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Prominent Non-Motor Symptoms in Patients with Parkinson's Disease and Pain

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Abstract

Sensory disorders including pain and other non-motor symptoms occur frequently in patients with Parkinson's disease (PD). Studies on the correlation between pain and non-motor symptoms such as depression and sleep disorders are relatively more, so further investigations of the correlation between pain and other non-motor symptoms of PD are needed. A total of 142 patients with PD with or without pain were included in the study. PD severity was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (H/Y) stage scale. Pain severity was analyzed using the Visual Analog Scale (VAS) and the Brief Pain Inventory (BPI). The Hamilton Rating Scale for Depression (HRSD; 24 items), Montreal Cognitive Assessment Beijing Version (MoCA), and non-motor questionnaire NMSQT) measured symptoms of depression, cognitive function, and non-motor symptoms. The incidence of pain was 47.9% in patients with PD, most of whom had moderate pain levels. Patients with pain showed higher HRSD, UPDRS, H/Y, and NMSQT scores and lower MoCA scores compared to patients without pain. HRSD and NMSQT scores were closely related with pain ($p<0.001$). The incidence of pain is higher in patients with PD in pain than in those without pain. Musculoskeletal pain was commonly seen in patients with PD. Compared to controls and patients with PD without pain, non-motor symptoms were more prominent in patients with pain.

Keywords: Non-motor symptoms; Parkinson's disease; Pain; Depression; Manifestation; Predictors

Introduction

Non-motor symptoms of Parkinson's disease (PD) have received increasingly more recognition in recent years. Pain is among such non-motor sensory disorders and occurs frequently in patients with PD. Although chronic pain among patients with PD can be caused by motor symptoms, it has also been reported independently of these symptoms [1]. Extensive co morbidity has been reported between chronic pain syndromes and mood and anxiety disorders [2,3]. Dysfunction in endogenous pain inhibition caused by a dopaminergic deficiency in the basal ganglia, particularly in the striatum and mesolimbic areas, is the main pathophysiological mechanism involved in PD-associated nociceptive abnormalities [2,4]. In addition to the anatomic overlap between the brain regions associated with pain processing and those that comprise the dopamine system, there is substantial overlap between the cognitive and affective functions influenced by dompaminergic (DA) neurotransmission. DA neurotransmission plays an important role in outcome prediction, attention, response inhibition, and motivation [5] as well as in affective symptoms associated with anxiety [6,7] and depression [8].

Cognitive and affective factors also influence the subjective experience of pain. Depression may be one of the leading factors contributing to pain [9]. One study on the relationship between pain and olfactory dysfunction, the two most common sensation dysfunctions in patients with PD, showed that pain processing in these patients was impaired and significantly correlated with smell dysfunction [10]. Research on the relationship between cognitive dysfunction and non-motor symptoms in patients with PD has shown that sleep disturbances in this group may be an early marker of dementia [11]. Therefore, the relationships between non-motor symptoms in patients with PD are complex and multiplex. Previous research on pain and other non-motor symptoms in patients with PD has mainly focused on the relationship between pain and depression. Other than depression, the relationships between pain and other non-motor symptoms in these patients are not yet known.

The aims of the study were to: examine the pain frequency and clinical characteristics of pain and examine the relationship between pain and other non-motor symptoms; and identify and analyze the factors that are independently associated with pain in patients with PD.

Patients and Methods

General clinical characteristics and questionnaires

A total of 142 consecutive patients with PD (82 men and 60 women) who were recruited from the outpatient clinic of our hospital participated in the study. The clinical diagnosis of PD matched the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) criteria [12]. Patients who had undergone deep brain stimulation, who were showing clinical or electrophysiological evidence of peripheral neuropathy or a disease that might be associated with pain such as diabetes mellitus, or Parkinsonism-plus syndrome, epilepsy or other neurological disease, or severe dementia (Montreal Cognitive Assessment Beijing Version [MoCA]<10) were excluded from the study. A questionnaire was designed to collect

