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The correlation between possible RBD and cognitive function in Parkinson's disease patients in China

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Abstract

Objective: Cognitive impairment is an important symptom of Parkinson's disease (PD) and seriously affects patients' quality of life and prognosis. However, its cause is still uncertain. In about one-third of patients, PD is associated with rapid eye movement sleep behavior disorder (RBD), which is an independent risk factor for PD-associated dementia; but whether or not it relates to the cognitive function of patients with nondemented PD is still controversial. **Methods**: The data from 89 enrolled PD patients were retrospectively analyzed. The RBD Questionnaire Hong-Kong (RBD-HK) was used to diagnose possible RBD (pRBD). There are 46 patients with possible RBD (the PD-pRBD) and 43 without (the PD-npRBD). PD disease severity, neuropsychological function, overall cognitive function, and various cognitive functions were assessed. **Results**: There were significant between-group differences in scores on the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), Digit Symbol Test (DST), Trail Making Test-A (TMT-A)-Time, TMT-Trail Making Test-B (TMT-B)-Time, Stroop Color-word Test, Clock Drawing Test (CDT), Boston Naming Test (BNT), Verbal Fluency Test (fruit), etc. ($P < 0.05$). **Interpretation**: Patients in the PD-pRBD group had more cognitive impairment.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease of the elderly, which was first described by James Parkinson in 1817. Although motor symptoms are the main clinical manifestations in PD, nonmotor symptoms are the first symptom in some patients. Cognitive impairment is a major nonmotor symptom in patients with PD. A cross-sectional study reported that dementia occurs in 30% of patients with PD and a longitudinal study reported that 70–80% of patients with PD will develop cognitive impairment within 20 years of onset[1,2] and thereby seriously affect their quality of life and that of their caregivers. Currently, rapid eye movement sleep behavior disorder (RBD) is considered as an independent risk factor for dementia in PD patients,[3–5] but whether RBD predisposes nondemented PD patients to cognitive impairment remains unclear, with some studies suggesting greater susceptibility to severe cognitive impairment[6–8] and other studies contradicting this view.[9–11]

This study was designed to investigate whether RBD increases the likelihood of cognitive impairment, and whether and which cognitive domains are affected.

Methods

Participants

Eighty-nine PD patients, who were treated at the outpatient department or hospitalized at Jilin University's China-Japan Union Hospital from 2016 to 2018, were enrolled in this study. All patients signed informed consent forms. The only criterion for enrollment was PD diagnosed using the latest diagnostic criteria of the International Movement Disorders Society (MDS) revised in 2015. The exclusion criteria were (1) secondary parkinsonism caused by repeated episodes of cerebrovascular disease, encephalitis, drugs, poisoning, infections, traumatic brain injury, etc.; (2) Parkinson-plus syndromes such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, etc.; (3) severe autonomic dysfunction, speech, memory, or executive

dysfunction or severe dementia (Mini-Mental State Examination [MMSE] score <24 and diagnosis of dementia according to the MDS clinical diagnostic criteria)[12]; (4) a history of long-term alcohol abuse, abuse of sedative drugs, abuse of psychotropic substances or mental illness; (5) severe physical diseases; (6) inability to undergo testing. Demographics of all patients, such as their age, gender, and years of schooling, were recorded.

Grouping

The RBD-HK questionnaire[13] was used to group the enrolled patients. Patients with scores greater than the critical value of 18/19 were assigned to the pRBD group ($n = 46$), and those with scores less than the critical value were assigned to the npRBD group ($n = 43$).

Assessments

Disease severity, neuropsychological function, overall cognitive function, and cognitive function in various domains were assessed.

Assessment of disease severity

The unified Parkinson's disease rating scale part III (UPDRS-III) and the Hoehn-Yahr (H&Y) grading method were used to assess the severity of PD symptoms. H&Y stage 1–2 was defined as mild; H&Y stage 2.5–3, as moderate, and H&Y stage 4–5, as severe. All subjects in this study were PD patients in H&Y stage 1–3 (mild to moderate).

Cognitive tests

Experienced movement disorder neurologists performed the following tests of: (1) General global cognition: Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE); (2) Attention: Digit Symbol Test (DST) and Digit Span Test; (3) Executive function: Stroop Color-Word Association Test (CWT) and Trail Making Test (TMT); (4) Visuopatial function: Clock Drawing Test; (5) Verbal: Verbal Fluency Test (VFT) and Boston Naming Test (BNT); and (6) Memory Assessment: Rey Auditory Verbal Learning Test.

