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Original Article

Parkinson's disease and narcolepsy-like symptoms

Ari Ylikoski [a,b,*], Kirsti Martikainen [c], Tomi Sarkanen [a,d], Markku Partinen [a,e]

[a] Vitalmed Research Center, Helsinki Sleep Clinic, Helsinki, Finland
[b] Hospital of Laakso, Department of Neurology, Helsinki, Finland
[c] The Finnish Parkinson Association, The Finnish Parkinson Foundation, Turku, Finland
[d] Central Finland Central Hospital, Department of Neurology, Jyväskylä, Finland
[e] Institute of Clinical Medicine, Department of Clinical Neurosciences, University of Helsinki, Helsinki, Finland

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ABSTRACT

Objective: Various sleep-related problems, for example, insomnia and symptoms of rapid eye movement behavior disorder (RBD), are common in patients with Parkinson's disease (PD). We studied the prevalence of symptoms of narcolepsy (NARC), hallucinations, and RBD and their association with other symptoms.
Methods: Altogether, 1447 randomly selected patients with PD, aged 43–89 years, participated in a questionnaire study. A structured questionnaire with 207 items was based on the Basic Nordic Sleep Questionnaire. Questions on demographics, PD, RBD, and other issues were included.
Results: The response rate was 59.0%; of these patients, 73% had answered to all questions that were used in the analyses ($N = 623$). The occurrence of suspected narcolepsy (Ullanlinna Narcolepsy Scale ≥ 14 and Epworth Sleepiness Scale ≥ 11) was observed in 9.3% of the subjects (PD with NARC), RBD (REM Sleep Behavior Disorder Screening Questionnaire ≥ 6) in 39.2% of all patients with PD, and in 62.1% of those with PD and NARC. In patients with PD, hallucinations before going to bed in the evening occurred in 5.8%, hypnagogic hallucinations in 4.0%, hallucinations during night 8.3%, and hypnopompic hallucinations in 3.2%. Cataplexy symptoms occurred in 43.1% of subjects with PD and NARC. In a logistic regression analysis, PD with NARC was associated with RBD, all types of hallucinations, daytime sleepiness, fatigue, insomnia, and intense dreaming also when adjusted for age, sex, disease duration, and levodopa.
Conclusions: Narcolepsy-like symptoms may be present in patients with PD. Symptoms of RBD were associated with symptoms of narcolepsy including symptoms of cataplexy.

1. Introduction

Despite being different clinical entities, narcolepsy and Parkinson's disease (PD) share many symptoms. Patients with narcolepsy present with symptoms of unstable sleep–wake regulation (daytime sleep attacks and nightly multiple awakenings), rapid eye movement (REM) sleep dysregulation, cataplexy (loss of muscle tone during wakefulness), sleep paralysis, and hypnagogic hallucinations [1,2]. Hypocretin deficiency seems to be responsible for the symptoms of narcolepsy with cataplexy. The pathogenesis is less clear in narcolepsy without cataplexy, where only 10–31% of patients have low cerebrospinal fluid (CSF) levels of hypocretin-1 (Hcrt) [2–4]. REM behavior disorder (RBD) is common in narcolepsy with cataplexy but rarer in narcolepsy without cataplexy [5].

Among nonmotor manifestations of PD, sleep problems, sleep-related phenomena, and sleepiness are found to be common. Intrusions of REM sleep into the daytime (or sleep onsets in REM periods) have been observed in 14–15% of unselected PD patients [6,7], in 27–40% of PD patients with sleepiness [8,9], and in 60% of PD patients with hallucinations [10].

After the diagnosis of PD, sudden onset of sleep occurred in 12% while sitting and reading and in 3.8% while driving [11]. The RBD and hallucinations occurred in 22.1% and 4.3% of 70 PD subjects [12]. Cataplexy-like symptoms have not been reported to occur in PD. It is not known whether narcolepsy-like symptoms in PD patients are associated with RBD.

In PD subjects, there is an increasing loss of hypocretin cells from 23% (stage I) to 62% (stage V) as measured by the Hoehn and Yahr rating scale [13,14]. Therefore, the early loss of Hcrt cells may explain the frequent daytime sleep attacks in PD patients.

The aim of this study was to assess, by means of a structured questionnaire approach, the occurrence between daytime sleep attacks, cataplexy, RBD, and hallucinations in a nonselected population of patients with PD.

* Corresponding author. Vitalmed Research Center, Helsinki Sleep Clinic, Sitratori 3, 00420 Helsinki, Finland. Tel.: +358 44 5330566.
E-mail address: ari.ylikoski@fimnet.fi (A. Ylikoski).

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2. Subjects and methods

Altogether, 1500 patients with PD were randomly selected from the registry of the Finnish Parkinson Association including 5373 PD patients from a total of 10,000–12,000 Finnish PD patients. We computed random numbers, based on the registration number in the registry. This allowed us to obtain a representative sample of all subjects in the registry. After an initial selection, we found that 49 subjects were either deceased or hospitalized (unable to answer), two were relatives of patients with PD, one had dystonia without PD, 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 PD based on the following conditions: (a) if their diagnosis had been confirmed by a neurologist and (b) if they had used a typical antiparkinsonian medication including levodopa alone or in combination with other dopaminergic medications. Due to the nature of the questionnaire study, most likely subjects with a cognitive dysfunction, for example, patients with Lewy body disease, were among the nonrespondents.

