

Observation Study of the Retina with the Alzheimer's Disease or Amnesic Mild Cognitive Impairment Patients

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Abstract

Objective: We investigated the regularity changes of the retinal nerve fiber layer (RNFL) and macular ganglion cell complex (mGCC) of the Alzheimer's disease (AD) and amnesic Mild Cognitive Impairment (aMCI) patients.

Methods: 24 AD patients, 22 aMCI patients and 30 health controls whose age were above 60 years old were recruited in the study. The RNFL thickness and the mGCC average thickness were measured by Fourier-domain optical coherence tomography (FD-OCT).

Results: Compared with the controls, we found statistically significant lower of the intraocular pressure (IOP) in the AD and aMCI patients. When compared with the AD patients and controls, aMCI patients showed a significant decrease in RNFL thickness in ST (Superior Temporal), TU (Temporal Upper) and temporal (TU+TL) quadrants. The average thickness of the mGCC was significantly thinner in the aMCI patients than in the AD patients and Controls. The Gross Loss of Volume (GLV) was significantly higher in the aMCI group than in the patients and Controls.

Conclusion: AD and aMCI patients had lower IOP, but there was no evidence that IOP would decrease with the progression of disease. Retinal degeneration in the aMCI patients detected by OCT may be a pathological indicator of the disease.

Keywords: Alzheimer disease; Mild cognitive impairment; Optical coherence tomography; Retinal nerve fiber layer; macular ganglion cell complex

Introduction

Alzheimer Disease (AD) is a common type of dementia, which is related to age. AD affects approximately of 10% individuals aged 65 or over [1]. With advancing age, the prevalence of the disease increases to 19% in individuals aged 74-84 [2], and is 30-35% for those older than 85 years old [3]. Mild cognitive impairment (MCI) is defined as impairment in cognitive function with otherwise normal performance of activities of daily life [4]. A hypotype of MCI which firstly damaged the memory function is called amnesic mild cognitive impairment (aMCI). aMCI now is considered to s early phase of AD [5].

Retina as an extension sensory system of the central nervous system (CNS) could be a good observational window of CNS diseases. A variety of visual problems have been reported in patients with AD including loss of visual acuity, color vision, visual fields and contrast sensitivity [1]. Studies have confirmed the existence of AD-related pathology arising in both the brain and the retina [6-10].

Fourier-domain optical coherence tomography (FD-OCT) is a well-established and non-invasive examination that can measure the thickness of the retinal nerve fiber layer (RNFL) and analyze the macular ganglion cell complex (mGCC). There has been much debate about the fact that the degeneration of RNFL in AD and MCI patients. Owing to technology limitation, most of the researchers applied SD-OCT or TD-OCT to their studies, which resolution are relatively low and time costing. Benefit from the high-resolution, high-speed technique of the new scan system of FD-OCT, we measured the thickness of the inner three retinal layers (which are collectively known as the macular ganglion cell complex) and the RNFL in aMCI and AD patients.

Methods

After approval from the ethics committee of Xuanwu Hospital, Capital Medical University, Beijing, China and written informed consent, 22 subjects diagnosed with AD, 24 subjects diagnosed with aMCI and 30 age-matched controls were enrolled in the study.

All AD patients were diagnosed by the neurologists in Xuanwu Hospital according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria for

probable AD [11]. Mini-mental state examination (MMSE), clinical dementia rating (CDR), Hachinski ischemic scale (HIS) and Hamilton depression scale (HAMD) were used to assess the neuropsychological impairment. The routine brain CT or MRI scan was done to evaluate the hippocampal atrophy and to exclude the vascular dementia.

Each aMCI patient was diagnosed by the neurologists in Xuanwu Hospital according to the criteria as follows: (a) impaired memory performance on a normalized objective verbal memory test, (b) recent history of symptomatic worsening in memory, (c) normal or near-normal performance on global cognitive tests[MMSE score>24] as well as on activities of daily living scale, (d) global rating of 0.5 on the CDR scale, with a score of at least 0.5 on the memory domain, and (e) absence of dementia [12-14]. The criteria for controls were: (a) no memory complaints, (b) MMSE score \geq 28.

Criteria requirements for all the subjects were: Diopters: spherical -3.00 DS to $+3.00$ DS, cylinder -3.00 DC to $+3.00$ DC, anisometropia \leq 2D, (b) IOP measured three times <21 mmHg, (c) cup to disc ratio (C/D) <0.6 and the difference of two eyes <0.2 .

