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Original Article

Age, drugs, or disease: What alters the macrostructure of sleep in Parkinson's disease?

Friederike Sixel-Döring *,[1], Ellen Trautmann [1], Brit Mollenhauer, Claudia Trenkwalder

Paracelsus-Elena-Klinik, Kassel, Germany

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ABSTRACT

Objective: To describe the alterations in the macrostructure of sleep in a large cohort of sleep-disturbed patients with Parkinson's disease (PD) and investigate influencing factors.
Methods: A cohort of sleep-disturbed but otherwise unselected PD patients ($n = 351$) was investigated with video-supported polysomnography. We analyzed the influence of age, disease duration, disease severity, and dopaminergic medication on subjective sleep perception, sleep efficiency, the amount of slow wave sleep, awakenings, periodic leg movements in sleep (PLMS), and REM sleep behavior disorder (RBD).
Results: Sleep efficiency and slow wave sleep decreased with age ($p = 0.003$ and $p = 0.041$, respectively). The number of awakenings and the frequency of RBD increased with age ($p = 0.028$ and $p = 0.006$, respectively). Higher Hoehn & Yahr stages were associated with more PLMS ($p = 0.017$). A higher daily dose of levodopa corresponded to more RBD ($p < 0.001$). Neither disease duration nor levodopa dosage had any influence on sleep efficiency, slow wave sleep, awakenings, or PLMS. Dopamine agonists increased awakenings ($p < 0.001$) and lowered PLMS ($p < 0.001$). Subjective sleep perception was not influenced by any of the factors analyzed. The only path model that could be replicated identified disease severity and dopamine agonists as interdependent factors influencing awakenings and PLMS.
Conclusion: Age leads to less sleep and a higher risk for RBD, and disease severity increases motor phenomena such as PLMS; dopamine agonists reduce PLMS but increase awakenings. No single factor analyzed influenced subjective sleep perception in this cohort of sleep disturbed PD patients.

1. Introduction

Sleep complaints are reported by 60 to > 90% of patients with Parkinson's disease (PD) [1–3]. While nocturia and recurrence of PD motor symptoms such as akinesia, tremor, and nocturnal cramps may be alleviated by tailoring dopaminergic therapy, sleep disruption and the feeling of nonrestorative sleep may still persist and impact daytime performance as well as quality of life [4]. Our current understanding is that the underlying disease process with primary degeneration of sleep-regulating centers [5], the complex effects of dopamine deficiency, the involvement of other non-dopaminergic transmitter systems, as well as effects of medication, all contribute to the etiology of sleep disorders in PD patients [6,7]. Polysomnographic studies have revealed an altered macrostructure of sleep with reduced sleep efficiency and an increased number of arousals in PD patients compared to healthy controls [8–10]. Further alterations include the loss of cyclic sleep structure, the reduction of slow wave sleep, sleep fragmentation, periodic limb movements in sleep (PLMS), and REM sleep behavior disorder (RBD), all of which are understood as polysomnographic hallmarks of sleep in neurodegenerative disease presenting with Parkinsonism [10–13]. The loss of physiological sleep architecture appears to be correlated to the duration of the disease [12]. The role of dopamine replacement therapy on sleep is controversial: whereas early studies reported increased awakenings in medically treated versus untreated PD patients [14] and a dose-dependent detrimental effect of levodopa and dopamine agonists on REM sleep [15,16], more recently published PSG-based data shows no influence of any dopaminergic medication or sedatives on the degree of sleep destruction in PD patients [17] and no impact of levodopa/carbidopa CR on the altered sleep structure of PD patients [18].

With this study we attempted to characterize the macrostructure of sleep in a cohort of sleep-disturbed but otherwise unselected PD patients and explore the influence of age, disease duration, disease severity, and dopaminergic medication.

* Corresponding author. Address: Paracelsus-Elena-Klinik, Center of Parkinsonism and Movement Disorders, Klinikstr. 16, 34128 Kassel, Germany. Tel.: +49 0561 60090; fax: +49 0561 6009126.
E-mail address: friederike.sixel@pk-mx.de (F. Sixel-Döring).
[1] These authors contributed equally to this work.

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2. Methods

Using video-supported polysomnography (vPSG) we analyzed sleep macrostructure in sleep-disturbed and treated, but otherwise unselected, PD patients with and without RBD. The influence of clinical and demographic data concerning age, gender, disease duration, disease severity, and medication on subjective sleep perception, sleep efficiency, the amount of slow wave sleep, awakenings, and PLMS were investigated. Disease severity was defined by Hoehn and Yahr stage. The results presented here are part of a sleep database integrated into our hospital system for in-patients. This study reports details of polysomnography on patients from the same cohort of a previously published study [19] (for further details see reference).

