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Gender and onset age-related features of non-motor symptoms of patients with Parkinson's disease – A study from Southwest China

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ABSTRACT

Background: Non-motor symptom (NMS) differences between male Parkinson's disease (PD) and female PD, and between early-onset PD (EOPD) and late-onset PD (LOPD) in Chinese populations remain largely unknown.
Methods: A total of 522 PD patients from Southwest China were included. Patients were assessed using the Non-Motor Symptom Scale (NMSS) and Unified PD Rating Scale (UPDRS).
Results: More NMS and significantly higher NMSS score were found in LOPD patients than in EOPD patients (9.3 ± 5.9 vs. 7.7 ± 5.6, $P = 0.005$; 37.4 ± 32.2 vs. 30.5 ± 28.9, $P = 0.018$), while no such differences were found between male and female patients. The NMS of gastrointestinal and urinary domains were more common in LOPD patients than in EOPD patients, whereas sexual dysfunction was more common in EOPD than in LOPD. The sleep/fatigue domain, the mood/apathy domain and "pain" symptoms were more prevalent and severe in female patients than in male patients while urinary symptoms were more common and severe in male patients. Significant positive correlations were observed between disease duration, Hoehn & Yahr stage, UPDRS III, and NMSS score in the total sample, subgroups of both male and female patients as well as both EOPD and LOPD patients.
Conclusions: NMS are common in the Chinese PD population. LOPD patients are likely to present with more and severe NMS than EOPD patients. Males are subjected to urinary symptoms and females are subjected to mood/apathy, sleep and pain symptoms.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by cardinal motor symptoms including tremor, rigidity, bradykinesia and postural instability [1]. However, growing evidence suggests that PD is a disease with numerous non-motor symptoms (NMS) that affect multiple, non-dopaminergic neuronal populations aside from the dopaminergic system [2]. NMS include neuropsychiatric, autonomic and sensory symptoms, and sleep disorders [3–6]. Increasingly, studies have shown that NMS are prevalent in PD patients [3–6], and have a greater impact on the quality of life of PD patients than motor symptoms; the progression of which consequently worsen the quality of life of PD patients [7,8].

PD can be classified into early-onset PD (EOPD, <50 years) and late-onset PD (LOPD, >50 years) [9,10]. Some studies have recently found that age of onset and gender are important factors affecting NMS [5,11–15]. However, there is no consistency among the different studies. For example, Martinez-Martin, P. et al. found symptoms of fatigue, pain, feelings of nervousness and of sadness and constipation were more common in female PD patients, whereas symptoms of daytime sleepiness, drooling saliva and sexual dysfunction were more common in male PD patients [5]; Celikel, E. et al. reported that sexual dysfunction was more common in female PD patients [16]; Wullner, U. et al. found sleep disturbances were more common in female PD patients [11]; Barone, P. et al. found that the psychiatric domain of NMS was more prevalent in female PD patients; skin disorders were more prevalent in male PD patients [3]. In addition, some studies found no differences in NMS symptoms of fatigue, anhedonia, dementia and depression between male and female PD patients [12–14,17]. Several studies found that EOPD patients had a lower rate of dementia and higher rate of other NMS, such as anxiety, depression and restless legs [9,18,19]. However, Willis, A. W. et al. found that psychiatric symptoms and cognitive impairment were more common in EOPD patients than in LOPD patients [15]. In addition, Spica V et al. found

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a higher prevalence of NMS in LOPD patients than in EOPD patients [20]. Recently, Kagi G et al. found no differences in the prevalence of any NMS between EOPD patients without the *Parkin* mutation and LOPD patients [21].

Because of the difference in the findings and the lack of study on gender and age of onset related differences of NMS in the Chinese PD population, we conducted a cross-sectional, study in a large cohort to identify such differences.

2. Patients and methods

Our cross-sectional and observational study included 522 PD patients who attended the Department of Neurology, West China Hospital, SiChuan University, between January 2010 and November 2012. PD patients were diagnosed in accordance with the UK PD Society Brain Bank Clinical Diagnostic Criteria [1]. Patients who had any disorder other than PD were excluded from the study. At the time of inclusion into the study, all patients were "stable" on anti-parkinsonism treatment for at least 1 month. The demographic features and clinical data including age, age of onset, gender, diagnostic delay, disease duration, and anti-parkinson medication were collected using a standard questionnaire by movement disorder specialists during face-to-face interviews. Diagnostic delay was defined as the period between the onset of parkinsonism and making the PD diagnosis. The daily levodopa dose was calculated using a published formula. The Unified PD Rating Scale (UPDRS) part III [4] was used to assess motor disability and Hoehn and Yahr (H&Y) stage [22] was used to establish disease severity. The severity and frequency of NMS were assessed using the Non-motor Symptoms Scale (NMSS), which is an internationally accepted assessment instrument for measuring NMS [6,7]. The NMSS is composed of 30 items grouped in nine domains: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous. Each item is scored for severity (0, none to 3, severe) and frequency (1, rarely to 4, very frequent) and each item score was calculated by the combination of severity and frequency. A patient score of 1 or more in one NMS item indicated that the patient had a NMS. The maximum total score is 360, which indicates the greatest NMS severity. The study was approved by the local ethics committee. All patients gave written informed consent.

