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Fluctuating pain in Parkinson's disease: Its prevalence and impact on quality of life

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ABSTRACT

Pain is a common non-motor symptom in Parkinson's disease (PD) patients, and the incidence of fluctuating pain may be improved by taking levodopa. There are only a few detailed reports regarding fluctuating pain. In this study, 331 PD patients were classified into three groups: no-pain group (67.4%), non-fluctuating pain group (22.1%), and fluctuating pain group (10.6%). We evaluated patients' background and its impact on the quality of life (QOL) of each group. The pain group exhibited higher levels of depression ($p < 0.0001$), had a higher frequency of visual hallucinations ($p = 0.007$), and lower QOL ($p < 0.0001$) compared with the no-pain group. The fluctuating pain group had a younger onset ($p = 0.006$), higher Hoehn & Yahr stage ($p = 0.018$), and higher frequency of wearing-off ($p < 0.001$) and dyskinesia ($p = 0.007$) than the other groups. We compared the Parkinson's Disease Questionnaire-8 summary index (PDQ-8 SI) in each pain group to the no-pain group using analysis of variance. As a result, PDQ-8 SI was significantly higher in both the non-fluctuating and fluctuating pain groups ($p < 0.0001$). Pain is regarded as a non-negligible symptom that affects the QOL of PD patients, and given the unique characteristics, fluctuating pain might be considered as an independent clinical subtype of PD.

1. Introduction

Pain is a common non-motor symptom in patients with Parkinson's disease (PD) and the impact of this pain on quality of life (QOL) in PD patients is significant [1]. According to previous reports, the prevalence of pain complications in PD patients varies from 40% to 85% [2–4]. Ford's classification for PD-related pain entails the following five types: musculoskeletal pain, radicular-neuropathic pain, dystonic pain, central or primary neuropathic pain, and other pain [5]. Pain can antedate motor symptoms by years and occur at any disease stage of PD [6]; however, as the disease progresses, the prevalence of pain increases due to additional factors such as dyskinesia, dystonia, and postural abnormalities.

Both motor and non-motor symptoms in PD patients fluctuate, reflecting synaptic dopamine concentration, and pain can also be exacerbated during an off period [7]. PD patients with fluctuating pain have been reported to have a lower QOL than PD patients without fluctuating pain [8]; however, little is known about the overall rate of occurrence of fluctuating pain and its clinical characteristics. Therefore, in this study, we evaluated the prevalence and clinical characteristics of PD patients with fluctuating pain, we also estimated the impact of fluctuating pain on QOL by adding other variables.

2. Materials and methods

This cross-sectional retrospective study was performed at the Department of Neurology, Fukuoka University Hospital from December 14, 2016 to March 31, 2020. The study protocol was approved by the ethics committee of our hospital (U20–04-001). The subjects included 331 PD patients. A diagnosis of PD was made according to the Movement Disorder Society Clinical Diagnostic Criteria for PD [9] and those patients that met the diagnostic criteria for definite or probable PD were included in the study. Exclusion criteria included dementia and disagreement with this study. Dementia was defined by a Mini Mental State Examination (MMSE) score of ≤23 points.

Patient information including age, sex, age at disease onset, disease duration, as well as presence of wearing off, dyskinesia, REM sleep behavior disorder, and visual hallucinations were extracted from each

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patient's medical record. Disease severity of each patient was defined according to the Hoehn & Yahr stage [10]. Motor symptoms were evaluated using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III [11]. Cognitive function was assessed with the Japanese version of The Montreal Cognitive Assessment (MoCA) [12,13] and MMSE. The severity of depression was evaluated by the Zung self-rating depression scale (SDS) [14]. The evaluation of wearing-off was performed using 9-symptom Wearing-off Questionnaires (WOQ-9) [15,16]. We defined wearing-off as when anti-Parkinson's medication improved two or more symptoms according to a previous report [17]. The patient's QOL was evaluated by the Parkinson's Disease Questionnaire-8 (PDQ-8) [18], and the total score (PDQ-8 SUM) and summary index (PDQ-8 SI) were calculated [19]. The patients were classified into three groups: no-pain group, non-fluctuating pain group, and fluctuating pain group according to Question 5 of WOQ-9; we compared the backgrounds, the correlation with QOL, and the correlation with other scales. We performed these evaluations during patients' on state.

The data were analyzed using IBM SPSS v.26 and SAS software v.9.4. All data were presented as mean ± standard deviation (SD) or as n (%). Continuous variables were compared using analysis of variance (ANOVA) while categorical variables were compared using the chi-squared test. Age at the assessment, age at disease onset, disease duration, Hoehn & Yahr stage, MDS-UPDRS part III, PDQ-8 SUM, PDQ-8 SI, MMSE, and MoCA among the three groups were analyzed by one-way ANOVA with Tukey's post hoc test. Sex, wearing-off, dyskinesia, RBD, and hallucinations among the three groups were analyzed by chi-square test. We compared PDQ-8 SI and PDQ-8 SUM according to the subtypes of pain using ANOVA and analysis of covariance (ANCOVA) with Tukey's post hoc test including age, sex, duration, MDS-UPDRS Part III, and SDS as covariates. In addition, we compared these clinical parameters between the two groups: the no pain group and pain group, and the non-fluctuating pain group and fluctuating pain group, and analyzed these using the Mann-Whitney test and the chi-square test.