patients' demographic data and other information including history of onset, medical treatment, and features of motor disability, motor fluctuations, and dyskinesia. Symptoms of depression, cognitive function, and non-motor symptoms in patients with PD were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) [13], Hoehn and Yahr Stage (H/Y) [14], Hamilton Depression Rating Scale (HRSD; 24 items) [15], MoCA [16], and non-motor questionnaire (NMS Quest) [17]. The number of non-motor symptoms according to the NMS Quest was recorded as the NMSQT. At the time of the examination, the patients were asked to report any pain they had experienced for at least 3 months. Average pain was evaluated using the Visual Analog Scale (VAS; scale, 0–100) [18] and the Brief Pain Inventory (BPI; scale, 0–10). BPI contains seven interference items including general activity, mood, walking ability, normal work, and relationships with other people, sleep, and enjoyment of life [19]. A total of 54 healthy control subjects from our medical center also completed the NMS Quest, and the results were compared between groups.

All patients were at the "on" stage during the interview except those who were not being treated with medications. Daily equivalent levodopa dosage was calculated for those patients receiving treatments. To analyze the drug effect on the pain of patients with PD, the levodopa equivalent dose was calculated according to the following conversion formula: regular levodopa dose × 1 + slow release levodopa × 0.75 + bromocriptine × 10 + apomorphine × 10 + ropinirole × 20 + pergolide × 100 + piribedil × 1 + pramipexole × 100 + selegiline × 10 if taking entacapone + [regular levodopa dose + (slow release levodopa × 0.75)] × 0.2 were calculated [20]. Patient characteristics are shown in Table 1.

	PD with pain n=68	PD without pain n=74	Control n=54	P value
Age (years)a	66.85±9.54	69.61±10.17	68.39±7.82	0.346
Gender (male %)b	39(57.4)	43(58.1)	30(55.6)	0.155
Disease duration (months)a	69.18±48.30	71.65±34.10		0.723
Age onset (years)a	61.07±9.61	63.64±10.12		0.125
UPDRS Ⅰa	3.66±2.33	1.95±1.68		0.000
UPDRS Ⅱa	12.57±6.10	9.04±4.94		0.000
UPDRSⅢa	25.13±12.60	20.27±10.95		0.015
UPDRSⅣa	2.18±2.47	0.92±1.50		0.000
H/Y stagea	2.33±0.76	1.95±0.80		0.005
HRSDa	15.54±8.82	7.41±6.22		0.000
MoCAa	22.49±4.77	23.89±3.09		0.037
NMSQTa	8.38±4.87	4.61±3.16		0.000
Daily equivalent levodopa dosage (mg)a	313.92±189.50	375.35±250.10		0.104
Motor fluctuation (yes)c	33	17		0.001
Dyskinesias (yes)c	16	6		0.011

Table 1: Clinical features of patients and univariate statistical analysis, [a]means and standard deviations; [b]percentages; [c]number of patients say "yes".

Pain definition in patients with PD

PD-associated pain was divided into five categories according to Ford B [21]: musculoskeletal, dystonic, radicular-neuropathic, central, and akathitic pain. Other pain syndromes, such as peripheral neuropathic pain and oral and genital pain, may occur more frequently in the presence of PD and, as such, were recognized as other types of discomfort according to the review by Jankovic J [22,23]. The aching, cramping, and joint pain in patients with PD commonly result from a lack of mobility in the affected limbs and joints, deformities of posture, stiffness of limb movements, and awkward gait mechanics. Musculoskeletal pain tends to increase as the duration of PD increases. Frozen shoulder is one of the most common causes of musculoskeletal pain. Radicular or neuritic pain was well localized to the territory of a nerve or nerve root. Dystonic pain was associated with sustained twisting movements and postures and seemed to be closely related to medication dosing. Central pain was described as feelings of burning, tingling, formication, and "neuropathic" sensations that were often relentless and bizarre in quality and with or without an autonomic character with visceral sensations or dyspnea. Akathitic pain or other discomfort was considered inner restlessness, an urge to move, the presence of oral and genital pain, and burning mouth or vagina syndrome. This type of pain may represent a sensory wearing off and improve with levodopa.

