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Orthostatic hypotension and cardiac sympathetic denervation in Parkinson disease patients with REM sleep behavioral disorder

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ABSTRACT

Background: Rapid eye movement (REM) sleep behavioral disorder (RBD), orthostatic hypotension (OH), and cardiac sympathetic denervation were commonly observed in PD and are related in both the premotor and motor periods. This study is intended to evaluate if the OH and cardiac sympathetic denervation found in PD are associated with RBD.
Methods: Among 94 non-medicated and mild PD patients, 53 had RBD. Orthostatic vital signs and ambulatory 24-hour blood pressure values were recorded. ^{123}I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy as obtained in all patients. The association between orthostatic hypotension, supine hypertension, nocturnal hypertension, non-dipping, myocardial MIBG uptake, and RBD was analyzed.
Results: RBD was associated with orthostatic hypotension. Patients with RBD had higher systolic blood pressure changes during orthostasis and lower myocardial MIBG uptake than patients without RBD and controls. Patients with OH also had lower mean H/M ratios those in the non-OH group.
Conclusion: This study showed that RBD was closely associated with OH and cardiac sympathetic denervation in patients with early and mild PD. The result also suggests that impaired cardiac sympathetic innervation could be the mechanism behind OH in PD. This association may be closely correlated with Braak alpha-synuclein pathogenetic sequences, which would account for the clinical spectrum of PD.

1. Introduction

Rapid eye movement (REM) sleep behavioral disorder (RBD) is one of the commonest non-motor symptoms in Parkinson's disease (PD), affecting 15–60% of patients [1]. While it is not associated with the severity of motor symptoms, it is related to cognitive dysfunction and precedes dementia in PD [2]. RBD is an independent risk factor for the development of PD and may present several years before motor symptoms appear [2,3].

A variety of cardiovascular autonomic abnormalities have been noted in PD, including orthostatic hypotension (OH), supine hypertension (SH), nocturnal hypertension (NH), and absence of normal nocturnal blood pressure (BP) fall ("non-dipping") [4]. These abnormalities are related to each other. It can occur independently of levodopa treatment and early in the course of disease [5,6]. In addition, these disturbances appear more frequently as the disease progresses, and it can influence subjective symptoms, quality of life, and disease treatment [7].

Metaiodobenzylguanidine (MIBG) is a physiologic analogue of norepinephrine, and iodine-123 (123I) MIBG cardiac scintigraphy is a non-invasive tool used to estimate myocardial sympathetic denervation [8]. Cardiac MIBG uptake was decreased in patients with Lewy body diseases such as PD and dementia with Lewy bodies (DLB). Therefore, it is useful for early differentiation of PD from atypical Parkinsonism and DLB from Alzheimer's disease. MIBG may also be helpful in the early detection of a subject with premotor PD [8,9].

RBD, autonomic dysfunctions, and cardiac sympathetic denervation were commonly observed in PD [1,3,8–10]. PD patients with clinical RBD had reduced MIBG uptake compared to those with normal REM sleep [10]. The hypothesis tested in this study was that the cardiovascular autonomic dysfunctions and cardiac sympathetic denervation found in early PD are associated with RBD. We assessed whether RBD was related to orthostatic hypotension, supine hypertension, nocturnal hypertension, or non-dipping and cardiac sympathetic denervation in Korean patients with early and mild PD.

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2. Methods

2.1. Subjects

The institutional review board of St. Mary's Hospital approved this study's protocol, and each patient provided written informed consent for participation.

Ninety-four patients at the Department of Neurology at Seoul St. Mary's Hospital between March 2013 and December 2014 were diagnosed with PD according to the UK brain bank criteria [11]. None of the patients had ever taken anti-Parkinsonian medication. Twenty-five healthy elderly subjects free from Parkinsonism and RBD were enlisted to serve as controls. Clinical information obtained included age, sex, disease duration, history of arterial hypertension, history of diabetes mellitus (DM), history of cigarette smoking, and current medication use. All patients underwent detailed clinical evaluations, including laboratory tests for lipid profiles and serum homocysteine. Exclusion criteria were patients (1) with neurological abnormalities related to atypical PD or secondary Parkinsonism, (2) with a history of diabetic neuropathy or other peripheral/autonomic neuropathy, (3) with a previous relevant cardiac disease, or any abnormalities on routine chest radiography and electrocardiography, (4) taking medications known to influence autonomic functions and drugs reported to influence cardiac MIBG uptake. All patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the modified Hoehn and Yahr (H&Y) stage. All blood pressure monitoring was performed after discontinuing antihypertensive drugs for more than 7 days. Patients were educated to abstain from drinking alcohol or coffee the day before the study.

2.2. RBD diagnosis

Patients were administered the REM sleep behavior disorder screening questionnaire (RBDSQ), a 10-item questionnaire with scores ranging from 0 to 13 [12]. Bed partners were also asked question 1 of the Mayo questionnaire (MQ1) [13]: "Have you ever seen the patient appear to 'act out his/her dreams' while sleeping? (punched or flailed arms in the air, shouted or screamed)". Both the RBDSQ test scores ≥5 and a response of "yes" on the MQ1 were considered consistent with RBD. Single, isolated episodes were disregarded and only recurrent episodes were taken into consideration. Subjects reporting only a single episode of somniloquy and/or vivid dreams were not included in this group.

