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LRRK2-associated Parkinson's disease patients have better stereopsis than idiopathic Parkinson disease

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ABSTRACT

Objectives: Visual dysfunctions are frequent and have several manifestations in idiopathic Parkinson's disease (PD). However, the characteristics of these complications in LRRK2 (leucine-rich kinase 2)-associated PD patients still lack systematic research. The purpose of this study is to assess visual functions of LRRK2-associated PD patients.

Patients and methods: Twenty-five (25) PD patients with LRRK2 R1628P and G2385R variants were included in the study and compared to 28 PD patients without these variants and 28 age-matched healthy controls. The genotypes of PD patients were kept double-blinded. Information on age, sex, disease duration, the movement disorder society-unified Parkinson's disease rating scale (MDS-UPDRS), Hoehn and Yahr staging scale (H&Y), Mini-Mental Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were included. Visual functions assessment included color perception, contrast sensitivity and stereopsis.

Results: PD patients with or without LRRK2 R1628P and G2385R variants have declined contrast sensitivity, diminished color discrimination and damaged stereopsis. There was no significant difference in retinal level visual deficiency (color discrimination and contrast sensitivity) between PD with LRRK2 variants and those without, but cortex level visual function, i.e. stereopsis is better in PD with LRRK2 variants than non-carrier PD patients. The associated factors of stereopsis are different. The stereopsis is associated with MoCA scores independently in non-carrier PD patients, but with UPDRSIII scores in LRRK2-associated PD patients.

Conclusions: Visual functions are similarly affected in PD patients with and without LRRK2 R1628P and G2385R variants, but LRRK2-associated PD patients have better stereopsis than idiopathic PD patients.

1. Introduction

Visual dysfunctions are a group of non-motor symptoms in Parkinson's disease (PD) and have several manifestations. Deficits in color discrimination and contrast sensitivity are established visual deficits of PD patients and are considered to be due to retinal dopaminergic deficiency [1]. In addition, central visual system beyond retina may also be impaired as the deterioration of orientation selective vision [2], motion detection [3], visual attention [4] in PD patients. Stereopsis, which is governed by cerebral cortex, especially the extrastriatal cortex, is considered as cortical visual functions. Stereopsis dysfunction has been reported in a small sample of drug naïve PD patients, suggesting that extrastriatal cortex might be involved [5]. Our previous study also showed the same results [6].

Mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2) have been reported to be the most frequent genetic cause associated with Parkinson's disease (PD) [7]. The phenotype of LRRK2-associated PD has been described as similar to idiopathic PD (IPD) with minor exceptions [8]. However, the characteristics of non-motor symptoms of LRRK2-associated PD are still controversial and inadequately studied, and there are a few studies focused on the characteristics of visual functions of PD with LRRK2 variants.

In this study, we evaluated visual functions including color discrimination, contrast sensitivity and stereopsis in PD patients with LRRK2 G2385R and R1628P variants (PD patients of mutation carriers, PD-MC) and compared them with non-carrier PD patients (PD patients of non-carrier of mutation, PD-NC) and normal controls, trying to answer whether PD-MC is different from PD-NC in visual functions.

2. Patients and methods

PD patients were recruited from the cohort established by the

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movement disorder centre at Xuanwu Hospital Capital Medical University in Beijing. PD was diagnosed by movement disorders specialists using the United Kingdom PD Society Brain Bank Criteria. Patients with MRI identified brain lesions and any other neurological disorders were excluded. Because Asians rarely have the G2019S mutations, but the common polymorphic variants of G2385R and R1628P, LRRK2 G2385R and R1628P variants had been tested in this cohort. Participants included 25 PD-MC, and 28 age and disease duration matched PD-NC. 28 community age-matched volunteers were also enrolled as unrelated control group. None of the subjects has strabismus, nystagmus, ocular motility disturbance and poor corrected visual acuity (< 20/40 snellen fraction in either eye) by examination or in any of the following conditions by history inquiring: unoperated symptomatic cataracts, untreated glaucoma, diabetic eye disease and congenital color blindness. None of the subjects had significant cognitive impairment. All subjects were informed of the purpose of the study and signed the consent form, which was approved by the Local Ethics Committee. The genotypes of PD patients were kept to be double-blinded during the neurologic evaluation and visual function assessment.

