ORIGINAL RESEARCH

Sleep disturbances in Parkinson's disease are associated with central parkinsonian pain

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Introduction: Sleep disturbances and pain are common non-motor symptoms in Parkinson's disease (PD). This study aimed to explore the association between these two symptoms in a cohort of patients with PD.

Materials and methods: The Parkinson's Disease Sleep Scale (PDSS-2) was used to identify sleep disturbances in a series of 229 PD patients. The identification and characterization of pain was performed by a semi-structured interview and by the application of the Ford classification and the Brief Pain Inventory (BPI). The Unified Parkinson's Disease Rating Scale-III, Hoehn & Yahr (H&Y), and Schwab and England Independence Scale were used to assess motor symptoms and functional independence in off and on conditions. The Hospital Anxiety and Depression Scale (HADS) and SF-36 were applied to screen for anxiety and depression and to evaluate the quality of life. Non-parametric tests were used for group comparisons and logistic regressions were applied to explore predictors of sleep disturbances.

Results: Seventy-five (33%) patients had clinically relevant sleep disturbances (PDSS-2≥18) and 162 patients (71%) reported pain. Of those with pain, 38 (24%) had central parkinsonian pain. PD patients with sleep disturbances experienced more pain and had more severe motor symptoms, lower functional independence, more anxiety and depression symptoms, and worst quality of life. Among patients with pain, central parkinsonian pain was the subtype of pain with the highest odds of sleep disturbances, even when taking into account motor symptoms (H&Y off), motor fluctuations, intensity of pain (BPI), and symptoms of anxiety and depression (HADS).

Conclusions: The association between pain and sleep disturbances in PD appears to be dependent on subtype of pain. The close relationship between central parkinsonian pain and sleep disturbances in PD raises the possibility of common pathophysiological mechanisms. A better understanding of the relationship between sleep disturbances and central parkinsonian pain may contribute to the development of new care strategies in PD patients.

Keywords: Parkinson's disease, sleep disturbances, central parkinsonian pain

Introduction

Parkinson's disease (PD) has been classically described as a disease with motor symptoms, such as bradykinesia, tremor at rest, rigidity, and postural instability.[1] Though PD is a complex disorder that also includes non-motor symptoms, such as dementia, depression, sleep disorders, autonomic dysfunction, and sensory symptoms.[2] The co-occurrence of certain non-motor symptoms has raised the hypothesis of clinical non-motor subtypes with specific pathophysiological patterns.[3]

Sleep disturbances are a common disabling non-motor symptom in PD, its prevalence varies greatly from 40% to 90% in these patients, and may interfere

with patients' quality of life.[4] The association between poor sleep quality in PD and symptoms of depression and anxiety has been well established.[5] There is also evidence that common sleep problems, such as sleep-onset insomnia and sleep-maintenance insomnia, may be associated with motor symptoms (eg, nocturnal akinesia) and other non-motor symptoms (eg, nocturia, hallucinations).[6,7]

Pain is also a major and disabling non-motor symptom in PD, with a prevalence of up to 85%.[8] Pain is one of the most bothersome non-motor symptoms and is known to be associated with lower quality of life[9] and more severe non-motor symptoms.[10]

In general population, sleep disturbances and pain are frequent co-morbidities. There is evidence from experimental and longitudinal studies that pain and sleep interact in a bidirectional manner and negatively affect each other.[11] In PD, studies have shown that sleep disturbances are a risk factor for pain and vice versa.[10,12–16]

Pain in PD can be classified according to its clinical features in five subtypes.[17] One of the subtypes is central parkinsonian pain, which is believed to be the only subtype of pain that is a direct consequence of the disease itself, resulting from abnormal painful information processing, and not the result of dystonia, rigidity, or a musculoskeletal cause, and is considered a neuropathic pain.[17–20] The association between this subtype of pain with sleep disturbances has yet to be investigated.

The general aims of this study were to identify in a cohort of PD predictors of sleep disturbances and to explore the relationship between sleep disturbances and pain, according to pain features.

