Stereopsis in Drug Naïve Parkinson's Disease Patients

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ABSTRACT: *Background:* Motor deficits associated with Parkinson's disease (PD) have been well described, yet little attention has been paid to non-motor symptoms, especially cortical visual dysfunction. We investigated stereopsis, as well as the relationship between stereopsis and other cognitive function, in a sample of PD patients. *Methods:* We used Titmus stereotest plates for assessing stereopsis. Fifty-nine subjects (29 PD patients and 30 normal controls) were included in this study. The included patients underwent a neurological examination, clinical rating scale and neuropsychological tests. *Results:* Drug naïve PD patients showed decreased stereopsis on the Titmus fly stereopsis test (Pearson χ^2=23.80, p<0.001) compared to PD patients with normal stereopsis. The Hoehn-Yahr stages and Unified Parkinson's Disease Rating Scale motor scores were significantly higher in patients with PD with abnormal stereopsis than in patients with PD with normal stereopsis (p=0.026; p=0.046). The frequency of abnormal visual perception/constructive function was greater in patients with PD with abnormal stereopsis compared to patients with PD with normal stereopsis (Pearson χ^2=5.11, p=0.024). *Conclusion:* These findings suggest that stereopsis deficits and visual perception/constructive dysfunction are common in *de novo* PD patients.

RÉSUMÉ: La stéréopsie chez les patients atteints de la maladie de Parkinson jamais traités. *Contexte :* Les déficits moteurs associés à la maladie de Parkinson (MP) ont été bien décrits. Cependant, on s'est peu intéressé aux symptômes qui ne sont pas des symptômes moteurs, particulièrement à la dysfonction du cortex visuel. Nous avons étudié la stéréopsie ainsi que la relation entre la stéréopsie et les fonctions cognitives dans un échantillon de patients atteints de la MP. *Méthodes :* Nous avons utilisé les plaques pour le stéréotest de Titmus pour évaluer la stétéopsie. Cinquante-neuf sujets (29 sujets atteints de MP et 30 sujets normaux) ont été inclus dans l'étude. Les patients ont subi un examen neurologique, une échelle d'évaluation clinique et des tests neuropsychologiques. *Résultats :* Les patients atteints de MP jamais traités présentaient une stéréopsie diminuée au test de stéréopsie de Titmus avec la mouche (χ^2 de Pearson = 23,80 ; p < 0,001) par rapport aux patients atteints de MP ayant une stéréopsie normale. Les stages de Hoehn-Yahr et les scores moteurs à la Unified Parkinson's Disease Rating Scale étaient significativement plus élevés chez les patients atteints de MP dont la stéréopsie était anormale que chez les patients qui avaient une stéréopsie normale (p = 0,026 ; p = 0,046). La fréquence d'une perception/fonction constructive visuelle anormale était supérieure chez les patients atteints de MP dont la stéréopsie était anormale par rapport à ceux chez qui elle était normale (χ^2 de Pearson = 5,11 ; p < 0,024). *Conclusion :* Selon nos données, des déficits de la stéréopsie et une dysfonction de la perception/constructive visuelle sont fréquentes au moment du diagnostic de la MP.

Cortical visual dysfunction (CVD) is commonly defined as a loss of visual function in the absence of damage to afferent visual pathways or ocular structures. Although many patients with Parkinson's disease (PD) may be visually asymptomatic, the pathological pattern of the PD brain suggests that CVD may be present in PD patients.[1] Most previous studies of visual signs of PD were concerned with basic visual functioning and subjective visual symptoms.[2,3]

Stereopsis, or binocular depth perception, depends on the disparity between the views perceived by each eye.[4] The two images are fused in the cerebral cortex and experienced as a single three-dimensional representation under normal circumstances. Parkinson's disease patients are known to have deficits in the perception of visual stimuli.[5] However, it remains unclear whether these visual deficits could lead to dysfunction of stereopsis.

In this study, we identified cases of dysfunction of stereopsis in PD patients. We also evaluated the relationship between stereopsis and cognitive function.

SUBJECTS AND METHODS

Study Participants

We recruited drug naïve PD patients from the Movement Disorders Unit of Korea University Guro Hospital, Seoul, Korea from November 2008 to March 2009. All patients met the clinical diagnostic criteria for PD, as described by the United Kingdom Parkinson's Disease Society Brain Bank.[6] Patients with MRI identified brain lesions were excluded. Thirty age-matched normal subjects were screened for participation in this study as controls. None of the study subjects suffered from any

other neurological disorders. None of the control subjects had a positive history of PD, or had any clinical findings suggesting PD. For ascertainment of dopaminegic drug treatment response we reviewed medical records of all included patients for more than one year. To exclude the dementia with Lewy body (DLB), we reviewed medical records and evaluated all patients according to the diagnostic criteria developed by the DLB Consortium after one year.[7]

