Neurol Sci (2015) 36:1141–1146
DOI 10.1007/s10072-014-2055-3

ORIGINAL ARTICLE

The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness

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Received: 27 August 2014 / Accepted: 26 December 2014 / Published online: 10 January 2015

Abstract The goal of the present study is to investigate the relationship between the degree of cognitive impairment and retinal nerve fiber layer (RNFL) thickness which is measured by the optical coherence tomography (OCT). Thirty-five patients with Alzheimer's disease (AD), 35 patients with mild cognitive impairment (MCI), and 35 healthy volunteers, between the ages of 60–87, who were examined in the neurology outpatient clinic among 2012–2013 were prospectively involved in our study. Mini mental state examination (MMSE) test, montreal cognitive assessment (MOCA), and also neuropsychological test batteries were used for the neurocognitive evaluation. RNFL thickness was measured by the OCT technique and the differences among groups were studied. The relationship between RNFL thickness and MMSE scores with demographic characteristics was investigated. RNFL thickness was significantly lower in AD and MCI groups compared with the control group ($p < 0.01$). No significant differences of RNFL were found between the MCI and the AD groups ($p > 0.05$). Significant correlation was found between MMSE scores and the RNFL values ($p < 0.05$). Significant thinning in RNFL along with age was detected ($p < 0.05$). In our study, it is thought that retinal nerve fiber degeneration and central nervous system degeneration may be concurrent according to the thinning of RNFL measured by OCT in AD and MCI groups. RNFL measurement may also be useful for early diagnosis and evaluation of the disease progression. Further studies are needed to optimize the utility of this method as an ocular biomarker in AD.

Keywords Retinal nerve fiber layer · Optical coherence tomography · Alzheimer's disease · Mild cognitive impairment

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Introduction

Alzheimer disease (AD) is the most common type of dementia, which causes permanent loss in more than one cognitive area sufficient to impair daily living activities [1]. Mild cognitive impairment (MCI), on the other hand, is a term used to define a period when there is a cognitive loss that is non-proportional to age and educational status but daily functions remain unaffected [2–5]. MCI is accepted as a risk factor and considered to be the early stage of AD. Discovery of markers allowing diagnosis of AD at a preclinical phase can delay or even prevent the clinical phase by starting therapeutic interventions early in the course of the disease. AD can affect eye, visual pathways, and visual cortex and lead to various visual signs and symptoms even at early stages. Among various visual disturbances reported by studies are a decrease in contrast sensitivity and the ability to perceive motion,

abnormal mydriatic response of pupils, reduced visual acuity, visual field defects, impaired color discrimination, changes in smooth and saccadic eye movements, alterations in visual evoked potentials, fixation defects, and disorders of complex visual functions such as reading and visuospatial functions [6, 7]. In AD, one of the most significant pathological changes related to visual system is the decrease of the optic nerve fiber density [6, 8, 9]. Various histopathological studies have shown the degeneration of retinal ganglionic cell layer (GCL) and optic neuropathy in AD [10]. Retinal nerve fiber layer (RNFL) resembles gray matter of brain, and changes in its thickness are only dependent on axonal injury. Axons of retinal ganglionic cells form a synapse in the lateral geniculate nucleus, mesencephalon, pretectum, or hypothalamus. From this perspective, retina is considered as a part of brain, which can be easily observed [11, 12]. The aim of our study was to assess the correlation of RNFL thickness measured with optic coherence tomography (OCT) technique with the level of cognitive impairment.

Patients and method

This prospective study included patients aged equal to or greater than 60 years who presented to Baskent University Faculty of Medicine, Department of Neurology between 2012 and 2013 and diagnosed with AD or MCI after detailed neurological evaluation, as well as healthy individuals without cognitive impairment. A total of 135 subjects were enrolled.

Cognitive assessment was done with the standardized mini mental state examination (MMSE) and the montreal cognitive assessment (MOCA) test, which were adapted to Turkish society, as well as a wide-scale battery of neuropsychological tests focused on such functions as attention, executive functions, learning and memory, language, and visual-spatial perception [13–18]. The battery of tests is composed of Rey auditory-verbal memory test, stroop test, digit span test, trail making test, and Rey complex figure test. AD and MCI were diagnosed on the basis of DSM-IV and Petersen criteria, respectively [20, 21].

