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Short communication

Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease

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ABSTRACT

Background: The association between sleep disorders and other non-motor symptoms (NMS) in Parkinson's disease (PD) has been scarcely investigated.
Objective: To describe the prevalence of insomnia and hypersomnia in PD and analyze their relationship with other NMS.
Methods: Cross-sectional, multicenter study including 388 PD patients evaluated with Hoehn and Yahr, Clinical Impression of Severity Index for PD, Scales for Outcomes in Parkinson's Disease (SCOPA)-Sleep(S), SCOPA-Cognition, SCOPA-Psychiatric Complications, SCOPA-Autonomic, Hospital Anxiety and Depression Scale, and fatigue and pain visual analogue scales. Spearman correlation coefficients, Mann–Whitney test and multiple linear regression analysis were applied.
Results: Mean age (54% male) was 65.9 ± 11.2 years old, with disease duration of 8.1 ± 6.0 years and median HY = 2 (range: 1–5). Mean SCOPA-S nocturnal sleep (NS) was 5.4 ± 4.0 (range: 0–15), daytime sleepiness (DS) was 3.76 ± 3.04 (range: 0–15). Most of the sample declared nocturnal or daytime sleep problems (87.4%). Weak-to-moderate correlations were found between sleep disturbances and other NMS (range: 0.14–0.37). SCOPA-S subscales showed higher scores with the presence of most other NMS such as psychiatric complications and autonomic dysfunctions ($p < 0.05$). Regression models showed that fatigue, depression, urinary, cardiovascular, and thermoregulatory dysfunctions were significant determinants of SCOPA-NS score (variance: 23%); cognitive impairment, urinary, cardiovascular, and pupillomotor disorders influenced SCOPA-DS score (variance: 14%).
Conclusions: Insomnia and daytime sleepiness are extremely prevalent in PD. Depression, fatigue, cognitive impairment, cardiovascular, urinary and thermoregulatory dysfunctions may contribute to insomnia/hypersomnia. This is the first clinical study to relate cardiovascular and thermoregulatory dysfunctions with sleep in PD.

1. Introduction

Although Parkinson's disease (PD) is traditionally defined by the presence of motor symptoms, the relevance of non-motor symptoms (NMS), even before the onset of motor manifestations [1], has been progressively recognized. The array of NMS described in PD includes pain, fatigue, depression, anxiety, cognitive impairment, autonomic dysfunction and sleep disorders. Non-motor manifestations significantly contribute to symptoms' burden, disability, quality of life deterioration, and institutionalization of patients [2].

Sleep disorders in PD can consist of onset or maintenance insomnia, restless legs syndrome, vivid dreams, rapid eye movement sleep behavior disorder and excessive daytime sleepiness (EDS). They affect up to 60–90% of PD patients, with increasing prevalence as the disease progresses [3–5]. Several factors are thought to contribute to the presence and severity of sleep disorders: neuropathological changes related to the disease itself, age-related changes, nighttime motor symptoms, cognitive impairment, mood disorders, primary sleep disorders such as restless legs, periodic leg movements and obstructive sleep apnea, and side effects of PD treatment (mainly, levodopa and dopamine agonists). A few studies have suggested a relationship between sleep disorders and other NMS, but there is a lack of research specifically focusing on this question [4].

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Thus, the main objective of the present study is to address this gap and analyze the link between two sleep disorders, insomnia and EDS, and other NMS in a large representative PD cohort. The prevalence of these disorders is also described.

2. Methods

2.1. Design

Multicenter, observational, cross-sectional study.

2.2. Sample

The sample was recruited in the framework of the ELEP (Longitudinal Parkinson's Disease Patient Study) [6], and included 388 patients, diagnosed with PD by a neurologist with expertise in movement disorders as per the United Kingdom PD Society Brain Bank modified criteria, aged ≥30 years at disease onset and having a main caregiver. Patients who did not fulfill the inclusion criteria, or whose limitations or comorbidities were barriers for evaluation, were excluded.

2.3. Ethical aspects

The study was approved by the Institutional Review Board of the Carlos III Institute of Health. Patients gave their informed consent prior to participating in the study.

2.4. Assessments

Socio-demographic characteristics and clinical data were collected. The following motor and non-motor rating scales were applied:

- For motor disease severity, the Hoehn and Yahr scale (HY), and for global evaluation, the Clinical Impression of Severity Index for PD (CISI-PD) [6].
- For sleep evaluation: Scales for Outcomes in Parkinson's Disease (SCOPA)-Sleep (S) [7]. The SCOPA-S is a disease-specific scale comprised of two subscales: nocturnal sleep (NS), with 5 items evaluating insomnia; and daytime sleepiness (DS), evaluating propensity to falling asleep during the day, with 6 items. All items are scored from 0 (not at all, never) to 3 (a lot, often). A single question on global assessment of NS quality, scored by a 7-point scale (from very well to very badly), is also included but not taken into account in the NS subscale score.
- For other NMS: SCOPA-Cognition (Cog), SCOPA-Psychiatric Complications (PC), SCOPA-Autonomic (Aut), Hospital Anxiety and Depression Scale (HADS), and fatigue and pain visual analogue scales (VAS) were used. For all scales used, higher scores indicate worse symptomatology, with the exception of the SCOPA-cog, where higher scores mean better function. A description of the applied rating scales has been previously published [6].

