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Sleep Problems Are Related to a Worse Quality of Life and a Greater Non-Motor Symptoms Burden in Parkinson's Disease

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Abstract

Introduction: The aim of the present study was to examine the frequency of self-reported sleep problems and their associated factors in a large cohort of PD patients. **Methods**: PD patients and controls, recruited from 35 centers of Spain from the COPPADIS cohort were included in this cross-sectional study. Sleep problems were assessed by the Spanish version of the

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Parkinson's disease Sleep Scale version 1 (PDSS-1). An overall score below 82 or a score below 5 on at least 1 item was defined as sleep problems. **Results**: The frequency of sleep problems was nearly double in PD patients compared to controls: 65.8% (448/681) vs 33.5% (65/206) ($p < 0.0001$). Mean total PDSS score was lower in PD patients than controls: 114.9 $\pm$ 28.8 vs 132.8 $\pm$ 16.3 ($p < 0.0001$). Quality of life (QoL) was worse in PD patients with sleep problems compared to those without: PDQ-39SI, 19.3 $\pm$ 14 vs 13 $\pm$ 11.6 ($p < 0.0001$); EUROHIS-QoL8, 3.7 $\pm$ 0.5 vs 3.9 $\pm$ 0.5 ($p < 0.0001$). Non-motor symptoms burden (NMSS; OR = 1.029; 95%CI 1.015–1.043; $p < 0.0001$) and impulse control behaviors (QUIP-RS; OR = 1.054; 95%CI 1.009–1.101; $p = 0.018$) were associated with sleep problems after adjustment for age, gender, disease duration, daily equivalent levodopa dose, H&Y, UPDRS-III, UPDRS-IV, PD-CRS, BDI-II, NPI, VAS-Pain, VAFS, FOGQ, and total number of non-antiparkinsonian treatments. **Conclusion**: Sleep problems were frequent in PD patients and were related to both a worse QoL and a greater non-motor symptoms burden in PD. These findings call for increased awareness of sleep problems in PD patients.

Keywords

non-motor symptoms, Parkinsońs disease, Parkinsońs disease sleep scale, quality of life, sleep

Introduction

Parkinsońs disease (PD) is not only characterized by classic motor symptoms but also by non-motor symptoms (NMS), which are sometimes present before diagnosis and worsen with disease progression. Sleep problems are one of the most disabling NMS in PD and have a negative impact on patient́s quality of life (QoL).[1] Moreover, sleep problems are frequent, affecting more than 60% of PD patients.[2] However, sleep problems are underdiagnosed and studies have suggested the use of a disease-specific instrument to measure of sleep disturbances.[3] The etiology of nocturnal disabilities in PD is multifactorial: sleep apnea, difficulty falling asleep (insomnia), frequent awakening (sleep fragmentation), nighttime urinary frequency, vivid dreams/nightmares often accompanied by physical action (REM behavioral disorder), nighttime confusion, hallucinations, and delusions.[4-6] Neurodegenerative processes within sleep regulatory brain circuitries, antiparkinsonian (e.g., levodopa and dopamine agonists) concomitant medication (e.g., antidepressants), as well as comorbidities or other non-motor symptoms (such as depression), are discussed as causative factors for sleep disturbances.[7] Therefore, although the management of sleep disorders in PD is complex, it is crucial to ask about different nocturnal and diurnal problems. For identifying sleep problems in PD, the Parkinsońs Disease Sleep Scale version 1 (PDSS-1) can be used as a simple bedside screening tool.[8] Furthermore, although related motor and neuropsychiatric symptoms are important causes of sleep disturbance in PD,[9,10] the frequency and association of different symptoms with sleep disorders varies according to the type of study and methodology used.[11] Therefore, studies in large PD populations are required.

The aim of the present study was to evaluate in a large cohort of PD patients the frequency of self-reported sleep problems in comparison to a control group. Moreover, the effect of sleep problems on patient́s QoL, the relationship between sleep problems and other NMS, and associated factors with sleep problems were investigated as well.

Methods

Patients with PD recruited from 35 centers of Spain from the COPPADIS cohort[12] were included in this study. Methodology about COPPADIS-2015 study can be consulted in https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9.

This is a multi-center, observational, longitudinal-prospective, 5-year follow-up study designed to analyze disease progression in a Spanish population of PD patients. The data for the present study (cross-sectional study) was obtained from the baseline evaluation of PD patients from the COPPADIS cohort between January 2016 and October 2017. All patients included were diagnosed according to UK PD Brain Bank criteria. Exclusion criteria were: non-PD parkinsonism, dementia (Mini Mental State Examination [MMSE] < 26), age < 18 or > 75 years, inability to read or understand the questionnaires, to be receiving any advanced therapy (continuous infusion of levodopa or apomorphine, and/or with deep brain stimulation), and the presence of comorbidity, sequelae, or any disorder that could interfere with the assessment.

