Parkinsonism and Related Disorders 33 (2016) 51–57

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The course of insomnia in Parkinson's disease

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form
1 September 2016
Accepted 7 September 2016

Keywords:
Parkinson's disease
Insomnia
Risk factors

ABSTRACT

Introduction: Insomnia is a debilitating symptom in Parkinson's disease (PD) that has been scarcely investigated in a longitudinal design. Knowledge of factors associated with occurrence of insomnia may provide clues for an increased understanding of underlying pathophysiology and facilitate early detection.

The objective of this study is to examine the course and factors associated with longitudinal changes in insomnia severity in patients with PD.

Methods: Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year longitudinal cohort study (2003–2011) of 421 PD patients who have been examined annually. Linear mixed models were used to identify factors associated with longitudinal changes in scores of the SCOPA-SLEEP-Nighttime sleep (NS) problems section. A generalized estimating equations (GEE) analysis was performed to determine which baseline variables were associated with the different aspects of insomnia (sleep initiation or maintenance difficulty).

Results: Baseline SCOPA-SLEEP-NS scores were available for 412 patients, of whom 110 (27%) had insomnia (i.e. score $\geq$ 7). Of the remaining 302 patients, 99 (33%) developed insomnia at some point during follow-up. More severe depressive symptoms, motor fluctuations, higher dopamine agonist doses and sleep medication use were independently associated with higher SCOPA-SLEEP-NS scores over time. GEE analysis did not identify an unique set of determinants that affected specific aspects of insomnia.

Conclusion: The presence of depressive symptoms, motor fluctuations and the use of higher doses of dopamine agonists are associated with more severe insomnia. Attention to these aspects could potentially contribute to a better management of insomnia symptoms in PD.

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1. Introduction

Insomnia is a common sleep disorder in Parkinson's disease (PD) and affects up to 60% of patients according to earlier population-based prevalence studies [1]. The American Academy of Sleep Medicine defines insomnia as problems involving initiating sleep, maintaining sleep, early awakenings and poor overall sleep quality [2]. In PD, sleep fragmentation and early awakenings are the most common complaints, whereas initiation of sleep is often unimpaired [3]. Insomnia may be related to ageing, the progression of the disease or the use of drugs with a sleep-altering effect [1–4]. Insomnia has a great negative impact upon health-related quality of life [5,6] and is one of the most frequently reported non-motor symptoms in PD, with larger studies finding prevalence rates between 37 and 45% [7,8]. Remarkably, there are only a few longitudinal studies on insomnia in PD and information on its course and possible determinants is therefore scarce. To date only one large longitudinal study (n = 231) has been performed [1], which showed that insomnia often exhibits a fluctuating course and is associated with female gender, longer disease duration and coexistent depression.

Cross-sectional studies on this topic showed that increased levels of anxiety and depression, impulsivity, excessive daytime sleepiness (EDS), fatigue, autonomic dysfunction and higher doses of dopaminergic medication are associated with insomnia in PD, whereas conflicting results emerged regarding disease severity [3,4,9–12]. However, cross-sectional studies provide limited information on the course and features that are longitudinally associated with insomnia. A thorough knowledge of factors that are associated with occurrence and severity of insomnia may provide clues for an enhanced understanding of the underlying pathophysiology, facilitate early detection and guide future intervention

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http://dx.doi.org/10.1016/j.parkreldis.2016.09.010
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strategies. The aim of the current study was to use a prospective cohort design to determine the frequency, course, longitudinal associations and risk factors of insomnia in PD.

2. Methods

2.1. Study design and participants

Since 2013, post-hoc analyses on the PROPARK cohort have been performed to determine the longitudinal course of several non-motor domains [13]. The original purpose of the PROPARK cohort study was to evaluate the longitudinal course of several motor and non-motor symptoms in PD. The cohort included 421 PD patients who have been examined annually and followed for up to five years (i.e., six assessments) on several motor and non-motor features; this makes this study very well-suited for the purpose of identifying factors associated with longitudinal changes in insomnia in PD [14]. Patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD [15]. The majority of patients were evaluated at the Leiden University Medical Centre, but more severely affected patients were offered the possibility to be examined at their homes to minimize selective drop-out. In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied. We intended to recruit at least 100 patients in each of the four strata [14]. The medical ethical committee of the Leiden University Medical Centre approved the PROPARK study and written informed consent was obtained from all patients [14].