Exclusion criteria were: (a) retinal detachment, retinal artery occlusion, optic neuropathy, ocular trauma or surgery, diabetes mellitus, hypertension, cerebral infarction and other diseases which may affect RNFL thickness; (b) personal or family history of

psychiatric disorders, anxiety, depression, dementia associated with lewy body formation, frontotemporal dementia, Vascular dementia, Creutzfeldt–Jakob disease, Binswanger disease, Parkinson's disease, and Multiple Sclerosis, and others; (c) some other serious chronic diseases.

All the subjects were examined for visual acuity, refractive error, intraocular pressure (IOP), anterior and posterior segment biomicroscopy, dilated fundus examination. RNFL 3.45 and GCC procedures were taken by using RTVue OCT of FD-OCT (Optovue, Fremont, CA, USA). All scans were repeated three times and the threshold of signal strength index was above 50.

Data are reported as mean \pm SD and statistical analysis was performed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The differences of gender constituent ratio among controls, aMCI, AD and control subjects were compared with chi-square test. The differences about age, IOP, RNFL thickness and mGCC values among three groups were evaluated with one-way ANOVA followed by post hoc Turkey's comparison with Bonferroni corrections. And p value <0.05 was considered to be of statistical significance.

Result

		AD (n=24)	aMCI(n=22)	Control (n=30)		P value
Sex	M	12	10	16	$\chi^2=0.315$	p=0.854
	F	12	12	14		
Age(yrs.)		74.4 \pm 7.5	72.3 \pm 9.1	70.7 \pm 6.6	F=1.248	p=0.294
Education (yrs.)		11.27 \pm 3.56	11.55 \pm 3.5	10.23 \pm 4.75	F=0.653	p=0.524
MMSE		17.35 \pm 6.03	25.29 \pm 2.2	28.26 \pm 1.51	F=56.299	p=0.000*
MoCA		15.36 \pm 4.68	19.33 \pm 2.96		t=-2.455	p=0.023*
CDR		1.03 \pm 0.30	0.5 \pm 0.00		t=6.715	p=0.000*

*p<0.05

Table 1: Demographic characteristics and Cognitive assessment (means \pm SD).

IOP in AD, aMCI patients and controls

The IOP value in AD (12.7 \pm 2.8 mmHg) and aMCI (12.6 \pm 3.0 mmHg) patients showed a significant reduction (p<0.05) to the controls (14.4 \pm 3.3 mmHg). There are no significant differences between AD and aMCI group (Table 2).

	AD(n=24)	aMCI (n=22)	Control(n=30)
IOP mean \pm SE(mmHg)	12.7 \pm 2.8 Δ	12.6 \pm 3.0 \diamond	14.4 \pm 3.3

Δ p<0.05, AD vs Control; \diamond p<0.05, aMCI vs Control.

Table 2: The IOP data of the three groups (means \pm SD).

RNFL thickness in AD, aMCI patients and controls

There were significant differences (p<0.05) between aMCI, AD and Control groups in Temporal quadrant and ST (Superior Temporal), TU (Temporal Upper) section. The RNFL thickness of aMCI patients showed a significant reduction (p<0.05) in those three quadrants when compared to AD and Control groups. In the TL (Temporal Lower) section aMCI patients showed a significant reduction (p<0.05) compared to AD patients. But in all quadrants we didn't find RNFL thickness differences between AD and Control groups (p>0.05). And the overall average RNFL thickness among three groups were also no significant differences (p>0.05) in our study (Table 3).

Table 3 The RNFL data of the three group (means±SD)

Parameter	Location	AD (n=24)	aMCI (n=22)	Control (n=30)
Peripapillary RNFL thickness, mean ± SE(μm)	Superior RNFL thickness	136.36 ± 25.97	129.64 ± 22.08	136.90 ± 20.30
	ST	144.69 ± 25.25	134.05 ± 21.37 Δ◇	144.81 ± 16.85
	SN	128.04 ± 24.18	125.23 ± 22.14	129.00 ± 20.55
	Nasal RNFL thickness	74.15 ± 12.60	73.62 ± 14.59	73.04 ± 13.50
	NU	78.48 ± 12.64	78.49 ± 15.40	76.97 ± 13.40
	NL	69.81 ± 11.09	68.74 ± 12.05	69.10 ± 12.55
	Inferior RNFL thickness	135.09 ± 24.27	130.85 ± 21.71	134.37 ± 23.90
	IN	121.54 ± 18.77	119.58 ± 17.69	121.64 ± 18.87
	IT	148.64 ± 21.52	142.14 ± 19.10	147.10 ± 21.65
	Temporal RNFL thickness	84.68 ± 17.69	77.80 ± 12.40 Δ◇	84.56 ± 14.87
	TL	80.69 ± 18.10	74.51 ± 9.62 Δ	80.38 ± 13.10
	TU	88.67 ± 16.52	81.09 ± 14.01 Δ◇	88.73 ± 15.50
	Average RNFL thickness	107.27 ± 10.97	102.88 ± 8.54	107.21 ± 8.05