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment was collected. Patient baseline evaluation included motor assessment (Hoehn and Yahr [H&Y], Unified Parkinson's Disease Rating Scale [UPDRS] part III and part IV, Freezing of Gait Questionnaire [FOGQ]), non-motor symptoms (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale-Pain [VAS-Pain], Visual Analog Fatigue Scale [VAFS]), cognition (MMSE, Parkinson's Disease Cognitive Rating Scale [PD-CRS], completing a simple 16-piece puzzle), mood and neuropsychiatric symptoms (Beck Depression Inventory-II [BDI-II], Neuropsychiatric Inventory [NPI], Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale [QUIP-RS]), disability (Schwab & England Activities of Daily Living Scale [ADLS]), health related QoL (the 39-item Parkinson's disease Questionnaire [PDQ-39]), and global QoL (PQ-10, EUROHIS-QOL 8-item index [EUROHIS-QOL8]).

Sleep problems were assessed by the Spanish version of the Parkinson's Disease Sleep Scale version 1 (PDSS-1).[13] The PDSS addresses the following features: overall quality of night's sleep (item 1), sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10–13), sleep refreshment (item 14), and daytime dozing (item 15). The response format is a 0–10 cm visual analogue scale, where 0 indicates that a symptom is severe and always experienced, while 10 means being free of symptoms. The score on each item is summarized into a total score which ranges from 0 (most severe) to 150 (free of symptoms).

The NMSS was used for assessing NMS.[14] This includes 30 items, each with a different non-motor symptom. The symptoms refer to the 4 weeks prior to assessment. The total score for each item is the result of multiplying the frequency (0, never; 1, rarely; 2, often; 3, frequent; 4, very often) x severity (1, mild; 2, moderate; 3, severe) and will vary from 0 to 12 points. The scale score ranges from 0 to 360 points. The items are grouped into 9 different domains: 1) Cardiovascular (items 1 and 2; score, 0 to 24); 2) Sleep/fatigue (items 3, 4, 5 and 6; score, 0 to 48); 3) Depression/apathy (items 7, 8, 9, 10, 11 and 12; score, 0 to 72); 4) Perceptual problems/hallucinations (items 13, 14 and 15; score, 0 to 36); 5) Attention/memory (items 16, 17 and 18; score, 0 to 36); 6) Gastrointestinal tract (items 19, 20 and 21; score 0 to 36); 7) Urinary symptoms (items 22, 23 and 24; score, 0 to 36); 8) Sexual dysfunction (items 25 and 26; score 0 to 24); 9) Miscellaneous (items 27, 28, 29 and 30; score, 0 to 48). The score per domain can be expressed as a percentage to be able to compare the degree of involvement between them.

As mentioned before, 3 different instruments were used to assess QoL: 1) the PDQ-39[15]; 2) a rating of global perceived QoL (PQ-10) on a scale from 0 (worst) to 10 (best)[16]; and 3) the EUROHIS-QOL8.[17] The PDQ-39 is a PD-specific questionnaire that assesses the patients' HRQoL. There are 39 items grouped into 8 domains: (1) Mobility (items 1 to 10); (2) Activities of daily living (items 11 to 16); (3) Emotional well-being (items 17 to 22); (4) Stigma (items 23 to 26); (5) Social support (items 27 to 29); (6) Cognition (items 30 to 33); (7) Communication (items 34 to 36); (8) Pain and discomfort (items 37 to 39). For each item, the score may range from 0 (never) to 4 (always). The symptoms refer to the 4 weeks prior to assessment. Domain total scores are expressed as a percentage of the corresponding maximum possible score and a Summary Index is obtained as average of the domain scores. The EUROHIS-QOL8 is an 8-item GQoL questionnaire (quality of life, health status, energy, autonomy for activities of daily living, self-esteem, social relationships, economic capacity, and habitat) derived from the WHOQOL-BREF. For each item, the score ranges from 0 (not at all) to 5 (completely). The total score is expressed as the mean of the individual scores. A higher score indicates a better QoL.

Data Analysis

Data were processed using SPSS 20.0 for Windows. Participants responded to the PDSS, where an overall score below 82[18] or a score below 5 on at least 1 item[11] was defined as a sleep problem.[19] NMS burden was defined as: slight (NMSS 1-20); moderate (NMSS 21-40); severe (NMSS 41-70); and very severe (NMSS > 70).[20] Each domain of the NMSS was expressed as a percentage: (score/total score) x 100. PSQ-39 was expressed as a summary index PDQ-39SI: (score/156) x 100.

