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Relationships between optic nerve damage and the severity of cognitive impairment in patients with mild cognitive impairment and Alzheimer's disease.

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Abstract

This study was to analyse the degeneration of the Retinal Nerve Fiber Layer (RNFL) and optic disc and the relationship between optic nerve damage and the severity of cognitive impairment in patients with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). The RNFL thickness and optic disc variables were assessed by optical coherence tomography in patients with MCI and AD and control subjects. Moreover, the correlation coefficients among RNFL thickness, optic disc parameters, and Mini-Mental State Examination (MMSE) scores were investigated in AD and MCI patients. RNFL thickness was significantly thicker in control group than that in the other two groups (P<0.05). The significant difference was detected between groups AD and MCI (P<0.05). Cup-to-disc ratio and pallor area-to-disc area ratio were increased but disc rim area was reduced in groups MCI and AD compared with in normal group (P<0.05). The significant difference was existed between groups AD and MCI (P<0.05). Pearson's correlation test showed that compared with MMSE scores there was negative correlations in cup-to-disc ratio (P<0.05) and pallor-to-disc area ratio (P<0.01), but positive correlations in total RNFL thickness (P<0.01) and disc rim area (P<0.01). These results indicated that there was the degeneration of RNFL in MCI and AD patients. Moreover, the correlations among RNFL thickness, optic disc parameters and MMSE scores revealed that the severity of the optic nerve damage was increased along with the aggravation of the disease.

Keywords: Retinal nerve fiber layer, Optic disc, Alzheimer's disease, Mild cognitive impairment, Optical coherence tomography.

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Introduction

As people grow older, the incidence of Alzheimer's disease (AD) increases gradually. By some estimates more than 100 million persons will suffer from AD by 2050 [1]. As everyone knows, patients with AD have visual problems including reduced visual acuity, visual field defects, impaired color discrimination, changes in smooth and saccadic eye movements, alterations in visual evoked potentials and fixation defects [2,3]. Mild Cognitive Impairment (MCI) is a broad term that encompasses several subtypes, among which amnestic MCI may be an early transitional stage to AD [4]. MCI is more likely to progress to AD by 10% per year, compared with 1% of normal subjects [5,6]. Due to the increasing incidence of AD and MCI more researches are needed to prevent AD as well as the related retinal changes. Thus, many ways have been tried to investigate the Retinal Nerve Fiber Layer (RNFL) thickness and optic disc in AD and MCI.

Optical Coherence Tomography (OCT) is a new non-invasive examination that can assess the RNFL thickness and optic disc variables, and is used in various ophthalmologic diseases including ocular hypertension, glaucoma, Alzheimer's disease, Parkinson's disease and multiple sclerosis [7]. RNFL is thin in Alzheimer's disease and multiple sclerosis, which may be a structural biomarker for the damage of the optic nerve [8]. Some reports have described the degeneration of the RNFL and optic disc in AD [9-12]. Hinton et al. [9] first reported the study of retinal damage which showed widespread damage in the optic nerve with reduced RNFL thickness. Berisha et al. [10] hypothesized that a specific superior RNFL loss could be detected by OCT in patients with early AD. Tsai et al. [11] found that cup-to-disc ratio, optic disc volume and disc rim area in patients with AD were significantly changed compared with normal group. However, there still were contradictory standpoints about RNFL and optic disc changes in AD or MCI. For example, Kergoat et al. [13] found no difference in RNFL thickness was observed between AD and healthy subjects. All

in all, these findings indicated that different methodologies may be responsible for the results discrepancy. In addition, the data about optic disc (cup-to-disc ratio, pallor area-to-disc area and disc rim area) were scarce.

The aim of the present study was to assess whether the RNFL and optic disc were degenerate definitely and whether there was a relationship between optic nerve damage and the severity of cognitive impairment in patients with AD and MCI.

Material and Methods

Subjects

Forty nine MCI patients and forty six AD patients were obtained from department of neurology; forty nine age-matched controls were obtained from department of ophthalmology in the First Affiliated Hospital of Zhengzhou University in 2014 and 2015. All patients signed informed consent. The study adhered to the guidelines of the Declaration of Helsinki, and was approved by ethic committee of the First Affiliated Hospital of Zhengzhou University, China.