Furthermore, the patient population that had wearing-off and dyskinesia was also classified into three groups: no-pain group, non-fluctuating pain group, and fluctuating pain group; the same analyses were performed across these groups. Age, age of onset, disease duration, Hoehn & Yahr stage, UPDRS part III, PDQ8-SUM, PDQ-8-SI, MMSE, and MoCA were analyzed by one-way ANOVA. Sex, wearing-off, dyskinesia, RBD, and hallucinations among the three groups were analyzed by chi-square test. All p-values <0.05 were considered significant.

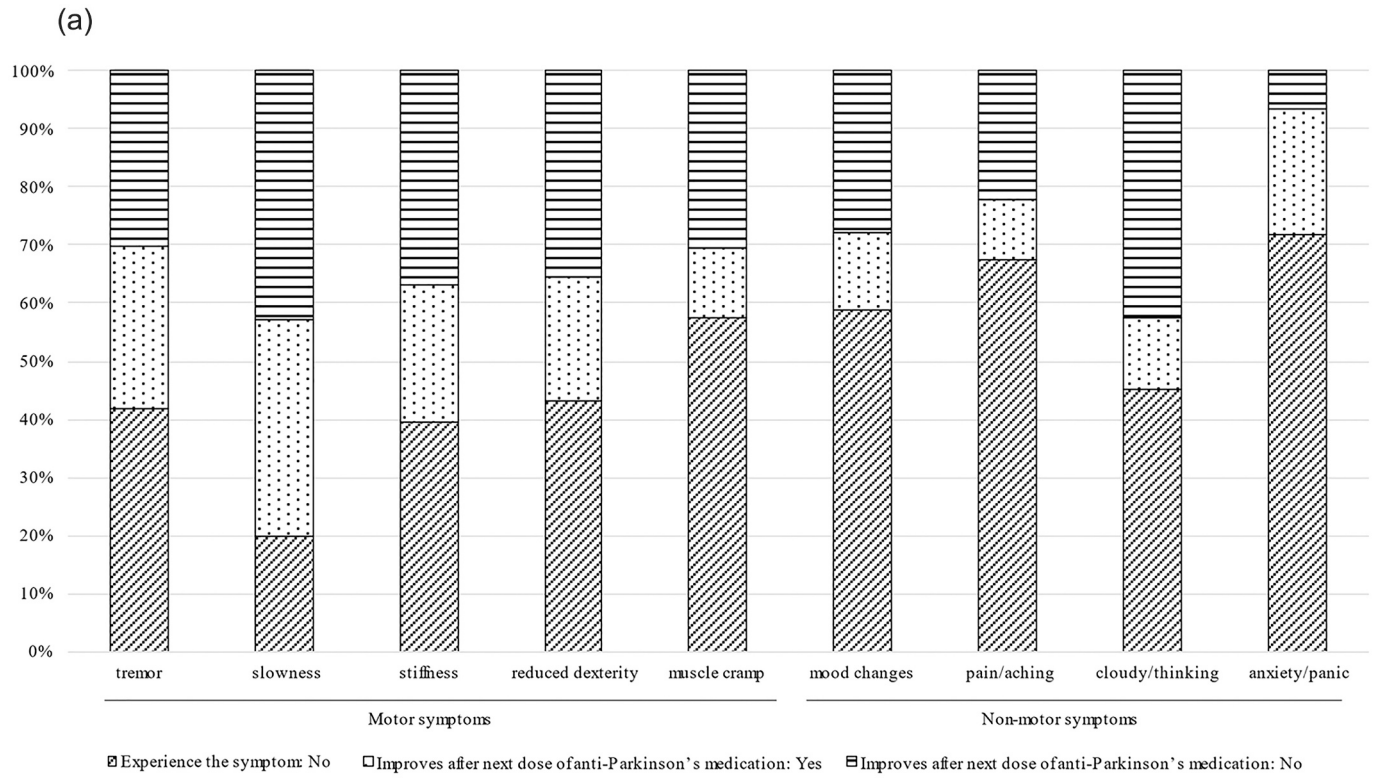
3. Results

In a total of 331 subjects (female: 208), 223 (67.4%) were classified into the no-pain group, 73 (22.1%) into the non-fluctuating pain group, and 35 (10.6%) into the fluctuating pain group. Table 1 shows the clinical characteristics of the patients and comparisons among the three groups. Fig. 1a summarizes the ratio of the patients, who had symptoms and whether or not they had improved with anti-Parkinson's medication for each item of WOQ-9. Fig. 2b shows the same analysis among those patients who experienced wearing-off. There was no significant difference among the groups regarding sex, age at the assessment, disease duration, MDS-UPDRS part III, MMSE, MoCA, and presence of RBD. The mean age at disease onset was lower in the fluctuating pain group (vs. no pain: $p = 0.004$, vs. non fluctuating pain: $p = 0.028$ with Tukey's post hoc test). There was no significant difference in the mean disease duration across the three groups after adjusting for multiple comparisons using Tukey's post hoc test (fluctuating pain vs. no pain: $p = 0.067$, fluctuating pain vs. non fluctuating pain: $p = 0.120$). The no pain group had lower mean PDQ-8 SUM scores (vs. fluctuating pain: $p = 0.003$, vs. non fluctuating pain: $p < 0.0001$ with Tukey's post hoc test) and PDQ-8 SI (vs. fluctuating pain: $p < 0.0001$, vs. non fluctuating pain: $p < 0.0001$ with Tukey's post hoc test), lower mean SDS scores (vs. fluctuating pain: $p = 0.0004$, vs. non fluctuating pain: $p < 0.0001$ with Tukey's post hoc test), and lower prevalence of visual hallucination ($p = 0.007$) compared to the other group. The fluctuating pain group had a higher Hoehn & Yahr stage (vs. no pain: $p = 0.017$, vs. non fluctuating pain: $p = 0.024$ with Tukey's post hoc test), and higher frequency of wearing-off ($p < 0.0001$) and dyskinesia ($p < 0.0001$) compared to the other groups. The frequency of comorbid fluctuating pain according to the severity of PD was 4.8% of the patients with Hoehn & Yahr stage ≤2.5, and 15.1% of patients with Hoehn & Yahr stage >2.5 (Fig. 2). In addition, we