For comparisons between patients and/or controls with and without sleep problems, the Student's t-test, Mann-Whitney U test, Chi-square test, or Fisher test, as appropriate, were used (distribution of values and scores was verified by 1-sample Kolmogorov-Smirnov test). Spearman's or Pearson's correlation coefficient, as appropriate, were used for analyzing the relationship between continuous variables. Correlations were considered weak for coefficient values ≤ 0.29, moderate for values between 0.30 and 0.59, and strong for values ≥ 0.60. Binary regression model was used for determining what variables were related to sleep problems (sleep problems as the dependent variable). A p-value < 0.05 was considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

For this study, we received approval from the Comité de Ética de la Investigación Clínica de Galicia from Spain (2014/534; 02/DEC/2014). Written informed consents from all participants in this study were obtained before the start of the study. COPPADIS-2015 was classified by the AEMPS (Agencia Española del Medicamento y Productos Sanitarios) as a Post-authorization Prospective Follow-up study with the code COH-PAK-2014-01.

Data Availability

The protocol and the statistical analysis plan are available on request. De-identified participant data are not available for legal and ethical reasons.

Results

A total of 681 and 206 out of 694 and 207 PD patients and controls, respectively, were considered valid for the analysis. The rest of the COPPADIS cohort participants were excluded due to lack of data. The frequency of sleep problems was nearly double in PD patients compared to controls: 65.8% (448/681) vs 33.5% (65/206) ($p < 0.0001$). In regard to the criteria defining sleep problems, 11.2% of the patients vs 1.9% of the controls had a total PDSS score under 82 ($p < 0.0001$), whereas 65.8% of the patients vs 33.5% ($p < 0.0001$) of the controls had a score under 5 on any item on the PDSS. Considering all items of the PDSS, PD patients more frequently presented a score under 5 in all items and presented a significantly lower mean

Figure 1. Sleep quality in PD patients vs controls regarding to PDSS. A. Percentage of patients vs controls with a score < 5 for each item of PDSS; $p < 0.0001$ except for PDSS-2 ($p = 0.001$) and PDSS-7 ($p = 0.08$). B. Comparison between patients and controls in mean score for each item of PDSS; $p < 0.0001$ except for PDSS-1 ($p = 0.001$) PDSS-2 ($p = 0.02$) and PDSS-7 ($p = 0.016$).

score on all items than controls (Figure 1 and Table 1 SM). Item 8 (Do you get up at night to pass urine?) was the lowest score in both patients and controls. Mean total PDSS score was lower in PD patients than controls: 114.9 ± 28.8 vs 132.8 ± 16.3 ($p < 0.0001$).

Sleep problems were not significantly associated with age or gender but did to disease duration (Table 1). In regard to motor symptoms, the score on H&Y, UPDRS-III, UPDRS-IV and FOGQ was significantly higher in patients with sleep problems vs those without. Specifically, the frequency of sleep problems regarding to H&Y stage was: stage 1, 59.6%; stage 2, 65.5%; stage 3, 87.3%; stage 4-5, 88.9%. Although there were no differences in motor phenotype, the frequency of dyskinesia was double in patients with sleep problems (21.5% vs 10.8%; $p < 0.0001$). To suffer from sleep problems was related to motor features (H&Y, UPDRS-III and dyskinesia) even after adjustment for disease duration, age, and gender: H&Y, OR = 1.674; 95%CI 1.188 – 2.359 ($p = 0.003$); UPDRS-III, OR = 1.024; 95%CI 1.006 – 1.041 ($p = 0.007$); dyskinesia, OR = 2.089; 95%CI 1.245 – 3.507 ($p = 0.005$).

When NMS were considered, it was observed that the score on all scales for assessing NMS showed a worse status for each symptom evaluated in patients with sleep problems except in the Parkinson's Disease Cognitive Rating Scale (PD-CRD) (a trend to significance; $p = 0.056$). However, cognitive impairment (PD-CRS ≤ 84) was more frequent in patients with sleep problems than in those without (34.5% vs 23.1%; $p = 0.003$). Mean total NMSS score was higher in patients with sleep problems (52 ± 37.7 vs 32.3 ± 36; $p < 0.0001$; Figure 2A) and the frequency of severe or very severe NMS burden (NMSS > 40) was higher in these patients too (51.8% vs 24.1%; $p < 0.0001$; Figure 2B). Except for domain-4 (perceptual symptoms), scores on all domains of the NMSS were significantly higher in patients with sleep problems compared to those without (Figure 2C and Table 2.SM). Mean score of all domains of the NMSS was inversely correlated with mean total PDSS score, being the most significant for domain-2 (sleep/fatigue; $r = -0.572$; $p < 0.0001$).