METHODS

Neurologic Evaluation

Patients underwent a neurologic examination and a clinical assessment. The Hoehn and Yahr (H&Y) stage was determined[8] and the degree of disease severity was quantified by the Unified Parkinson's Disease Rating Scale (UPDRS)[9] by Dr. S.B. Koh, a movement disorder specialist. Neuropsychological tests were performed to assess the cognitive function of patients using a standard neuropsychological test battery. The neuropsychological battery was composed of the following: (1) indexes, including the Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA); (2) a frontal/executive function test with contrasting program, fist-edge-palm, alternating square and triangle, Go-No-Go test, alternating hand movement, Luria loop test, controlled oral word association test, and Stroop test; (3) a verbal/visual memory test with Korean version-Seoul Verbal Learning Test and Korean version complex figure copying test; (4) a language function test; and (5) a visual perception/constructive function (VPCF) test with interlocking pentagon and Rey complex figure copy test. The results for H-Y stage, UPDRS motor scores, MMSE, and MoCA were assessed using the relevant scores. The results of frontal/executive function tests, verbal/visual memory tests, language function tests and VPCF were categorized as normal or abnormal. That is, scores below the fifth percentile and above the 95th percentile of normal reference values were considered to be abnormal.

Stereopsis Assessment

The two step test for stereopsis was performed by two experienced ophthalmologists, Drs. S-H. Kim, and J-H. Park. The first step tests for visual acuity and strabismus. Patients with strabismus, nystagmus, ocular motility disturbance and poor visual acuity in either eye (< 20/40 Snellen fraction) were excluded from the study sample. The second step involves the measurement of stereopsis. Stereopsis was assessed using Titmus stereotest plates (Stereo Optic Co., Inc., IL, USA). Normal stereopsis was defined as an arc < 60 seconds in the Titmus fly test. Previous studies of adult stereoacuity reported that a reduction of the Titmus fly test score was observed in five patients among a group of 60 normal subjects.[10] All tests were conducted at a distance of 40cm, under 200 Lux illumination.

Statistical Analysis

Data were tabulated and analyzed using SPSS, version 15.0 for Windows (SPSS, Chicago, IL, USA). An independent t-test was used to compare the results of clinical rating scales between patients and controls, or between PD patients with normal stereopsis (PDNrS) and PD patients with abnormal stereopsis (PDAbS) for continuous variables. The stereopsis test results of the patients and control were compared with Pearson's chi-square test. To characterize the relationship between stereopsis and the cognitive function, we used Pearson's chi-square test for categorical variables. Differences were considered to be significant if the p value was <0.05.

RESULTS

Baseline Data

A total of 66 subjects (36 patients and 30 controls) were screened for inclusion in this study; seven patients were excluded because of concomitant brain lesions (3/7), poor visual acuity (2/7), and incomplete study (2/7). Finally, 29 patients (15

Table 1: Demographic features and clinical rating scales in PD patients

	PD with normal stereopsis (n=8)	PD with abnormal stereopsis (n=21)	p value
Age (years)	57.88±15.39	68.76±8.98	0.093
H&Y stage	1.56±0.68	2.29±0.75	0.026*
MMSE	26.12±3.23	22.10±5.99	0.085
MoCA	20.71±3.90	17.72±7.65	0.339
UPDRS, motor	9.25±5.20	13.14±4.79	0.046*
Duration of motor disease (months)	14.17±9.27	17.32±11.38	0.093

*$p < 0.05$; PD: Parkinson's Disease; H&Y: Hoehn and Yahr; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; UPDRS: Unified Parkinson's Disease Rating Scale

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Table 2: Association of cognitive function and stereopsis

		Stereopsis			
		Normal	Abnormal	Pearson chi-square value	p value
Frontal/ Executive Function	Normal	3	9	0.069	0.793
	Abnormal	5	12		
Verbal memory test	Normal	5	10	0.514	0.474
	Abnormal	3	11		
Visual memory test	Normal	5	5	3.839	0.05
	Abnormal	3	16		
Language test	Normal	7	12	2.363	0.124
	Abnormal	1	9		
VPCF	Normal	5	4	5.110	0.024*
	Abnormal	3	17		

* $p < 0.05$; VPCF: Visual perception/constructive function

men and 14 women; mean age 65.75 years, ranging from 34 to 80 years) and 30 controls (18 men and 12 women; mean age 63.13 years, ranging from 59 to 74 years) were enrolled in the study. The PD patients had the following descriptive characteristics: mean Hoehn-Yahr stage: 2.09±0.79; mean UPDRS motor scores: 12.07±5.13. On the basis of medical records and follow-up evaluation, all PD patients showed the dopaminergic drug treatment response and there was no patient compatable to the "probable" DLB.

