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Pain is common in early onset Parkinson's disease and pain severity is associated with age and worsening of motor and non-motor symptoms

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ABSTRACT

The consequences of pain in early onset Parkinson's disease (EOPD) remain under appreciated even though pain may exert an increasingly negative impact on patient quality of life as motor and non-motor symptoms worsen.

In this prospective study, we investigate the prevalence and severity of pain in 135 Vietnamese patients with EOPD from three medical centers using the King's PD Pain Scale (KPPS), the Mini Mental Status Exam (MMSE), the Unified Parkinson's Disease Rating Scale (UPDRS) and the Non-Motor Symptoms Scale (NMSS).

Pain was reported by 79.3%. The most common subtype of pain was musculoskeletal (70.1%), followed by nocturnal (43.9%), radicular (43.0%), chronic (42.1%), fluctuation-related (34.6%) and orofacial pain (16.8%). Most patients (74.8%) experienced more than one pain subtype. Fluctuation-related pain and orofacial pain were significantly more prevalent among patients with higher Hoehn & Yahr (H&Y) stages (3–5) versus lower H&Y stages (1–2). Pain subtype and severity were not significantly related to gender or age of PD onset.

Patients with H&Y stages 3–5 had statistically significantly higher KPPS scores for fluctuation-related pain ($p = 0.018$) and radicular pain ($p = 0.026$). Independent associations were found between pain severity and age ($p = 0.028$), depression severity ($p = 0.018$), perceptual problems/hallucinations ($p = 0.033$) and sexual function ($p = 0.024$).

Patients with depression and higher H&Y stages (3–5) had statistically significantly higher mean KPPS scores versus patients without depression and at lower H&Y stages (1–2).

Pain may be more common and severe in EOPD patients than previously appreciated. Older age, depression, perceptual problems/hallucinations and sexual dysfunction were independently associated with higher pain severity.

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1. Introduction

Pain is one of the most common non-motor symptoms in patients with Parkinson's disease (PD), with an estimated prevalence of up to 88.6% [1–4]. Pain is associated with worsening motor symptoms such as rigidity [1], freezing of gait, falls [5], and dyskinesias. Pain is also associated with exacerbations of non-motor symptoms such as depression, sleep disturbances, and cardiovascular co-morbidities [3,4].

Pain is frequently under recognized in patients with PD [3,6,7]. Standard clinical assessments of patients with PD such as the Unified Parkinson's Disease Rating Scale (UPDRS) do not include pain as part of their assessment. Despite previous attempts to include pain as the "fifth" vital sign, reliable, repeatable and convenient measurements of pain remain underutilized in routine clinical practice. This lack of adoption may be due to the nebulous nature of pain symptoms. Different patients may have different perceptions for what "pain" may mean. Pain for a particular patient may conjure reports of a physical ailment or psychological stress or simply a general sense of lack of wellness. Therefore, incorporating a validated clinical assessment of pain may be helpful to capture the full extent of a patient's condition.

The King's PD Pain Scale (KPPS) is the first reliable and validated scale developed specifically to assess pain in patients with PD [8]. Previous studies exploring the association between the KPPS pain assessment and motor/non-motor symptoms have been in patients with onset of PD in their 60s and 70s.

However, this approach fails to acknowledge the unique challenges faced by patients diagnosed before the age of 50, otherwise known as early onset Parkinson's disease (EOPD). Patients with EOPD are more likely to suffer sustained decrements in quality of life when in pain. Approximately 5–10% of all patients with PD fall into this category [9]. Patients with EOPD have higher expectations with regard to their clinical care, as PD progression during the most productive years of their life may have a disproportionate impact on their quality of life [9,10]. These challenges require a personalized, multidisciplinary approach to assessment and management [11].

This study sought to investigate the prevalence and severity of pain in Vietnamese patients with EOPD as measured by the KPPS, and to characterize the association of pain severity with both motor and non-motor symptoms.

2. Methods and assessments

2.1. Methods

2.1.1. Overview

This was a prospective, cross-sectional study. A total of 135 Vietnamese patients with EOPD were recruited from Military Hospital 103 (in Hanoi City), Viet Tiep Hospital (in Hai Phong province) and Hospital of Ho Chi Minh City Medicine and Pharmacy University from April 2019 to December 2021. Patients willing to participate in the study had their information collected on a standardized medical record form during outpatient consultations by a trained neurologist with a subspecialty interest in movement disorders. All patients provided informed consent to participate in this study. This study was approved by the ethics committee at the Institute of Genome Research, Vietnam Academy of Science and Technology.

