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Research Article

Inner Retinal Layers as Biomarkers of Disease in Patients with Mild Cognitive Impairment

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ABSTRACT

Purpose: To investigate whether inner retinal thickness can be used as a reliable biomarker in patients with mild cognitive impairment (MCI) for early diagnosis and correlate these changes with cognitive decline.

Material and methods: Using spectral domain optical coherence tomography (SD-OCT) in MCI and control subjects we assess peripapillary Retinal Nerve Fiber Layer (RNFL) thickness, macular thickness and volume and macular Ganglion Cell Complex (mGCC was defined as the combination of retinal fiber, ganglion cell and inner plexiform layers) thickness, Ganglion Cell Complex Global Volume Loss (GCC GVL%) and Ganglion Cell Complex Focal Volume Loss (GCC FVL%). We assessed cognitive function using Mini Mental State Examination (MMSE) score. A database was created with the use of the Statistical Program for Social Sciences (SPSS® ver12). Descriptive Statistics were utilized to find means, medians, standard deviations and interquantile ranges. Statistical significance was set to 95%. Independent t-tests were used to compare means between patients and control group when variables reached normal distribution. Mann-Whitney U test was used to compare medians between patients and control group when variables did not reach normal distribution.

Results: In MCI patients there was found a statistically significant decrease in overall RNFL thickness (Mann-Whitney test, p: 0.009) and temporal RNFL thickness (T-test, p: 0.013) and increased macular GCC FVL% (Mann-Whitney test, p: 0.001) compared to the controls. There was found no significant correlation between retinal thickness and cognitive decline in MCI patients.

Conclusion: Our study showed decreased inner retinal thickness in MCI patients. The potential use of inner retina thickness as a reliable biomarker in early diagnosis needs to be further explored in longitudinal studies with large cohorts.

Keywords: Cognitive impairment; Optical coherence tomography; Retinal structural changes; Mini mental state examination; Ganglion cells

INTRODUCTION

Alzheimer's disease (AD) is the most common age-related dementia and is characterized by the accumulation of amyloid-β protein (Aβ) plaques and aggregates of hyperphosphorylated tau as neurofibrillary tangles in the brain [1]. These neuropathological changes develop many years before the onset of dementia [2].

It has been recognized that patients with early AD experience abnormalities in visual acuity [3,4], contrast sensitivity [5], color perception [6], visual field [7,8], and motion perception [9,10].

Mild Cognitive Impairment (MCI) is considered a prodromal stage of AD and presents a transitional stage between expected age-related cognitive decline and AD dementia [11-15]. MCI is categorized into amnestic and non-amnestic subtypes [16]. Amnestic MCI, where episodic memory is impaired without impairment of executive function, language or other domains, is most likely to progress into AD [17-21].

Current diagnostic modalities for AD are presented by magnetic resonance imaging (MRI) or positron emission tomography

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(PET), cerebrospinal fluid biomarkers, genetic markers, serum amyloid [22] and neuropsychological evaluation which is the "gold standard" for pre-mortem diagnosis of AD [23]. However, these modalities are invasive, expensive and time consuming.

Retina and brain have common embryological origin and share many tissue similarities. The link between these two central nervous system tissues poses the question of whether the retina may represent the brain in healthy and neurodegenerative conditions. Indeed, structural changes in brain due to AD could be reflected in the retina [24]. The retina is easily accessible through high-resolution optical imaging. Optical Coherence Tomography (OCT) is a noninvasive, non-contact and patient friendly way to view in vivo the retina of patients. OCT provides high resolution two-dimensional cross-sectional imaging and three-dimensional volumetric measurements of the retina. OCT is used to evaluate a variety of ophthalmic conditions, such as glaucoma and various retinal diseases and is able to measure the thickness of individual retinal layers including Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell-Inner Plexiform Layer (GCIPL). Ganglion cell layer contains ganglion cell somata and inner plexiform layer contains ganglion cell dendrites. Retinal Nerve Fiber Layer (RNFL) consists of the axons of the retinal ganglion cells, which together form the optic nerve and the anterior visual pathways [25]. Deviation from the age-matched normal range of the thickness of these layers, is a biomarker for neurodegenerative disease such us multiple sclerosis [26,27]. Parkinson's disease [28] and amyotrophic lateral sclerosis [29].

The results of previous OCT studies on retinal thickness in MCI patients are inconsistent. Various studies revealed retinal thinning, other found retinal thickening and other did not find any significant difference in thickness between MCI patients and controls. Possible explanations of these variable results may be the variability in exclusion criteria, the variability in evaluating the cognitive function, the variability in rigor of adjustment of confounders and finally the presence of gliosis (hypertrophy and proliferation of astrocytes and other glial cells) in inner retinal layers in MCI patients which probably precedes the final stage of thinning and makes inner retinal layers appear thicker than normal. There is also disagreement in correlation between retinal thickness and cognitive decline.

In this study, we measured peripapillary RNFL thickness, macular thickness and volume, macular Ganglion Cell Complex (mGCC) thickness, Ganglion Cell Complex (GCC) Global Volume Loss (%) and Ganglion Cell Complex (GCC) Focal Volume Loss (%) in the macula and we sought to correlate these retinal findings with cognitive decline using MMSE.