Δ p<0.05, aMCI vs. AD; ◇ p<0.05, aMCI vs. Control.

Table 3: The RNFL data of the three group (means ± SD).

mGCC in AD, aMCI and controls

The overall average thickness of macular GCC in aMCI subjects was significantly decreased (p<0.05) compared to AD and Control subjects. Goss Loss of volume was also significant decreased (p<0.0017) in the aMCI patients than in the Controls (Table 4).

Parameter	AD (n=24)	aMCI (n=22)	Control(n=30)
GCC-average (μm)	93.42 ± 7.73	88.83 ± 9.20 Δ◇	94.81 ± 6.97
GLV (%)	10.33 ± 6.24	13.76 ± 8.26*	8.67 ± 5.04

Δ p<0.05, aMCI vs. AD; ◇p<0.05, aMCI vs. Control; *p<0.0017, aMCI vs. Control.

Table 4: The mGCC data of the three groups (means ± SD).

Discussion

Reduction of IOP in AD and aMCI patients

In our study, the IOP of AD and aMCI patients were significantly lower than the healthy controls. In pathological conditions, the reason of lower IOP usually came from the reducing aqueous humor production or over outflow of the aqueous humor. In reviewing literature, we haven't found any published studies that showed the pathological changes of trabecular meshwork in AD or aMCI patients. As we have noticed that the vascular hypothesis emerged as an alternative to the amyloid cascade hypothesis for the pathophysiology of AD. Destruction of the organization of the blood brain barrier, decreased cerebral blood flow, and the establishment of an

inflammatory context would be responsible for the neuronal damage [15].

For instance, dural arterovenous fistulas and jugular venous reflux may lead to chronic cerebral venous hypertension and decreased cerebral blood flow [1617]. Roher et al. [18] reported that total cerebral blood flow was 20% lower in the AD group than the Control group and those values were directly correlated with pulse pressure and cognitive measurements. Gietl et al. [19] found that MCI patients also had lower regional cerebral blood flow indicating a reduction uptake of [11C]-Pittsburgh Compound B. It could be postulated that cerebral lower blood flow of brain may cause the reducing aqueous humor production in AD and aMCI patients.

Previous reports have demonstrated that secretion, synthesis, and transport of choroid plexus are impaired and related to decrease of cerebrospinal fluid in AD patients [20-22]. Thus it may influence the trans-lamina cribrosa pressure difference (TLCPD). There is still some debate about the high prevalence of glaucoma in AD patients due to TLCPD. Some reported that high TLCPD plays an important role in glaucomatous optic damage [23-25], while others thought difference between cerebrospinal fluid pressure (CSFP) and IOP cannot alter the position or shape of the lamina cribrosa [26]. In our study, we excluded the high C/D patients and didn't have their CSFP, thus we cannot prove either side of view. But as we found in the study that overall RNFL average thickness haven't showed significant differences between three groups, we assumed that a potential regulating mechanism to balance the CSFP and IOP besides the atrophy of CNS. Thus this may play as a self-protection mechanism to induce the decreased IOP level of aMCI and AD patients to prevent the optic nerve damage induced by fluctuating TLCPD.

IOP didn't demonstrate a difference between AD and aMCI patients, which may indicate that the unknown factors which may alter the IOP level had developed in aMCI stage. For further study of IOP in AD patients, we would add central cornea thickness (CCT) measurement and CSFP monitoring to analyze the role of IOP reduction in AD duration.

The changes of RNFL and mGCC in aMCI patients

With the development of OCT technology, the revolutionary advances in the image resolution and scanning speed have benefited the retina examination. RTVue OCT is a widely used FD-OCT in ophthalmology clinic with unparalleled advantages in scanning speed and resolution Time Domain OCT. We can have reliable and reproducible retina data of AD and aMCI patients, taking advantage of the benefits by FD-OCT.