The patients diagnosed as AD or MCI with neurocognitive evaluation and the healthy subjects underwent ophthalmological examination that includes assessment of visual acuity, intraocular pressure measurement, ocular motility, and examination of anterior chamber and retina. After the physical examination, RNFL thickness was measured with OCT. RNFL measurement was performed with Zeiss Cirrus HD 5000 model OCT device on the same day with the neurocognitive tests. RNFL thickness measurements were recorded in microns and the mean value of the measurements from both eyes was recorded for statistical analyses. The measurement of RNFL was performed one time in the same patient.

Thirty patients were excluded, either due to having certain conditions that are capable of affecting RNFL thickness, such as glaucoma, advanced cataract, degenerative myopia, optic neuropathy, or diabetic retinopathy, or being unable to undergo measurements due to lack of cooperation. The patients were then divided into three groups, namely AD ($n = 35$), MCI ($n = 35$), and the control ($n = 35$) groups.

This study was approved by Baskent University Institutional Review Board and Ethics Committee with a project code of KA11/115. All subjects gave informed consent.

Statistical analysis

Statistical analyses were performed with IBM SPSS for Windows Version 21.0 software package. Numerical variables were expressed as mean ± standard deviation or median (minimum−maximum) and categorical variables as numbers and percentages. Normality of the continuous variables was tested by Shapiro Wilks test. Levene test was used to show the homogeneity of variances. Independent samples t test was used to determine the differences between two independent groups. More than two independent groups were compared by one-way ANOVA or Welch ANOVA as appropriate. Post-hoc comparisons were done by Tukey HSD or Games Howell test. Chi square test was used to compare the groups with respect to the categorical variables. Correlation between numerical variables was tested with Pearson's correlation test when parametric test assumptions were met and with Spearman's correlation coefficient when those assumptions were not met. A p value less than 0.05 was considered statistically significant.

Results

This study evaluated the data of 35 control subjects and two groups of patients with AD and MCI, each containing 35 patients, who presented to Baskent University Faculty of Medicine, Department of Neurology between 2012 and 2013 and diagnosed by means of detailed history, clinical features, imaging techniques, and detailed neurocognitive evaluation.

Descriptive data of AD, MCI, and control groups with respect to age, sex, and educational status are summarized in Table 1. There were no significant differences between the groups with respect to sex. All three groups had a mean age equal to or greater than 70 years.

Comparison of RNFL thicknesses on the basis of demographic features, independent of the groups, is shown

Table 1 The demographic properties of the participants

	Control ($n = 35$)	MCI ($n = 35$)	AD ($n = 35$)
Sex			
F	23 (65.7 %)	20 (57.1 %)	21 (60 %)
M	12 (34.3 %)	15 (42.9 %)	14 (40 %)
Age	70.2 ± 8.0 (60–87)	74.1 ± 6.3 (62–85)	75.4 ± 6.9 (62–87)
Educational status			
Primary school	6 (17.1 %)	9 (25.7 %)	14 (40 %)
Secondary school	1 (2.9 %)	2 (5.7 %)	8 (22.9 %)
High school	13 (37.1 %)	9 (25.7 %)	8 (22.9 %)
Higher education	15 (42.9 %)	15 (42.9 %)	5 (14.3 %)

Table 2 The correlation of RNFL with sex and educational status

	RFNL (mean ± SD)	p
Sex		
F ($n = 64$)	85.2 ± 9.6	0.656
M ($n = 41$)	84.4 ± 8.9	
Age		
60–68	89.3 ± 7.1	0.005*
69–77	83.1 ± 9.9	
78–87	82.8 ± 9.2	
Educational status		
Primary school ($n = 29$)	84.4 ± 9.8	0.803
Secondary school ($n = 11$)	84.5 ± 9.5	
High school ($n = 30$)	84.0 ± 8.0	
Higher education ($n = 35$)	86.1 ± 10.1	

* Mean RNFL of 60–68 years age group was significantly different than those of other groups