compared PDQ-8 SI and PDQ-8 SUM in each pain group to the no-pain group by analysis of variance and analysis covariance using Tukey's post hoc test which was performed with age, sex, Hoehn & Yahr stage, UPDRS Part III, SDS, and duration of illness as covariates. As a result, PDQ-8 SI and PDQ-8 SUM were significantly higher in both the non-fluctuating and fluctuating pain groups (Table 2). Among PD patients with wearing-off, a longer disease duration, higher Hoehn & Yahr stage, higher PDQ-8 SI and PDQ-8 SUM, and higher SDS were seen in the fluctuating pain group (Supplementary Table 1). Among PD patients with dyskinesia, a higher age, younger age of onset, higher PDQ-8 SI and PDQ-8 SUM, and higher SDS were seen in the fluctuating pain group (Supplementary Table 2). A comparison between the no pain group and the pain group showed higher PDQ-8 SI and PDQ-8 SUM, higher SDS, and a higher frequency of wearing-off and hallucination in the pain group (Supplementary Table 3). A comparison between the non-fluctuating pain group and the fluctuating pain group showed a younger age at disease onset, longer disease duration, higher Hoehn &

Table 1
Baseline clinical characteristics and comparison among three groups.

	Total (n = 331)	No pain (n = 223)	Non-fluctuating pain (n = 73)	Fluctuating pain (n = 35)	p-value
Sex, male (n)	123 (37.2%)	83 (37.2%)	29 (39.7%)	11 (31.4%)	0.705
Age (y)	68.2 (10.6)	69.0 (10.0)	67.8 (11.5)	63.4 (12.0)	0.057
Age at onset (y)	61.2 (11.4)	62.2 (10.6)	60.9 (12.2)	54.4 (13.3)	0.006
Duration (y)	7.1 (4.8)	6.9 (4.9)	6.9 (4.7)	9.1 (3.6)	0.008
H&Y	2.6 (0.8)	2.6 (0.7)	2.6 (0.8)	3.0 (0.7)	0.018
UPDRS Part III	29.1 (13.8)	28.4 (13.6)	30.0 (14.4)	32.2 (14.7)	0.257
SDS	42.8 (10.2)	41.1 (9.5)	45.6 (10.8)	49.2 (10.2)	<0.0001
MMSE	28.0 (1.8)	27.9 (1.9)	27.9 (1.8)	28.6 (1.4)	0.523
MoCA	24.0 (3.6)	24.0 (3.5)	23.5 (3.7)	25.5 (3.7)	0.095
Wearing off (n)	139 (42.0%)	84 (37.7%)	23 (31.5%)	32 (91.4%)	<0.0001
Dyskinesia (n)	80 (24.2%)	47 (21.1%)	17 (23.3%)	16 (45.7%)	0.007
RBD (n)	159 (48.0%)	101 (45.3%)	37 (50.7%)	21 (60%)	0.236
Hallucination (n)	74 (22.4%)	40 (17.9%)	26 (35.6%)	8 (22.9%)	0.007
PDQ-8 SI	20.7 (19.0)	16.0 (15.7)	29.3 (20.6)	35.8 (23.5)	<0.0001
PDQ-8 SUM	6.7 (6.1)	4.9 (4.9)	10.2 (6.6)	11.6 (7.3)	<0.0001

H&Y: Hoehn & Yahr scale.
UPDRS: Unified Parkinson's Disease Rating Scale.
PDQ-8 SI: The Parkinson's Disease Questionnaire-8 summary index.
PDQ-8 SUM: The Parkinson's Disease Questionnaire-8 sum score.
SDS: Self-rating Depression Scale.
MMSE: Mini-Mental State Examination.
MoCA: The Montreal Cognitive Assessment.
RBD: REM sleep behavior disorder.
All data are presented as mean (standard deviation) or n (%).