2.1.2. Inclusion and exclusion criteria

Vietnamese patients with EOPD were included in this study. PD was diagnosed according to the 2015 Clinical Diagnostic Criteria for Parkinson's Disease as published by the Movement Disorders Society (MDS-PD) [12]. The MDS-PD criteria include a three-step process for PD diagnosis. EOPD was defined as PD patients with the age of onset $\leq$50 years old but older than 20 years [13].

Patients with cognitive impairment (MMSE $<$24) were excluded from participating, as were those with comorbidities known to be independently associated with significant chronic pain (See Appendix A).

2.2. Assessments

Baseline demographic information and clinical history were collected at the beginning of the study. The clinical history form included information such as age, gender, family history, time since initial PD diagnosis, clinical PD subtype (tremor dominant, akinetic-rigid dominant, or mixed phenotype), motor complications, Hoehn and Yahr (H&Y) stage, and Levodopa Equivalent Daily Dose (LEDD) (See Appendix B).

The following structured questionnaires were translated into Vietnamese and subsequently administered by a trained neurologist.

1) Unified Parkinson's Disease Rating Scale (UPDRS) part III was used to assess PD severity. Items from questions 18 to 31 were scored on a 0–4 rating scale. Higher total scores (range 0 to 108) indicate worsening disease severity.
2) Beck's Depression Inventory (BDI) was used to assess the degree of depressive symptoms. BDI consists of 21 self-reported on four scales, each item rated from 0 to 3. Higher total scores indicate more severe depressive symptoms.
3) Mini Mental State Examination (MMSE) was used to evaluate cognitive impairment. The maximum score for the MMSE is 30. A score of 23 or less indicates possible cognitive impairment. Although the Montreal Cognitive Assessment (MoCA) is often preferred over the MMSE for assessing cognitive dysfunction in PD patients, the author's' choice of the MMSE was influenced by the specific circumstances of medical practice in Vietnam. In this region of the world, the authors face certain limitations, including the absence of a standardized version of the MoCA that has been culturally adapted and validated for use in Vietnamese populations.
4) King's PD Pain Scale (KPPS) [8]. The KPPS consists of 14 Likert-type items, divided into seven domains: (1) musculoskeletal pain; (2) chronic pain; (3) fluctuation-related pain; (4) nocturnal pain; (5) orofacial pain; (6) discoloration, edema/swelling and (7) radicular pain. Each item is scored from 0 (no pain) to 3 (very severe pain) multiplied by frequency from 0 (never) to 4 (very frequently), to generate sub-scores that range from 0 to 12 and a total score from 0 to 168. Higher score indicates higher levels of pain. A KPPS score $>$ 0 indicates the patient has pain. Severe, moderate, and mild pain are defined by scores of three, two and one on any KPPS item, respectively.
5) The Non-Motor Symptoms Scale (NMSS) was used to assess non-motor symptoms [14]. The NMSS has a total of 30 items in nine different domains: (1) cardiovascular, (2) sleep/fatigue, (3) mood/apathy, (4) perception/hallucinations, (5) attention/memory, (6) gastrointestinal tract, (7) urinary, (8) sexual and (9) miscellaneous including pain, taste or smell, weight change and excessive sweating. Each item is quantified by multiplying severity (score 0–3) and frequency (score 1–4). The range of possible total scores is 0–360. Higher scores indicate more frequent and severe non-motor symptoms in PD patients.

6) A subset of the NMSS was used to help assess the degree of dysautonomia. Specifically, questions 1, 2, 19–24, 26 and 29–30 were used to assess dysautonomia severity.
7) A subset of the UPDRS part IV questions 32 to 39 were used to assess the severity of dyskinesias. Higher total scores indicate worsening disease severity.
8) Levodopa Equivalent Daily Dose (LEDD)(mg/day) was calculated according to Tomlinson's scale [15]. Higher LEDD totals indicate need for more levodopa replacement.

