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Original Article

Clinical manifestations of Parkinson disease and the onset of rapid eye movement sleep behavior disorder

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ABSTRACT

Objective: To identify whether the presence and/or timing of rapid eye movement (REM) sleep behavior disorder (RBD) onset were associated with differences in clinical features and sleep parameters of Parkinson disease (PD).

Methods: In all, 112 PD patients were enrolled and all underwent extensive clinical evaluations and video-polysomnography (PSG). Clinical features and PSG parameters were compared in PD patients with (PD + RBD) or without (PD − RBD) RBD, RBD preceding (RBD > PD), or not (PD ⩾ RBD) PD onset.

Results: Sixty-three of the 112 PD patients were affected by RBD. Adjusted for age, gender, education, body mass index (BMI), levodopa equivalent daily dose (LED) and PD duration, PD + RBD patients had higher Hoehn & Yahr stage, higher scores for UPDRS parts I, II and III, more dyskinesia, higher ratio of axial/limb manifestations, and more hallucinations. Their cognitive and quality-of-life status was significantly lower (all $P < 0.05$). For PSG, PD + RBD patients exhibited higher percentages of phasic and tonic EMG activities, lower apnea hypopnea (AHI) and oxygen desaturation index (ODI), and less time in arterial oxygen saturation (SaO_2) <90% during REM sleep (all $P < 0.05$). PD ⩾ RBD ($n = 22$) patients did not significantly differ from RBD > PD ($n = 41$) patients in clinical manifestations, whereas the PD ⩾ RBD subgroup had significantly higher UPDRS part I score, lower PDQ score and lower AHI during REM than the PD − RBD group (all $P < 0.05$), but not RBD > PD subgroup. Correlation analysis showed that worse cognition was associated with shorter interval of RBD preceding PD onset ($r = 0.297$, $P = 0.018$), but not RBD duration ($P = 0.202$).

Conclusions: Clinical manifestations of PD may vary depending on the presence and timing of RBD onset. These findings are compatible with the hypothesis that RBD may be a marker of complex subtypes of PD.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by a loss of normal muscle tone during REM sleep and motor activity associated with dream content [1]. Brainstem lesions have been mainly associated with REM sleep without atonia (RWA), whereas action-filled and violent dreams are based on cortical dysfunction [2,3]. RBD constitutes an increased risk of developing neurodegenerative diseases, such as multiple system atrophy (MSA), Parkinson disease (PD), and dementia with Lewy bodies (DLB) [4].

RBD is one of most widespread non-motor symptoms of PD, but not all PD patients exhibit RBD. Moreover, RBD not only precedes or coincides with the motor symptoms of PD, but may occur during the progression of PD. According to Braak et al.'s staging system for PD [5], clinical expression with presymptomatic stages were characterized by Lewy body inclusions confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. These nuclei are often affected in PD prior to the involvement of the substantia nigra. This would explain why RBD precedes motor parkinsonism in PD patients. However, it does not explain why a certain proportion of PD patients does not develop RBD and why RBD may precede or develop with or after PD onset. Many studies have been performed to explore the potential

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relationships between PD and RBD [6–10]. Most previous studies found that RBD was associated with longer PD duration and higher doses of dopaminergic therapy [7,10,11]. However, disease duration and medication may impact on sleep parameters and/or other clinical manifestations of PD [12]. On the other hand, the timing of RBD onset may play a role in the specificity of RBD to degenerative process of PD [13]. Nonetheless, data on the potential relationships between PD patients with RBD preceding and developing with or after PD onset are rare [11,13].

We hypothesized that RBD may be a marker of complex subtypes of PD and that PD might constitute distinct clinical and pathological subtypes related to the presence and/or timing of RBD onset. To test our hypothesis, by controlling age, gender, education, body mass index (BMI), levodopa equivalent daily dose (LED) and PD duration, we performed extensive clinical evaluations and video-polysomnography (PSG) to compare clinical features and PSG parameters in PD patients with (PD + RBD), without RBD (PD − RBD), RBD preceding (RBD > PD), or developing with or after (PD ⩾ RBD) the onset of PD.

2. Methods

2.1. Subjects

PD patients were recruited from the Center of Parkinsonism and Movement Disorders in our hospital from September 2010 to February 2013.

2.1.1. Inclusion criteria

The diagnosis of PD was established according to the UK Parkinson's Disease Society Brain Bank clinical diagnosis criteria [14].

