parkinson's disease. J Neurol Sci 2012;323:33–9.
[12] Guo X, Song W, Chen K, et al. Gender and onset age-related features of non-motor symptoms of patients with Parkinson's disease–a study from Southwest China. Parkinsonism Relat Disord 2013;19:961–5.

[13] Nicoletti A, Vasta R, Mostile G, et al. Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk? Parkinsonism Relat Disord 2017;35:69–74.

[14] Coelho M, Ferreira JJ. Late-stage Parkinson disease. Nat Rev Neurol 2012;8:435–42.

[15] Puschmann A, Brighina L, Markopoulou K, et al. Clinically meaningful parameters of progression and long-term outcome of Parkinson disease: an international consensus statement. Parkinsonism Relat Disord 2015;21:675–82.

[16] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.

[17] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–42.

[18] Fahn S, Elton R, Marsden C. Fahn S, Marsden C, Goldstein M, Calne D. Unified Parkinson's disease rating scale. Recent Developments in Parkinson's Disease Florham Park, NJ: McMillan Healthcare Information; 1987;153–63.

[19] Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 2007;22:1901–11.

[20] Kang Y, Na DL, Hahn S. A validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. J Korean Neurol Assoc 1997;15:300–8.

[21] Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 1974;7:151–69.

[22] Buysse DJ, Reynolds CF3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

[23] Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990;40:1529–34.

[24] Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease-east versus west. Mov Disord Clin Pract 2017;5:14–28.

[25] Chung W, Kim R. A reversal of the association between education level and obesity risk during ageing: a gender-specific longitudinal study in South Korea. Int J Environ Res Public Health 2020;17: 6755.

[26] 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. ScientificWorldJournal 2015;2015: 787451.

[27] 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.

[28] Gatto NM, Deapen D, Stoyanoff S, et al. Lifetime exposure to estrogens and Parkinson's disease in California teachers. Parkinsonism Relat Disord 2014;20:1149–56.

[29] Mahale R, Yadav R, Pal PK. Does gender differences have a role in determining sleep quality in Parkinson's disease? Acta Neurol Belg 2021;121:1001–7.

[30] Martinez-Martin P, Falup Pecurariu C, Odin P, et al. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. J Neurol 2012;259:1639–47.

[31] Szewczyk-Krolikowski K, Tomlinson P, Nithi K, et al. 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.

[32] 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.

[33] Högl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. Mov Disord 2010; 25:2704–16.