Both health-related (PDQ-39SI, 19.3 ± 14 vs 13 ± 11.6; $p < 0.0001$) and global (PQ-10, 7.1 ± 1.6 vs 7.6 ± 1.5 [$p = 0.001$]; EUROHIS-QoL8, 3.7 ± 0.5 vs 3.9 ± 0.5

Table 1. Disease Related Characteristics, Motor and Non-Motor Symptoms, Autonomy for Activities of Daily Living and Quality of Life in PD Patients With Sleep Problems Vs Those Without Sleep Problems (n = 681).

	No sleep problems (n = 233)	Sleep problems (n = 448)	p
Age	62.8 ± 7.9	62.4 ± 9.4	0.694
Males (%)	59.7	60.5	0.448
Disease duration (years)	5 ± 4	5.7 ± 4.5	0.037
Motor phenotype (%)			0.105
- Tremoric dominant	51.3	41.9	
- PIGD	32.8	41.7	
- Indeterminate	15.9	16.4	
Hoehn & Yahr	1.8 ± 0.5	2 ± 0.6	0.001
- Stage 1 (%)	27.1	20.3	0.015
- Stage 2 (%)	68.6	67.4	
- Stage 3 (%)	3.8	10.3	
- Stages 4 – 5 (%)	0.5	2	
UPDRS-III	20.7 ± 9.5	23.9 ± 11.9	0.001
UPDRS-IV	1.5 ± 1.9	2.3 ± 2.6	<0.0001
Motor fluctuations (%)	30.9	35.8	0.116
Dyskinesia (%)	10.8	21.5	<0.0001
FOG-Q	3 ± 4.2	4.2 ± 4.7	<0.0001
- Patients with falls (%)	10	14.7	0.088
PD-CRS	92.8 ± 15.1	90.5 ± 16.2	0.056
- Cognitive impairment (PD-CRS ≤ 84) (%)	23.1	34.5	0.003
NMSS	32.3 ± 36	52 ± 37.7	<0.0001
- Very severe NMS burden (NMSS > 70) (%)	11.2	24.3	<0.0001
BDI-II	6 ± 6	10.2 ± 7.6	<0.0001
- Depressive symptoms (%)	40.9	54.4	<0.0001
- Major depression (%)	8.9	19.6	
- Minor depression (%)	17.1	16.3	
- Subthreshold depression (%)	14.9	18.5	
NPI	4.6 ± 6.3	6.7 ± 8.5	0.002
QUIP-RS	2.3 ± 5.2	5.3 ± 9.3	<0.0001
- ICD and/or CB (%)	7.3	18.4	<0.0001
- Patients with ICD (%)	5.4	12.8	<0.0001
- Patients with CB (%)	3.5	10.6	<0.0001
PDSS	134.4 ± 13	104.7 ± 26.8	<0.0001
VAS-PAIN	1.9 ± 2.6	3 ± 3	<0.0001
- Patients with pain (%)	46.4	62.5	<0.0001
VASF – physical	2.2 ± 2.6	3.3 ± 2.8	<0.0001
VASF – mental	1.5 ± 2.2	2.5 ± 2.7	<0.0001
ADLS	90.2 ± 8.6	87.7 ± 11.2	0.009
- Patients with functional dependency (%)	9	21.5	<0.0001
PDQ-39SI	13 ± 11.6	19.3 ± 14	<0.0001
PQ-10	7.6 ± 1.5	7.1 ± 1.6	0.001
EUROHIS-QoL8	3.9 ± 0.5	3.7 ± 0.5	<0.0001
L-dopa eq. daily dose (mg)	494.2 ± 353.6	588.6 ± 439.2	0.022
Total number of pills/day	6.4 ± 3.9	7.8 ± 4.2	<0.0001
Total number of non-antiparkinsonian drugs / day	2.3 ± 2.3	2.8 ± 2.5	0.014
Use of antidepresive agent (%)	16.7	28.1	0.003
Use of benzodiacepins (%)	15	16.5	0.674
Use of dopamine agonist (%)	63.5	71.2	0.117

Chi-squared and Mann-Whitney-Wilcoxon test were applied. The results represent percentages or mean ± SD. Data about H&Y and UPDRS-III are during the OFF state (first thing in the morning without taking medication in the previous 12 hours).

ADLS, Schwab and England Activities of daily living Scale); BDI, Beck Depression Inventory-II; CB, compulsive behaviors (hobbyism, punding, and/or dopaminergic dysregulation síndrome); ICD, impulse control disorders (gambling, buying, sex, and/or eating). NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinsońs disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Inestability Gait Dificulty; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale;[21] UPDRS, Unified Parkinson's Disease Rating Scale; VAFS, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale-Pain.