2.2. Assessment of baseline variables

Baseline assessments were performed between 2003 and 2005. In the five subsequent annual visits, all patients received standardized assessments. The last assessments of individual patients were performed between 2008 and 2011. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA) [16]. Diagnosis of PD and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment [17].

The following instruments were administered by qualified examiners: the SPES/SCOPA [18] (including sections on motor examination, activities of daily living and motor complications), the SCOPA-COG (cognitive function) [19], and the SCOPA-PC (psychiatric complications; items 1–5) [20]. Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients were assessed during "on" and patients completed the following instruments themselves: the SCOPA-AUT (subscales gastrointestinal, urinary tract and cardiovascular) [21], the SCOPA-SLEEP (nighttime sleep problems [NS] and daytime sleepiness [DS]) [22], and the Beck Depression Inventory (BDI) [23]. For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype into those with and without postural-instability-and-gait difficulty (PIGD) by using a ratio of tremor score over PIGD score [19]. Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values ≥1.0 were classified as non-PIGD dominant [18,24].

2.3. Ascertainment of insomnia

Insomnia was assessed using the nighttime sleep (NS) section of the SCOPA-SLEEP questionnaire [22], an instrument that was appraised as "recommended" by the Movement Disorder Society Sleep Scale Task Force (MDS-SSTF) [25]. It consists of 5 items that evaluate problems with sleep initiation, sleep maintenance, early awakenings and subjective sleep quality. Patients were considered to suffer from insomnia if they scored ≥7 [22].

2.4. Statistical analysis

The objectives of the statistical analysis in this study were: 1) to examine which factors are associated with the presence of insomnia; 2) to evaluate which variables are associated with longitudinal variations in SCOPA-SLEEP-NS scores; and 3) to determine which specific aspects of insomnia are affected by the different baseline variables.

For objective 1 we evaluated which features were associated with insomnia in the baseline data of our population. Cross-sectional analyses were performed to assess differences at baseline between patients with and without insomnia using the appropriate tests.

For objective 2 a linear mixed models (LMM) analysis was performed using the data of all patients included in the follow-up. This method is suitable for identifying baseline variables that are associated with variation in SCOPA-SLEEP-NS scores over time. LMM takes into account that repeated measures in the same patient are correlated and a restricted maximum likelihood model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses; this covariance structure takes into account that measurements performed closer in time are more strongly correlated than those that have been performed over longer intervals. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and slopes were used. Variables that have been found associated with insomnia in earlier studies were considered in the LMM. The H&Y stage was not included because it is partly determined by motor phenotype and the sumscore of motor impairment.

The relationship between variables that were associated with variation in SCOPA-SLEEP-NS scores over time were first analyzed including only one variable at a time (unadjusted model). Additionally, an adjusted model was performed that considered the main effects of all significant baseline variables from the unadjusted model. The final model only included the variables that were significant from the adjusted model.

A generalized estimating equations (GEE) method was applied to determine if the same or different baseline variables determined the various characteristics of insomnia (i.e. the different items of the SCOPA-SLEEP-NS, e.g., difficulty initiating sleep, sleep maintenance or early awakenings) (objective 3). This method is suitable for identifying variables that are associated with variation in a binary outcome over time (here: the presence or absence of a particular insomnia symptom). Similar to the LMM procedure, an autoregressive (heterogeneous) covariance structure type was used. Scores on different items of each annual SCOPA-SLEEP-NS assessment were dichotomized, and patients were classified as impaired if they scored ≥1 on a specific item. Baseline variables that are significant from the unadjusted model were entered in the multivariate analysis. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

3. Results

Of the 412 patients of whom a baseline SCOPA-SLEEP-NS score

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