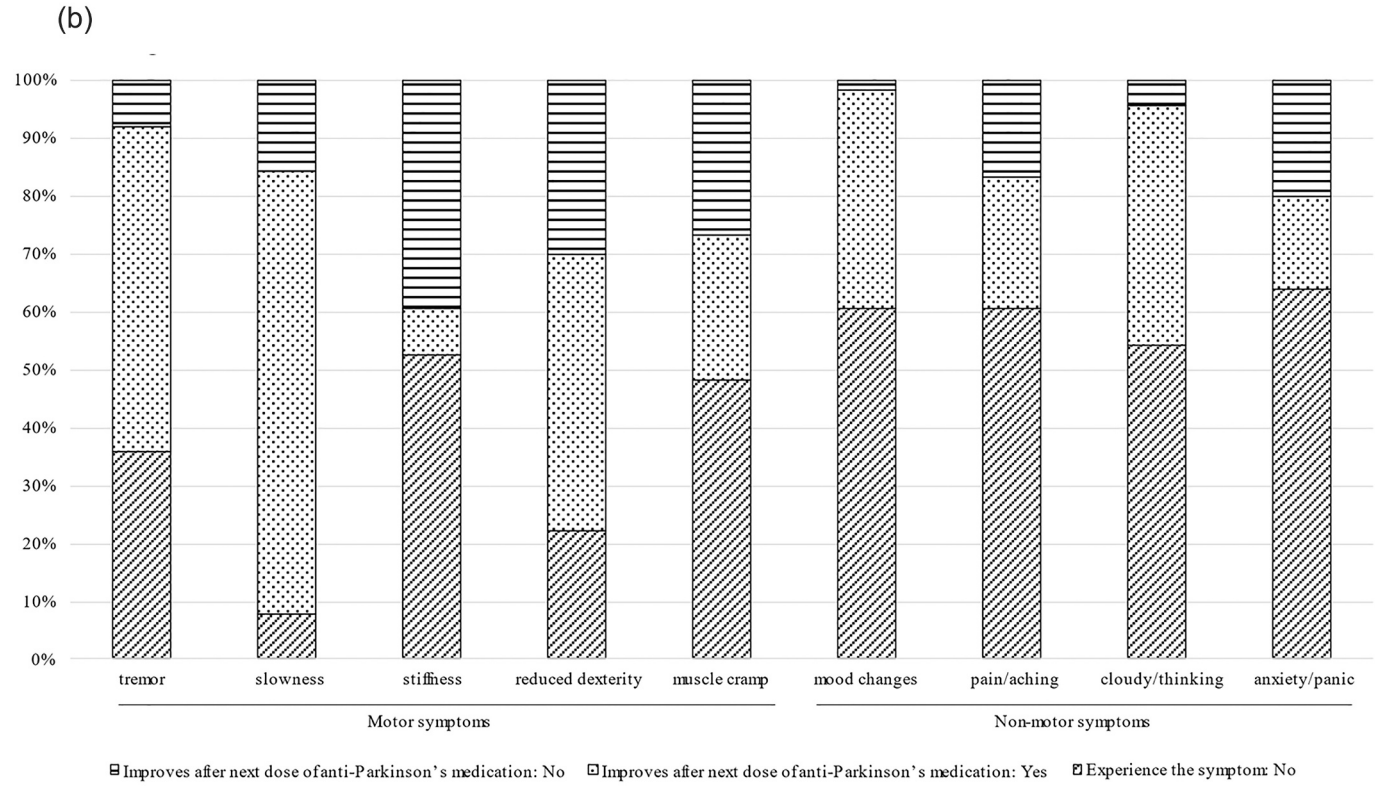


Fig. 1. a. The percentage of patients with each symptom of WOZ-9 and their details. b. The percentage of patients with each symptom of WOQ-9 among the patients experiencing wearing-off.

Yahr stage, and higher frequency of wearing-off and dyskinesia in the fluctuating pain group. PDQ-8 SI and PDQ-8 SUM were higher in the fluctuating pain group but this was not statistically significant (Supplementary Table 4).