Statistical analysis

Statistical analyses were performed using SPSS 10.0 statistical analysis software (SPSS Inc. Chicago, IL, USA). Chi-square and student t-tests were used to compare constituent ratios and means in patients with and without pain and in controls. A logistic regression model was conducted to examine the predictors of pain. Bivariate correlations about gender, age, disease duration, age onset, score of UPDRS Ⅰ, UPDRS Ⅱ, UPDRSⅢ, UPDRSⅣ, HRSD, MoCA, and NMSQT score, motor fluctuation, dyskinesia, and the equivalent dosage of levodopa were analyzed between patients with and without pain. Each UPDRS score, H/Y stage, HRSD, MoCA, and NMSQT score, motor fluctuation, and dyskinesia was included in the covariance model. Values of $P<0.05$ were defined as statistically significant.

The regional ethics committee of Soochow University approved the study. Informed consent was obtained from each patient.

Results

Subject characteristics

A total of 142 patients with PD but without dementia and 54 healthy control subjects were included in the study (Table 1). Patients and controls were age and gender-matched. The control population's mean age was 68.4 years, and 55.6% (30/54) were men. The patients' mean age was 68.3 years, and 57.4% were men (Table 1). Mean age at onset was 62.4 years and the average PD duration was 70.5 months with a median H/Y stage of 2.1. Mean scores for each part of the

UPDRS were 2.8, 10.7, 22.6, and 1.5. Mean HRSD and MoCA scores were 11.3 and 23.22, respectively. According to the NMSQ, there was a mean of 6.4 occurrences of non-motor symptoms. In all of the patients with PD, the mean daily equivalent levodopa dosage was 343.3 mg. Motor fluctuation was present in 35.2% of the sample and the prevalence of dyskinesia was 15.5%.

A total of 47.9% (68/142) of the patients with PD had pain symptoms. The difference in disease duration between the two groups was not statistically significant. However, patients with pain had higher scores on each part of the UPDRS and a higher H/Y stage than did patients without pain. The mean HRSD score in patients with PD and pain was 15.5; this was higher than the mean score of 7.4 in patients with PD but without pain. In patients with PD and pain, the mean MoCA and NMSQT scores were 22.5 and 8.4, respectively. In patients with PD but without pain, the mean MoCA and NMSQT scores were 23.9 and 4.6, respectively. Differences in these items were significant between the two groups (P=0.037, P=0.000). The prevalence of motor fluctuation and dyskinesia was 48.5% (33/68) and 23.5% (16/68) in patients with pain and 23.0% (17/74) and 8.1% (6/74) in patients without pain.

Clinical types of pain in PD patients

PD-associated pain was recorded in 47.9% (68/142) of cases. Of these, 47.1% (32/68) of patients with PD and pain had musculoskeletal pain. Dystonic pain occurred in 23.5% (16/68) of patients with PD and pain, while neuropathic pain, central pain, akathitic discomfort, and other pain was present in 19.1% (13/68), 7.4% (5/68), and 2.9% (2/68), respectively. Nine patients (13.2%) reported more than one type of pain. The mean VAS score was 5.79. The mean BPI scores for seven interference items were 4.53 (general activity), 4.65 (mood), 4.66 (walking ability), 5.00 (normal work), 2.71 (relationships with other people), 3.76 (sleep), and 4.56 (enjoyment of life).