The structured questionnaire with 207 items included questions derived from the Basic Nordic Sleep Questionnaire (BNSQ) [15]. The basic five alternatives for the responses were as follows: (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." In the questions concerning hallucinations, a sixth response alternative was given by separating (0) "never" from (1) "less than once per month." Hallucinations were separated into four different questions: (1) hallucinations during evening when awake, (2) hallucinations at the moment of falling asleep, (3) hallucinations during night, and (4) hallucinations at the moment of awakening. The time period was the last year.

Sleepiness and overall narcolepsy symptom severity were ascertained with two well-known validated instruments, the Epworth Sleepiness Scale (ESS) [16] and the Ullanlinna Narcolepsy Scale (UNS) [17]. In both cases, higher scores indicated greater sleepiness and worse narcolepsy symptom severity. In ESS, a cutoff point of 11 out of 24 points is commonly used as an indication of excessive daytime sleepiness. An 11-item UNS score varies between 0 and 44 points. UNS includes separate questions about the frequency of daytime sleep attacks and cataplexies. The four cataplexy questions concern the frequency of muscle weakness (weak knees/buckling of the knees, sagging of the jaw, nodding of the head, or collapsing to the ground) during emotions such as laughing, happiness, suspense, or anger. A UNS score ≥14 indicates narcolepsy [17]. As the primary and most prominent sleep symptom in narcolepsy is excessive daytime sleepiness, in this study, a subject was considered as having suspected narcolepsy if UNS ≥14 and ESS ≥11 simultaneously. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) [18] is a patient self-rating instrument with 10 questions (yes/no) assessing various aspects of sleep behavior. RBDSQ as a screening tool for secondary RBD among PD patients has been validated (the cutoff value is 6 points, with a sensitivity of 0.842 and a specificity of 0.962) [19].

The validated BNSQ included a separate question on the presence of obstructive sleep apnea (OSA): "Have you had breathing pauses (sleep apnea) at sleep (have other people noticed that you have pauses in respiration when you sleep)?" Daytime fatigue was asked as "Do you feel fatigued during daytime?" Intense dreaming was defined as seeing dreams every night. Restless legs syndrome (RLS) was defined using international definition criteria [20].

The International Classification of Diseases (ICD)-10 criteria of insomnia are as follows:

A. Difficulties falling asleep, maintaining sleep, or non-refreshing sleep
B. Symptoms occur on at least three nights per week and for longer than 1 month
C. The sleep problems cause marked personal distress or interference with personal functioning in daily living.

In our study, persons were defined as having insomnia if:

A. they had at least one of the following symptoms:
   a. difficulties falling asleep on at least three nights per week
   b. waking up too early at night without being able to sleep again on at least three nights per week
   c. waking up at least three times per night on at least three nights per week
   d. unrefreshing (non-restorative) sleep during at least 1 month
B. they had suffered from insomnia at least for 1 month, and
C. the sleep disturbance affected their social life, working life, or leisure time negatively.

Sleep maintenance insomnia (SMI; criterium A.c. of the ICD-10) was evaluated with two questions as "How often weekly have you awakened at night during the past three months?" and " If you use to wake up during night, how many times do you usually wake up during one night?": (1) "usually I don't wake up at night," (2) "once," (3) "2 times," (4) "3–4 times," or (5) "at least 5 times." The sum of the questions was named as the Sleep Maintenance Insomnia Index (SMII) with a score from 2 to 10. SMI occurred when the index was at least 8. Anosmia was defined as a subjective inability to perceive odor. Constipation was defined as infrequent bowel movements (≤3 times per week).

All statistical analyses were conducted using Stata 12.0 (Copyright 1985–2011 StataCorp LP). Quantitative values were expressed as medians, means, standard deviations (SDs), 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 on the distribution. Categorized values were expressed in numbers and percentages, and they were analyzed by Pearson's chi-squared test and Fisher's exact test. Values of $P < 0.05$ were considered statistically significant. Logistic regression analysis was used to compute the odds ratios (ORs) and their 95% confidence intervals (CI). As narcolepsy is a rare event, CIs were computed using Poisson distribution. 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% ($N = 854$); of these patients, 73% returned fully answered questionnaires ($N = 623$). In this cohort, the mean age of the respondents was 67.7 years (SD 8.6; median 67 years; range 41–89), and 56.3% of them were male. The mean duration of PD was 5.9 years (SD 4.9; median 5). The akinetic–rigid subtype of PD was found in 39.4% of the participants. Table 1 shows the demographics and medication details of the subjects with PD (PD without NARC) and PD and suspected narcolepsy (PD with NARC). Both groups had similar ages, genders, educations, body mass index (BMI), and manners of living. The PD with NARC group tended to exhibit a higher usage of levodopa.

The occurrence of narcolepsy-like symptoms (UNS ≥14) was 11.0% (95% CI 8.6–13.5), weekly daytime sleep attacks 13.8%, and cataplexy symptoms 22.2% (monthly 2.9%). Answers indicating RBD (RBDSQ ≥6) were found in 39.2% of the subjects, hallucinations before going to bed in the evening in 6.1%, hypnagogic hallucinations in 4.0%, hypnopompic hallucinations in 3.4% (combined hypnagogic