Materials and methods
Participants
A cross-sectional study of PD patients (diagnosis according to the United Kingdom Brain Bank criteria)[21] was carried out in the Movement Disorders Clinic of Centro Hospitalar Universitário do Porto. Exposition to drug-induced parkinsonism, vascular parkinsonism, possible or probable atypical parkinsonian syndromes, and advanced therapies (subcutaneous apomorphine pump, levodopa-carbidopa intestinal gel, or deep brain stimulation) were considered a priori exclusion criteria. From a consecutive series of 322 possible subjects (Figure 1), 229 participated in the study. One patient refused to participate in the study. Twenty-six were excluded before assessment (ie, seven died, two developed other debilitating conditions, thirteen moved geographically to a region not dependent from our center or could not be reached between inclusion and assessment, and four could not be assessed due to logistic problems) and 66 were excluded after the assessment (ie, one due to misdiagnosis and 65 due to incomplete data set).

All the patients (or legal representatives) were informed about the nature of the study and gave written informed consent, in compliance with the Declaration of Helsinki. The ethics committee of Centro Hospitalar e Universitário do Porto approved the study.

Procedures
Based on an interview and clinical records, the following data were collected: sex, age, age at PD onset, first motor symptom, and current treatments. Current antiparkinsonian
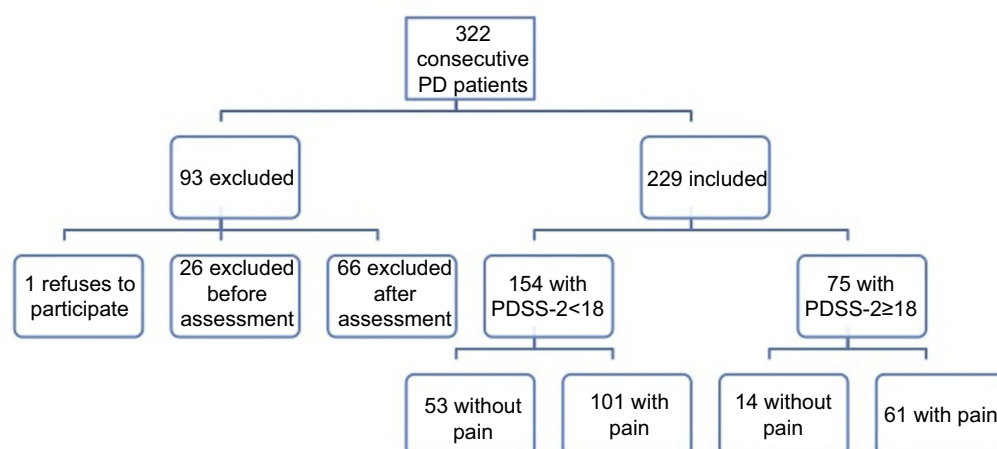

Figure 1 Flowchart of the study sample.
Abbreviation: PDSS-2, Parkinson's Disease Sleep Scale.

medication was converted to levodopa equivalent dose.[22] A movement disorders specialist performed a neurological examination to all participants. Thirty patients (12%) were evaluated at home due to the severity of their motor symptoms. PD patients were evaluated in the morning without antiparkinsonian medication for 12 hrs (off medication condition), using the Unified Parkinson's Disease Rating Scale (UPDRS)[23] and the modified Hoehn & Yahr Scale (H&Y).[24] Presence of motor fluctuations was identified by UPDRS-IV items 36, 37, and 38. After the assessment in off, patients took their usual first dose of antiparkinsonian medication and were re-evaluated 1 hr later (on medication condition), using the same instruments. Then, the Schwab and England Independence Scale (S&E) was applied regarding their state on and off.[25]

The Parkinson`s Disease Sleep Scale (PDSS-2) was used to screen for sleep disturbances.[26] The applied cutoff score for clinically relevant sleep disturbances was PDSS-2≥18.[27]