3. Statistical analysis

All data were analyzed using SPSS 11.5. All continuous data including mean age, age of onset, diagnostic delay, disease duration, H&Y stage, UPDRS part III and NMSS scores, were presented as mean ± standard deviation. For comparisons, the Student's *T* test was applied as the variables met the normal distribution, whereas the Mann–Whitney test was used for the variables that did not meet the norms for using parametric statistics. Statistical comparisons in terms of prevalence of NMS between male and female patients as well as between EOPD and LOPD patients were performed using Chi-square test. Spearman's correlation test was used to analyze the relationship between age, age of onset, diagnostic delay, disease duration, H&Y stage, UPDRS part III and NMSS scores. A value of $P < 0.05$ was considered statistically significant.

4. Results

Among 522 patients, 296 (56.7%) patients were males and 226 (43.3%) were females, 135 (25.9%) patients were EOPD and 387 (74.1%) were LOPD. The demographic and clinical features of the study patients are listed in Table 1. No statistical differences in disease duration, H&Y stage, UPDRS part III, and daily levodopa dose were observed between male and female PD patients, and between EOPD and LOPD patients (Table 1). The mean diagnostic delay was much longer in EOPD patients than in LOPD patients (2.4 ± 2.4 years vs. 1.6 ± 2.0, $P = 0.001$, Table 1), but there was no difference between male and female patients.

A total of 497 patients (95.2%) reported at least one item of NMS. Only 25 patients (4.8%), including 17 males and 8 females (9 EOPD and 16 LOPD), had no NMS. The mean number of NMS was 8.9 ± 5.8 and the mean total NMSS score was 35.6 ± 31.5 in the total sample. There were no differences in the mean number of NMS and mean total NMSS score between the male and female patients (Table 1). However, LOPD patients had more NMS and had significantly higher NMSS scores than EOPD patients (9.3 ± 5.9 vs. 7.7 ± 5.6, $P = 0.005$; 37.4 ± 32.2 vs. 30.5 ± 28.9, $P = 0.018$, Table 1).

The prevalence of each domain and item of NMS between male and female PD patients as well as those between EOPD and LOPD were shown in Tables 2 and 3 respectively. The most prevalent NMS domain observed in our patients was sleep/fatigue (76.6%), followed by attention/memory (67.8%), mood/apathy (65.1%), miscellaneous (61.5%). In the total sample, the most prevalent item of NMS was "forget things or events" (61.3%), followed by "feelings of sadness" (54.4%), "difficulty falling asleep" (47.9%), "difficulty experiencing pleasure" (43.9%).

The sleep/fatigue domain with the item "difficulty falling asleep" and "restless legs", the mood/apathy domain with the items "lost interest in surroundings, lack motivation, feelings of nervousness, feelings of sadness and difficulty experiencing pleasure", and "pain" from the miscellaneous domain were more prevalent and severe in female PD patients than in male PD patients (Table 2). However, the urinary domain with its item of "frequency" and the item "problems having sex" from sexual dysfunction domain were more prevalent in males than in females (Table 2). Furthermore the urinary domain with all of its items was more severe in male patients than in female patients (Table 2). There were no differences between male and female patients in the remaining NMS (Table 2).

The prevalence and severity of "daytime sleepiness" from the sleep/fatigue domain, the perceptual problems/hallucinations domain with the item "double vision", the attention/memory domain with the items of "forget things or events" and "forget to do things", the gastrointestinal domain with every item, urinary domain with every item, and "taste or smell" of the miscellaneous domain were higher in LOPD patients compared with EOPD patients; however, the sexual dysfunction domain with all its items was more common and severe in EOPD patients than in LOPD patients (Table 3).

The correlations between the NMSS scores and clinical variables are listed in Table 4. Significant positive correlations between age,

Table 1
Demographic and clinical features of the study PD patients (*significant difference).

	Total sample	Male	Female	*P*-value	EOPD group	LOPD group	*P*-value
N (%)	522 (100%)	296 (56.7%)	226 (43.3%)		135 (25.9%)	387 (74.1%)	
Mean age (years)	61.6 ± 11.4	63.0 ± 11.2	59.7 ± 11.5	0.001*	46.7 ± 7.1	66.9 ± 7.4	<0.001*
Mean age of onset (years)	57.2 ± 11.6	58.6 ± 11.5	55.5 ± 11.5	0.002*	41.8 ± 6.1	62.6 ± 7.4	<0.001*
Diagnostic delay (years)	1.8 ± 2.1	1.8 ± 2.1	1.8 ± 2.1	0.660	2.4 ± 2.4	1.6 ± 2.0	0.001*
Disease duration (years)	4.4 ± 4.1	4.4 ± 4.3	4.3 ± 3.8	0.756	5.0 ± 4.4	4.2 ± 4.0	0.065
Hoehn & Yahr stage	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	0.515	2.4 ± 0.9	2.5 ± 0.9	0.131
UPDRS III	27.7 ± 13.9	28.5 ± 14.6	26.8 ± 13.0	0.429	25.6 ± 14.7	27.7 ± 13.7	0.964
Use of levodopa	335 (64.2%)	185 (62.5%)	150 (66.4%)	0.361	73 (54.1%)	262 (67.7%)	0.005*
Daily dose of levodopa (mg)	341.4 ± 214.0	348.9 ± 196.7	332.3 ± 233.6	0.483	343.8 ± 184.5	340.7 ± 221.9	0.685
Mean number of NMS	8.9 ± 5.8	8.5 ± 5.7	9.3 ± 6.0	0.151	7.7 ± 5.6	9.3 ± 5.9	0.005*
Total NMSS score	35.6 ± 31.5	33.7 ± 29.7	38.0 ± 33.6	0.124	30.5 ± 28.9	37.4 ± 32.2	0.018*

EOPD: early-onset Parkinson's disease; LOPD: late-onset Parkinson's disease; NMS: non-motor symptoms; NMSS: non-motor symptoms scale.