2.1.2. Exclusion criteria

Patients with psychiatric disease or severe dementia were excluded, according to the Diagnostic and statistical manual (DSM-IV). The primary reason was that these patients were unable to co-operate with PSG or clinical tests. Patients who had taken selective serotonin reuptake inhibitor (SSRI) and/or selective noradrenaline reuptake inhibitor (SNRI) were excluded. Patients who were unable to give detailed information on the occurrence of RBD or PD motor symptoms were also excluded.

2.1.3. Patient consent and standard protocol approvals

All patients provided written informed consent to participate in this study and signed additional consent forms to agree with the use of their night-time video for scientific purposes. This study was approved by our hospital's ethical committee.

2.2. Polysomnography

All participants completed an overnight video-PSG study (Compumedics-E series, Australia). The basic recordings included standard electroencephalogram (EEG; F3–A2, F4–A1, C3–A2, C4–A1, O1–A2, O2–A1), electro-oculogram (EOG; LE–A2, RE–A1), chin electromyogram (EMG), bilateral leg EMG (anterior tibialis muscles), electrocardiogram (ECG), nasal–oral pressure transducer airflow, thermal oro-nasal airflow, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, snoring sound, and body position. Awakenings, sleep stages, periodic leg movements during sleep (PLMS), and respiratory-related parameters including apnea hypopnea index (AHI), oxygen desaturation index (ODI), and percentage of time spent at oxygen saturation (SaO_2) <90% (time – [SaO_2 < 90%]), were visually scored by experienced PSG technologists and clinicians, according to American Academy of Sleep Medicine guidelines [15]. On the basis of video-PSG and clinical evaluations, a diagnosis of RBD was made according to the criteria of the International classification of sleep disorders, 2nd edition (ICSD-2) [15]. According to a previously published method, the REM sleep without atonia (RSWA) PSG criteria were either >30% of REM sleep with tonic chin EMG activity (tonic density), or >15% of REM sleep with phasic chin EMG density activity (phasic density) [16].

2.3. Clinical evaluations

Evaluations were performed at the Center of Parkinsonism and Movement Disorders. A specialist in movement disorders and sleep disease carried out a complete evaluation of each patient's disease while blinded to the PSG evaluation. Evaluations were carried out in the medication 'on' state. All participants underwent the following assessments and interviews at the time of PSG.

2.3.1. Demographics and detailed clinical history

The following information was obtained from all patients: gender, age, education, BMI, PD and RBD duration, and LED [17] at the time of PSG. Particular attention was paid to the clinical history regarding the timing of RBD and PD motor symptoms onset. Because of the relative difficulty in reconstructing the precise dates for the onset of each disease, we evaluated whether RBD clearly preceded (at least one year) the occurrence of the earliest PD symptoms to define RBD onset preceding (RBD > PD), or not (PD ⩾ PD), the onset of PD. The RBD questionnaire – Hong Kong (RBDQ-HK) [18] was used to assess RBD symptom severity for PD patients with RBD. This information was collected during clinical interviews with patients, their family, and their bed partners.

2.3.2. Motor manifestations

According to Unified PD Rating Scale (UPDRS)-based criteria developed by Schiess et al. [19], patients were divided into tremor-dominant, akinetic, and mixed subtypes. Hoehn & Yahr (H–Y) stage and all parts of UPDRS were measured. The presence of dyskinesia was assessed according to questions 32–35 of UPDRS IV. Additionally, according to location, UPDRS III was subdivided into axial (items 18, 19, 22, 27, 30) and limb (items 20–26). The ratio between the summed axial and limb scores was then calculated. The presence of falls and freezing was evaluated, according to score ⩾1 for questions 6 and 7 on UPDRS II [20].

2.3.3. Non-motor manifestations and quality of life: non-motor symptom questions (NMSQ)

These approaches were initially used to investigate the occurrence of non-motor symptoms, including olfactory dysfunction, constipation, and hallucinations. Cognition function, hypersomnia, autonomic dysfunction, and quality of life were respectively assessed with the Montreal Cognitive Assessment (MOCA, Beijing Version), Epworth Sleepiness Scale (ESS), the scale for outcomes in PD for autonomic symptoms (SCOPA-AUT), and the PD Questionnaire (PDQ).

2.4. Statistical analysis

SPSS software version 17.0 (Chicago, IL, USA) was used for the statistical analyses. Descriptive data are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage). All comparisons were performed by means of analysis of covariance (ANCOVA) or Kruskal–Wallis ANOVA, for control gender, age, education, BMI, LED, and PD duration, as appropriate. Pearson's and Spearman's correlations were used to analyze the correlations between clinical manifestations with RBD duration and interval of RBD preceding PD onset. Statistical significance was defined as $P < 0.05$.