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Clinical markers of neurodegeneration in Chinese patients with idiopathic rapid eye movement sleep behavior disorder

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ABSTRACT

Objective: It is reported that neurodegenerative markers of Parkinson's disease occur in patients with idiopathic rapid eye movement sleep behavior disorder (idiopathic RBD); however, it has been unknown in Chinese patients. This study aims to provide a detailed understanding of the clinical features of Chinese patients with idiopathic RBD.
Methods: We conducted a series of Parkinson related motor and non-motor assessments in 181 participants including 41 patients with idiopathic RBD, 35 Parkinson's patients without RBD, 42 Parkinson's patients with RBD, and 63 healthy controls. The RBD questionnaire –Hong Kong (RBDQ-HK) was used to confirm clinical RBD symptoms and evaluate the severity. Motor function including Unified Parkinson's disease Rating Scale (UPDRS), alternative tap test, Purdue Pegboard test and Timed Up and Go test, and non-motor functions including olfaction, cognition, and autonomic function were assessed in each group.
Results: Motor assessments of UPDRS, Purdue Pegboard, and Timed Up and Go, and the systolic blood pressure (BP) drop in patients with idiopathic RBD were intermediate between controls and Parkinson's patients. However, the alternative tap test and some non- motor functions including olfaction and orthostatic symptoms in idiopathic RBD were impaired as seriously as in Parkinson's disease. No difference was found in urinary and bowel function between idiopathic RBD and controls. In idiopathic RBD, functional impairment was associated with age and the severity of RBD symptoms ($p < 0.05$). In addition, systolic BP drops closely correlated to motor function and bowel function ($p < 0.05$).
Conclusions: Chinese patients with idiopathic RBD demonstrated an extensive and heterogeneous functional impairment. The association between functional impairment and age and the severity of RBD symptoms needs to be determined in future studies.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a disease featuring a loss of atonia during the stage of rapid eye movement sleep. RBD is closely connected with Parkinson's disease (PD). Many studies have found that a portion of patients with RBD (idiopathic RBD) eventually progressed to PD after years of follow-up [1–3]. RBD could also be an accompanying symptom of PD. Postuma et al. [4] reported that mild PD-like functional impairment occurred in idiopathic RBD. However, it was unknown whether similar clinical features would occur in Chinese patients with idiopathic RBD. Hence, using comparisons to Parkinson's patients and healthy controls, we conducted a small case-control study to show characteristics of patients with idiopathic RBD in east China.

2. Patient and methods

2.1. Patient

Between October 2012 and February 2014, 181 participants were recruited for this research. Among the subjects, 77 outpatients with PD were from the Movement Disorders Clinics at the Department of Neurology of Xinhua hospital (affiliated with the medical school of Shanghai JiaoTong University, Shanghai, China). All of them conformed to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for the diagnosis of idiopathic PD [5]. Forty-one patients with idiopathic RBD were recruited from different communities in Shanghai and surrounding counties. We confirmed RBD in the group of idiopathic RBD and the PD group by both of the following conditions: (1) a history of problematic and harmful or potentially harmful sleep behaviors to self and/or sleep partner in the past year, which adhere to ICSD-II criteria for the diagnosis of RBD [6]; (2) a score on the RBD questionnaire-HK (RBDQ-HK) above 17 for idiopathic RBD and 18 for Parkinson's

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disease [7]. Sixty-three healthy controls were recruited from different communities in Shanghai and surrounding counties, with matched gender and age. Healthy controls were excluded if they had either of the above two conditions. The exclusion criteria for this study were: (1) dementia (defined as Mini–Mental State Examination(MMSE) <24 with functional impairment); (2) a past history of psychiatric illness and treatment with antidepressants; (3) a past history of other sleep disorders including obstructive sleep apnea syndrome, periodic limb movement during sleep, and narcolepsy; (4) a past history of nasal cavity operation, chronic rhinitis, use of other medicinal remedies, abuse of alcohol and tobacco.

2.2. Methods

Every participant was interviewed by two movement disorder neurologists. One neurologist was responsible for screening RBD and the other was responsible for all motor and non-motor assessments and was blind to the score of the RBDQ-HK. Demographic characteristics were also collected. Parkinson's patients were evaluated one hour after medication. Approval was obtained from the Research Ethics Committee of this hospital and all participants gave their informed consent to participate. Motor and non-motor assessments were completed using the appropriate tools as described in the following section.

The RBD questionnaire-HK (RBDQ-HK) [7] is a self-rating scale composed of 13 questions which uses the ICSD-II and its related clinical manifestations as the basic design. This questionnaire was conducted by the patient and the bedroom partner together. Questions 1–5 and Question 13 were factors related to dreams, and included if there was dreaming, frequency of dreaming, content, if it disturbs sleeping, and so on. Questions 6–12 were factors related to abnormal behaviors during RBD, which included somniloquence, shouting, body movements, falling from the bed, self-injury or injury by other factors. The presence of RBD was defined as achieving a score above 18 on the RBD-HK questionnaire. The overall score on the scale positively correlated to the severity of clinical RBD symptoms.