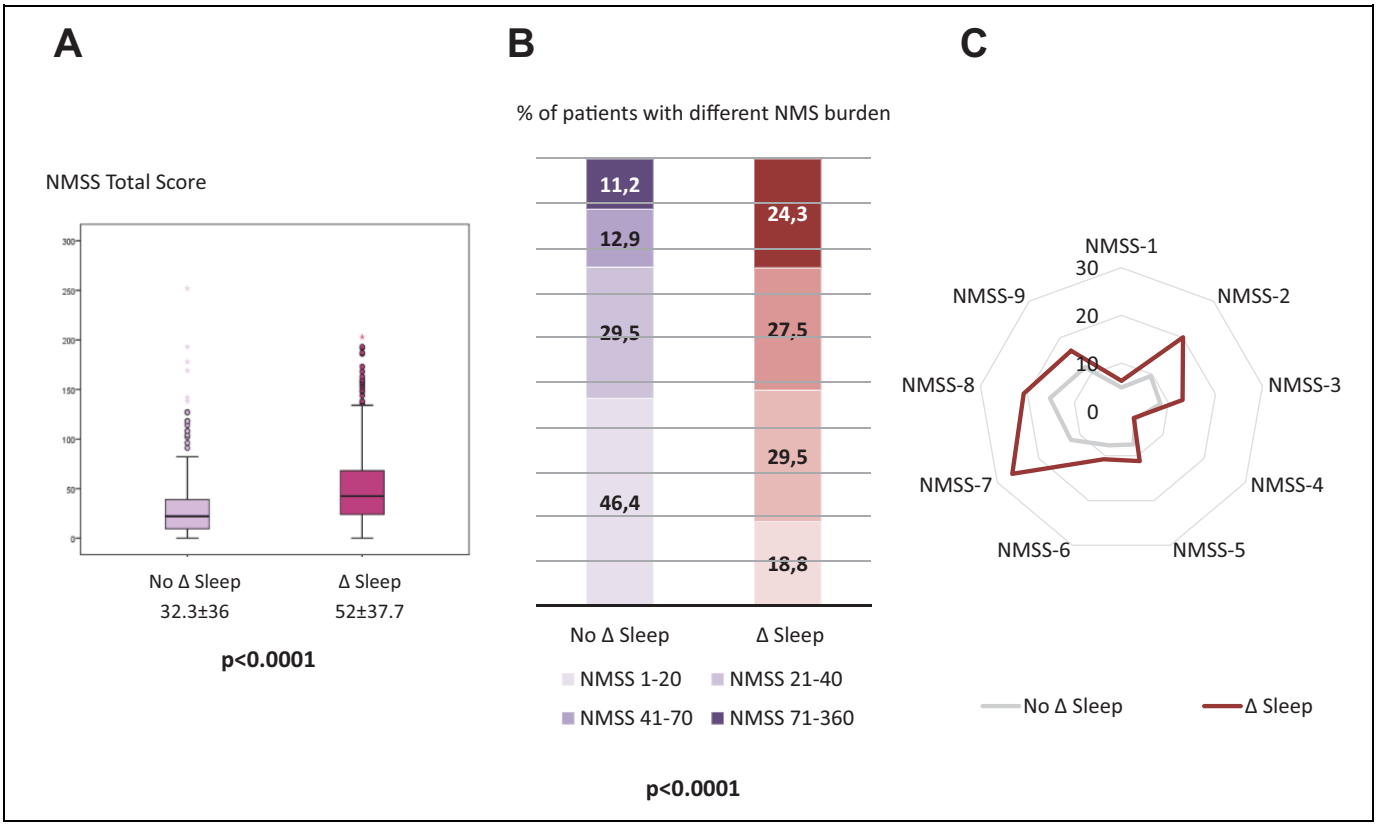

Figure 2. A. NMSS total score in PD patients with vs without sleep problems. B. Percentage of PD patients with slight (NMSS 1-20), moderate (NMSS 21-40), severe (NMSS 41-70) and very severe (NMSS > 70) NMS burden in PD patients with vs without sleep problems. C. Comparison in PD patients with vs without sleep problems of mean NMSS score on each domain of the scale; $p < 0.0001$ except for NMSS-1 (cardiovascular; $p = 0.06$), NMSS-4 (perceptual symptoms; $p = 0.024$), NMSS-8 (sexual dysfunction; $p = 0.009$).

Table 2. Binary Logistic Regression Model About Factors Related to Sleep Problems (n = 681).