Standardized neurologic examination and clinical assessments were performed in all PD patients. All evaluations were carried out in the morning, and patients were asked to come without taking anti-parkinsonian medications for at least 12 h (18 h for levodopa-carbidopa [Sinemet]), to be sure on a "practically defined off" state [9]. The Hoehn and Yahr (H&Y) staging scale (non-weighted and weighted Kappa scores = 0.44–0.71)was used to describe the severity of PD [10]. Unified Parkinson's Disease Rating Scale (UPDRS), with excellent inter-rater reliability (Cronbach's alpha = 0.96) and intra-rater reliability (intraclass correlation coefficient [ICC] = 0.92) was used to measure parkinsonian signs and symptoms [11]. Purdue Pegboard Test (PPT) [12] was used to test hand dexterity and motor speed. Briefly, it requires the subject to place as many pins as possible in a vertical column of holes on a board within 30 s. The pins were placed in by right, left and both hands for three times each, and the average numbers of the pins placed on the three conditions were recorded. The total average numbers (TAN, test–retest reliability: ICC = 0.89) [13] were used as the measured scores. The Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to assess patients' cognitive functions. All visual functions were tested under natural daylight, avoiding direct sunlight. PD patients were evaluated in the morning in the medication-off state. Stereopsis was assessed using the Fly Stereo Acuity Test (P/N 1000, Vision Assessment Co., Inc., IL, USA). We administered the test according to the manufacturer's guidelines. Subjects wearing polarized viewers looked at the test material at a viewing distance of 40 cm and reported which circle was out of the plane of the other three (zero plane). The graded circle included 10 grades, testing from 400 s (Grade 1) down to 20 s (Grade10). We started the test with the easiest condition 400 s (Grade 1) and gradually increased its difficulty. The limited grades (LG) of fly stereo acuity test that were normal distribution data was used as the index of subjects' stereopsis function, and normal stereopsis was defined as LG ≥ 5 (arc ≥ 63 s) according to previous studies [14]. Color perception was tested with Farnsworth-Munsell 100 Hue test (FMT), no time limit was imposed, the total error score(TES) was determined. Contrast sensitivity was measured with a sine-wave grating at spatial frequencies of 3, 6, 12, and 18 cycle/ degree (cpd) using the Vector Vision CSV-1000E chart (Vector Vision, Haag-Streit, Harlow, UK). Sensitivity values were transformed into a logarithmic scale, and compared respectively in the four spatial frequencies.

Data were analyzed using SPSS, version 17.0 (SPSS, Chicago, IL, USA). One-way ANOVA was used to assess the data among three groups and the Newman-Keuls test was applied for further two-two comparison. T-test was used to compare the characteristics of two independent samples. Pearson correlation analysis was applied for correlation analysis, and multiple linear regression analyses were used to remove interference between variables. Differences were considered to be significant if the p value was < 0.05.

3. Results

3.1. Patient characteristics

25 PD-MC (16 men and 9 women, mean age of 65.76 years, ranging from 46 to 81years), 28 PD-NC (18 men and 10 women, mean age of 67.75 years, ranging from 53 to 85 years) and 28 controls (10 men and 18 women, mean age of 64.93 years, ranging from 47 to 81 years) were enrolled in the study. There were no statistical differences in age and gender distribution among three groups. The TAN of PPT in PD-MC and

Table 1
Demographic features and visual functions comparison of PD-MC, PD-NC and controls.

	PD-MC (n = 25)	PD-NC (n = 28)	CONTROL (n = 28)
Age(years)	65.76 ± 10.07	67.75 ± 9.96	64.93 ± 9.31
Gender(male, %)	64.0	64.3	35.7
Hoehn and Yahr stage	2.20 ± 0.76	2.48 ± 0.95	NA
UPDRS III	25.60 ± 15.63	27.26 ± 13.50	NA
UPDRS	39.44 ± 20.70	41.96 ± 18.25	NA
PPT, TAN	33.81 ± 9.93	32.17 ± 10.51	50.17 ± 6.83**
MMSE	27.92 ± 2.43	27.14 ± 2.68	
MoCA	24.84 ± 3.77	23.88 ± 4.93	
Duration of motor disease (years)	6.76 ± 2.74	8.07 ± 4.54	NA
Color Perception	137.04 ± 72.69* (p = 0.035)	139.23 ± 128.20* (p = 0.0001)	83.04 ± 48.14
Farnsworth			
TES			
Contrast Sensitivity			
3cpd	1.47 ± 0.20	1.52 ± 0.31	1.67 ± 0.33
6cpd	1.48 ± 0.48* (p = 0.0001)	1.67 ± 0.23* (p = 0.012)	2.05 ± 0.20
12cpd	0.63 ± 0.37* (p = 0.0001)	1.07 ± 0.40* (p = 0.0001)	1.77 ± 0.21
18cpd	0.23 ± 0.53* (p = 0.0001)	0.60 ± 0.50* (p = 0.001)	1.31 ± 0.22
Stereopsis			
LG	5.58 ± 2.90*# (p = 0.037) (#p = 0.007)	3.67 ± 2.59* (p = 0.0001)	7.04 ± 1.84
Abnormality rate(%)	41.7*#	74.1*	14.3

**p = 0.0001. *p < 0.01, PD-MC or PD-NC compare with control in the Newman-Keuls test. #p < 0.01, PD-MC compare with PD-NC in the Newman-Keuls test. UPDRS, unified Parkinson's disease rating scale. PPT, TAN, total average number of Purdue Pegboard Test. MMSE, minimal mental status examination. MoCA, Montreal cognitive assessment.TES, total error score. PES, partial error scores. LG, limited grade.