2.3. Data analysis

Categorical and continuous variables are expressed as frequency, percentage, mean ± standard deviation (SD) (range), median with range or interquartile range (Q1–Q3), where appropriate and analyzed using SPSS Statistics for Windows, version 22. 0 (SPSS Inc., Chicago, Ill., USA). Crude differences between groups were analyzed using the chi-square test, Fisher's test (categorical data), independent samples *t*-test (numerical data were normally distributed), Mann-Whitney *U* test (numerical data were not normally distributed) or ANOVA-test (analysis of variance). Pearson correlation tests were used to test for possible correlations between KPPS score and other continuous variables. Correlations were classified as strong ($r \geq 0.60$), moderate ($r = 0.40$–0.59), or weak ($r = 0.2$–0.39). To test whether the KPPS score is associated with other clinical variables , multivariable mixed-effect linear regression models were applied. All covariates used for the adjusted analyses were tested for multicollinearity. In addition, question 27 (evaluating pain) in NMS-domain 9 A was also excluded to avoid bias when calculating correlation coefficients and multivariable regression analysis. Two-tailed *p* values of <0.05 were considered statistically significant.

3. Results

A total of 135 EOPD patients (72 men, 53.3%) was included in the study, with mean age of 45.5 (± 8.1) years, mean onset age of 38.1 (± 6.1) years and mean disease duration of 7.9 (± 5.3) years. The patients with a positive PD family history accounted for 23/135 (17%). The clinical motor phenotypes were distributed as follows: akinetic–rigid dominant in 89/135 (65.9%), tremor dominant in 34/135 (25.2%) and mixed phenotypes in 12/135 (8.9%). Regarding the severity of disease, the mean H&Y score was 2.3 (± 0.7), and the median UPDRS-part III was 26 (range: 9–37). Depressive symptoms were evaluated by BDI which showed a median score of 13 (range: 6–22). The median total NMSS score was 32 (range: 1–63). 66.7% of patients received dopamine agonist treatment, while 61.5% of participants were treated with Levodopa. Baseline demographic and clinical features of the patients in this study are shown in Table 1.

Of the 135 patients, pain was reported by 107/135 (79.3%). The most common subtype of pain was musculoskeletal (70.1%), followed by nocturnal pain (43.9%), radicular pain (43.0%), chronic pain (42.1%), fluctuation-related pain (34.6%) and finally orofacial pain (16.8%). Of the patients who experienced pain, 74.8% experienced more than one subtype of pain. No significant differences were detected in the distribution of pain subtypes based on gender or age of PD onset. Fluctuation-related pain and orofacial pain were significantly more prevalent among patients with H&Y stages 3, 4 and 5 compared to patients with H&Y stages 1 and 2 (see Table 2a, Table 2b, Table 2c and Table 3).

The pain subtypes were subsequently stratified by KPPS score, age, H&Y stage and onset age. No significant differences were detected in the severity of pain among the groups based on gender or age of onset. Patients with more advanced PD, such as those with H&Y stages 3, 4 and 5, had statistically significantly higher KPPS scores in fluctuation-related pain ($p = 0.018$) and radicular pain ($p = 0.026$). No

Table 1
Baseline demographics and clinical features of Vietnamese patients with EOPD ($n = 135$).

Features		Overall	With Pain ($n = 107$)	Without pain ($n = 28$)	P value
Age (year), mean ± SD		45.5 ± 8.1	46 ± 8.4	43.8 ± 6.5	0.189
Gender (Male/Female)		72/63	56/51	16/12	0.677
Age at onset (year), mean ± SD		38.1 ± 6.1	38.3 ± 6.2	37.3 ± 5.5	0.422
Time since PD diagnosis (year), mean ± SD		7.9 ± 5.3	8.2 ± 5.4	7.0 ± 4.9	0.281
Family history of PD, n (%)		23 (17)	17 (15.9)	6 (21.4)	0.572
Clinical motor phenotypes, n (%)	Tremor dominant	34 (25.2)	26 (24.3)	8 (28.6)	0.944
	Akinetic–rigid dominant	89 (65.9)	71 (66.4)	18 (64.3)	
	Mixed phenotypes	12 (8.9)	10 (9.3)	2 (7.1)	
Hoehn and Yahr stage, mean ± SD		2.3 ± 0.7	2.3 ± 0.5	2.4 ± 0.4	0.165
UPDRS III, median (Q1- Q3)		26 (9–37)	32 (24–44)	26 (18.2–34)	0.013*
BDI score, median (Q1- Q3)		13 (6–22)	14 (7–24)	7.5 (5–16)	0.012*
MMSE score, median (Q1- Q3)		28 (25–29)	28 (25–29)	28.5 (27–29.8)	0.162
NMSS score, median (Q1- Q3)		32 (1–63)	47 (25–85)	26.5 (15.3–38.8)	0.001*
Treatment, n (%)	Levodopa	83 (61.5)	64 (59.8)	19 (67.9)	0.516
	Dopamine agonist	93 (66.7)	69 (64.5)	21 (75)	0.371
	Anticholinergic	67 (49.6)	54 (50.5)	13 (46.4)	0.832
	Amantadine sulphate	1 (0.7)	1 (0.9)	0 (0)	
	COMT/MAO B inhibitor	4 (3.0)/0 (0)	4 (3.0)/0 (0)	0 (0)/ 0(0)	
Levodopa Equivalent Daily Dose (mg/day), median (Q1- Q3)		100 (0–393)	99 (0–385)	150 (25–475)	
Patients with dyskinesia, n (%)		51 (37.8)	42 (39.3)	9 (32.1)	0.521
Patients with motor fluctuations, n (%)		108 (80.0)	86 (80.4)	22 (78.6)	0.796
KPPS score (Pain), median (Q1- Q3)		7 (1–16)	10 (5–19)		

