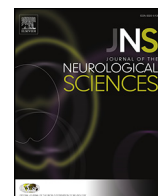




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## Parasomnias and isolated sleep symptoms in Parkinson's disease: A questionnaire study on 661 patients

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### ABSTRACT

**Background:** Sleep disorders are among the most common non-motor symptoms in Parkinson's disease.

**Method:** The prevalence of parasomnias and their association with other symptoms were studied in a questionnaire study among 1447 randomly selected Parkinson patients, aged 43 to 89 years. The response rate was 59.0% and of these 77% had answered to all questions that were used in the analyses ( $N = 661$ ).

**Results:** The prevalence of REM sleep behavior disorder (RBD) evaluated by the RBDSQ  $\geq 6$  was 39.0%. The occurrences of other parasomnias ( $\geq 1$ /week) in patients with PD were: nightmares 17.2%, night terrors 3.9%, sleepwalking 1.8%, enuresis 21.0%, and hallucinations 15.3%. Occurrences ( $\geq 1$ /week) of the isolated sleep symptoms were: nocturnal sweating 28.8%, bruxism 4.7%, and sleep talking 21.7%. Association of RBD with sleepwalking (parasomnia overlap disorder) was found in 1.7% of all PD patients. Adjusted logistic regression analysis showed that weekly nightmares (OR 12.5; 95% CI 5.3 to 29.7), hallucinations (OR 5.1; 2.1 to 12.4), sleep talking (OR 11.6; 5.9 to 22.8), male gender (OR 1.9; 1.1 to 3.1), and restless legs syndrome (OR 4.7; 1.7 to 13.2) associated with the presence of RBD.

**Conclusion:** Parkinson patients with RBD have often also other parasomnias and/or isolated sleep symptoms.

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### 1. Introduction

Although Parkinson's disease is defined by its motor symptoms, the non-motor symptoms of the disease such as sleep disorders have a significant impact on patients' well-being and quality of life as well. The majority of patients suffer from sleep disturbances affecting their ability to fall asleep, ability to stay asleep, dreams, motor activity during sleep, post-sleep behavior, or day-time somnolence. Among different sleep disorders parasomnias have often been overlooked.

According to the latest International Classification of Sleep Disorders (ICSD-3) three sleep disorders are classified as REM sleep parasomnias, namely REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder [1].

The NREM parasomnias are disorders of arousal from NREM sleep, with impaired sleep–wake transitions that can result in activation of physiologic systems. Sleepwalking (SW), confusional arousals, sleep terrors and sleep related eating disorder may occur when the transition from slow-wave sleep to wakefulness is disrupted [1].

The third category of parasomnias, classified as “other parasomnias”, includes sleep-related dissociative disorder, sleep enuresis, exploding head syndrome, and sleep related hallucinations [1]. Additionally to these, parasomnias may be due to drug, other substance, or medical condition.

Sleep talking (ST), sleep bruxism (SB), and nocturnal sweating are classified in the new classification as isolated symptoms [1]. ST is a common phenomenon that may occur during REM or NREM sleep. SB is a parafunctional activity during sleep that is characterized by clenching (tonic activity) and/or the repetition of phases of muscle activity (phasic activity) that produce grinding of the teeth. Most SB episodes (60–80%) occur in light non-REM sleep [2].

Autonomic physiology in PD is of particular interest, since it underlies several non-motor symptoms, including orthostatic dizziness, constipation, urinary problems, erectile dysfunction, drooling, sweating and swallowing problems [3]. Of these hyperhidrosis and urinary problems can disturb the sleep of PD patients. It is important to make the distinction between nocturnal enuresis (a parasomnia, i.e. urinary incontinence while asleep), and nocturia, i.e. frequent urgency to urinate during night, which can also lead to bedwetting especially when combined with rigidity and slow movements.

According to the ICSD-3 the diagnosis of a typical parasomnia can be based on history and clinical examination. A polysomnography is not necessary, but in case of doubt it is recommended [4]. The diagnosis of

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RBD can be based on history but the definitive diagnosis of RBD requires polysomnographic (PSG) documentation as one of the essential diagnostic criterion is REM sleep without muscle atonia (RWA). Therefore the diagnosis is usually based on questionnaires and interviews. Several RBD screening instruments have been developed to facilitate the identification of clinical RBD, e.g. RBDSQ [5]. In addition to the Marburg questionnaire at least three other questionnaires exist: RBDSQ-J [6], RBDQ-HK [7] and MSQ [8]. Nomura et al. used RBDSQ (Marburg) in patients with PD [9].

For the majority of PD patients, sleep is disrupted. On the other hand, factors that fragment sleep, e.g. PD, can facilitate or precipitate parasomnias in predisposed individuals [4]. Previous studies of the occurrence of parasomnias in patients with PD are scarce [10,11]. Our aim is to evaluate in a Parkinsonian population the occurrence of different parasomnias and isolated symptoms, as defined in the ICSD-3.

## 2. Subjects and methods

Total 5373 subjects with a diagnosis of PD were included in the registry of the Finnish Parkinson Association. Altogether 1500 patients with Parkinson's disease were randomly selected from the registry. We computed random numbers, based on the registration number in the registry. This allowed us to have a representative sample of all subjects in the registry. After an initial selection we found that forty-nine subjects were either deceased or hospitalized (unable to answer), two were relatives of Parkinson's patients, one had dystonia without Parkinson's disease and one was a healthy person. These persons were excluded and the remaining number of eligible patients was 1447. A new questionnaire was sent to those participants who did not respond within three months. The patients were defined as having Parkinson's disease, a) if their diagnosis had been confirmed by a neurologist and b) they used a typical antiparkinsonian medication. Due to the nature of a questionnaire study, most likely subjects with a cognitive dysfunction, e.g. patients with Lewy body disease, were among non-responders.

