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Original Article

Mutant of leucine-rich repeat kinase 2 is not associated with non-motor symptoms in Chinese Parkinson's disease patients

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Abstract: Non-motor symptoms (NMS) are common in patients with Parkinson's disease (PD). However, little is known about NMS in patients with mutant of leucine-rich repeat kinase 2 (LRRK2). This study aimed to elucidate the relationship between NMS in Chinese PD patients and to ascertain if there were differences in NMS between PD patients and mutant of LRRK2. 200 sporadic PD (sPD) patients were recruited from a Provincial Hospital Affiliated to Shandong University. The Non-motor Symptom Questionnaire (NMSQ) was used to screen for the presence of NMS. A mean of 9.73 NMS (SD=4.53) was reported per patient. Forgetfulness, constipation and daytime sleepiness were found to be the most frequent NMS. No differences were found in 9 domains analysis between PD with and without LRRK2 variants. Non-motor symptoms in PD are too important to remain undetected. There are no Clinical characteristics of NMS tend to be similar between LRRK2 variants carriers and non-carriers in Chinese sPD patients.

Keywords: LRRK2 variants, on-motor symptoms, NMS Quest, nocturia, Parkinson's disease

Introduction

Parkinson's disease is caused by inexorable deterioration of dopaminergic neurons from the substantia nigra [1]. Parkinson's disease (PD) commonly occurred between 55 and 65 years [2]. The motor disorders of PD include resting tremor, rigidity, bradykinesia, and difficulties with balance. Usually, patients with established PD often experience a wide variety of non-motor symptoms (NMS) [3, 4], which have been identified as having a significant impact on QOL in individuals with PD [5, 6] and risk of institutionalization at advanced stages of PD [7]. Utilizing a validated Queen Square Brain Bank (QSBB) [8] clinical criteria for the diagnosis of PD, Martinez-Martin and colleagues [3] surveyed 545 PD patients of multiethnic origins. They found nocturia, urgency, constipation, sad and impaired concentration were the top five most common NMS. Similar findings were also reported by Chaudhuri and colleagues [9] when the QSBB was used in their study of 242 European PD patients.

Associations between the genotype and clinical phenotype such as NMS in sporadic PD (sPD) patients have attracted research attention in recent years [10, 11]. It is known mutations in Leucine-rich Repeat Kinase 2 gene (LRRK2) are the most common known genetic cause of sPD [12]. Previous study mainly focuses on one or several specific NMS, rather than the general profile of NMS. The NMS characteristics of sPD patients who are carriers of LRRK2 G2385R or R1628P variants are currently unknown.

To our knowledge, LRRK2 variants carriers and non-carriers of Chinese sPD may suffer from different sets of NMS. Thus, we prioritized obtaining patient-reported needs and barriers.

Methods

Subjects and clinical assessments

PD patients were identified from a PD cohort of Provincial Hospital Affiliated to Shandong University from May 2011 to July 2013.

Table 1. Demographic and clinical characteristics between participants with LRRK2 positive and negative PD

Items	Total PD (n=200)	LRRK2(+) PD (n=35)	LRRK2(-) PD (n=1062)	*P* Value
Men	118	80	38	0.35
Age (years)	62.43±10.47	60.24±10.48	61.34±9.28	0.58
Age at onset (years)	53.82±5.92	56.29±10.86	56.97±10.91	0.74
Duration of the disease (years)	3.7±1.01	3.96±3.28	3.35±4.25	0.40
UPDRS-III	22.17±14.74	21.63±13.37	22.61±14.35	0.71
MMSE	26.77±3.64	26.78±3.61	26.77±3.81	0.98
The number of NMS	9.73±4.53	9.58±5.16	9.8±5.35	0.83

Mean ± SD. Abbreviations: MMSE = Mini-Mental State Examinations; LRRK2 = leucine-rich repeat kinase 2; NMS = Nonmotor Symptom; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 2. Comparison of scores in each NMS Quest domain between LRRK2 positive and negative PD

Domain	Number of items	LRRK2(+) PD	LRRK2(-) PD	*P* Value
Gastrointestinal tract	7	1.63±1.40	1.84±1.53	0.46
Urinary tract	2	0.54±0.24	0.62±0.35	0.16
Cognitive	3	1.21±1.12	1.38±1.13	0.45
Hallucination/delusions	2	1.12±0.42	1.18±0.24	0.42
Neuropsychiatric	2	0.83±0.49	0.80±0.47	0.75
Sexual function	2	0.97±0.40	0.94±0.49	0.07
Cardiovascular	2	0.36±0.45	0.45±0.33	0.28
Sleep	5	1.61±1.23	1.75±1.35	0.58
Miscellany	5	1.43±1.23	1.34±1.06	0.70

Mean ± SD. Abbreviations: LRRK2 = leucine-rich repeat kinase 2; NMS Quest = Non-motor Symptom Questionnaire; PD = Parkinson disease.