Reported as # (%), mean ± standard deviation, or median (interquartile range); PD: Parkinson's Disease; UPDRS III, Unified Parkinson's Disease Rating Scale Part III (motor examination); KPPS: King's Parkinson's Disease Pain Scale; BDI: Beck Depression Inventory; NMSS: Non-Motor Symptoms Scale for Parkinson's Disease; MAO monoamine oxidase, COMT catechol-O-methyl transferase.
* Mann-Whitney Test.

Table 2
Vietnamese patients with EOPD who experienced pain ($n = 107$).

Pain subtypes stratified by gender, H&Y stage and age of onset < 50 (n = 107)										
Pain subtypes	Overall n (%)	Male $n = 56$	Female $n = 51$	*p values*	H&Y 1 and 2 $n = 65$	H&Y 3,4 and 5 $n = 42$	*p values*	Onset age (≤40) $n = 78$	Onset age (>40) $n = 29$	*p values*
Musculoskeletal pain	75 (70.1)	38 (67.9)	37 (72.5)	0.597	46 (70.8)	29 (69)	0.849	53 (67.9)	22 (75.9)	0.427
Chronic pain	45 (42.1)	20 (35.7)	25 (49)	0.164	28 (43.1)	17 (40.5)	0.790	30 (38.5)	15 (51.7)	0.217
Fluctuation-related pain	37 (34.6)	20 (35.7)	17 (33.3)	0.796	17 (26.2)	20 (47.6)	**0.023**	25 (32.1)	12 (41.4)	0.367
Nocturnal pain	47 (43.9)	25 (44.6)	22 (43.1)	0.875	24 (36.9)	23 (54.8)	0.069	32 (41)	15 (51.7)	0.322
Orofacial pain	18 (16.8)	10 (17.9)	8 (15.7)	0.764	7 (10.8)	11 (26.2)	**0.037**	11 (14.1)	7 (24.1)	0.217
Discoloration; edema/swelling pain	24 (22.4)	11 (19.6)	13 (25.5)	0.469	13 (20)	11 (26.2)	0.453	16 (20.5)	8 (27.6)	0.436
Radicular pain	46 (43)	24 (42.9)	22 (43.1)	0.977	24 (36.9)	22 (52.4)	0.115	34 (43.6)	12 (41.4)	0.837

Table 2b
Accumulated number of pain subtypes and pain intensity.

Accumulated number of pain subtypes	N = 107
Patients who experienced 1 subtype of pain	27 (25.2%)
Patients who experienced 2 subtypes of pain	31 (29.0)
Patients who experienced 3 subtypes of pain	24 (22.4%)
Patients who experienced >3 subtypes of pain	25 (23.4%)
Pain intensity*	***N* = 107**
Mild	37 (34.6%)
Moderate	40 (37.4%)
Severe	30 (28.0%)

* Severe, moderate, and mild pain are defined by scores of three, two and one on any KPPS item, respectively.

significant differences were present between patients in high vs low H&Y scores in musculoskeletal, chronic, nocturnal, or orofacial pain, or in discoloration, edema/swelling.

Next, a multivariable regression model was performed between the KPPS score and certain clinical features as collected on the UPDRS, BDI and NMS questionnaires. NMS-Domain 3 (Mood/cognition) showed a multicollinearity with depression (VIF > 5) and therefore this NMS-domain was excluded from multivariable analysis. Multivariable mixed-effects linear regression models showed an independent association between pain severity (KPPS score) and age ($p = 0.028$), depression severity ($p = 0.018$), perceptual problems/hallucinations ($p = 0.033$) and sexual function ($p = 0.024$) (See Table 4).