Statistical analysis

SPSS22.0 was used for statistical analysis. The numerical data were analyzed using the Chi-square and Fisher tests. Continuous data are expressed as median (25th percentile, 75th percentile). Nonparametric rank sum test was used for comparison between groups. A P value of less than 0.05 was considered statistically significant.

Results

Demographic comparison

There were 40 males and 49 females overall, with 21 males and 25 females in the PD-pRBD group and 19 males and 24 females in the PD-npRBD group. There was no statistically significant between-group difference in gender distribution ($P > 0.05$), mean age (66 [60,74] years in the PD-pRBD group and 65 [54,73] years in the PD-npRBD group) ($P > 0.05$), length of education (9 [9,12] and 12 [9,12], respectively) ($P > 0.05$), and disease duration(4 [3,7] and 3 [2,5]) ($P > 0.05$) (Table 1).

Disease severity

There was no statistically significant between-group difference in disease severity (UPDRS-III and H&Y stage distribution) ($P > 0.05$) (Table 1).

Cognitive functions

Overall cognitive functions

An analysis of MMSE and MoCA scores in the two groups showed that they were statistically significantly lower in the PD-pRBD group, indicating statistically significantly lower overall cognitive function ($P < 0.05$) (Table 2).

Various cognitive domains

(1) Attention: the PD-pRBD group had statistically significantly lower Digit Symbol Test (DST) score ($P < 0.05$) but nonsignificantly lower Digit span test (forward digit span and backward digit span) score ($P > 0.05$). (2)

Table 1. Comparison of demographic and clinical symptoms between the PD-pRBD group and the PD-npRBD group, UPDRS, and H&Y were used to assess disease severity.

	PD-pRBD ($n = 46$)	PD-npRBD ($n = 43$)	Z	P
Sex (M/F)	21/25	19/24		0.63[#]
Age (years)	66 (60, 74)	65 (54, 73)	−0.715	0.475[#]
Years of schooling (years)	9 (9, 12)	12 (9, 12)	−1.173	0.241[#]
Duration of disease (years)	6 (5, 7.5)	6 (5.5, 7)	−1.36	0.174[#]
Disease severity				
H-Y stage	2 (2, 2.5)	2 (1.25, 2.25)	−1.732	0.064[#]
UPDRS III	26 (14, 30)	23 (17, 30)	−0.476	0.634[#]

[#]Not statistically significant, $P > 0.05$.

Table 2. Comparison of cognitive function between the PD-RBD group and the PD-NRBD group.

Groups	PD-pRBD (n = 46)	PD-npRBD (n = 43)	Z	P
MMSE	27 (25, 28)	28 (26, 29)	−1.773	0.021*
MoCA	19 (17, 22)	22 (18.5, 26)	−2.411	0.016*
Rey Auditory Verbal Learning Test (immediate memory)				
Rey Auditory Verbal Learning Test (delayed memory)	26 (17, 29)	27 (23, 34)	−1.29	0.197#
Boston Naming Test				
Verbal Fluency Test (animal)	3 (0, 5)	4 (2, 6.5)	−1.581	0.114#
Digit Symbol Test	15 (11, 17)	18 (15, 20.5)	−3.114	0.002*
Digit Span Test (forward digit span) Digit Span Test (backward digit span)	10 (9, 14)	13 (11, 16)	−1.86	0.063#
	18 (11, 29)	25 (17.5, 32.5)	−1.971	0.049*
StroopColor-Word Test A (second)	8 (7, 9)	8 (8, 9)	−0.565	0.572#
StroopColor-Word Test B (second)	4 (3, 4)	4 (3, 4)	−1.527	0.127#
StroopColor-Word Test C (second)	34 (27, 37)	31 (25, 33)	−1.693	0.09#
Trail Making Test A	44 (40, 82)	43 (38, 48)	−2.022	0.043*
Trail Making Test B	85 (71, 143)	82 (71, 95)	−1.296	0.012*
Clock Drawing Test	83 (69, 160)	48 (32, 55)	−4.275	0.000*
	283 (181, 300)	160 (110, 300)	−2.225	0.006*
	18 (9, 22)	24 (22, 25.5)	−3.291	0.001*

*Statistically significant, $P < 0.05$.
#Not statistically significant, $P > 0.05$.