2.1. Patients

2.1.1. Inclusion criteria

Diagnosis of PD had to be established in all patients according to UK brain bank criteria. All patients complained about nocturnal sleep disturbances or excessive daytime sleepiness. vPSG was performed as part of a clinical work-up to correctly diagnose and treat these clinically relevant nocturnal disturbances reported by the patients themselves or by a bed partner/caregiver, and after an observational period of at least three days/nights as in-patients, if the nocturnal disturbance could not be clarified clinically. None of the patients were investigated on the first night of their stay. In some cases, severe daytime vigilance problems were the reason for performing vPSG.

2.1.2. Exclusion criteria

Patients with acute psychosis or severe dementia (Mini-Mental State Examination MMSE values <10), patients not able to cooperate in the sleep laboratory, and patients who did not sign a consent form for the sleep laboratory investigation were excluded from vPSG.

2.1.3. Consent

All patients consented to scientific evaluation of their clinical data. Additional consent forms were signed agreeing with the use of nighttime videos for scientific and medical educational purposes. The Ethical Committee of the Landesärztekammer Hessen approved the project.

2.2. Polysomnography

All patients were studied in the sleep laboratory of the Paracelsus-Elena-Klinik for at least one night. Some patients required a second night for clinical reasons. This second night was not used for this analysis because first night effects are less relevant in PD patients compared to insomnia patients [12] (for details see [19]). Nighttime sleep recordings started immediately after connecting the patient and calibration with lights off at 22:00 and ended at 6:00 the next morning. All patients were on their habitual nighttime medication and daytime medication had been kept constant for at least two days prior to PSG. Cardiorespiratory polysomnography (Xltec: Excel Tech Ltd; Oakville, Ontario, Canada) was applied, including bilateral monopolar central electroencephalography (EEG) with two channels, electrooculogram (EOG), chin and bilateral tibialis anterior surface electromyography (EMG), airflow registration, tracheal sound registration by microphone, thoracic and abdominal belts to measure respiratory movements, electrocardiogram, and oximetry. All patients were documented with an infrared video recording synchronized to the PSG. A sleep lab technician monitored each recording. Sleep (including sleep stages), periodic limb movements, and apneas were scored visually by a trained technician according to standard criteria. All sleep evaluations were reviewed and supervised by board-certified sleep specialists (FSD & CT). Sleep efficiency was defined as total sleep time (TST)/time in bed (TIB). Quantitative analysis of sleep stages was calculated as a percentage of TST. Awakenings (defined by AASM criteria as appearance of occipital alpha (8–13 Hz) rhythm or higher frequencies for >50% of an epoch) but not arousals (defined by AASM criteria as an abrupt increase in frequency lasting for a minimum of three seconds after a minimum of 10 s of sleep) were counted as the most robust measure for sleep fragmentation. RBD was diagnosed by second per second review in time-synchronized video analysis of all REM episodes by experienced raters (FSD & CT) and in accordance with EEG, EOG, and chin EMG. RBD was defined as the presence of REM sleep without atonia (RWA) together with complex movements and/or vocalizations during REM sleep apparently associated with dreaming or dream-enacting behaviors visible in time-synchronized video PSG as described previously [19].

2.3. Clinical data

The following information was obtained from all patients: gender and age at the time of vPSG, disease duration and Hoehn & Yahr stage rated under medication upon hospital admission, the daily dose of levodopa and dopamine agonists calculated as a levodopa equivalent according to German guidelines [20], and the use of benzodiazepines, opioids, selective serotonin re-uptake inhibitors (SSRI), atypical neuroleptics (clozapine, quetiapine), and amantadine.

2.4. Subjective sleep perception

Subjective sleep quality was assessed with the Parkinson's disease sleep scale (PDSS) [21]. Until 2008, the original 2002 version of the scale was used – a visual analogue scale in which a maximum score of 10 for each of the 15 items indicated an absence of symptoms. From 2008 onwards the revised PDSS (PDSS-2), a 5-point rating scale, was administered [22]. Here, severity for each of the 15 items is assessed on a scale ranging from 0 to 4, "0" signifying absence of symptoms and "4" signifying constant presence of symptoms, with a maximum sum score of 60 implying subjectively severely impaired sleep.

2.5. Statistical analysis

The first step consisted of characterizing the study population by descriptive analysis. Linear regressions and binary logistic regressions for dichotomous variables were performed using SPSS 17.0. In the second step, path analyses were performed using AMOS 18.0 (lit.). Hypothesized and improved path models were additionally tested with the chi-square statistic: in case of significance the model displayed no good acceptance. The first set of analyses focused on testing the hypothesized path models and revised models. For additional model evaluation the comparative fit index (CFI) and the root mean square error of approximation (RMSEA) were calculated. A CFI >0.95 usually indicates a good fit; RMSEA values around 0.05 are considered a good fit and models with values >0.10 are not accepted. The final models were retested on two separate random samples from the entire sample. Multigroup analyses of the final model were then performed to investigate the influence of benzodiazepines, selective serotonin reuptake inhibitors (SSRI), and atypical neuroleptics.

3. Results

Over a period of 3 years a total of 356 patients were investigated. Complete datasets from 351 PD patients were available for