4. Discussion

Storch et al. first reported that QOL was poorer in those PD patients with fluctuating pain compared to those with non-fluctuating pain as assessed by univariate analysis [8]. In our study based on a single center

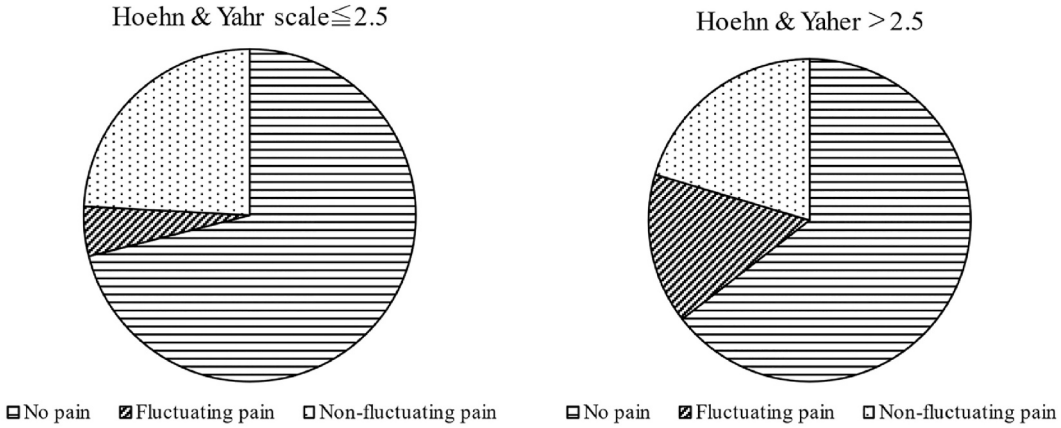


Fig. 2. Prevalence of pain by classification using the Hoehn & Yahr scale.

Table 2
PDQ-8 SI and PDQ-8 SUM according to the subtypes of pain.

	Univariable model			Multivariable model		
	No pain	Non-fluctuating pain	Fluctuating pain	No pain	Non-fluctuating pain	Fluctuating pain
PDQ-8 SI						
Difference (95% CI)	reference	13.8 (9.1–18.5)	20.7 (14.4–27.9)	reference	9.3 (5.3–13.3)	12.1 (6.3–17.8)
p-value		<0.00001	<0.0001		<0.0001	0.0001
PDQ-8 SUM						
Difference (95% CI)	reference	3.3 (1.9–4.6)	3.1 (1.3–5.0)	reference	2.5 (1.1–3.9)	3.1 (1.1–5.0)
p-value		<0.0001	0.0025		0.0011	0.0067

PDQ-8 SI: The Parkinson's Disease Questionnaire-8 summary index.
PDQ-8 SUM: The Parkinson's Disease Questionnaire-8 sum score.
CI: confidence interval.
For univariable analysis, mean differences, 95% confidence intervals and *p* values were estimated using one-way ANOVA with Tukey's post hoc test.
For multivariable analysis, mean differences, 95% confidence intervals and *p* values were estimated using ANCOVA with Tukey's post hoc test which included age, sex, duration, MDS-UPDRS Part III and SDS as covariates.

database, overall prevalence of pain in PD patients was 32.6%, and 32.4% of the patients who experienced pain showed fluctuating pain. The fluctuating pain group had a younger disease onset, greater disease severity, and higher frequency of wearing-off and dyskinesia.

Wearing-off is more likely to occur in PD patients who have received levodopa treatment for a longer period of time, have a younger disease onset, and a greater disease severity [20–22]. In our study, the patient characteristics of the fluctuating pain group were quite similar to those of patients who had risk of developing wearing-off. Alternately, the no-pain group and non-fluctuating pain group did not show a significant difference between the groups related to the items. The fluctuating pain of PD, as evaluated by the King's Parkinson's Disease Pain Scale, was present in 41.3% of the patients with pain, and the results showed no difference between the severity of PD and the prevalence of fluctuating pain [23]. Of all the patients who experienced pain in our study, 32.4% reported fluctuating pain. Of all the patients in our study, 10.6% reported fluctuating pain. In addition, 4.8% of patients with Hoehn & Yahr stage ≤2.5 had fluctuating pain, whereas 15.1% of the patients with Hoehn & Yahr stage >2.5 had fluctuating pain. The fluctuating pain group had a higher Hoehn & Yahr stage ($p = 0.003$). This result may show that, although pain can develop at any PD stage, fluctuating pain tends to occur in the advanced stage (Fig. 2). Fluctuating pain may have a higher complication rate as the disease progresses, similar to wearing off [24].

Longer duration of PD and younger onset have been reported to be a risk for the development of dyskinesia [21] [25]. In our study, PD patients with fluctuating pain shared common characteristics such as early disease onset and longer duration with dyskinesia patients. There is a report demonstrating that PD patients with dyskinesia show increased cold pain threshold and tolerance after levodopa administration [26]. Therefore, it is suggested that the pain could perhaps be the fluctuating type, as opposed to the persistent type, in advanced PD patients due to a change in pain threshold.

In this study, the overall proportion of patients with fluctuating pain was 10.6%, but the proportion among patients with wearing-off and dyskinesia increased to 23.0% and 20.0% (Supplementary Table 1 and 2), respectively. In conclusion, both wearing-off and dyskinesia are important factors that cause fluctuating pain.