This analysis revealed a significant positive correlation between KPPS scores and depression and H&Y stage. EOPD patients with depression and higher H&Y stages (3,4, and 5) had statistically significantly higher mean KPPS score compared to EOPD patients without depression and at lower H&Y stages (1 and 2). The differences among

Table 2c
Patients with pain by accumulated number of pain subtypes (n = 107).

Accumulated number of pain subtypes	Overall N = 107 (%)	Male n = 56 (%)	Female $n = 51$ (%)	*p values*	H&Y 1 and 2 $n = 65$ (%)	H&Y 3,4 and 5 $n = 42$ (%)	*p values*	Onset age (≤40) $n = 78$ (%)	Onset age (>40) $n = 29$ (%)	*p values*
Patients who experienced 1 subtype of pain	27 (25.2)	15 (26.8)	12 (23.5)	0.824	21 (32.3)	6 (14.3)	*0.042*	21 (26.9)	6 (20.7)	*0.621*
Patients who experienced 2 subtypes of pain	31 (29)	15 (26.8)	16 (31.4)	0.672	19 (29.2)	12 (28.6)	*0.942*	22 (28.2)	9 (31)	*0.813*
Patients who experienced 3 subtypes of pain	24 (22.4)	15 (26.8)	9 (17.6)	0.354	13 (20)	11 (26.2)	*0.484*	20 (25.6)	4 (13.8)	*0.297*
Patients who experienced >3 subtypes of pain	25 (23.4)	11 (19.6)	14 (27.5)	0.369	12 (18.5)	13 (31)	*0.163*	15 (19.2)	10 (34.5)	*0.124*

Table 3
Pain severity (KPPS score) according to disease stage (Hoehn and Yahr scale), gender and age at onset (N = 107).

pain subtypes	KPPS score (n = 107)	Male (n = 56)	Female (n = 51)	*p values*	H&Y 1 and 2 (n = 65)	H&Y 3,4 and 5 ($n = 42$)	*p values*	Onset age (≤40) (n = 78)	Onset age (>40) (n = 29)	*p values*
Musculoskeletal pain	3.8 ± 3.6	3.7 ± 3.8	3.9 ± 3.7	0.820	3.6 ± 3.7	4.0 ± 3.9	0.659	3.6 ± 3.8	4.3 ± 3.6	0.403
Chronic pain	2.3 ± 3.7	2.0 ± 3.3	2.6 ± 4.0	0.377	2.2 ± 3.5	2.4 ± 3.9	0.770	2.0 ± 3.4	3.0 ± 4.2	0.206
Fluctuation-related pain	3.0 ± 6.1	3.4 ± 6.6	2.5 ± 5.5	0.478	**1.9 ± 5.0**	**4.7 ± 7.3**	**0.018**	2.8 ± 5.8	3.5 ± 7.0	0.589
Nocturnal pain	3.1 ± 4.9	3.2 ± 5.4	2.9 ± 4.2	0.727	2.5 ± 4.4	4.0 ± 5.5	0.124	2.7 ± 4.5	4.0 ± 5.7	0.232
Orofacial pain,	1.0 ± 2.9	1.1 ± 3.2	0.8 ± 2.7	0.600	0.6 ± 2.2	1.6 ± 3.7	0.097	0.8 ± 2.7	1.4 ± 3.5	0.321
Discoloration; edema/ swelling pain	1.1. ± 2.8	1.0 ± 2.5	1.1 ± 3.2	0.884	0.8 ± 2.6	1.5 ± 3.1	0.243	0.9 ± 2.2	1.5 ± 4.0	0.303
Radicular pain	1.7 ± 2.9	1.8 ± 3.0	1.7 ± 2.9	0.911	**1.2 ± 2.2**	**2.5 ± 3.7**	**0.026**	1.7 ± 2.8	1,9 ± 3.3	0.706
KPPS total	15.9 ± 17.3	16.2 ± 18.2	15.5 ± 16.4	0.844	**12.8 ± 14.3**	**20.6 ± 20.5**	**0.023**	14.5 ± 14.5	19.7 ± 23.2	0.168

Table 4
Multivariable regression model between pain severity (KPPS score) and clinical features in Parkinson's patients ($n = 135$).