All patients were tasked whether they had pain in the last month. Those who responded "yes" to the previous question were asked a series of questions regarding their pain: onset; duration; localization; features (including burning, tingling, formication, stabbing, aching, tension, tightness, or radiating); intensity; frequency; precipitating/relieving factors; temporal and topographical relationship with PD symptoms; and influence of motor complications, dyskinesias, and dopaminergic medication. Based on the patients' description, the neurologist categorized the pain, according to Ford framework,[17] as central parkinsonian pain, musculoskeletal pain, dystonia-related pain, radicular or neuropathic pain, and akathitic discomfort. Central parkinsonian pain was defined, according to Ford criteria,[17] as burning, tingling, formication, or "neuropathic" sensations, often relentless and bizarre in quality, not confined to root or nerve territory, and not explained by rigidity, dystonia, musculoskeletal, or internal lesion. The Brief Pain Inventory (BPI) was applied.[28]

The Hospital Anxiety and Depression Scale (HADS) was applied to measure anxiety and depression; a cutoff score of ≥8 was used for each subscale.[29] The SF-36 was used to evaluate the quality of life. Two summary scores, physical and mental health, were calculated with adjustment for the Portuguese population.[30]

Statistical analysis

Descriptive statistics were used for group characterization and non-parametric tests (ie, chi-square test, Fisher's exact test, and Mann–Whitney test) were applied for group comparisons. Simple and multiple logistic regression analyses were used to explore associations between the presence of sleep disturbances and subtypes of pain. The backward wald method was used for variable selection, with $p > 0.100$ criterion for variable removal.

The threshold for statistical significance for group comparisons and for logistic regressions was $p < 0.05$. The statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0 (SPSS, USA).

Results

Characteristics of the sample

Of the 229 PD patients examined, 122 (53%) were men, mean age was 69 years (sd=11), mean age at disease onset was 60 years (sd=12), and mean duration of the disease was 9 years (sd=6). Ninety-six (42%) were taking dopamine agonist (ie, 91 ropinirole, 2 pramipexole, 3 piribedil) and the mean levodopa equivalent dose was 900 mg/day (sd=542). The mean ropinirole dose was 10 (sd=5). Mean scores in motor scales were: 32 (sd=11) in UPDRSS-III off and 22 (sd=9) in on; 2.7 (sd=0.7) in H&Y off and 2.3 (sd=0.5) in on. One hundred and thirty-one (57%) had motor fluctuations. Mean in the functional independence scale S&E were 75 (sd=17) in off and 87 (sd=11) in on. At the time of the assessment, 162 patients (71%) reported pain. Of those with pain, 99 (61%) had musculoskeletal pain, 43 (27%) had dystonia-related pain, 38 (24%) had central parkinsonian pain, and 19 (12%) had radicular or neuropathic pain. No patient reported akathitic discomfort. The frequencies of HADS ≥8 on anxiety and depression subscales were, respectively, 102 (45%) and 111 (49%). Mean SF-36 summary scores for physical and mental health were, respectively, 40 (sd=11) and 46 (sd=12).

Characterization of sleep disturbances

Mean PDSS-2 total score was 15 (sd=10). One hundred and fifty-four (67%) patients scored PDSS-2<18 and 75 patients (33%) scored ≥18. Table 1 shows the demographic and clinical features of these patients. Patients with sleep disturbances (PDSS-2≥18) had more severe motor symptoms (UPDRS in off and on and H&Y in off), more motor fluctuations, lower functional independence (S&E in off and on), and were taking higher doses of antiparkinsonian medication ($p < 0.05$). Patients with PDSS-2≥18 reported more frequent pain and greater pain intensity were more

Table 1 Demographic, clinical, and therapeutic characteristics of PD patients according to PDSS-2 total score