The AD patients were diagnosed by neurologists in the First Affiliated Hospital of Zhengzhou University and met criteria for AD set by the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [14,15]. We used Petersen criteria for the diagnosis of MCI [16]. Each patient with AD or MCI underwent a detailed neurological examination including laboratory and neuro-imaging evaluations, and psychometric test. Cognitive function was evaluated by means of the Mini-Mental State Examination (MMSE) [17] in AD, MCI and control groups. The criteria for normal control were: (1) no dementia or cognitive impairment; (2) MMSE scores above 28. The criteria for MCI were: (1) memory complaints; (2) MMSE scores above 25; (3) abnormal behaviors at the MMSE (missing two or three words).

Some patients were excluded due to some certain conditions that are capable of affecting RNFL thickness, such as glaucoma, increased intraocular pressure, optic neuropathy, diabetic retinopathy, macular degeneration, retinal artery occlusion, cerebral infarction, Parkinson's disease, cerebral apoplexy and other diseases.

Method

All subjects underwent ophthalmological examination including visual acuity, diopter, slit lamp biomicroscopy, Intraocular Pressure (IOP), direct ophthalmoscopy, indirect ophthalmoscopy and optical coherence tomography. The examinations were performed by an experienced technician with blinded method. The IOP was measured by Goldmann applanation tonometer. By OCT total RNFL thickness and optic disc parameters were measured in both eyes of every subject and only one eye for high quality image was selected into the study (Stratus 3000, Carl Zeiss). The RNFL thickness scan mode with a diameter of 3.4 mm centered on the optic disc was used and the software automatically calculated the RNFL thicknesses. The optic disc scan was got from six linear scans centered on the optic disc and the software automatically measured the optic disc parameters. Every eye was repeatedly scanned for three times and the average value was considered to be the reliable data.

Statistical analysis

SPSS 16.0 data analysis software (SPSS Inc., USA) was used. All clinical data were expressed as mean ± Standard Deviation (SD). The chi-square test was used to compare the difference in sex among three groups. One way Analysis of Variance (ANOVA) was used to compare the differences in age, IOP, RNFL thickness and optic disc parameters among three groups following post hoc comparison between groups by Bonferroni correction. Spearman's correlation coefficient analysis was applied to analyse the correlations among the retinal nerve fiber layer thickness, optic disc variables and MMSE scores. P value less than 0.05 was statistically significant.

Results

There were 49 patients participated in our research. The descriptive data in MCI, AD and control groups were summarized in Table 1. No significant differences in sex, age, or IOP were found among three groups ($P>0.05$). The results indicated that sex, age and IOP had no effect on the comparison of RNFL thickness and optic disc.

Total RNFL thickness and optic disc variables values in patients with MCI, AD and control subjects were illustrated in Table 2. The results showed (1) RNFL thickness: RNFL thickness was significantly thicker in the control group compared to the other two groups ($P<0.05$), the significant difference was detected between groups AD and MCI ($P<0.05$); (2) optic disc variables: cup-to-disc ratio and pallor area-to-disc area ratio were increased but disc rim area was reduced in groups MCI and AD compared with the normal group ($P<0.05$), the significant difference was existed between groups AD and MCI ($P<0.05$). These data suggested the thinner RNFL consistent with higher cup-to-disc ratio and pallor area-to-disc area ratios and lower disc rim area proved the damage of optic nerve in MCI and AD patients.

From the Table 3, the correlation coefficient among RNFL thickness, cup-to-disc ratio, pallor-to-disc area ratio, disc rim area and MMSE scores were revealed. Pearson's correlation test showed that compared with MMSE scores there was negative correlations in cup-to-disc ratio ($P<0.05$) and pallor-to-disc area ratio ($P<0.01$), but positive correlations in total RNFL thickness ($P<0.01$) and disc rim area ($P<0.01$). The correlation coefficient among RNFL thickness, optic disc parameters and MMSE scores revealed that the severity of the optic nerve degeneration increased along with the aggravation of the disease.