2.3. Tilt testing

Continuous electrocardiographic and noninvasive blood pressure monitoring leads were connected in each patient (YM6000, Mediana Tech, Redmond, WA, USA). After 30 min of supine rest, head-up tilt testing (20 min at 60°) was performed using the Manumed Special Tilt1-section (ENRAF NONIUS, Rotterdam, The Netherlands). Blood pressure was measured in the upper limb every 5 min before and 1, 3, 5, 10, 15 and 20 min during tilt, 1 min post-tilt, and as indicated for patient safety. Supine baseline and the lowest tilt values for blood pressure were recorded. For statistical analysis, the lowest values between 3 and 5 min were chosen. Orthostatic hypotension was defined as a fall in BP of at least 20 mm Hg systolic BP and/or 10 mm Hg diastolic BP measured between 2 and 5 min after the tilt [14,15]. Subjects with systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg were considered to have supine hypertension [16–18].

2.4. Ambulatory blood pressure monitoring

Automated 24-hour BP recording instruments (Mobil-O-Graph NG, I.E.M., Stolberg Germany) with an upper arm cuff were used to measure blood pressure and heart rate every 15 min during the day and every 30 min at night. The accuracy of this device was validated previously [19]. The following parameters were evaluated: average systolic and diastolic blood pressure and heart rate for daytime, nighttime and 24-h periods. Daytime and nighttime blood pressure was defined using narrow clock-time intervals (day from 10.00 to 20.00 and night from midnight to 06.00) [20]. Nocturnal falls in blood pressure and heart rate were calculated as percent changes between daytime and nighttime mean values. Subjects with <10% nocturnal fall in mean blood pressure were considered "non-dippers" [21]. Nocturnal hypertension was defined according to the 2007 European Hypertension Society/European Cardiology Society guidelines (i.e., average nighttime BP ≥ 120/70 mm Hg) [22,23].

2.5. MIBG scintigraphy

MIBG scintigraphy was performed and data was collected for 30 min (early) and 2 h (late) after injecting 111 MBq of ^{123}I-MIBG using a dual head camera (Siemens, Munich Germany), and a static image was obtained with a 128 × 128 matrix. Regions of interest were manually drawn around the heart, mediastinum and thyroid. Tracer uptake was measured within each region of interest to calculate the heart to mediastinum (H/M) ratio. Patients were stratified to normal and low MIBG uptake group according to healthy controls; the range of normal H/M ratio was calculated as above mean (2.26280) − 2 × stanstandard deviation (0.23117) of age-matched normal controls (cutoff value = 1.80046).

2.6. Statistical analysis

Statistical analysis was performed with SPSS software version 22.0. Independent sample *t*-tests or one-way ANOVAs (with Bonferroni post-hoc testing) were used to compare groups and Pearson's χ^2 tests were used to compare frequencies for categorical variables. A forward binary logistic regression model was performed to study factors that may contribute to the development of RBD in PD patients. The presence of RBD was considered a dependent variable while age, sex, disease duration, hypertension, diabetes mellitus, nonsmoking, UPDRS score, supine hypertension (or supine SBP), orthostatic hypotension (or ΔSBP during tilt test), nocturnal hypertension (or nighttime SBP), nondipping (percent of dipping), and late H/M ratio were considered covariables. A p-value < 0.05 was considered significant.

3. Results

All blood pressure monitoring was performed after discontinuing antihypertensive drugs for 8.5 ± 1.1 days. During the period, no serious clinical problem was observed. Ambulatory blood pressure was recorded without interruption in all subjects with a mean measurement period of 23.1 ± 1.4 h and the average number of measurements obtained during the recording was 67.7 ± 6.7. Among patients with OH, the mean tilting time of tilt before orthostatic symptoms was 3.6 ± 1.2 min. All patients without OH were tested for 20 min of tilt.

Among the 94 PD patients, 50 were women (53.2%). Mean age (±SD) was 66.8 ± 10.8 years, and mean disease duration was 1.8 ± 1.4 years. Total UPDRS and H&Y stage scores were 27.3 ± 15.2 and 1.7 ± 0.7, respectively. Compared to controls, the proportion of arterial hypertension and orthostatic hypotension in PD patients was higher (Tables 1 and 2).

Fifty-three (56.4%) patients had RBD, based on the both questionnaires. The PD + RBD group and PD–no RBD group were similar in sex, medical history, and severity of PD. The PD + RBD group was older than the PD–no RBD group (Table 1). Patients with PD + RBD had more orthostatic hypotension than the PD–no RBD group and controls (Table 2). The nadir pressure during tilt was lower in the PD + RBD group than in the PD–no RBD group and controls (ΔSBP during tilt, mm Hg; controls vs. no RBD vs. RBD, 3 ± 9 vs. 6 ± 13 vs. 15 ± 13,