According to our study, the RNFL thickness in ST, TU and Temporal quadrants of aMCI subjects are significantly thinner than Control groups. It has been suggested that peripapillary RNFL thickness is a marker of axonal loss, which would reflect central nervous system axonal loss [27]. Several studies also shows thinner of the retina in aMCI patients [28-31]. While Cheung et al. [32] observed that there aren't differences between aMCI patients and Control group in RNFL thickness. But in their study, they found that compared with normal controls, aMCI patients had significantly reduced ganglion cell-inner plexiform layer thickness at the macular. This might indicate that the degeneration of the retina in aMCI patients had existed. And the negative results of RNFL thickness changes might due to the severity condition of aMCI patients they enrolled and different procedure to evaluate the retina. In our previous research, we found there are reduction of RNFL thickness in superior quadrant selectively in MCI and early AD patients [30] and with the development of AD, the degeneration of the RNFL appeared not only in superior quadrant, but also in inferior quadrant [30,33]. In this study, we didn't found significant thinning changes in inferior quadrant of RNFL thickness in aMCI patients compared to Control, which partly supported our point view of RNFL changes during the progression of AD.

Our study showed that the thinner changing of mGCC thickness and GLV are parallel to the RNFL thickness. FD-OCT can measure the thickness of the mGCC layer, which extends from the internal limiting membrane to the inner nuclear layer and includes the retina ganglion cell (RGC) layer [34]. RGCs became myelinated when they leave the eyes, forming the optic nerve and providing the connection between the eye and central nervous system (CNS) [35]. There is increasing evidence that neurodegenerative conditions occurs both in the CNS and in the retina [8-10,35]. Therefore, observing RGCs might be a direct evidence to retina degeneration. Our results also proved those facts with a non-invasive way.

The changes of RNFL in AD patients

Interestingly, unlike the most reports (including our previous studies) in the past [29,30,33], our results didn't show a significant difference between AD and Control subjects in RNFL thickness and mGCC value. We assumed that in this study, we excluded the subjects that C/D>0.6 and the difference of C/D in two eyes >0.2. Thus it is likely that the thinner RNFL subjects of AD patients excluded.

Also, according to previous studies, there was high prevalence of glaucoma in AD patients. Bayer et al. [36] reported that 29 out of 112 patents with AD find glaucoma. Tamura et al. [37] also had a similar

result. So our inclusion criteria may exclude some subjects with AD and glaucoma as well. In other hand, some severe AD patients also excluded from the study because of their poor recognition function for hardly cooperating nasal fixation. But in aMCI group we found the retinal degeneration without the cupping, which might indicate that the high ratio of the C/D and the prevalence of glaucoma may develop with the progression of AD. In our previous studies, bigger cup and disc ratio was not an exclusion criteria. Based on results of the previous and this study, we were inclined to think that in the early stage of AD, patients' RNFL began to thin but whose C/D didn't change. As the disease progresses, thinning RNFL would accompany with the cupping. As our results showed that in 3 groups of our study, their RNFL thickness had a consistency of the mGCC average thickness and GLV, which might infer that the OCT value could be an indicator to predict the cupping. This rule of pathological changes hypotheses may explain that after excludes the bigger C/D, AD patients' RNFL thickness had high consistency of the control group while aMCI group showed a significant decreasing RNFL thickness. Thus, we can infer that the high prevalence of glaucoma in AD patients and the RNFL thinner changing in AD patients are mainly due to glaucomatous injury rather than RGC axonal degeneration caused by CNS axonal losses which have known ever. Because of this, after we applied the exclusion standard of large C/D, AD patients had high consistency with Control group in RNFL and mGCC thickness, and also, all 3 groups showed no significantly differences in overall RNFL thickness.

We should realize that some AD patients had a normal RNFL thickness and mGCC value although their CNS had been suffering from a neurodegenerative disease. The protective factor to their retina remained unknown. But according to our results, we assumed that AD patients' low IOP contributed a low TLPD, thus normal axoplasmic flow could be one possible factor [38].

Conclusions

We found that AD and aMCI patients had lower IOP, which may be a self-protective mechanism. FD-OCT is an effective and non-invasive method for us to evaluate the retinal degeneration in aMCI patients.

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