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Original Research

Gender Differences in Pain Subtypes among Patients with Parkinson's Disease

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Abstract

Background: To determine the influence of gender on the different pain subtypes experienced by patients with Parkinson's disease (PD). **Methods**: Two hundred patients with PD were recruited for this research. Demographic features for all patients were recorded, as well as clinical data on age, disease duration, levodopa equivalent daily dose (LEDD), and scores for Unified Parkinson's Disease Rating Scale-III (UPDRS III), Hoehn-Yahr Scale (H&Y), King's Parkinson's disease Pain Scale (KPPS), Pittsburgh Sleep Quality Index (PSQI), Mini-mental State Examination (MMSE), activities of daily living scale (ADL), Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA) scales. **Results**: Male and female patients showed no significant differences in terms of age, disease duration, LEDD, H&Y stage, and UPDRS III, HAMD, HAMA, PSQI and ADL scores. Women showed significantly lower MMSE than men, but their KPPS scores were higher (both $p < 0.05$). Female also showed significantly higher scores for chronic, fluctuation-related pain and oro-facial pain and more discoloration;edema/swelling than males ($p < 0.05$). **Conclusions**: Female gender was associated with pain in PD patients, with stronger associations for certain subtypes of PD-related pain.

Keywords: Parkinson's disease; pain; gender; King's Parkinson's disease Pain Scale

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by both motor (resting tremor, rigidity, bradykinesia, and postural instability) and non-motor symptoms (pain, sleep disturbance, anxiety, depression, cognitive dysfunctions, autonomic dysfunctions, apathy, and fatigue) [1–4]. Pain is now recognized as a frequent and troublesome symptom that reduces quality of life in PD patients.

Published evidence suggests gender differences exist for many features of PD, including epidemiological characteristics and the clinical presentation of both the motor and non-motor symptoms of PD [5]. PD is more common and has earlier onset in males, while females have more tremors but are less rigid. Females are also more likely to exhibit postural instability and to develop L-dopa-related motor complications. Sleep disturbance, anxiety, depression, cognitive dysfunctions, apathy and fatigue are more frequent in women with PD, whereas men with PD have greater sexual dysfunction and urinary problems [6–9].

Previous studies on PD have shown that female gender may be associated with more pain, and that pain symptoms differ between male and female patients [3,10–13]. Moreover, men showed greater improvement in pain following deep brain stimulation (DBS) of the subthalamic nucleus (STN) than women [14]. So far, however, the relationship between gender and different pain subtypes in PD is still unclear [10]. Here, the King's Parkinson's disease Pain Scale (KPPS) was used to investigate the influence of gender on different pain subtypes in PD patients.

2. Methods

2.1 Participants

This cross-sectional and observational study was carried out with 200 PD patients recruited from the Neurology Department at the First Affiliated Hospital of Nanchang University from March 2018 to March 2021. All subjects from both the ward and the outpatient department were examined by experienced neurologists and met the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD [15]. Excluded from the study were individuals with secondary or atypical parkinsonism, known causes of pain, or prior neurosurgery. Also excluded were individuals with parkinsonian syndromes such as progressive supranuclear palsy, multiple system atrophy or corticobasal degeneration, as well as those with serious medical diseases or psychological illness. Written informed consent was obtained from all subjects before participation in the study. The study received approval from the ethics committee of the First Affiliated Hospital of Nanchang University.

2.2 Clinical Assessment Protocol

Movement disorder specialists recorded data on demographic and clinical features, including age, gender, disease duration and the use of anti-Parkinson medication. This was carried out during face-to-face interviews and using a standard questionnaire. Motor disability was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part III and disease severity with the Hoehn-Yahr (H&Y) scale. Pain symptoms were assessed using the KPPS and global cognitive function was assessed with the The Mini-Mental State Examination (MMSE). Affective disorders were evaluated using the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Rating Scale (HAMA) rating scales. Sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI) and ability to carry out daily activities using the quality of the activities of daily life scale (ADL) scale.

2.3 Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 23.0 (SPSS, Chicago, IL, USA). Levene's test was used to assess the homogeneity of variance for different variables. Measurements were presented as the mean $\pm$ standard deviation. Independent two-tailed *t*-tests were used to analyze for differences in demographic and clinical features Comparisons between men and women were adjusted using MMSE scores as the covariate by univariate analysis of covariance. Numerical data were expressed as a percentage (%), while *p* values of <0.05 were assumed to represent statistical significance.

3. Results

3.1 Clinical Characteristics

A total of 200 PD patients were recruited to the study. Table 1 shows shows all demographic data and clinical characteristics available for this cohort. No significant differences between males and females were seen in terms of age, disease duration, levodopa equivalent daily dose (LEDD) and H&Y stage, as well as for UPDRS III, HAMD, HAMA, PSQI and ADL scores. Women had lower MMSE scores than men but higher KPPS scores (both $p < 0.05$).