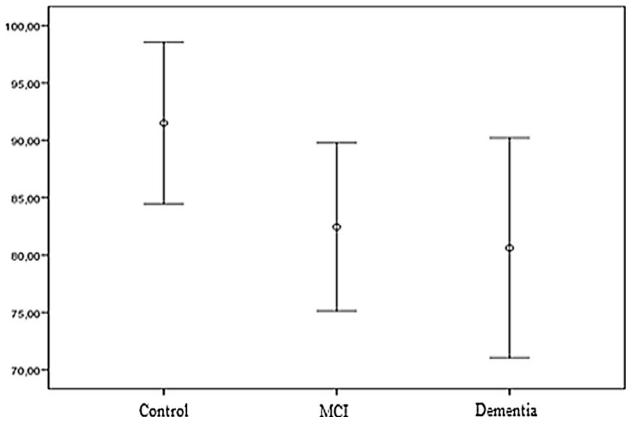

Fig. 1 RNFL thickness (mean ± SD) in all groups

in Table 2. Women participating in the study collectively had a mean RNFL of 85.2 ± 9.6 μm, while men collectively had a mean RNFL of 84.4 ± 8.9 μm. According to these data, there was no significant difference between both sexes with respect to RNFL thickness ($p > 0.05$). To ensure a homogenous distribution, the patients were divided into three equal parts based on age range, and three age groups were formed. Mean RNFL of 60–68 years age group, the youngest age group in our study, was significantly different than those of other groups ($p \leq 0.05$). No correlation was found between educational status and RNFL thickness.

Mean MMSE and MOCA test scores and RNFL thickness measurements are shown in Table 3. RNFL thickness was significantly greater in the control group compared to the other two groups ($p < 0.001$). No significant difference was detected between AD and MCI groups ($p \geq 0.05$) (Table 3; Fig. 1).

A significant correlation was present between MMSE test and RNFL thickness ($p < 0.05$) upon examination of the relationship between MMSE test scores and RFNL thickness measurements of all study participants. A comparison of MOCA test scores, which is applicable only to the MCI and the control groups, and mean RNFL thickness revealed that RNFL thickness also increased in parallel with the MOCA test scores, although no significant difference existed statistically.

Discussion

In AD, a wide variety of visual symptoms and signs of visual disturbance may be observed. It is believed that the

Table 3 Mean test scores and RNFL values of the groups

* RNFL thickness was significantly greater in the control group compared to the other 2 groups

	Control ($n = 35$)	MCI ($n = 35$)	AD ($n = 35$)	p
MMSE	29	28	18	
MOCA	25.3 ± 2.2	22.2 ± 3.2	15.6 ± 5.0	
RNFL	91.5 ± 7.1	82.5 ± 7.3	80.6 ± 9.6	<0.001*

exact cause of visual complaints is related to neurodegeneration in central nervous system, especially in visual cortex [22, 23]. Many studies have shown that in AD, abnormalities also existed in primary visual system including retina and optic nerve in addition to cortical changes [24–27]. A limited number of histopathological studies have demonstrated retinal ganglionic cellular loss and axonal loss in optic nerve without coexisting amyloid accumulation and neurofibrillary tangle (NFT) formation [10, 28].

RNFL thickness has recently been used to study these pathological alterations in retina in AD. RNFL is a region that is very sensitive to axonal and neuronal loss, since it contains ganglionic cell neurons originating from optic nerve and their axons. Thus, RNFL thinning of any reason points to the axonal and neuronal loss. RNFL studies in healthy individuals showed that its thickness is reduced with age but no significant inter-gender differences exist [29–31]. We also found no significant difference between both sexes with respect to RNFL thickness. When we grouped all patients and the control group on the basis of age, we found that, in line with the literature findings, RNFL was significantly thinner in subjects equal to or over the age of 68, although no significant difference existed between advanced age groups.