Non-motor manifestations in patients with PD with and without pain

Completed NMS Quest data were compared between patients with and without pain and to the control population (Table 2). Not surprisingly, the tenth item (pain presence percentage) was significantly different since patients with PD were divided according to pain status but controls were not. Constipation (55.9%, 38/68) was the most prominent non-motor symptom in patients with PD and pain, followed by memory impairment (51.5%, 35/68). The least common symptom was delusions. Patients with PD and pain had higher incidences of weight loss, memory disturbances, depression, insomnia, restless leg syndrome, and swelling than did patients without pain (P=0.003, P=0.000, P=0.048, P=0.003, P=0.043, P=0.016, respectively). Comparisons between PD patients with pain and control subjects showed that patients with PD and pain were more likely to experience dribbling, loss of taste or smell, swallowing and choking difficulties, constipation, incomplete bowel emptying, weight loss, memory loss, loss of interest, difficulty concentrating, sad or blue mood, anxiety, decreased sex drive, insomnia, intense and vivid dreams, acting out during dreams, and swelling (P=0.012, P=0.001, P=0.002, P=0.000, P=0.017, P=0.014, P=0.045, P=0.000, P=0.000, P=0.000, P=0.017, P=0.015, P=0.017, P=0.018, P=0.000, P=0.001, P=0.041, respectively). Results comparing the patients without pain to control subjects were similar for all above symptoms with the exception of weight loss, memory loss, anxiety, insomnia, and swelling (P=0.822, P=0.194, P=0.096, P=0.733, P=0.887, respectively). Constipation (54.1%, 40/74) was also the most prominent non-motor symptom in patients with PD but without pain, followed by nocturia (31.1%, 23/74), although its incidence was not significantly different from that of control subjects. The least common symptom was also delusions.

	PD- pain(+) (n=68) yes (%)	**PD- pain(-) (n=74)yes (%)**	**Control (n=54)yes (%)**	**P 1 value**	**P2 value**	P3 value
1. Dribbling	13(19.1)	15(20.3)	2(3.7)	0.863	0.012	0.006
2. Loss of Taste/Smell	18(26.5)	14(18.9)	2(3.7)	0.282	0.001	0.010
3. Swallowing/Choking difficulties	5(7.4)	11(14.9)	1(1.9)	0.268	0.002	0.013
4. Nausea/Vomiting	3(4.4)	2(2.7)	3(5.6)	0.581	0.772	0.411
5. Constipation	38(55.9)	40(54.1)	9(16.7)	0.827	0.000	0.000
6. Bowel incontinence	2(2.9)	1(1.4)	1(1.9)	0.510	0.700	0.822
7. Bowel emptying incomplete	16(23.5)	16(21.6)	4(7.4)	0.786	0.017	0.029
8. Urgency	17(25.0)	14(18.9)	10(18.5)	0.381	0.392	0.954
9. Nocturia	20(29.4)	23(31.1)	9(16.7)	0.829	0.100	0.063
10. Pains	32(47.1)	0(0)	16(29.6)	0.000	0.050	0.000
11. Weight loss	10(14.7)	1(1.4)	1(1.9)	0.003	0.014	0.822
12. Remembering	35(51.5)	17(23.0)	18(33.3)	0.000	0.045	0.194
13. Loss of interest	23(33.8)	15(20.3)	0(0.0)	0.068	0.000	0.000
14.Halucinations Delusions	6(8.82)	4(5.4)	1(1.9)	0.426	0.100	0.305

15.Concentrating	15 (22.1)	8(10.8)	0(0.0)	0.069	0.000	0.013
16. Sad, blues	26(38.2)	17(23.0)	3(5.6)	0.048	0.000	0.007
17. Anxiety	14(20.6)	11(14.9)	3(5.6)	0.371	0.017	0.096
18. Sex_drive	5(7.4)	3(4.1)	2(3.7)	0.394	0.015	0.013
19. Sex_difficulty	7(10.3)	2(2.7)	2(3.7)	0.064	0.017	0.012
20. Dizziness	18(26.5)	13(17.6)	8(14.8)	0.200	0.118	0.626
21. Falling	8(11.7)	12(16.2)	3(5.6)	0.446	0.234	0.064
22. Daytime sleepiness	11(16.2)	10(13.5)	3(5.6)	0.655	0.068	0.141
23. Insomnia	26(38.2)	12(16.2)	10(18.5)	0.003	0.018	0.733
24. Intense, vivid dreams	29(42.7)	21(28.4)	5(9.3)	0.075	0.000	0.008
25. Acting out during dreams	20(29.4)	22(29.7)	3(5.6)	0.967	0.001	0.001
26. Restless legs	23(33.8)	14(18.9)	11(20.4)	0.043	0.100	0.838
27. Swelling	14(20.6)	5(6.8)	4(7.4)	0.016	0.041	0.887
28. Sweating	20(29.4)	15(20.3)	8(14.8)	0.207	0.057	0.427
29. Diplopia	6(8.8)	3(4.1)	3(5.6)	0.244	0.493	0.691
30. Delusions	0	0	0	constant	constant	constant