3.2 Gender Differences in Pain Subtypes Severity

KPPS is a 14-item, interview-based rating scale that is separated into 7 domains. These assess musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, oro-facial and radicular pain, as well as discoloration;edema/swelling [16]. Females had higher scores than males for chronic, fluctuation-related pain and oro-facial pain, as well as for discoloration;edema/swelling (each $p < 0.05$). In the 14 items for KPPS, female PD patients also had higher scores than males for central pain, visceral pain, dyskinetic pain, "off" period pain, restless leg syndrome, teeth grinding during the night, burning mouth syndrome, burning pain in the limbs and generalized lower abdominal pain than those of males group (each $p < 0.05$). Table 2 shows these specific findings.

4. Discussion

This is the first study to our knowledge that uses KPPS to investigate gender differences in pain subtypes amongst patients with PD Our results showed that pain intensity was higher in female patients, and that females were more likely to develop chronic, fluctuation-related and oro-facial pain, as well as discoloration;edema/swelling.

Consistent with previous studies, female PD patients in this cohort also had more severe pain symptoms [11–13]. However, other studies found no significant associations between gender and pain in PD patients [17–19]. A recent study reported that women with bilateral PD and the DRD2 rs2283265 polymorphism have significantly risk of PD-related pain [20]. The rs1044397 polymorphism may be associated with age of PD onset in females with pain, rather than with the course or severity of this disease [21]. Furthermore, an earlier study found that female gender might be associated with the appearance of spontaneous pain in subjects who are at risk of PD [22]. Together, these findings suggest that females are genetically and physiologically predisposed to develop PD-related pain.

A frequent problem in PD patients is chronic pain. The current study found that the intensity of chronic pain was higher in females than males. An earlier study also found that female gender was an independent predictors of chronic pain in PD patients [23]. Spinal-paravertebral pain is a dominant form in the spectrum of chronic pain associated with PD. This pain subtype was previously shown to be more common and to have a higher mean pain intensity in women compared to men [10]. According to Skogar *et al*. [24], women more often described their chronic pain as troublesome, whereas men more often described their pain as irritating.

Fluctuation-related pain, including dyskinetic pain and "off" period pain, is associated with motor complications in PD. In the current study, this pain subtype was observed to be more severe in female PD patients. Females are also more likely to develop L-dopa-related motor complications including dyskinesias and "wearing-off" [5]. Another recent study reported that females had an increased hazard ratios (HRs) for wearing-off [25]. These findings may partially explain the gender difference observed for fluctuation related pain in PD patients.

Female patients in the current study had a higher intensity of oro-facial pain associated with grinding their teeth during the night and burning mouth syndrome. A recent study on PD patients found that sleep bruxism was possibly associated with female gender and could lead to negative health outcomes including temporomandibular disorder (TMD) pain and tooth wear [26]. In addition, female

Table 1. Demographic data and clinical characteristics of patients with Parkinson's disease in the total sample and stratified by gender.

	Total	Females	Males	*p* value
Number of subjects (%)	200 (48.9%)	92(47.6%)	108(49.3%)	–
Age, years	64.6 ± 10.2	65.2 ± 9.2	64.1 ± 10.9	0.458
Disease duration, years	4.7 ± 3.7	4.4 ± 3.5	5.0 ± 3.8	0.215
LEDD, mg/d	461.3 ± 244.5	441.2 ± 236.5	478.4 ± 251.0	0.349
UPDRS III score	23.4 ± 7.6	22.9 ± 7.8	23.9 ± 7.4	0.285
H&Y stage	2.4 ± 1.0	2.4 ± 1.1	2.4 ± 0.9	0.937
MMSE score	25.7 ± 2.9	24.8 ± 3.4	26.4 ± 2.3	<0.001
HAMD score	18.8 ± 8.5	19.0 ± 9.7	18.5 ± 7.3	0.660
HAMA score	14.0 ± 5.2	14.36 ± 5.9	13.7 ± 4.6	0.390
ADL score	78.0 ± 19.6	76.1 ± 21.8	79.6 ± 17.4	0.209
PSQI score	8.7 ± 5.4	9.34 ± 5.8	8.2 ± 5.0	0.137
KPSS score	18.3 ± 27.2	22.8 ± 31.1	14.5 ± 22.8	0.032

Dose conversion: 100 mg levodopa = 1 mg pergolide = 10 mg bromocriptine = 50 mg piribedil = 1 mg pramipexole = 10 mg selegiline. LEDD, levodopa equivalent daily dose; UPDRS-III, Unified Parkinson's Disease Rating Scale III; H&Y, Hoehn and Yahr scale; MMSE, Mini Mental State Examination; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; ADL, Activities of Daily Living; PSQI, Pittsburgh Sleep Quality Index; KPPS, King's Parkinson's disease Pain Scale.

Table 2. King's Parkinson's disease Pain Scale scores of patients with Parkinson's disease in the total sample and stratified by gender.