In the PRIAMO study, depression was seen in 23.6% and anxiety in 24.9% at the onset of PD [27]. As the stage progresses, the complication rate of depression increases [28]. Depression sometimes causes hyperalgesia and can be a major cause of chronic pain [29]. Pain can also be a cause of depression [30]. In our study, the SDS was higher in the PD patients with pain, indicating that pain and depression often coexist in PD patients.

Intriguingly, the pain group showed a higher rate of visual hallucination compared to the no pain group. Visual hallucinations in patients with PD probably result from a complex interaction of many variables, including cognitive, affective, medication, sensory, and even personality and environmental factors [31]. Dopaminergic, serotonergic, and cholinergic dysfunctions are indicated as the cause of visual hallucination [32]. Dopamine can also modulate pain threshold at several levels of the nervous system, including the spinal cord, thalamus, periaqueductal grey, basal ganglia, and cingulate cortex [33]. No studies have shown an association between visual hallucinations and pain in PD, and further studies are needed to search for a link between these two non-motor symptoms in the future.

Previous studies have shown that pain in PD patients is an

independent factor in lowering QOL [8] [34] [35]. Musculoskeletal pain, radial-neuropathic pain, dystonic pain, and central pain all affect patient's QOL [36]. In our study, the PDQ-8 SI and PDQ-8 SUM were significantly lower in the no pain group in comparisons made among the three groups, indicating that the group with pain had a lower QOL. The fluctuating pain group showed a higher PDQ-8 SI and PDQ-8 SUM compared to the non-fluctuating pain group, but this finding was not statistically significant. Our results also revealed that the characteristics of the fluctuating pain group were: a younger age at disease onset, higher Hoehn & Yahr stage, and higher frequency of wearing-off and dyskinesia.

In our consecutive database, the number of females was as high as 208/331 (68.8%). Unlike the incidence in Europe and the United States, it has been reported that the prevalence of PD is higher in females in Japan [37]. Therefore, in our study, the trend reflected a larger number of females, and there was no sex-related difference among the no pain group, non-fluctuating pain group, and fluctuating pain group.

PD is a clinically heterogeneous disease, which can be classified into subtypes of mild motor predominant, intermediate form, and diffuse malignant form [38]. Classification of clinical subtypes with these characteristics may lead to the greater use of personalized medicine. In this study, it was shown that the fluctuating pain group had a characteristic background, which may be considered to be a PD clinical subtype. Because patients in the fluctuating pain group were able to improve pain in response to dopaminergic medication, they are suggested to be a population that requires more aggressive treatment intervention. In addition to oral medication, device-assisted therapies such as deep brain stimulation and levodopa-carbidopa intestinal gel can relieve pain or pain fluctuation and improve the patient's QOL [39,40]. It is necessary to evaluate pain before and after the treatment and consider the evidence.

The limitations of our study include it being a single-center retrospective evaluation and having a small number of participants in the fluctuating pain group. In addition, we did not evaluate data regarding therapeutic drugs which may have affected pain, hallucinations, motor complications, and QOL or levodopa equivalent doses. Other factors that may affect QOL such as fatigue, anxiety, insomnia, urgency, and nocturia [41] were not evaluated. In a previous study, patients with postural instability and gait difficulty (PIGD) subtypes have also been reported to have higher KPPS scores compared to other subtypes [42]. In our study, we found a strong association between fluctuating pain and disease severity; however, we did not classify or analyze the PD subtypes. Therefore, it is necessary to clarify whether fluctuating pain is also associated with clinical subtypes in the future. We also showed that the fluctuating pain group had a higher frequency of dyskinesia; however, we did not examine whether the pain appeared at the same time as the dyskinesia. In the future, an examination of the relationship between the appearance of dyskinesia and pain and the pain threshold during dyskinesia should be considered.

5. Conclusion

In this study, we demonstrated the characteristics of patients who experienced fluctuating pain and their QOL. Given that pain is a factor affecting their QOL, it is suggested that appropriate levodopa supplementation may be actively considered for the fluctuating pain group. Pain is regarded as a non-negligible symptom that affects the QOL of PD patients; therefore, fluctuating pain might be considered as an independent clinical subtype of PD. Although the symptoms of PD are diverse, we suggest that understanding each characteristic can lead to individually tailored treatment.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Y. Tsuboi: Conceptualization. **Y. Tsuboi, S. Fujioka, T. Mishima, S. Ouma**: Data curation. **M. Kawazoe, K Kurihara**: Formal analysis. **K. Kurihara**: Writing original draft. **Y. Tsuboi**: Project administration and supervision.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2021.100371.