	OR	95% IC	p
Age	0.989	0.958 – 1.020	0.469
Gender	0.811	0.645 – 1.750	0.811
Disease duration	0.984	0.932 – 1.074	0.984
L-dopa eq. daily dose (mg)	0.101	1.000 – 1.001	0.101
Hoehn & Yahr	0.944	0.508 – 1.571	0.695
NMSS	1.029	1.015 – 1.043	**<0.0001**
BDI-II	1.020	0.967 – 1.076	0.464
QUIP-RS	1.054	1.009 – 1.101	**0.018**

Non-Motor Symptoms Scale; PD, Parkinsońs disease; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Model adjusted by UPDRS-III, UPDRS-IV, PD-CRS, NPI, VAS-Pain, VAFS, FOG and total number of non-antiparkinsonian treatments as covariates.

[$p < 0.0001$]) perceived QoL were worse in PD patients with sleep problems than those without (Table 1 and Figure 3). Mean score on all domains of the PDQ-39SI was higher in patients with sleep problems except on domain-4 (stigma), whereas the contrary was observed for all domains of the EUROHIS-QoL8 except for enough money and habitat ($p = 0.981$) (Figure 3). With regard to independence for activities of daily living, 21.5% of the patients with sleep problems were functional dependent vs 9% of those without sleep problems ($p < 0.0001$).

Non-motor symptoms burden (NMSS; OR = 1.029; 95%CI 1.015 – 1.043; $p < 0.0001$) and impulse control behaviors (QUIP-RS; OR = 1.054; 95%CI 1.009 – 1.101; $p = 0.018$) were associated with sleep problems after adjustment for age, gender, disease duration, daily equivalent levodopa dose, H&Y, UPDRS-III, UPDRS-IV, PD-CRS, Beck Depression Inventory-II (BDI-II), Neuropsychiatric Inventory (NPI), VAS-Pain (Visual Analog Scale-Pain), VAFS (Visual Analog Fatigue Scale), FOGQ, and total number of non-antiparkinsonian treatments (Table 2). Similar results were observed when symptoms of domain 2 (sleep/fatigue) were excluded of the NMSS total score (NMSS total score – NMSS domain 2 score): NMSS, OR = 1.028; 95%CI 1.013 – 1.043 ($p < 0.0001$); impulse control behaviors (QUIP-RS; OR = 1.059; 95%CI 1.014 – 1.106; $p = 0.010$). When NMSS was considered as a categorical variable in the same model (I: slight burden, NMSS 1-20; II: moderate burden, NMSS 21-40; III: severe burden, NMSS 41-70; IV, very severe burden, NMSS > 70), OR was 1.891 (95%CI 1.350 – 1.650; $p < 0.0001$). Again, it was significant when NMSS total score – NMSS domain 2 score was considered as a categorical variable in the model: OR = 1.849; 95%CI 1.307 – 2.617 ($p = 0.001$). To suffer from an impulse control disorder (ICD)