The diagnosis of PD was defined according to the QSBB criteria [8]. Exclusion criteria were individuals with significant memory impairment (defined as Mini-Mental State Examinations core<24) [13]. The Non-motor Symptom Questionnaire (NMSQ) was used to determine the NMS. NMS Quest contains 9 relevant domains: gastrointestinal tract, urinary tract, cognitive, hallucination/delusions, neuropsychiatric, sexual function, cardiovascular, sleep, miscellaneous disturbances [3, 14, 15]. The severity of motor symptoms was established via the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Assessments and data collection was conducted in the outpatient department of the participating clinical centers. Blood samples were obtained in accordance with protocols as reported by Wang et al. [16] and both the LRRK2 R1628P and G2385R variants were genotyped in each patient [16-18]. PD patients who carried either G2385R or R1628P variant were considered to be carriers of LRRK2 variants.

Ethical approval

Ethical approval was obtained from the Human Research Ethics Committee of Shandong University. All subjects or their legal guardians gave their written informed consents.

Data analysis

Statistical analysis was performed using SPSS 18.0. The prevalence for every domain is the sum of items positive response. The chi-square test was used to analyze categorical data. Student's unpaired t-test was used to analyze the differences between PD with and without LRRK2 variants for age, gender, the use of dopamine agonist and levodopa, duration of disease, the score UPDRS-III. A value of $P<0.05$ was considered statistically significant.

Results

Of 200 subjects included in our study, 135 patients met the selection criteria. Data analysis shown there was no difference in the frequency of LRRK2 variants between study participants and non-participants. Analysis revealed 24 participants had the LRRK2 variants. **Table 1** revel the characteristics of subjects included in our study. No significant differences were found between these two groups.

This study found the mean number of NMS occurrences was 9.73 (SD=4.53) ranging from 0 to 29. All symptoms listed in NMSQ (n=30) was observed in the current study population. No differences were found in 9 domains analy-

sis between PD with and without LRRK2 variants (**Table 2**).

Discussion

The findings of this study suggest that clinicians should pay more attention to forgetfulness, constipation, daytime sleepiness, sad, and loss of interest in Chinese sPD patients.

In our study, the mean number of NMS was found to be lower than what were reported by Martínez-Martín et al. [3] and Chaudhuri et al. [9] but higher than that of Barone et al.'s study [19], and similar with khoo et al [20] studied 159HYPERLINK "app:ds:the%20United%20Kingdom" \t "_self" United Kingdom newly diagnosed PD patients. On the other hand, the prevalence of forgetfulness, constipation, daytime sleepiness, loss of interest in our study were higher than above 4 studies [3, 9, 19, 20], urinary urgency was lower than them, and sad, nocturia, impaired concentration were in between them. The disparity between the prevalence of NMS in China and the West may be related to differences in disease duration and staging of the study populations, sample size, in addition to racial diversity.

Previous literatures on clinical features of PD patients with LRRK2 variants suggested that their phenotypes might not be distinguishable from sPD patients without LRRK2 variants. However, some non-motor symptoms of PD patients with LRRK2 variants were more benign than those of PD without LRRK2 variants [10]. Olfactory malfunction in PD with LRRK2 variants might be less severe compared with PD without LRRK2 variants [10, 11, 21]. While a study conducted by HYPERLINK "javascript:void(null)" Silveira-Moriyama et al., found that the frequency of hyposmia was similar in PD patients with and without LRRK2 G2019S mutation [22]. However, these studies mainly focused on G2019S mutation. In this study, NMS in sPD were examined comprehensively via the use of NMSQ. The current study found three are non different between LRRK2 variants carriers and non-carriers in sPD patients for frequencies of NMS.

Non-motor symptoms in PD result in significant disability and worsen the health and quality of life of the patient and their family [23]. Gallagher et al reported that nonmotor Nocturia is commonly found in the elderly, and it often cause significant distress and can reduce patients' quality of life [24]. Findings from two neuropathological studies confirmed that sPD with LRRK2 mutations can be associated with nonspecific nigral degeneration without Lewy bodies [25, 26]. This may partly explain this phenomenon, although the exact mechanism remains unknown. It is postulated that there may be fewer Lewy bodies deposit in lower urinary tract which results in preserved urinary tract functions. Given that the risk factors for nocturia also include obesity, prostatic enlargement, diabetes mellitus, and certain medications [27], future investigation should consider to exclude these potential confounders.

In conclusion, this study suggests that NMS are quite common in Chinese sPD population. Nonmotor symptoms in PD are too important to remain undetected. Clinical characteristics of NMS appear to be similar between LRRK2 G2385R and R1628P Variants carriers and non-carriers in Chinese sPD patients.

Disclosure of conflict of interest

None.

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