Domain	Total	Females	Males	*p* value*
Domain 1: musculoskeletal pain	2.3 ± 3.3	2.7 ± 3.1	2.0 ± 3.1	0.200
Domain 2: chronic pain	1.7 ± 3.7	2.3 ± 4.7	1.2 ± 2.5	0.003
Central pain	1.3 ± 2.7	1.7 ± 3.1	1.00 ± 2.2	0.027
Visceral pain	0.4 ± 1.3	0.5 ± 1.7	0.2 ± 0.7	0.003
Domain 3: fluctuation related pain	5.2 ± 7.8	6.35 ± 9.2	4.2 ± 6.7	0.021
Dyskinetic pain	2.0 ± 3.1	2.3 ± 3.4	1.8 ± 2.8	0.012
"Off" period dystonia	1.7 ± 2.6	2.1 ± 3.0	1.4 ± 2.2	0.063
"Off" period pain	1.5 ± 2.5	2.0 ± 3.0	1.1 ± 2.0	0.009
Domain 4: nocturnal pain	3.8 ± 6.0	4.4 ± 6.5	3.3 ± 5.6	0.074
Restless leg syndrome	1.9± 3.0	2.1 ± 3.2	1.7± 2.9	0.043
Pain related to difficulty turning in bed	1.9 ± 3.3	2.3 ± 3.6	1.6 ± 3.0	0.133
Domain 5: oro-facial pain	1.0 ± 3.0	1.6 ± 4.0	0.5 ± 1.3	0.004
Pain when chewing	0.2 ± 1.0	0.3 ± 1.5	0.1 ± 0.3	0.137
Grinding their teeth during night	0.1 ± 1.0	0.2 ± 1.5	0.1 ± 0.2	0.008
Burning mouth syndrome	0.7 ± 1.9	1.1 ± 2.4	0.4 ± 1.2	0.034
Domain6: discoloration;edema/swelling	2.1 ± 4.1	2.7 ± 4.9	1.6 ± 3.2	0.003
Burning pain in limbs	1.4 ± 2.6	1.8 ± 3.0	1.1 ± 2.1	0.014
Generalized lower abdominal pain	0.7 ± 1.9	0.9 ± 2.3	0.5 ± 1.5	0.002
Domain 7: radicular pain	2.0 ± 3.1	2.3 ± 3.4	1.7 ± 2.8	0.100

* Adjusted for Mini-mental State Examination scores.

patients in the present study had higher scores for discoloration;edema/swelling, including burning pain in the limbs and generalized lower abdominal pain. Gender differences in autonomic symptoms have been found before in PD patients, with females having more gastrointestinal symptoms than males [27].

Although musculoskeletal pain is the most frequent PD-related pain, we did not find a significant gender difference for this subtype of pain. PD patients with musculoskeletal pain have lower bone mineral density (BMD) than those without pain, and females have lower BMD in the lumbar spine, femoral neck, and hip than males [28]. Kim *et al*. [29] found that musculoskeletal problems such as frozen shoulder, low back pain, osteoporosis and fracture were more frequent in the PD patients than healthy controls, while also being more common in females with PD.

Consistent with an earlier report, female PD patients in our study had more severe cognitive dysfunctions [7]. Mogil *et al*. [30] demonstrated that pain was a form of memory and that gender differences in pain memory (found only in males) could be observed across species. Brain imaging studies in adults have shown differential activation in the pain matrix between males and females. Regions activated by painful stimuli show increased reactivity in the parietal cortex and sensory cortex S2 of men, and increased reactivity in the cingulate cortex and thalamus of women [31,32]. However, additional research is required to better understand these gender differences in PD-related pain and the association between cognitive dysfunction and pain perception.

A cross-sectional study recently investigated the prevalence and characteristics of chronic pain in elderly Chinese living in the community [33]. The most frequent sites for pain were the legs and feet, head, and abdomen/pelvis. However, significant gender differences were not found in the study by Li *et al*. [33]. Some workers reported that women in the general population have a higher prevalence of headache, musculoskeletal pain, arthritis, irritable bowel syndrome and neuropathic pain than men [31]. The discrepancies in the above findings may be partly explained by different socio-cultural characteristics of various patient cohorts rather than by biological sex characteristics alone [34].

Several limitations should be mentioned in order to appropriately interpret the results of the current study. First, it is possible the findings were partly influenced by the characteristics of the patients enrolled in our study and by limitations of the methodology. We did not address gender differences in experimental pain perception. Furthermore, our study did not have a control group and hence any PD-related pain could not be distinguished from pain in healthy subjects. Finally, a larger cohort of PD patients would increase the statistical power for the detection of PD-related pain.

5. Conclusions

Female gender is not only associated with the severity of pain symptoms in PD patients and with certain pain subtypes of pain, such as chronic, fluctuation-related and orofacial pain, as well as with discoloration;edema/swelling.

Abbreviations

PD, Parkinson's disease; LEDD, levodopa equivalent daily dose; UPDRS III, Unified Parkinson's Disease Rating Scale-III; H&Y, Hoehn-Yahr Scale; KPPS, King's Parkinson's disease Pain Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini-mental State Examination; ADL, activities of daily living scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

Author Contributions

LG and YY conceived and designed the research; LG, LC and YY collected materials; LC and YX analyzed the data; LG and YY wrote the paper. YX and LG revised and edited the final version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University (2020956). All participants gave written informed consent to participate.

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Conflict of Interest

The authors declare no conflict of interest.

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