Stereopsis

Three (10%) subjects among the control group (n=30) and 21 patients (87.5%) among the PD group (n=29) showed abnormal stereopsis results. Relative to normal controls, drug naïve PD patients showed decreased stereopsis function on the Titmus fly test (Pearson χ^2=23.80, p<0.001).

Clinical Rating Scales and Stereopsis

The H&Y stage and the UPDRS motor scores were significantly higher in PDAbS than in PDNrS (p=0.026; p=0.046). There were no significant differences in age, MMSE and MoCA between the two groups. Demographic factors and clinical rating scales are summarized in Table 1.

Cognitive Function and Stereopsis

The frequencies of abnormal cognitive function tests, including frontal/executive function (p=0.793), verbal memory (p=0.474), visual memory(p=0.05) and language function (p=0.793) were not associated with the results of stereopsis tests (Table 2). Compared to PDNoS, abnormal VPCF was more common in PDAbS (Pearson χ^2=5.11, p=0.024; Table 2).

DISCUSSION

Human beings have a remarkable ability to perceive depth and three-dimensional shape.[4] The process of stereopsis[4] is governed by the cerebral cortex, especially the extrastriatal cortex.[11,12] Abnormalities of steropsis have been reported in patients with supratentorial structural lesions.[12] However, the presence of stereopsis in neurodegenerative disorders has not previously been evaluated.

The results of our pilot study suggest that deficits of stereopsis are common in drug naïve PD patients. Although PD is characterized by a reduction in dopamine concentrations in the nigrostriatal pathway, both dopamine and other monoamines are depleted in the cortex and brainstem outside the nigrostiatal system. Since dopamine is found in many regions of the central nervous system related to visual processing,[13] it may play an important role in vision.[13] However, it is difficult to identify distinctive contributions from different cortical areas to the binocular representation of 3D surfaces.[14] The results of our previous study suggested that there is a relationship between stereopsis and the extrastriate cortex.[12] Therefore, we hypothesized that the stereopsis deficits in PD patients were caused by the involvements of cortical areas, especially visual association areas including the extrastriate cortex.

Another significant finding of our study was that the clinical progression of PD was more advanced in patients with abnormal stereopsis. We found that deficits of stereopsis were related to disease stage. According to Braak pathological staging of PD,

cortical areas, including multimodal association and primary cortices, are affected in advanced stages.[1] These pathological findings may explain the finding that deficits of stereopsis, which are related to involvement of the visual association area, are more common in advanced PD. Our study has a shortcoming in that our sample includes a large number of patients with early PD. To define the relationship between deficits of stereopsis and disease progression, we must study stereopsis not only in drug naïve PD patients but also in patients with advanced PD.

The findings of our study demonstrate that stereopsis is related to visual perception/constructive function in cognitive domains. Visual memory function may also be related to stereopsis, although in the results of this study, this relationship was not statistically significant (p=0.05). However, we found no significant relationships between stereopsis and frontal/executive function, language function, of verbal memory. Therefore, we believe that the deficits of stereopsis observed in PD are closely related to the involvement of visual association areas. Abe et al demonstrated that occipital and posterior parietal hypometabolism in PD with single photon emission computed tomography study.[15] They suggested that occipital hypometabolism is likely to underlie impairment of visual cognition. We thought that stereopsis deficits may represent non-motor signs of PD.

Our study has several shortcomings. Dopamine depletion at the level of the retina and findings of altered retinal optical coherence tomography findings in PD have been previously demonstrated.[16] We did not check the visual contrast sensitivity or color discrimination. While stereopsis may indeed be a cortical process, if normal cortex is fed erroneous information from upstream structures (such as the retinal ganglion cells) there may be deficits. Lack of checking retinal level abnormality in this present study may limit the robustness of our results. A morphometric neuroimaging study could provide further evidence for understanding the mechanisms of stereopsis abnormality in PD. The lack of patients with advanced PD in our study limited the interpretation of our results.

CONCLUSIONS

The Titmus stereopsis plate test is a simple method to evaluate stereoacuity. It is the most commonly used method to evaluate stereoacuity, and is usually used for children who have underdeveloped visual perception. However, the relationship between visual acuity and stereopsis remains controversial. We did not exclude vision-affecting eye diseases including cataracts (which is the most prevalent disease in the age group included in this study). Several studies have shown that a reduction of visual acuity does not increase the stereoscopic threshold, even if visual acuity was as low as 20/60.[17] In the present study, we included patients with visual acuity 20/40 or better in both eyes. In conclusion, we demonstrated that a stereopsis test is a simple and useful test for cortical vision and that it could be used as an indicator of cortical involvement and evaluation of non-motor signs of PD.

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