Table 2: Percentage of non-motor manifestations in PD patients with and without pain and in controls, P1: differences between PD patients with pain and without pain; P2: differences between PD patients with pain and controls; P3: differences between PD patients without pain and controls.

Independent predictors of pain in patients with PD

A logistic regression model between pain and variables was established to confirm the independent predictors of pain in patients with PD. These variables included gender, age, disease duration, age at onset, location of onset, onset symptoms, UPDRS I, UPDRS II, UPDRS III, and UPDRS IV scores, H/Y stage, dyskinesia, motor fluctuations, HRSD score, MoCA score, daily equivalent levodopa dosage, and NMSQT. UPDRS I, UPDRS II, UPDRS III, and UPDRS IV, H/Y stage, dyskinesia, motor fluctuation, HRSD, MoCA, and NMSQT scores were included in the logistic regression model.

HRSD and NMSQT scores were entered into the model. On multivariable analysis, HRSD (P=0.000) and NMSQT (P=0.012) scores were associated with pain in patients with PD (Table 3). The Hosmer-Lemeshow goodness-of-fit test supported the validity of our regression model.

Variable	B	SE	Wald	P value	95%CI
NMSQT	-0.196	0.078	6.338	0.012	0.705~0.957
HRSD	-0.133	0.038	12.138	0.000	0.813~0.944

Table 3: Logistic regression model examining predictors of pain, Abbreviations: B=B coefficient; SE=standard error.

Discussion

Although there has been a lot of research on pain and other non-motor symptoms, particularly depression, in patients with PD [24,25], the unique aspect of the current study was the correlation between pain and an extensive range of other non-motor symptoms. This was accomplished through the use of NMS Quest and by comparing responses on the NMS Quest questionnaire between patients with PD with and without pain and controls. The aim of the study was to observe the pain characteristics and examine the relationship between pain and other non-motor symptoms as well as factors that are independently associated with pain in patients with PD.

The prevalence of all types of PD-associated pain has been shown to be 24–83% [22,23]. However, we cannot conclude whether the pain is the result of dysfunction in basal ganglia pathway or the deterioration of clinical manifestations. In our study, the prevalence of pain in patients with PD was 47.9% (68/142). Musculoskeletal pain was the most common type of pain occurring in Chinese patients with PD, similar to the results of other studies [4,24,26]. The prevalence of musculoskeletal pain in the current study was 47.1% (32/68), while the prevalence of dytonic, neuropathic, central, and akathitic discomfort and other pain was 27.9% (19/68), 22.1% (15/68), 10.3% (7/68), and 5.9% (4/68), respectively. Nine patients (13.2%) described more than one type of pain. VAS and BPI were completed simultaneously. Pain in patients with PD is generally relatively mild or moderate [27]. The mean VAS (1–100) score was 57.9 in our study.

The patients' clinical characteristics showed that those with PD and pain had higher scores on each part of the UPDRS and a higher H&Y

stage than did those without pain. Patients with pain had more severe PD symptoms. Patients with pain may progress more rapidly than patients without pain because disease duration did not differ between the two groups, but clinical symptoms were more severe in patients with pain than in patients without pain. Lack of mobility may also contribute to the occurrence of pain in patients with PD. Mean HRSD, MoCA, and NMSQT scores were 15.5, 22.5, and 8.4 in patients with pain and 7.41, 23.9, and 4.6 in those without. These findings in patients with PD suggested that patients with pain were more likely to be depressed and have a cognitive impairment and a corresponding increase in non-motor symptoms related to pain occurrence [28].