Executive function: the PD-pRBD group took statistically significantly longer to complete the Stroop CWT-B, TMT-A, and TMT-B ($P < 0.05$) (Table 2). (3) Visuospatial ability: the PD-pRBD group had statistically significantly lower CDT score ($P < 0.05$). (4) Language: the scores on the Boston naming test ($P < 0.05$) but not the VFT ($P > 0.05$) were significantly lower in the PD-pRBD group. (5) Assessment of memory: although the Rey Auditory Verbal Learning Test(immediate memory, delayed memory) scores were lower in the PD-pRBD group, they were not significantly lower ($P > 0.05$) (Table 2).

Discussion

There have been many recent studies on the factors affecting cognitive impairment in PD. These factors may include age, sex, duration of disease, impairment of motor function, education, and nonmotor symptoms.[14,15] Recent studies have also suggested that RBD is an independent risk factor for cognitive impairment in PD,[3-5] and patients with PD-RBD are more likely to have mild cognitive impairment. A study of Gagnon et al.[2] showed that the incidence of mild cognitive impairment was 73% in PD-RBD patients and only 11% in PD-NRBD patients. Postuma et al.[16] performed polysomnographic monitoring in a 4-year follow-up study of 42 patients with nondemented PD (27 with RBD, 15 without RBD) and found dementia in 48% of patients in the PD-RBD group and 0% of patients in the PD-NRBD group. Nomura et al.[17] studied 82 patients with PD, and found that clinical RBD symptoms were associated with the development of dementia in PD. Studies have also shown no significant difference in the incidence of cognitive impairment between the PD-RBD group and the PD-nRBD group.[9-11,18] Thus, whether RBD can be used as a predictor of cognitive impairment in PD patients remains controversial.

Change in cognitive function at the early stage of PD in nondemented patients (i.e., early-stage mild cognitive impairment in PD [PD-MCI]) is subtle and easy to overlook in an overall assessment of cognitive function. Based on diagnostic criteria developed by the International Parkinson and Movement Disorder Society (MDS) in 2012,[19] PD-MCI can be diagnosed by evaluating five cognitive domains including verbal memory, visuospatial ability, attention, and executive function.[2,20] Although the domains affected in RBD patients are attention, executive function, verbal memory, visuospatial ability, etc.[21,22], the different domain of cognitive impairment of PD-RBD differ between East and West because of research method differences and cultural differences. Postuma et al. 14 conducted an overall neuropsychological assessment in 27 patients with PD-RBD and 15 patients with PD-nRBD and found that the former were more likely than the latter to exhibit a decrease in attention, executive function, episodic memory, and visuospatial ability, which is similar to previously reported findings.[2,8] In the study by Chahine et al., 423 PD patients were followed up for 3 years, divided into a PD-RBD group and PD-NRBD group based on RBD sleep questionnaire data, and underwent neuropsychological assessments that showed

significant impairment of delayed memory and attention, but not of visuospatial ability and executive function.[5]

In this study, age of onset, gender, length of disease, degree of motor impairment, and years of education were similar between the groups, while overall cognitive function (evaluated using the MoCA and MMSE) was statistically significantly worse in the PD-pRBD group.

It is reported in the literature (The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010;75:1717–25.) that the specificity and sensitivity of MoCA is higher than MMSE, MoCA can be used as a screening scale for comprehensive cognitive function. The results of our study suggest that the scores of MoCA and MMSE both have the statistic difference between PD-pRBD and PD-npRBD, which is different from previous literature, it can be related to the fewer cases.

Using the 2012 International Parkinson and Movement Disorder Society (MDS) diagnostic criteria for PD-MCI,[18] we evaluated five cognitive domains and compared domain scores between groups. PD-pRBD patients performed statistically significantly worse than PD-npRBD patients in the executive function, language, visuospatial ability, and attention domains, but similarly in the memory domain. These results are different from those of others, and the difference may be due to a difference in assessment scales.