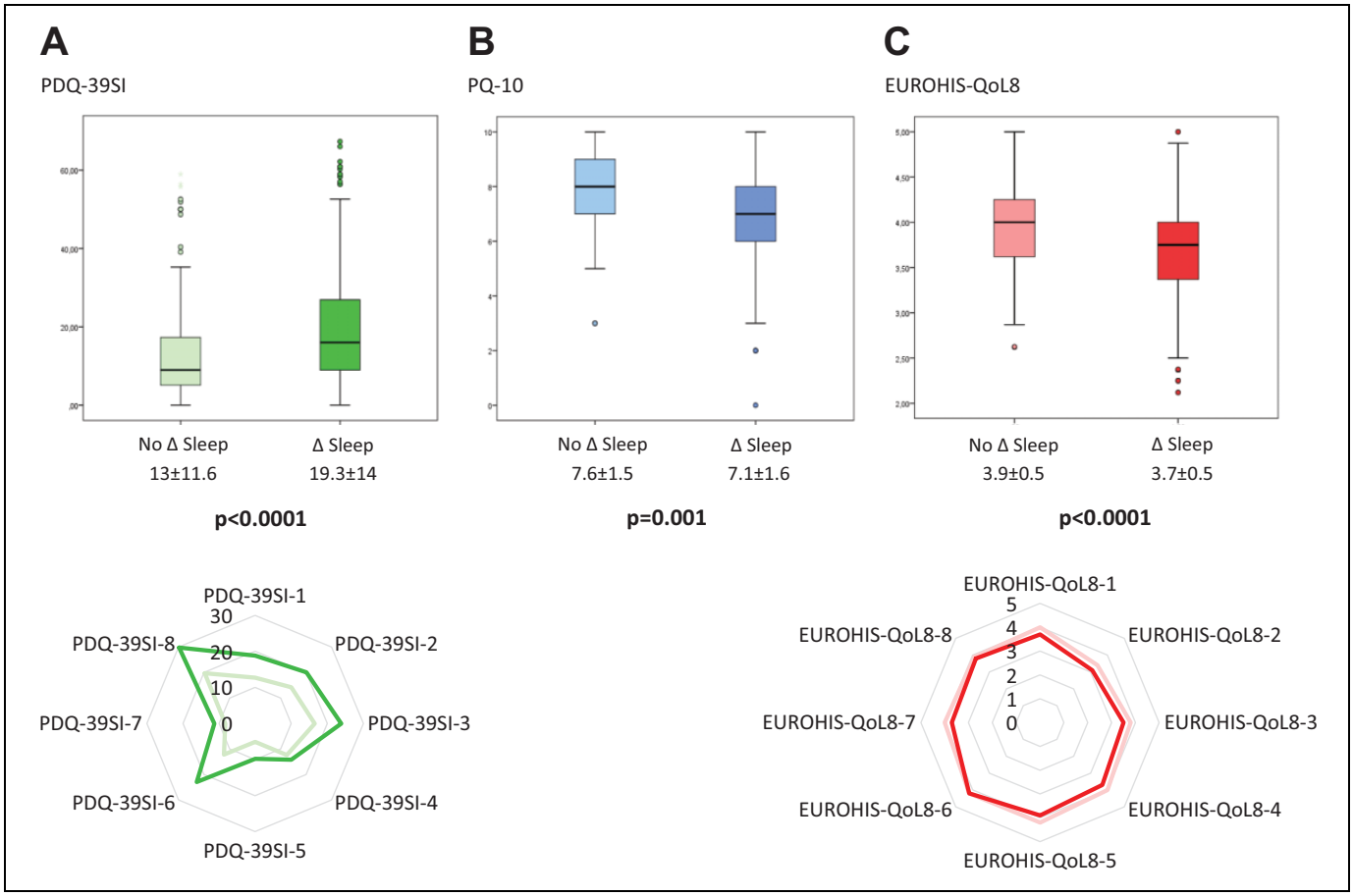

Figure 3. Health-related (A) and global (B, C) perceived quality of life in PD patients with vs without sleep problems. Regarding to PDQ-39SI domains, p was < 0.0001 except for PDQ-39SI-4 (stigma; p = 0.408) and PDQ-39SI-7 (communication; p = 0.009). Regarding to EUROHIS-QoL8, p was < 0.0001 except for EUROHIS-QOL8-6 (enough money; p = 0.338), EUROHIS-QOL8-7 (social relationships; p = 0.003) and EUROHIS-QOL8-8 (habitat; p = 0.981).

and/or CB (compulsive behavior) was associated with sleep problems (OR = 2.064, 95%CI 1.024 – 4.161; p = 0.002) after adjustment to age, gender, disease duration, daily equivalent levodopa dose, H&Y stage, motor status (UPDRS-III), motor complications (UPDRS-IV), NMS burden (total NMS score), and neuropsychiatric symptoms (total NPI score).

Discussion

The present study finds that self-reported sleep problems are frequent in PD. PD patients who have sleep problems also perceive a worse QoL. Sleep problems associate with advanced PD with greater NMS burden and worse motor status. After adjustment for many covariates, suffering from impulse control behavior was related to sleep problems as well.

Prevalence of sleep problems in PD can vary anywhere from 50% to 81%.[22,23] Community studies have reported that about 60% of PD patients have a sleep disorder compared to 33% of the controls[2] The frequency depends in part on the methodology used. The PDSS, a simple bedside screening instrument for evaluation of sleep disturbances in PD, has been used in different studies and it has demonstrated good psychometric characteristics.[24] The scale is "recommended" by the MDS Task Force as a screening tool and severity measure for sleep symptoms in PD as it includes most of the patient's possible disturbances[25] For this scale, a cutoff score of 82/83[18] or a score below 5 on at least 1 item[19] have been suggested and both have been recently used for defining sleep problems in a study conducted in 176 PD patients,[11] presenting only 17% of the patients a PDSS score under 82 but 70% a total score under 5 on 1 or more items. In our study, the frequency was 11.2% and 65.8%, respectively. To our knowledge, this is the largest study by far in which sleep problems were assessed with the PDSS and in which a control group was included.

As in previous studies, symptoms concerning to item 8 (nocturia) of the PDSS were the most frequently reported by not only patients but controls as well.[8,9,11,18] In our study, the difference between score in patients and controls was significant for all items of the PDSS. However, in Chaudhury et al.[8] study, in which 143 PD patients and 137 healthy age matched controls were included, there were no significant differences in items 1, 2, and 14. PDSS scores were markedly different

between patients with early/moderate PD and advanced disease in previous studies,[8,7] as in ours. In regard to motor symptoms, the finding most interesting was that dyskinesia was double in patients with sleep problems compared to those without. In line with this, Mao et al.[26] observed very recently that poor nighttime sleep was positively associated with dyskinesia in PD patients, suggesting that physicians caring for PD patients should pay attention to night-time sleep quality, especially in patients with a relatively large amount of daily LED and longer disease duration who are at high risk for dyskinesia.