Parkinson's Disease Clinical Features	Unstandardized Coefficients B (S. Error)	95% CI	Beta	t	p value
Age at examination (year)	***−0.535 (0,240)***	***(−1.01; −0.059)***	***−0.259***	***−2.225***	***0.028***
Age at onset (year)	0.362 (0.294)	(−0.220; 0.944)	0.132	1.232	0.220
Total UPDRS III score	−0.068 (0.064)	(−0.195; 0.060)	−0.089	−1.050	0.296
Hoehn – Yahr	2.040 (2.509)	(−2.929; 7.008)	0.059	0.813	0.418
Depression (BDI score)	***0.305 (0.128)***	***(0.052; 0.558)***	***0.207***	***2.389***	***0.018***
Domain 1: Cardiovascular including falls	0.607 (0.492)	(−0.366; 1.580)	0.134	1.235	0.219
Domain 2: Sleep/fatigue	0.344 (0.224)	(−0.099; 0.786)	0.179	1.537	0.127
Domain 4: Perceptual problems/hallucinations	***0.986 (0.456)***	***(0.083; 1.889)***	***0.189***	***2.161***	***0.033***
Domain 5: Attention/memory	−0.104 (0.229)	(−0.558; 0.350)	−0.046	−0.454	0.651
Domain 6: Gastrointestinal tract	0.232 (0.465)	(−0.689; 1.153)	0.099	0.499	0.619
Domain 7: Urinary	0.076 (0.172)	(−0.265; 0.418)	0.041	0.443	0.658
Domain 8: Sexual function	***0.630 (0.276)***	***(0.084; 1.176)***	***0.236***	***2.286***	***0.024***
Domain 9: Miscellaneous (except for question 27)	0.213 (0.350)	(−0.480; 0.905)	0.069	0.607	0.545
Dysautonomia (NMSS questions 1, 2, 19–24, 26, 29–30).	0.132 (0.345)	(−0.551; 0.815)	0.112	0.382	0.703
NMSS score total (except for question 27)	0.010 (0.100)	(−0.189; 0.209)	0.030	0.103	0.918

Table 5
Previous studies on pain in Parkinson's disease.

Author	Date of publication	Study title	Study design	PD Type and number of patients	Pain scale	Pain Prevalence
Silverdale, Monty A et al. [7]	2018	A detailed clinical study of pain in 1957 participants with early/ moderate Parkinson's disease	prospective	PD 1957 patients	Short Form McGill Pain Questionnaire, Visual Analogue Scale and KPPS	85%
Pritha Ghosh et al. [3]	2020	A Dual Centre Study of Pain in Parkinson's Disease and Its Relationship with Other Non-Motor Symptoms	prospective	PD 167 patients	Brief Pain Inventory and KPPS	88.6%
Mao, Cheng-Jie et al. [16]	2015	Parkinson's disease patients with pain suffer from more severe non-motor symptoms	prospective	PD 142 patients	Visual Analogue Scale	47.9%
Buhmann, Carsten et al. [6]	2017	Pain in Parkinson disease: a cross-sectional survey of its prevalence, specifics, and therapy	prospective	PD 181 patients	German Pain Questionnaire the PainDetect, and a self-developed Parkinson's disease Pain Questionnaire	95.4%
Behari, Madhuri et al. [17]	2020	Pain Assessment in Indian Parkinson's Disease Patients Using King's Parkinson's Disease Pain Scale	prospective	PD 119 patients	KPPS	52.1%
Agrawal et al. [18]	2021	Predictors of Pain Severity and its Impact on Quality of Life in Patients with Parkinson's Disease	prospective	PD 119 patients	KPPS	70%
Yoritaka et al. [19]	2013	Motor and non-motor symptoms of 1453 patients with Parkinson's disease: Prevalence and risks, Parkinsonism and Related Disorders	retrospective	PD and EOPD 1453 PD (711 EOPD)	Pain was defined as pain that requires treatment including pain related to wearing off excluding pain related to bone fracture, myocardial infarction, respiratory and abdominal diseases	25%

mean KPPS score of different gender groups, familial PD, clinical motor phenotypes, drug regimens and motor fluctuations such as dyskinesias were not statistically significant ($p > 0.05$). This finding suggests that pain severity may not be impacted by demographic or clinical features such as gender, family history, clinical disease subtypes, use of anti-Parkinsonian medications, and motor complications such as dyskinesias (Table 4).