The cross-culturally adapted and validated Spanish version of all rating scales was used.

2.5. Data analysis

Socio-demographic and clinical characteristics of the sample were analyzed using frequency and central tendency measures: mean and standard deviation or median and inter-quartile range (IR), as appropriate. For treatment, levodopa equivalent dose (LED) was calculated using standardized conversion formulas [8]. Frequencies of insomnia and daytime sleepiness were calculated based on subjects scoring ≥1 in SCOPA-S subscales.

Non-parametric statistics were used because the main variables in the study did not meet assumptions for use of parametric tests. To determine the relationship between sleep scores and other NMS, Spearman rank correlation coefficients were calculated. We hypothesized weak to moderate correlations between the SCOPA-S subscales and the rest of NMS scales applied in the study [4,9].

The sample was divided in groups by variables of interest: SCOPA-Cog and HADS cut-off values (19/20 and 10/11, respectively), and presence of psychiatric complications, autonomic symptoms, pain and fatigue (scores ≥1 in the corresponding scales and subscales). Mann–Whitney test was used to compare groups with respect to SCOPA-S subscales scores.

Multiple linear regression models were built to identify NMS that could influence insomnia or daytime sleepiness, controlling for basic epidemiological factors. The independent variables (excluding those showing collinearity) were: sex, age, disease duration, agonist LED, and cognition, psychiatric complications, dysautonomia (excluding sexual dysfunction), depression, fatigue, and pain scores.

3. Results

The patient cohort (54% men) had a mean age of 65.9 ± 11.2 years old, with age at onset of 57.8 ± 12.1 years and disease duration of 8.1 ± 6.0 years. HY distribution was as follows: stage 1, 25% of the sample (97 subjects); stage 2, 49.5% (192); stage 3, 19.3% (75); stage 4, 4.6% (18); and stage 5, 0.5% (2). More than 70% of patients were on a combination of levodopa and agonist therapy, with mean total LED of 547 ± 372 mg (of which, agonist LED was 186 ± 166 mg). In total, 24 patients had undergone DBS surgery. About 16% of patients were on medication known to influence sleep: 16% took antidepressants, 13% were on anxiolytics and 7.2% took hypnotic drugs. Mean SCOPA-NS score was 5.4 ± 4.0 (range: 0–15), 22.6% of patients complained of sleeping poorly/very poorly, while 87.4% reported some nocturnal sleep problem (SCOPA-NS score ≥1). Mean SCOPA-DS score was 3.8 ± 3.0 (range 0–15), and 87.4% of the sample declared some daytime somnolence (SCOPA-DS score ≥1). Mean and median NMS scales scores are presented in Table 1. Most correlation coefficients between the SCOPA-S subscales and NMS rating scales were relatively weak (Table 1). Only the SCOPA-Aut total score showed moderate correlations with both NS and DS subscales (0.37 and 0.31 respectively). Fatigue, depression and anxiety scores also correlated moderately with nocturnal sleep scores.

Table 2 shows the SCOPA-NS and DS subscales scores broken down by the presence or not of other NMS as defined by threshold level where available (SCOPA-Cog, depression and anxiety scales), above 0 on the analogue scales (pain and fatigue) or a positive answer to any of the questions (SCOPA-PC and subscales of SCOPA-aut). Insomnia was significantly worse in those patients with psychiatric complications, anxiety, depression, pain, and fatigue and various autonomic dysfunctions (gastrointestinal, cardiovascular, thermoregulatory, and pupillomotor symptoms) evaluated by the SCOPA-Aut (Mann–Whitney, $p < 0.01$). SCOPA-DS showed significantly higher scores with the presence of psychiatric complications, cognitive difficulties and gastrointestinal, urinary, cardiovascular, and pupillomotor symptoms of the SCOPA-Aut (Mann–Whitney, $p < 0.05$). Concomitant use of antidepressants, anxiolytics, and hypnotic drugs did not significantly change either subscale score.

The multiple linear regression model for SCOPA-NS showed that the NMS fatigue (standardized beta = 0.17) and thermo-regulatory function (0.16), depression (0.12), urinary (0.13), and cardiovascular dysfunction (0.11) independently influenced insomnia. Other retained variables were age (−0.10) and agonist LED (0.16). The model explained the 23% of the variance. The multiple linear regression model for SCOPA-DS identified the NMS cardiovascular dysfunction (0.17), urinary dysfunction (0.15), SCOPA cog (−0.14), and pupillomotor autonomic domain scores (0.011) as determinants. Sex (−0.15) and agonist LED (0.15) were also included in the model which accounted for 14% of the variance.

4. Discussion

This study informs about the declared prevalence of insomnia and daytime hypersomnia in a large PD cohort and characterizes their association with other NMS such as cognitive difficulties, psychiatric complications, mood disorders, pain, fatigue and dysautonomia. About 9 out of 10 patients reported some kind of insomnia, which is in line with previous studies [4]. Results showed a similarly high prevalence for EDS (87% of patients), differing from the previously reported 43% using the same scale in a Dutch population [10] and most epidemiological studies where figures range from 20 to 50% [3]. Possible reasons for the discrepancy may be differences in methodology, patient cohort demographics and cultural bias that may influence questionnaire interpretation.