Assessment of motor function was performed by a movement disorders specialist with a neurological examination which applied the Unified Parkinson Disease Rating Scale part III (UPDRS-III) and three quantitative tests including the alternative tap test, Purdue Pegboard test, and Timed Up and Go (TUG) test. The motor severity was assessed by UPDRS-III. The motor phenotype was classified into tremor dominant type, and postural instability and gait disability (PIGD) dominant and intermediate types according to the Unified Parkinson Disease Rating Scale (UPDRS) tremor score (items 16, 20, 21) and PIGD phenotype (items 13, 14, 15, 29, 30): tremor dominant type (mean tremor score/mean PIGD score $\geq$1.5), PIGD dominant type (mean tremor score/mean PIGD score <1.5) and intermediate motor type [8]. The alternative tap test [9] is a rapid and objective test to assess rigidity and bradykinesia of the upper limbs. Subjects are asked to alternately tap with each index finger on two 1.5 cm diameter keys on two counters placed 20 cm apart. The total number of keys tapped on the two keys within one minute is regarded as the score. The Purdue Pegboard test [10] is another test to measure the dexterity and moving speed of the hand as well as its coordination with the eyes. In the test, the subjects are asked to transfer round metal pegs one at a time with each hand from a dish into fixed holes within a period of time of 30 s. The average number of pegs inserted by both hands is regarded as the score. The Timed Up and Go [11] is a simple test to measure the moving speed and stability of gait by requiring the subject to stand up from a chair and then walk straight for 3 m, and finally come back to the chair and sit down. The whole process is timed and constitutes the score.

Assessment of non-motor functions was performed by appropriate methods. Olfaction was measured by "Sniffin' Stick" method [12,13] which consisted of olfactory threshold (T), odor discrimination (D), and odor identification (I). In the odor threshold test, the subject is presented with 16 triplets of pens, among which there is one pen in a triplet filled with stepwise-diluted *n*-butanol. The subject is asked to correctly identify the pen with a certain concentration of *n*-butanol from the other two odorless pens in a fixed sequence. The process is repeated seven times, and the threshold was the mean of the last four reversals of the staircase. In the odor discrimination test, the subject is presented with 16 triplets of pens in intervals of 30 s and asked to pick out the pen that smelled different from the other two pens in each group. The number of correct discriminations is considered the score. In the odor identification test, the subject is provided with 16 pens filled with different kinds of odors and asked to match the odor of each pen to the odor shown on a given card. The right answers are considered to be the score. Cognition was assessed with the MMSE. Autonomic symptoms were assessed with a structured interview based on the Multiple System Atrophy Rating Scale [14]. The scale consists of four questions that reflect orthostatic symptoms, urinary function, sexual function, and bowel function. Each question is graded from 0 to 4 and the score positively correlates to the severity of autonomic dysfunction. In addition, systolic blood pressure (BP) drop was also calculated by measuring blood pressure in the supine position and after standing for one minute.

Statistic analysis Descriptive statistics were used as required. One-way analysis of variance was used for comparison of age, alternate tap test, Purdue Pegboard test, and olfaction. A post hoc test was evaluated with the Bonferroni test. Kruskal–Wallis test was used for comparison of UPDRS-III, Timed Up and Go test, systolic blood pressure drop, and other non-motor functions (orthostatic symptoms, urinary function, sexual function, bowel function, MMSE). The post hoc test was evaluated with the Nemenyi test. A Spearman correlation was used to analyze the association between idiopathic RBD variables including age, duration of RBD, scores on RBDQ-HK, and measures of motor and non-motor function. The chi-square test was used for comparison of gender ratios between the four groups. Unpaired student *t*-test was used for comparison of variables including age, duration, measures of motor function, and systolic BP drop between male and female patients in idiopathic RBD. The Mann–Whitney *U* test was used for comparison of orthostatic symptoms, urinary function, sexual function, and bowel function between male and female patients in idiopathic RBD. The significance was set at $p < 0.05$, with a two-tailed approach. Statistical computations were performed by SPSS 17.

3. Results

A total of 181 participants were enrolled in this study. There were 41 patients with idiopathic RBD, with a mean age of 67.0 ± 8.9 years old, mean RBD duration of 9.5 ± 7.0 years, and male percentage of 58.5%. There were 63 healthy controls, 42 Parkinson's patients with RBD, and 35 Parkinson's patients without RBD. Age, gender ratio, and MMSE score showed no difference between groups (Table 1). Parkinson's patients mainly presented with PIGD dominant type (48/77, 62.3%). The duration of these PD patients was 4.26 ± 3.77 years and the daily levodopa dose was 309.09 ± 276.66 mg. Although the percentage of patients with PIGD dominant type in PD patients with RBD (28/42, 66.7%) was higher than in PD patients without RBD (20/35, 57.1%), no significant difference was found between the two groups ($p = 0.45$). In addition, no difference was found in the duration or daily levodopa dose between PD patients with or without RBD.

Compared with controls, the patients with idiopathic RBD demonstrated worse results in all measures of motor function (UPDRS-III, alternative tap test, Purdue Pegboard, and Timed Up and