4. Discussion

The findings of this study demonstrate that pain may be more common and more severe in patients with EOPD than previously reported in the existing literature. In this prospective study of 135 Vietnamese patients from three medical centers, 79.3% of patients with EOPD reported experiencing pain. Older age, depression, perceptual problems/hallucinations and sexual dysfunction were independently associated with higher pain severity scores.

4.1. Prevalence of pain in early-onset Parkinson's disease

The prevalence of pain observed in this study differs from the extant literature, where a wide range of estimates has been reported [1]. The lack of consensus on the prevalence of pain in patients with EOPD may be that previous studies have rarely delineated between the general population of patients with PD versus patients with EOPD. To the best of our knowledge, only a single study has previously investigated the relationship between pain and PD as stratified by EOPD vs the general PD population [20]. Please see Table 5 for a comparison summary of previous studies.

Furthermore, a standardized pain assessment is rarely incorporated into population-based PD studies. The lack of a uniform standard for pain assessment in patients with PD makes detailed research in this area more challenging. The KPPS has several advantages including its ability to assess multiple pain subtypes, ease of use in a busy clinical setting, and well-established use in previous PD populations. The KPPS does

require the presence of a skilled clinician and remains a subjective measure of pain, both of which may introduce bias.

4.2. Association of pain severity and non-motor symptoms

The results of this study suggest that among patients with EOPD, higher UPDRS part III scores, advanced H&Y stages, and higher NMS scores are positively correlated with higher KPPS score indicating the presence of more severe pain. However, these covariates did not achieve statistical significance within the multivariate model. The multivariate regression analysis showed that pain severity, as measured by KPPS score, is independently correlated with age, depression, perceptual disturbances/hallucinations and sexual dysfunction.

The association between pain and depression has been well established in patients with PD [1,6,20,21]. In previous studies, pain in idiopathic PD patients has been associated with a host of clinical factors including: 1) poorer health-related quality of life; [22,23] 2) higher disease severity evaluated by the UPDRS and H&Y stage; [3,16,24] 3) and higher NMS scores in the sleep/fatigue subgroup [2,3,25].

However, certain non-motor symptoms such as hallucinations and sexual dysfunction are rarely incorporated alongside pain severity in a standardized assessment. The UPDRS, a commonly used, standardized evaluation of PD severity does assess hallucinations but does not assess sexual dysfunction or pain. The potential interplay between pain, depression, and sexual dysfunction is complex and the exact relationships have yet to be clearly understood. Several proposed pathophysiologic mechanisms may account for this association. From an epidemiological perspective, central oxytocin, a sex hormone, has an effect on the pain descending modulatory system, pain-related symptoms in PD and analgesic effect; [26,27]. Additionally, testosterone levels have been found to be decreased in PD and are related to non-motor symptoms including pain [28]. Lastly, sexual activity results in benefits and is associated with better non-motor symptoms [29].

Further research is needed to clarify the relationship between pain, depression and sexual dysfunction in patients with PD.

4.3. Study limitations

The Vietnamese versions of the structured questionnaires such as the UPDRS and BDI have not been previously validated in prior studies though these questionnaires are standard of practice in the three medical centers who participated in this study. The design of this study relies on voluntary patient participation, which raises the potential for selection and information bias. We have tried to mitigate these potential confounders to the extent possible utilizing the statistical analysis plan as previously elucidated. As mentioned, this study included only 135 Vietnamese patients with PD onset <50 years of age which limits the generalizability of our study results. Lastly, the KPPS was selected as the pain assessment tool used in this study. The KPPS was previously validated in a generalized PD population. The application of this assessment to patients with EPOD is reasonable but potential unforeseen confounders within this population cannot be excluded.

4.4. Future directions

The assessment of pain severity is an underappreciated area of exploration in patients with PD. The insidious nature of pain symptoms may be deleterious, especially in patients with EOPD who are at a stage in life where they still expect to retain a high standard of living. This study emphasizes the importance of further studies of pain using a standardized pain assessment such as the KPPS. In current clinical practice, pain is not often emphasized or uniformly assessed in patients with PD. However, the results of this study bring to light the unmet clinical need in this patient population. We hope this study will raise the astute clinician's suspicion when a patient with EOPD presents with uncontrolled pain.

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Declaration of Competing Interest

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The other authors have no financial conflicts of interest.

Appendix A. Appendix

The chronic medical conditions excluded during enrollment.

Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, chronic headache including chronic migraine, medication overuse headache, cervical/lumbar disc herniation, polyneuropathy and cancer.

Appendix B. Appendix

STUDY MEDICAL RECORD

Patient records number:..... Case number:……

Address of hospital:.....