References

[1] J.H. Roh, B.J. Kim, J.H. Jang, et al., The relationship of pain and health-related quality of life in Korean patients with Parkinson's disease, Acta Neurol Scand 119 (6) (2009 Jun) 397–403, https://doi.org/10.1111/j.1600-0404.2008.01114.x.
[2] G. Wasner, G. Deuschl, Pains in Parkinson disease–many syndromes under one umbrella, Nat. Rev. Neurol. 8 (5) (2012) 284–294, https://doi.org/10.1038/nrneurol.2012.54.
[3] M.P. Broen, M.M. Braaksma, J. Patijn, W.E. Weber, Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool, Mov. Disord. 27 (4) (2012) 480–484, https://doi.org/10.1002/mds.24054.
[4] B. Ford, Pain in Parkinson's disease, Mov. Disord. 25 (Suppl. 1) (2010), https://doi.org/10.1002/mds.22716 pp. S98–103.
[5] B. Ford, Pain in Parkinson's disease, Clin. Neurosci. 5 (2) (1998) 63–72.
[6] M.T. Tseng, C.H. Lin, Pain in early-stage Parkinson's disease: Implications from clinical features to pathophysiology mechanisms, J. Formos. Med. Assoc. 116 (8) (2017) 571–581, https://doi.org/10.1016/j.jfma.2017.04.024.
[7] A. Nebe, G. Ebersbach, Pain intensity on and off levodopa in patients with Parkinson's disease, Mov. Disord. 24 (8) (2009) 1233–1237, https://doi.org/10.1002/mds.22546.
[8] A. Storch, C.B. Schneider, M. Wolz, et al., Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications, Neurology. 80 (9) (2013 Feb) 800–809, https://doi.org/10.1212/WNL.0b013e318285c0ed.
[9] R.B. Postuma, D. Berg, M. Stern, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601, https://doi.org/10.1002/mds.26424.
[10] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology 50 (2) (1967) 427–442, https://doi.org/10.1212/wnl.17.5.427.
[11] K. Kashihara, T. Kondo, Y. Mizuno, et al., Official Japanese version of the International Parkinson and Movement Disorder Society–Unified Parkinson's Disease Rating Scale: validation against the original English version, Mov Disord Clin Pract (Hoboken) 1 (3) (2014 June) 200–212, https://doi.org/10.1002/mdc3.12058.
[12] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, et al., The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment, J Am Geriatr Soc 53 (4) (2005 Apr) 695–699, https://doi.org/10.1111/j.1532-5415.2005.53221.x.
[13] Y. Fujiwara, H. Suzuki, M. Yasunaga, et al., Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal cognitive assessment, Geriatr Gerontol Int 10 (3) (2010 Jul) 225–232, https://doi.org/10.1111/j.1447-0594.2010.00585.x.
[14] W.W. Zung, A self-rating depression scale, Arch. Gen. Psychiatry 12 (1965) 63–70, https://doi.org/10.1001/archpsyc.1965.01720310065008.
[15] M.A. Stacy, J.M. Murphy, D.R. Greeley, et al., The sensitivity and specificity of the 9-item wearing-off questionnaire, Parkinsonism Relat Disord 14 (3) (2008) 205–212, https://doi.org/10.1016/j.parkreldis.2007.07.013.
[16] T. Kondo, K. Takahashi, Translation and linguistic validation of the Japanese version of the wearing-off questionnaires (WOQ-19 and WOQ-9), Brain Nerve 63 (11) (2011) 1285–1292 (Article in Japanese).