A relationship between the presence of sleep problems and the presence of greater NMS burden as a whole, as well as greater individual symptoms such as depression, pain, fatigue, or impulse control behaviors, is known. A cross-sectional study conducted in 86 PD patients observed that the presence of comorbid sleep disorders was related to more NMS including increased sleep complaints, more depressive symptoms, poorer cognition, and more fatigue.[27] In our cohort of 681 PD patients, the probability of suffering from sleep problems nearly doubled for each increment in the grade of NMS burden (slight, moderate, severe, very severe). The reason for this association is not clear. Sleep disruption in PD patients is likely due to a multitude of factors. Dopamine circuitry is also thought to be implicated in several major sleep disorders. There are reports suggesting that patients with PD exhibit dopamine dysfunction in the hypothalamus, a key area in the regulation of sleep-wake that may contribute to symptoms of insomnia, circadian rhythm disruption, and daytime sleepiness.[7] In addition, brain stem deterioration is reported in PD and is also implicated in the REM sleep processes. Other factors may also be responsible for disturbed sleep in PD, including the medications used to treat the PD, motor symptoms, pain, nocturia, and other sleep disorders common in this age group. Nonetheless, our results suggest that even when controlling for disease (dopaminergic treatment and PD severity), age and many other covariates, sleep disorders are associated with NMS in PD. Moreover, suffering from sleep problems was related to impulse control behaviors. The relationship between sleep problems and ICDs is bidirectional and complex.[28] Sleep disturbances and fragmentation may play a crucial role in increasing susceptibility to impulsive behavior and they may represent a risk factor for developing ICDs in PD patients. On the other hand, ICDs may lead to sleep restriction and fragmentation as well.

The present study observed that sleep problems is associated with a poorer QoL. Previous studies have reported the negative impact of sleep disorders on QoL.[29,30] Additional studies are now required to determine whether the treatment of sleep disorders in PD patients may be beneficial in terms of overall NMS and QoL. While treating sleep disorders will likely not affect PD progression, it has the potential for improving NMS and may potentially reduce overall disability and thereby improve the lives of PD patients and their caregivers.[27,28,31]

The present study has some limitations. The PDSS is a subjective semiquantitative scale which attempts to provide a holistic and clinical assessment of the complex etiology of sleep problems in PD. Sleep problems was defined as sleep disturbances as a whole and no specific sleep disorders were analyzed in detail. Moreover, objective studies like polysomnography were not performed and the data were based on subjective answers provided by the patients. All scales or questionnaires used to assess motor and NMS are validated except PQ-10. This is a very simple question about global QoL from 0 to 10 used in previous studies that takes very little time and provides information similar to the EUROHIS-QOL8 total score.[32] A specific tool for assessing comorbidity, like Charlson Index or others, has not been used. However, the total number of non-antiparkinsonian medications has been suggested as a useful marker of comorbidity in PD.[33] For some variables, the information was not collected in all cases. Our sample is not fully representative of the PD population due to inclusion and exclusion criteria (i.e., age limit, no dementia, no severe comorbidities, no second line therapies, etc.) which subsequently entails a bias toward early PD. Finally, although this is a cross-sectional study, the aim of the COPPADIS-2015 study[12] is to follow-up the cohort for 5 years so that predictors of sleep disorders in PD may be analyzed.

In conclusion, this study demonstrates that, in PD, suffering from sleep problems are frequent and related to a worse QoL and greater NMS burden. These findings call for increased awareness of sleep problems in PD patients.

Appendix 1.

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Abbreviations

BDI-II	Beck Depression Inventory-II
CB	compulsive behavior
FOG-Q	Freezing Of Gait Questionnaire
ICD	impulse control disorder
NMS	non-motor symptoms
NMSS	Non-Motor Symptoms Scale
NPI	Neuropsychiatric Inventory
QoL	quality of life
PD	Parkinsońs disease
PD-CRS	Parkinson's Disease Cognitive Rating Scale
PDQ-39SI	39-item Parkinson's Disease Quality of Life Questionnaire Summary Index
PDSS	Parkinson's Disease Sleep Scale
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
S&E	Schwab & England Activities of Daily Living Scale
UPDRS	Unified Parkinson's Disease Rating Scale
VAFS	Visual Analog Fatigue Scale
VAS-Pain	Visual Analog Scale-Pain

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Supplemental Material

Supplementary material for this article is available online.

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