		PDSS-2		p
		<18 (n=154)	≥18 (n=75)	
Sex, men		87 (57%)	35 (47%)	0.162
Age (years)		69 (63–77)	71 (63–75)	0.830
Age at disease onset (years)		60 (53–70)	61 (53–67)	0.626
PD disease duration (years)		7 (4–11)	8 (5–14)	0.214
UPDRS III	Off	29 (22–36)	37 (29–45)	<0.001
	On	19 (14–26)	25 (19–32)	<0.001
H&Y	Off	2.5 (2–3)	3 (2–4)	0.006
	On	2 (2–2.5)	2.5 (2–2.5)	0.051
Motor fluctuations		78 (51%)	53 (71%)	0.004
S&E	Off	80 (70–90)	70 (50–80)	<0.001
	On	90 (80–90)	80 (70–90)	<0.001
Dopamine agonists		64 (44%)	29 (35%)	0.486
LED (mg/day)		700 (460–1040)	1,027 (600–1410)	0.001
Hypnotic medication				0.439
	No medication	56 (36%)	26 (35%)	
	BDZ	48 (31%)	22 (29%)	
	BDZ agonist	2 (1%)	0 (0%)	
	Tricyclic and tetracyclic antidepressants	14 (9%)	5 (7%)	
	Antipsychotic	5 (3%)	8 (11%)	
	Anticonvulsant	3 (2%)	1 (1%)	
	Other antidepressants	11 (7%)	7 (9%)	
	Combination of hypnotic medications	15 (10%)	6 (8%)	
Pain		101 (66%)	61 (81%)	0.014
BPI		23 (21–31)	34 (24–43)	<0.001
HADS	Anxiety ≥8	55 (36%)	47 (63%)	<0.001
	Depression ≥8	59 (38%)	52 (69%)	<0.001
SF-36	Physical health	42 (33–51)	32 (28–43)	<0.001
	Mental health	50 (41–57)	43 (34–49)	<0.001

Notes: UPDRS-III on, H&Y on, and S&E on were not applied to untreated patients. Data are presented as frequencies (%) and as medians (25th–75th percentiles). Chi-square test (or Fisher's exact when appropriate) and Mann–Whitney test were used for group comparisons.
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr scale; S&E, Schwab and England Independence Scale; LED, Levodopa Equivalent Dose; BZD, Benzodiazepines; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form (36 itens) Health Survey.

anxious and depressed (HADS), and had poorer quality of life (SF-36 physical and mental health summary scores) than patients with PDSS-2<18. These two groups did not differ (p>0.05) regarding sex, age, age at disease onset, disease duration, and use of dopamine agonists (including type and dose) and hypnotic medication.

Sleep disturbances and subtypes of pain

The frequency of sleep disturbances was 20% for patients without pain and 38% for patients with pain (p=0.014). In comparison with patients without pain, the frequency of sleep disturbances was significantly higher for patients with central parkinsonian pain (53%, p=0.001), but not for musculoskeletal pain (32%, p=0.107), dystonia-related pain (37%, p=0.061), or radicular/neuropathic pain (26%, p=0.755).

Among patients with pain, a simple logistic regression revealed that the odds of having sleep disturbances were higher among patients with central parkinsonian pain (odds=2.25, 95% CI: 1.08–4.71; p=0.031). No significant association was found with musculoskeletal pain, dystonia-related pain, or radicular/neuropathic pain (Table 2). When adjusted for severity of motor symptoms in off (H&Y), presence of motor fluctuations, pain intensity (BPI), anxiety, and depression (HADS), the odds of having sleep disturbances remained higher in patients with central parkinsonian pain (adjusted odds=2.46, 95% CI: 1.06–5.74; p=0.037).

Discussion

In a series of 229 PD patients, the prevalence of sleep disturbances was 33% and of pain was 71%. The frequency of sleep disturbances is similar to another study that used PDSS-2≥18.[31] Although it is lower than other published series, with prevalence estimates of sleep disturbances ranging between 40% and 90%.[4,32] This wide variation is likely due to methodological differences (ie,

assessment instruments and applied cutoffs). The prevalence of pain in our series is consistent with other cohorts of PD.[8,9,33]

In accordance with a recent study,[15] PD patients with sleep disturbances had more severe motor symptoms, more anxiety and depression symptoms, lower functional independence, and poorer quality of life. As previously identified in other cohorts,[13,32] the intensity of pain among PD patients with sleep disturbances was significantly higher than in patients without clinically relevant sleep disturbances.

Presence of motor fluctuations was also more frequent among patients with sleep disturbances. Previous studies have demonstrated that motor fluctuations are more common in PD patients who report pain.[34–36] This pattern of findings raises the possibility that motor fluctuations may have a modulating effect on the relationship between pain and sleep.