The above-mentioned studies show that PD-patients with RBD have more cognitive impairment, but the mechanism is not yet clear. However, on the basis of the previous studies, we consider that cognitive impairment in patients with PD-RBD is caused by the following:

First: The REM sleep control center is mainly located in the central pons and the locus coeruleus. The pathophysiology of RBD is not fully understood, but dysfunction of the dopaminergic pathway has been proposed. SPECT studies found that dopamine innervation is reduced in RBD patients.[24–26] Another important subcortical system of RBD pathogenesis is the serotonergic system in the brainstem. Serotonergic nuclei modulate cortical and subcortical structures, such as the striatum, via the striatal complex. Serotonin in the brainstem may be the pathophysiological basis of RBD occurrence.[27] Another study suggesting a strong correlation between cholinergic denervation and the development of RBD raises the possibility that the cholinergic projection system in the basal forebrain complex might play a key role in the pathogenesis of RBD.[28]

Cognitive impairment in PD patients may be related to dopaminergic, noradrenergic, and serotonergic disturbances. Degeneration of dopaminergic neurons in the substantia nigra leads to decreased levels of dopamine in the striatum, damage to the cortical-subcortical dopamine loop between basal ganglia and frontal lobe, and depletion of dopamine in frontal lobe, resulting cognitive impairment.[29,30]

Meanwhile, a study about dementia and nondementia in PD patients found that dementia occurrence was significantly correlated with the loss of dopaminergic neurons in the medial portion of the substantianigra in PD patients.[31] Moreover, dopamine concentration in the neocortex is significantly lower in PD patients with dementia than in PD patients without dementia.[32] Studies have also found that noradrenergic and serotonergic pathways are also involved in cognitive impairment and that locus damage, neuronal damage, and norepinephrine depletion are more severe in PD patients with cognitive impairment.[33,34] In patients with cognitive impairment, there is the possibility that cholinergic defects have a role in promoting cognitive impairment, cholinergic innervation is decreased in the cerebral cortex, and cells of the nucleus basalis of Meynertare severely depleted.[35–37] At the same time, Dubors et al.[38] found memory impairment after low-dose anticholinergic drug treatment in PD patients, which did not appear in the healthy control group. In summary, RBD is related to common neurological changes in several brainstem nuclei and changes in the signaling of their corresponding neurotransmitters (i.e., dopaminergic, cholinergic, norepinephrine, and serotonergic signaling) in PD-MCI patients.

Second: It was reported that the occipital EEG rhythm slows down in PD-RBD patients without cognitive impairment, and that obvious θ-wave dominance in each lobe during the awakening phase of sleep[39] is suggestive of mild cognitive impairment (MCI). Meanwhile, studies have also found that the cerebral blood flow in the frontal lobe, parietal lobe, and occipital cortex is reduced in PD-RBD patients.[28,40,41] These studies show that the slow cerebral EEG rhythm and the decreased cerebral blood flow may be used as indicators of cognitive impairment in patients with PD-RBD.

This study has certain shortcomings. First of all, when grouping patients, we considered that PSG was not commonly used in clinical practice to diagnose RBD and did not use it (as recommended in the 2005 International Classification of Sleep Disorders [ICSD-2]). Instead, we used the RBD-HK screening scale at the time of grouping. Despite its relatively high sensitivity and specificity, the screening scale is affected by certain subjective factors. Second, the study enrolled relatively few patients and was not longitudinal. In addition, even though cognitive impairment could differ in the early and late stages of the disease, there was no long-term follow-up to observe the progression of cognitive impairment. Moreover, since the assessment scales for the various cognitive domains were not uniform, the results might be different. Finally,

the effects of damage in each cognitive domain may not be independent because of possible domain interactions.

In conclusion, cognitive impairment is more severe in patients with PD-RBD than in patients with PD-NRBD. However, it will be necessary to improve the clinical studies of PD patients with REM sleep disorder in order to confirm that RBD is a predictor of cognitive impairment in early PD. Such predictors may help identify candidate patients for specific interventions that prevent cognitive decline or dementia development.

Limitations

However, we have excluded patients with symptoms duration less than 5 years, there may be few included LBD patients who have early cognitive decline, early manifestation of dysautonomia and high rates of RBD, we will continue to follow up our patients.

Conflict of Interest

The remaining authors have no conflicts of interest or disclosures and none of the authors have any financial associations with commercial entities that were involved with the project.

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