.....

1. General patient information

- Name:.....

- Phone.....E-mail:……..

- Address:.....

.....

- Date of hospital admission / outpatient visit): .....

- End date of examination:.....

- Date of birth:……

- Age group: 1. < 40 4. 60 – 69

2. 40- 49 3. 50-59 5.≥ 70

- Age of onset disease:.....

- Sex : 1. Male 2. Female

- Occupation: 1. Mannual labour 2. Mental labour

- Educational level:

1. Primary school 4. Vocation/College
2. Secondary school 5. Undergraduate
3. High school 6. Postgraduate

2. Post medical history

2.1. Personal history

1. Traumatic brain injury

3. Cerebrovascular disease:.....

2. Encephalitis:.....

4. Exposure to toxic chemicals.....

5. Other medical history (pain):……

……

2.2. Family history

- Relatives in 3 generations suffering from Parkinson's disease

1. Yes:.....

2. No

- Central nervous system genetic diseases:.....

.....

3. Clinical characteristics

- Disease duration:.....years

3.1 Symtoms at the onset of disease

<u>* Motor symptoms:</u>

+ Tremor:

Location.....

Characteristic of tremor.....

+ Bradykinesia:

Location.....

Characteristic:.....

+Rigidity

Location.....

Characteristic:.....

+ Postural instability:……..

+ Dystonia:……..

+ Progression of the disease:

Fast progress:.....

Slow progress.....

3.2 Symptoms at the time of examination

a. <u>Movement disorders sym</u>

+ Tremor:

Location.....

Characteristic of tremor.....

+ Slowness of movement:

Location.....

Characteristic:.....

+ Muscle stiffnes

Location.....

Characteristic:.....

+: Postural instability :…….

+ Dystonia:……..

+ ***Hoehn và Yahr (Appendix)***

Stages 1

Stages 2

Stages 3

Stages 4

Stages 5

+ *Motor disorder level according to UPDRS* (Appendix)

[1] Mild [2] Moderate

[3] Severe [4] Extreme severe

b. **Non-motor symptoms**

+ Before onset motor symptom …….....(....month.....year)

+ After onset motor symptom…….....(.....month.....year)

- Depression (total score):……..Severity.....*(according to BECK- appendix)*

- Cognition (total score)**:……**Severity.....*(according to MMSE - appendix)*

- Delusion: Yes.....No.....

- Hallucination: Yes.....No.....

+ Pain (total score)**:……**Severity.....*(according to KING- appendix)*

+ Restless Leg syndrome: Yes.....No.....Severity

***** *Autonomic nervous system disorder*

- Hyper hydration : Yes.....No

- Constipation: Yes.....No

- Postural hypotension: Yes.....No

- Bladder dysfunction: Yes.....No

- Sexual dysfunction: Yes.....No

- Olfactory dysfunction: Yes.....No

- Other symptoms:.....

- *Primitive brain stem reflex:*

+ Oral reflex : Yes.....No

+ Palmomental reflex: Yes.....No

4. Treatment

1. Never

2. Current drugs:

+ Anti-cholinergic: Yes.....No

+ Dopamine agonist : Yes.....No

+ L-Dopa Yes.....No

+ Dopamine decarboxylase inhibitor: Yes.....No

3. First drug for treatment

+ Anti-cholinergic: Yes.....No

+ Dopamine agonist : Yes.....No

+ L-Dopa Yes.....No

+ Dopamine decarboxylase inhibitor: Yes.....No

4. Treatment response

+ Anti-cholinergic: Yes.....No

+ Dopamine agonist : Yes.....No

+ L-Dopa Yes.....No

+ Dopamine decarboxylase inhibitor: Yes.....No

5. Side effect

+ Anti-cholinergic: Yes.....No…….

+ Dopamine agonist : Yes.....No……

+ L-Dopa Yes.....No……..

+ Dopamine decarboxylase inhibitor: Yes.....No……

Specific:.....

6. Determined Diagnose

Parkinson's disease : Yes.....No……

7. Disease stage: According to Hoehn và Yahr

1. Stage 1 3. Stage 3 5. Stage 5
2. Stage 2 4. Stage 4

8. Disease severity: According to UPDRS

1. Mild
2. Moderate
3. Severity
4. Extreme severity

9. Combination disease:.....

……

……

……

……..

....., date ..... month ..... year 20...

Patient (Signature)

Researcher (Signature)

. (*continued*).

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