The daily equivalent levodopa dosage was 313.9 mg in patients with PD and pain. This was not higher than that in patients without pain supposing that the use of anti-PD medications may not play a role in pain occurrence. Motor fluctuation was present in 48.5% of the PD patients with pain and the presence of dyskinesia was 23.5% in these patients. The frequency of motor fluctuation and dyskinesia was obviously higher in patients with pain than in patients without pain, indicating that dysfunction of the dopamine circuit may play a role in pain occurrence in patients with PD. Sensitization phenomena may explain the role of dyskinesia and motor fluctuations in patients with PD and pain. Lim SY et al. [29] considered that plasticity changes may also occur in pain responses in patients with dyskinesia.

To examine whether pain is related to other non-motor symptoms in patients with PD, the NMS Quest scale was used in this study. The NMS Quest is a useful clinical tool for screening non-motor symptoms in patients with PD [30]. These patients had a higher frequency of non-motor symptoms than did the controls. Constipation was the most common non-motor symptom in patients with PD regardless of pain status. The second most common non-motor symptom in patients with pain was memory impairment, while in patients without pain, the second most common non-motor symptom was nocturia. Delusion was not seen in any of the patients. These results suggest that patients with PD have a higher frequency of non-motor symptoms than control subjects, especially gastrointestinal, sensory, sleep disorders, autonomic, neuropsychiatric, cognitive impairment, weight loss, restless legs, and swelling. More severe degrees of weight loss, memory loss, depression, restless leg, and swelling were seen than in patients without pain. These findings may suggest that patients with PD who had a greater number of non-motor symptoms, such as weight loss, cognitive impairment, psychiatric problem, sleep disorder, and autonomic dysfunction, seemed to be at greater risk of pain occurrence. The neuronal degeneration in patients with pain may be more severe than patients without pain in basal ganglia as the disease progresses.

A logistic regression model comparing pain and multiple variables was established to help identify which variables may predict pain occurrence in patients with PD. HRSD and NMSQT scores were entered into the model. Dysregulation in dopamine signaling may directly and indirectly modulate the experience of pain by influencing affective and cognitive processes. Hypersensitivity to pain and high rates of comorbid chronic pain are common in disorders linked with deficits in the function of the dopamine system, including disorders of mood and affect, and PD [26]. Because there were no significant difference in the equivalent dosage of levodopa between patients with and without pain, these findings also suggest that common brain region such as the insular cortex, substantia nigra, amygdala, thalamus, prefrontal cortex, and anterior cingulated cortex, which affect cognitive function, emotional regulation, sleep, and autonomic functioning, may play a role in the occurrence of pain in patients with PD [31]. These non-motor symptoms became more prominent as the PD progressed. NMSQT score entered into the model revealed that the more non-motor symptoms, such as weight loss, memory disturbances, depression, insomnia, rapid eye movement disorder, and swelling, the patients had, the greater probability that pain would develop.

This study had several limitations. First, this was a cross-sectional study, which cannot determine the true risk of developing pain. Also, we cannot conclude whether the occurrence and degree of pain will change with disease progression. Second, although the daily equivalent levodopa dosage was calculated, different treatment groups were not established and the effect of different treatments and different drugs was not examined.

Conclusion

In summary, we found that pain in Chinese patients with PD is common. Non-motor symptoms were more prominent in patients with PD and pain, especially sensory, autonomic and neuropsychiatric symptoms, as well as sleep disorders, cognitive impairment, autonomic dysfunction, and weight loss. Patients with PD who had a greater number of non-motor symptoms, such as weight loss, cognitive impairment, psychiatric problems, sleep disorders, and autonomic dysfunction, seemed to be at higher risk of developing pain. Common brain region impairments affecting affective, cognitive, sleep and autonomic function may explain the common occurrence of pain in patients with PD.

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