Various studies have shown that RNFL thickness measured with the OCT technique is reduced in AD; however, there are only a few studies that have examined the relationship between RNFL and MCI and disease progression [24, 30, 32, 33]. In this study, we investigated if there was a difference between AD, MCI, and healthy control groups with respect to RNFL and examined the relationship between RNFL thickness and MMSE, MOCA scores. In a study by Parisi et al., which compared RNFL thicknesses measured with OCT between 17 Alzheimer patients and 14 healthy controls, there was a significant thinning in RNFL thickness in patients with AD. In that study, pattern electroretinogram (PERG) was also used in conjunction with OCT to assess retinal function. In Alzheimer patients, abnormal PERG responses have been shown in addition to RNFL examination. In contrast to our study, no significant difference has been reported between RNFL and MMSE scores [24]. Paquet et al. compared RNFL thickness measured by OCT between 15 healthy control subjects (MMSE $>$ 25), 23 subjects with MCI, 14 subjects with mild AD (MMSE 20–25), and 12 subjects with moderate-to-advanced AD (MMSE 11–19). As compared to the control group, all three groups showed significant thinning; however, no significant difference was found between mild AD and MCI. No significant correlation could be demonstrated between MMSE scores and RNFL measurement [33]. Iseri et al. compared 14 Alzheimer patients and 15 healthy subjects and showed that the mean total macular volume and RNFL thickness were significantly reduced in AD. A correlation was suggested between MMSE scores and total macular volume [25]. We also found that RNFL was significantly reduced in AD and MCI groups compared to the control group. On the other hand, no significant difference could be shown between AD and MCI groups. The reason of the latter finding may include a low sample size and inclusion of patients with mild AD. Unlike the existing literature data, our study revealed a significant correlation between MMSE scores and RNFL thickness. To our best knowledge, no study has ever investigated the correlation between detailed neurocognitive tests and RNFL thickness. In addition to MMSE test, we initially aimed to correlate RNFL thickness also with these tests, which are more sensitive than MMSE; however, as standardization with those tests would not be possible due to inability of the patients with advanced AD to accomplish those tasks, we considered it more feasible to compare RNFL thickness with MMSE test that is applicable to all stages of the disease. We did not find any significant correlation between MOCA scores and RNFL thickness in MCI and healthy controls that succeeded to finish the MOCA test. In a study by Kaya et al., which examined the validity of MOCA test score in persons with MCI and AD in Turkish society, educational status was shown to exert a significant effect on MOCA test score [34]. Also in our study, less than expected MOCA scores were attained, despite a lack of significant involvement in DLA (daily life activity) in patients with low educational status, especially in primary school graduates. We considered that this may have been linked to the lack of a significant correlation between MOCA scores and RNFL thickness.

Kesler et al. studied 24 patients with MCI, 24 control subjects, and 30 patients with Alzheimer disease and showed that RNFL thickness was significantly reduced in the AD and MCI groups than the control group and in the AD group compared to the MCI group. The thinning was particularly prominent in the lower quadrant [32]. Similarly, a study by Lu et al. [26] that examined 22 healthy control subjects and 22 patients with Alzheimer disease revealed that patients with AD had a thinner RNFL in the lower and upper quadrants. Our study, unlike others, made a comparison based on mean RNFL thickness.

Measurement of the retinal ganglion cell layer on OCT is one of the recent techniques used in retinal evaluation. Marziani et al. [35] showed that both the RNFL and RNFL + GCL thickness are reduced in AD patients compared with healthy subjects. In our study, we could not measure the retinal GCL for technical reasons. In addition to prepapillary evaluation, ganglion cell layer measurement could have reinforce our hypothesis and confirm the histopathological data.

Literature data suggest that neurodegenerative disorders other than AD are associated with RNFL thinning. In a post-mortem study, retinal dopamine loss and associated visual symptoms were shown in PD [36]. Based on this information, Inzelberg et al. showed a prominent thinning in OCT measured RNFL in patients with Parkinson disease [37].

Our study had some limitations. Since RNFL measurement with OCT requires patient cooperation and eye fixation, patients with advanced stage Alzheimer disease could not cooperate with the examination; therefore, advanced stage Alzheimer disease, when present, was considered an exclusion criterion. Hence, our study predominantly included patients with mild-to-moderate Alzheimer disease and this may have masked potential differences between them and the patients with MCI. Another limitation of our study is neither patients with cognitive decline nor healthy control group have a follow-up exam. The results of our study, which showed a significant correlation between MMSE scores and RNFL thinning and significant RNFL thinning in the AD and MCI groups compared to the control group, suggest that retinal nerve fiber degeneration and central nervous system degeneration may be simultaneous and RNFL measurement may be of benefit in follow-up of the disease in the future. However, studies with larger sample size and follow-up data are needed to confirm this hypothesis.

Acknowledgments This study was funded by Baskent University Research Fund with a project code of KA11/115.

Conflict of interest The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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