The study results also demonstrate that the association between quality of sleep and pain in PD depends on pain subtype. Similar to other cohorts,[9,16,33,37] musculoskeletal and dystonia-related pain were the most common subtypes of pain. Although only central parkinsonian pain was significantly related to an increased risk of sleep disturbances, both in comparison to patients without pain and to patients with other pain subtypes. Patients with musculoskeletal pain or dystonia-related pain tended to have more sleep disturbances than patients without pain. However, among patients with pain, these pain subtypes were not related to an increased risk of sleep disturbances. The relationship between central parkinsonian pain and sleep disturbances was not statistically dependent on disease severity, presence of motor fluctuations, pain intensity, or mood symptoms.

Ford's classification of pain is specific for patients with PD and is based on the likely etiology of pain.[17] Even though it has been widely accepted,[38] Ford's criteria are not universally used and have not been thoroughly validated. This limits the comparison with other cohorts.

In the general population, several studies have shown that sleep deprivation leads to changes in pain processing with increased sensitivity to pain and a hyperalgesic effect,[39] whereas longer nocturnal sleeping time may reduce pain perception.[40] Persistent pain is also known to have a great impact on sleep and is one of the most frequent causes of sleep disturbances in older adults.[41,42] In a recent study, Krause et al[43] provided a central brain framework for the underlying impact of sleep loss in

Table 2 Odds of patients with pain (n=162) having PDSS-2 total score ≥18 according to pain subtypes

Subtype of pain	Odds	P	Adjusted odds*	p
Central parkinsonian	2.25	0.031	2.46	0.037
Musculoskeletal	0.56	0.080	-	-
Neuropathic	0.56	0.283	-	-
Dystonic	0.974	0.994	-	-

Notes: *The odds of having PDSS-2 total score ≥18 for each subtype of pain adjusted for H&Y off, motor fluctuations, BPI score, HADS – anxiety ≥8, and HADS – depression ≥8, with backward – wald selection method.

pain. They demonstrated that acute sleep-deprivation amplifies pain reactivity within human primary somatosensory cortex, but blunts pain-reactivity in higher order valuation and decision-making regions of the striatum and insula cortex.

Both pain and sleep disturbances are known to involve brainstem structures and changes in neurotransmitter systems, namely dopamine.[44–46] The existing clinical evidence suggests an important role of the dopaminergic deficit in central parkinsonian pain[47] and it has been well demonstrated that dopamine contributes to the promotion and maintenance of arousal states and regulation of sleep and wakefulness.[11,48] The ascending reticular activating system, including parts of raphe nuclei which is a crucial sleep modulation center, has many dopaminergic receptors and pain induced alterations in dopaminergic system, that may deregulate raphe cells and contribute to long-term sleep loss.[44,45] Changes in the striatum and dopamine depletion are hallmarks of PD. However, the pathophysiological relationship between sleep and pain in PD is not yet understood.

The recruitment of participants to the study was consecutive. However, a significant number of subjects were unable to complete parts of the protocol due to cognitive impairment. The exclusion of participants with missing data set may have reduced the representativeness of the sample. The a priori exclusion of patients under advanced therapies for PD, namely deep brain stimulation, also reduces the representativeness of the sample, especially in the advanced stages of the disease. Another limitation of the study is the identification of sleep disturbances only by a self-report screening questionnaire, which is vulnerable to misrepresentation of the actual pattern and quality of sleep. As this study did not explore the characteristics of sleep disturbance, future studies ought to include polysomnographic recordings for further characterization and the level of arousal during the day should be taken into account. One major strength of this study is the diagnosis of PD and the clinical evaluation by movement disorders specialists, which reduces the risk of misdiagnosis.

In summary, sleep disturbances and pain are prevalent non-motor symptoms in PD. Poor quality of sleep is associated with more pain and more severe motor symptoms, anxiety, depression, and poorer quality of life. The study results revealed that the association between pain and sleep disturbances in PD appears to be dependent on the subtype of pain.

Conclusion

Patients with central parkinsonian pain are particularly prone to experience sleep disturbances. This relationship ought to be explored in future neurophysiological studies. A better understanding of the relationship between sleep disturbances and central parkinsonian pain may contribute to the development of new care strategies in PD patients.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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