The structured questionnaire with 207 items included questions derived from the Basic Nordic Sleep Questionnaire (BSNQ) [12,13]. The basic five alternatives for the responses were: 1) "never or less than once per month", 2) "less than once per week", 3) "on 1–2 days per week", 4) "on 3–5 days per week" and 5) "daily or almost daily". The diagnosis of the restless legs syndrome (RLS) is based in Finland on the four main criteria of the International RLS Study group and on the NIH criteria. In our study we asked if the diagnosis had been diagnosed by a physician. The presence of obstructive sleep apnea (OSA) was asked separately according to the validated BNSQ with a question: "Have you had breathing pauses (sleep apnea) at sleep (have other people noticed that you have pauses in respiration when you sleep)?" We asked separately for fatigue and daytime sleepiness. In this study, daytime fatigue was asked as "Do you feel fatigued during daytime?" Excessive sleepiness was evaluated by the Epworth Sleepiness Scale (ESS) [14]. In our experience, mentally fatigued people (often depressive) usually do not have high scores in the ESS as opposed to sleepy patients with, say, sleep apnea or narcolepsy. Intense dreaming was defined as recalling dreams nightly. RBDSQ as a screening tool for secondary RBD among PD patients has been validated [9].

The DSM-IV criteria were used to define chronic insomnia (primary insomnia). Persons were defined as insomniac if:

A. they answered positively to the question: "Have you suffered from insomnia at least for one month", and B. positively to at least one of the following three symptoms:

- "Have you slept 6 h or less per night at least 16 nights per month?"
- "Have you waked up too early without being able to sleep again at least three mornings per week"
- "Have you suffered unrefreshing (non restorative) sleep at least for one month?" and C. positively to "Is your sleep disturbance affecting negatively your social life, working life or leisure time?"

About different other parasomnias and isolated symptoms the questionnaire included 11 items including: nightmares, night terrors, SW, enuresis, hallucinations, ST, SB and nocturnal sweating. Hallucinations were separated in four different questions: 1) hallucinations during evening when awake, 2) hallucinations at the moment of falling asleep, 3) hallucinations at the moment of awakening and 4) hallucinations during night. The time period was the last year. In these questions a sixth response alternative was given by separating 0) "never" from 1) "less than once per month". In this study, other parasomnias and isolated symptoms were asked separately as "How often during last year you have had this disturbance?"

The health-related quality of life was evaluated using the Euroqol (EQ-5D) questionnaire and visual-analog scale (VAS) [15]. The quality of life is considered poor if the value is less than 60 [16]. Depression was evaluated using an easy screening method for general practice, i.e. Rimon's Brief Depression Scale (score 0–21). The limit for depression is 10 [17].

All statistical analyses were conducted using Stata 12.0 (Copyright 1985–2011 StataCorp LP). Quantitative values were expressed as medians, means, standard deviations and ranges. The normality of the distributions was tested with the Shapiro–Wilk normality test. For continuous variables parametric (Student's *t*-test) or nonparametric methods (Mann–Whitney *U*-test) were used depending of the distribution. Categorized values were expressed in numbers and percentages and analyzed by the Pearson's chi-square test and Fisher's exact test. Values of  $P < 0.05$  were considered statistically significant. Logistic regression analysis was used to compute odds ratios (OR) and their 95% confidence intervals (CI). Examples of predicted probabilities were computed with the *prvalue* command of the STATA. With the *prvalue* the predicted probability of having RBD can be computed, when the other characteristics of the defined model are known. The ethical permission was obtained from the local ethical committee and the study was conducted according to the declaration of Helsinki.

## 3. Results

The response rate was 59% ( $N = 854$ ), and of these 77% returned fully answered questionnaire ( $N = 661$ ). In this cohort, the mean age of the responders was 68.8 years (SD 8.5; median 69 years; range [43 to 89]), and 53.0% of them were male. The median duration of Parkinson's disease was 5 years (mean 6.1 y, SD 4.9). Quality of life measured using EQ VAS was poor ( $< 60$ ) in 43.6 % of patients. Answers indicating depression (Depression scale  $\geq 10$ ) were found in 20.9% of the subjects, and fatigue in 43.3%.

Occurrence of previously diagnosed restless legs syndrome (RLS) was 5.6%, obstructive sleep apnea (OSA) was 13.6%, chronic insomnia was 32.5%, excessive daytime sleepiness (ESS  $> 10$ ) was 30.6%, intense dreaming was 14.5%, and RBD according to the questionnaire study was 39.0% (258/661 PD patients).

REM sleep parasomnia (weekly nightmares), NREM sleep parasomnias (at least weekly occurring night terrors and sleep walking), other parasomnias (at least weekly enuresis and hallucinations), and isolated sleep symptoms (at least weekly nocturnal sweating, bruxism, and sleep talking) were all, i.e. as each and every one and as a group, significantly related to RBD. RBD without coexisting other parasomnias or isolated sleep symptoms was rare (35/661 PD patients; 5.3%). In other words 86.4% (223/258) of the PD patients with RBD had at least one other parasomnia or some isolated sleep symptoms as mentioned above. Their occurrences as such and as a whole group, and with and without RBD, are shown in Table 1. Association of RBD with sleepwalking (parasomnia overlap disorder) was found in 1.7% (95% CI 0.7% to 2.6%) of all participants. Sleepwalking at least once weekly was reported by only one (0.2%) PD patient without RBD while it was reported by 11 (4.3%) of the 258 patients with RBD ( $P < 0.001$ ).

Although 45/114 (39.5%) of the PD patients with weekly nightmares had also hallucinations, 69/114 (60.5%) were not hallucinating. On the

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