Table 1. *The descriptive data of patients with MCI, AD and control groups (mean ± SD).*

		Control (n=49)	MCI (n=49)	AD (n=46)		P value
Sex	M	24	22	24	χ^2=0.451	
	F	25	27	22		
Age (y)		71.1 ± 8.6	70.9 ± 6.1	72.8 ± 5.2	F=2.121	>0.05
IOP (mmHg)		15.1 ± 6.5	17.1 ± 7.6	16.1 ± 5.2	F=2.759	>0.05

MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; n: Eyes; M: Male; F: Female; IOP: Intraocular Pressure.

Table 2. *Total RNFL thickness and optic disc variables values in patients with MCI, AD and control subjects (mean ± SD).*

	Control	MCI	AD	F value
T	100.12 ± 15.01	92.52 ± 19.23▲	87.13 ± 17.05▲■	7.985**
C/D	0.42 ± 0.61	0.48 ± 0.65▲	0.53 ± 0.22▲■	5.115**
P/D	0.26 ± 0.11	0.35 ± 0.26▲	0.319 ± 0.32▲■	6.121**
D	2.01 ± 0.61	1.83 ± 0.29▲	1.51 ± 0.32▲■	8.923**

MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; T: Total (μm); C/D: Cup-to-Disc ratio; P/D: Pallor-to-Disc area ratio; D: Disc Rim Area (mm^3); Comparison to the control group: P<0.05; comparison to MCI: P<0.05; ANOVA: *P<0.05, **P<0.01.

Table 3. *Correlation coefficient among RNFL thickness, cup-to-disc ratio, pallor-to-disc area ratio, disc rim area and MMSE.*

	MMSE
Total RNFL thickness (μm)	0.256**
cup-to-disc ratio	-0.192*
pallor-to-disc area ratio	-0.251**
disc rim area (mm^3)	0.216**

MMSE: mini-mental state examination; Spearman's correlation analysis: *P<0.05, **P<0.01.

Discussion

Retinal nerve fiber layer thickness and optic disc

According to above results, several aspects would be addressed. The first question involves the changes of RNFL thickness and optic disc. RNFL thickness is thin in Alzheimer's disease and multiple sclerosis, which may be a structural biomarker for the damage of the optic nerve [8]. RNFL thickness by OCT in previous investigation showed that significantly thin RNFL was found in patients with AD compared with control subjects [10]. Paquet et al. [18] compared RNFL thickness by OCT among healthy control subjects, MCI, mild AD, and moderate-to-advanced AD. All three groups showed significant difference compared with the healthy control group. No significant difference was found between mild AD and MCI [18]. Other studies by Parisiet [19] and Iseri et al. [20] also indicated there was an obvious reduction of RNFL thickness for AD and MCI patients. In line with the findings, we also found significant difference with respect to RNFL thickness among AD, MCI, and healthy control groups, especially between AD and MCI.

There are more studies concerning RNFL thickness in AD with the OCT technique. However, there are only a few data that have assessed the optic disc variables. In this study, we investigated optic disc parameters by OCT among three groups. The research found that the patients with MCI and AD showed obviously changes in cup-to-disc ratio, pallor-to-disc area ratio and disc rim area. Consistent with our findings, in 1991, Tsai et al. [11] found that cup-to-disc ratio, optic disc volume and disc rim area were significantly changed and were related to MMSE and durations of disease with the use of retinal nerve fiber photography and computerized image analysis of the optic nerve head. Lu et al. [21] showed that the cup-disc ratio in AD patients was increased by 39-43% when compared to that in the control group. A case control study also showed that an obvious defection in AD patients' RNFL was found and that there was a 3-fold greater odds ratio demonstrating the increased cupping in AD [22]. The results of our study proved the optic nerve damage existed in AD and MCI.