[17] J. Fukae, M.A. Higuchi, S. Yanamoto, et al., Utility of the Japanese version of the 9-item wearing-off questionnaire, Clin Neurol Neurosurg 134 (2015 Jul) 110–115, https://doi.org/10.1016/j.clineuro.2015.04.021.
[18] V. Peto, C. Jenkinson, R. Fitzpatrick, R. Greenhall, The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease, Qual. Life. Res. 4 (3) (1995) 241–248, https://doi.org/10.1007/BF02260863.
[19] C. Jenkinson, R. Fitzpatrick, V. Peto, R. Greenhall, N. Hyman, The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire, Psychol. Health 12 (6) (1997) 805–814, https://doi.org/10.1080/08870449708406741.
[20] Y. Mizuno, S. Shimoda, H. Origasa, Long-term treatment of Parkinson's disease with levodopa and other adjunctive drugs, J. Neural. Transm. (Vienna) 125 (1) (2018) 35–43, https://doi.org/10.1007/s00702-016-1671-x.
[21] C.O. Warren, K. Kieburtz, O. Rascol, et al., Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease, Mov Disord 28 (8) (2013 Jul) 1064–1071, https://doi.org/10.1002/mds.25364.
[22] L.W. Ferguson, A.H. Rajput, A. Rajput, Early-onset vs. Late-onset Parkinson's disease: A Clinical-pathological Study, Can. J. Neurol. Sci. 43 (1) (2016) 113–119, https://doi.org/10.1017/cjn.2015.244.
[23] M. Rodríguez-Violante, A. Alvarado-Bolaños, A. Cervantes-Arriaga, P. Martinez-Martin, A. Rizos, K.R. Chaudhuri, Clinical determinants of Parkinson's disease-associated pain using the King's Parkinson's Disease Pain Scale, Mov. Disord. Clin. Pract. 4 (4) (2017) 545–551, https://doi.org/10.1002/mdc3.12469.
[24] Y. Wan, C. Yuan, X. Hou, et al., Wearing-off identification in Parkinson's disease: the shapd-woq study, Front Neurol 11 (2020 Mar) 116, https://doi.org/10.3389/fneur.2020.00116.
[25] T.N. Tran, T.N. Vo, K. Frei, D.D. Truong, Levodopa-induced dyskinesia: clinical features, incidence, and risk factors, J. Neural. Transm (Vienna) 125 (8) (2018) 1109–1117, https://doi.org/10.1007/s00702-018-1900-6.
[26] S.Y. Lim, M.J. Farrell, S.J. Gibson, R.D. Helme, A.E. Lang, A.H. Evans, Do dyskinesia and pain share common pathophysiological mechanisms in Parkinson's disease? Mov. Disord. 23 (12) (2008) 1689–1695, https://doi.org/10.1002/mds.22111.
[27] A. Antonini, C. Colosimo, R. Marconi, L. Morgante, P. Barone, The PRIAMO study: background, methods and recruitment, Neurol. Sci. 29 (2) (2008) 61–65, https://doi.org/10.1007/s10072-008-0863-z.
[28] B. Jasinska-Myga, J.D. Putzke, C. Wider, Z.K. Wszolek, R.J. Uitti, Depression in Parkinson's disease, Can. J. Neurol. Sci. 37 (1) (2010) 61–66, https://doi.org/10.1017/s0317167100009665.
[29] L.N. Piardi, M. Pagliusi, I. Bonet, et al., Social stress as a trigger for depressive-like behavior and persistent hyperalgesia in mice: study of the comorbidity between depression and chronic pain, J Affect Disord 1 (2020 Sep) 759–767, https://doi.org/10.1016/j.jad.2020.05.144.
[30] P.H. Hilderink, H. Burger, D.J. Deeg, A.T. Beekman, R.C.O. Voshaar, The temporal relation between pain and depression: results from the longitudinal aging study Amsterdam, Psychosom. Med. 74 (9) (2012) 945–951, https://doi.org/10.1097/PSY.0b013e3182733fdd.
[31] J. Barnes, A.S. David, Visual hallucinations in Parkinson's disease: a review and phenomenological survey, J Neurol Neurosurg Psychiatry 70 (6) (2001 Jun) 727–733, https://doi.org/10.1136/jnnp.70.6.727.
[32] M. Russo, C. Carrarini, F. Dono, M.G. Rispoli, et al., The pharmacology of visual hallucinations in yynucleinopathies, Front Pharmacol 10 (2019 Dec) 1379, https://doi.org/10.3389/fphar.2019.01379.
[33] K.R. Chaudhuri, A.H. Schapira, Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment, Lancet Neurol 8 (5) (2009 May) 464–474, https://doi.org/10.1016/S1474-4422(09)70068-7.
[34] P. Valkovic, M. Minar, H. Singliarova, et al., Pain in Parkinson's disease: a cross-sectional study of its prevalence, types, and relationship to depression and quality of life, PLoS One 10 (8) (2015 Aug), e0136541, https://doi.org/10.1371/journal.pone.0136541.
[35] S. Rahman, H.J. Griffin, N.P. Quinn, M. Jahanshahi, Quality of life in Parkinson's disease: the relative importance of the symptoms, Mov. Disord. 23 (10) (2008) 1428–1434, https://doi.org/10.1002/mds.21667.
[36] S.M. Choi, B.C. Kim, H.J. Jung, et al., Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease, J Clin Neurosci 45 (2017 Nov) 105–109, https://doi.org/10.1016/j.jocn.2017.08.002.
[37] W. Muangpaisan, H. Hori, C. Brayne, Systematic review of the prevalence and incidence of Parkinson's disease, Asia J Epidemiol 19 (6) (2009) 281–293, https://doi.org/10.2188/jea.je20081034 (Epub 2009 Oct 3).
[38] M.J. Armstrong, M.S. Okun, Diagnosis and treatment of Parkinson disease: a review, JAMA. 323 (6) (2020 Feb) 548–560, https://doi.org/10.1001/jama.2019.22360.
[39] W.A. Kamel, J.Y. Al-Hashel, LCIG in treatment of non-motor symptoms in advanced Parkinson's disease: review of literature, Brain Behav 10 (9) (2020 Jul), e01757, https://doi.org/10.1002/brb3.1757.
[40] H.S. Dafsari, L. Weiß, M. Silverdale, et al., Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease, Brain Stimul. 11 (4) (2018) 867–874, https://doi.org/10.1016/j.brs.2018.02.015.
[41] P. Barone, A. Antonini, C. Colosimo, et al., The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, Mov Disord 24 (11) (2009 Aug) 1641–1649, https://doi.org/10.1002/mds.22643.
[42] M. Rodríguez-Violante, A. Alvarado-Bolaños, A. Cervantes-Arriaga, et al., Clinical determinants of Parkinson's disease-associated pain using the King's Parkinson's disease pain scale, Mov Disord Clin Pract 4 (4) (2017 Feb) 545–551, https://doi.org/10.1002/mdc3.12469.