To our knowledge, RNFL is a region that is sensitive to axonal and neuronal loss as it contains ganglionic cell neurons originating from optic nerve and their axons [23]. Retinal nerve fibers converge together when they exit from the eye and descend through the lamina cribrosa becoming the optic disc. Retinal nerve fiber layer is association with optic disc closely. Therefore, the thin RNFL is consistent with large cup-to-disc ratio and pallor area-to-disc area ratios and small disc rim area. By OCT the changes in retina and optic disc had been identified in patients with AD, including significant decrease in RNFL thickness and disc rim area and increase in cup-to-disc ratio and pallor-to-disc area ratio. In addition, some scholars have speculated that the disc rim area more exactly and directly reflect the severity of optic nerve damage than the cup-to-disc ratio and pallor-to-disc area ratio [24]. The loss of disc rim area was typically morphological change of optic nerve degeneration, and it was less affected by age, refraction and optic disc size [24]. Thus, it is obvious that RNFL and optic disc, especially disc rim area, could be used as sensitive indicators of optic nerve damage in patients with AD and MCI by OCT.

Many previous reports indicated that the damage in retina and optic disc were attributed to nerve degeneration only in primary visual cortex [25-27]. Armstrong [28] found axons from retina project to primary visual cortex, senile plaques and neurofibrillary tangles in primary visual cortex may cause the damage in retina and optic nerve. Other studies revealed that patients with AD had senile plaques and neurofibrillary tangles in primary visual pathways (optic nerve and retina), leading to the damage of retina [29]. Tsai et al. [11] suggested that the degeneration of retinal nerve fiber layer and optic disc might possibly ascribe to both antegrade degeneration secondary to retinal ganglion cell degeneration and retrograde degeneration originating at optic tract or visual cortex. The question need to

be clarified is the relationship (succession or parallel) between visual cortex and primary visual pathways.

The relationship between optic nerve damage and the severity of cognitive impairment

Many studies have showed that RNFL thickness is measured by OCT in AD patients. However, the number of studies about the relationship between optic nerve damage and the severity of cognitive impairment is still limited [19,30,31]. In this study, we investigated the relationships among RNFL thickness, optic disc and MMSE scores. In 1991, Tsai et al. [11] found that cup-to-disc ratio, optic disc volume and disc rim area were significantly changed and were related to MMSE and durations of disease. Although pallor area-to-disc area ratio was not significantly different, the patients with higher pallor area-to-disc area ratios had a higher MMSE scores and longer durations of disease with the use of retinal nerve fiber photography and computerized image analysis of the optic nerve head between patients with AD and controls. Paquet et al. [18] found no significant relationship between MMSE scores and RNFL measurement by OCT among healthy control subjects, MCI, mild AD, and moderate-to-advanced AD [18]. Our results also showed that the RNFL thickness was thinner, disc rim area was decreased and cup-to-disc ratio and pallor area-to-disc area ratios were larger from MCI to AD. Like the existing data, our study revealed the severity of the optic nerve degeneration increased along with the aggravation of the cognitive impairment. The relationship played an important role for RNFL and optic disc analysis by OCT in monitoring the development of AD and in assessing the effect of treatment.

In contrast to these studies, no significant difference was reported between RNFL and MMSE scores. For example, a study proved that the damage in visual function occurring in dementia of the Alzheimer's type were not related to optic nerve head structural anomalies, at least in the earlier stage of AD [13]. Kergoat et al. [13] found no difference was observed between AD and control subjects in RNFL thickness by scanning laser polarimetry. The reason for difference may include a low sample size and methodological difference.

MCI

MCI is a risk factor for AD. Extensive research is being devoted to prevent MCI converting to AD. The damage of RNFL thickness and optic disc in MCI indicates that the change of retina and optic nerve is an early event in the development of this disease. OCT is a safe and reproducible method to assess retina and optic nerve degeneration in AD and MCI. By OCT we were able to early detect MCI and prevent MCI progress to AD.

Our study also had some limitations. First, the limitation of the study is the relatively small sample size because of the strict inclusion criteria. The study mainly included patients with mild-to-moderate Alzheimer disease due to poor coordination of severe Alzheimer' disease patients and this may affect the accuracy of the results. A follow-up study is needed to further prove the relationship between optic nerve damage and the severity of disease progression. Therefore, a larger cohort of MCI and AD patients and a follow-up study are needed to confirm these conclusions.

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Conflicts of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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