MATERIALS AND METHODS

Using high resolution Spectral Domain OCT (RTVue-100, Optovue) which acquires 26,000 axial scans (a-scans) per second and has a 5-μm depth resolution in tissue we sought to assess peripapillary Retinal Nerve Fiber Layer (RNFL) thickness, macular thickness and volume in all macular regions as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) [30] and macular Ganglion Cell Complex (mGCC was defined as the combination of nerve fiber, ganglion cell, and inner plexiform layers) thickness in MCI patients, and to correlate these findings with cognitive decline. We sought to find out if inner retinal thickness measured with OCT in MCI patients can be used as a reliable biomarker for MCI diagnosis.

Parameters measured in RNFL protocol scan are peripapillary RNFL overall thickness (μm), superior hemisphere peripapillary RNFL thickness (μm), inferior hemisphere peripapillary RNFL thickness (μm), temporal, superior, nasal and inferior quadrant peripapillary RNFL thickness (μm). Parameters measured in macular protocol scan are fovea, parafovea (superior and inferior hemisphere, temporal, superior, nasal and inferior quadrants), perifovea (superior and inferior hemisphere, temporal, superior, nasal and inferior quadrants) thickness (μm) and volume (mm^3). Parameters measured in mGCC scan are average, superior and inferior GCC thickness (μm), macular GCC focal volume loss percentage (FVL%), and macular GCC global volume loss percentage (GVL%). FVL% measures the amount of focal (isolated) loss over the entire GCC map while GLV% measures the average amount of GCC loss over the entire GCC map. FLV% shows isolated depressions or ''potholes'' on GCC thickness map while GVL% shows the extent of overall uniform depression on the GCC thickness map. FLV% will best detect localized ganglion cell loss and GVL% will best detect diffuse ganglion cell loss in the macula.

During OCT scanning, the examination eye was constantly fixed on an internal target provided by the equipment. An average of 3 consecutive measurements of RNFL thickness,macular scan parameters and GCC scan parameters were effectuated.

Cognitive impairment level is assessed by MMSE (Mini Mental State Examination) [31], FRSSD (Functional Rating Scale for Symptoms of Dementia), and GDS (Geriatric Depression Scale). Patients were diagnosed with MCI according to the criteria described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association).

In the study were enrolled 59 eyes of 31 MCI patients (mean age 64.08 ± 8.8 years) and 20 eyes of 10 age-matched controls (mean age 60.1 ± 4 years). The general inclusion criteria for MCI patients and controls were no evidence of vascular dementia, no dismetabolic diseases, no psychiatric disorders, no psychotropic therapy, no other neurological diseases, no arterial hypertension, no history of alcohol abuse and no heart disease or other serious chronic conditions.

A complete ophthalmic examination including best-corrected distance visual acuity, intraocular pressure (IOP) measured by Goldmann applanation tonometer, and pupil-dilated slit-lamp fundus biomicroscopy was performed in both eyes. Ocular inclusion criteria were best corrected visual acuity >8/10 with refractive error between ± 3 sph, intraocular pressure <18 mmHg, absence of glaucoma, retinal detachment, previous history

of optic media opacity, cataract or early lens opacity, retinal vascular diseases, early age-related macular degeneration or other maculopathies and optic neuropathy.

RESULTS

In MCI patients was found a statistically significant decrease in overall RNFL thickness (Mann-Whitney test, p: 0.009) and temporal RNFL thickness (T-test, p: 0.013) and increased macular GCC Focal Volume Loss (FVL%) (Mann-Whitney test, p: 0.001) compared to the control group and there was found a significant difference of MMSE score between MCI patients and controls (Mann-Whitney test, p:0.001)(Tables 1-4 and Figures 1-4).

There was also found a significant positive correlation between macular inner superior, inner nasal, inner inferior and inner temporal quadrant thickness, outer superior and outer temporal quadrant thickness(μm), parafoveal temporal, superior, nasal and inferior quadrant volume (mm^3), perifoveal temporal and superior quadrant volume (mm^3), RNFL temporal quadrant thickness(μm), GCC average thickness(μm), GCC superior thickness(μm) and GCC Global Volume Loss (GVL%) and level of MMSE score in control group (Spearman's rho). In MCI patients there was not found a correlation between retinal thickness and volume and level of MMSE score (Spearman's rho) (Supplementray Table 1).

Table 1: RNFL overall thickness of patients group compared to control group.

Patient		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
RNFL over all	Patient	60	100%	0	0%	60	100%
	Control group	20	100%	0	0%	20	100%
Descriptives							
Patient				Stastic		Std. Error	
RNFL over all	Patient	Mean		101		1.321273	
		95% confidence interval for Mean	upper bound	98.09406			
			lower bound	103.3818			
		5% trimmed Mean		101.3322			
		Median		99.8335			
		Variance		104.746			
		Std. Deviation		10.23454			
		Minimum		62.333			
		Maximum		120.67			
		Range		58.337			
		Interquartrile range		8.883			
		Skewness		-1.214		0.309	
		Kurtosis		4.845		0.608	
	Control group	Mean		107.0817		1.06889	
		95% confidence interval for Mean	upper bound	104.8444			
			lower bound	109.3189			
		5% trimmed Mean		106.85			
		Median		107			
		Variance		22.851			
		Std. Deviation		4.78022			
		Minimum		99			
		Maximum		119.333			
		Range		20.333			
		Interquartrile range		6.725			
		Skewness		0.633		0.512	
		Kurtosis		1.096		0.992	

Tests of normality							
Patient		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		statistic	df	sig.	stastistic	df	sig.
RNFL over all	Patient	0.16	60	0.001	0.869	60	0
	Control group	0.15	20	0.002*	0.956	20	0.463
Npar tests Mann-Whitney test							
Ranks							
Patient		**N**	**Mean rank**		**Sum of ranks**		
RNFL overall	Patient	60	35.53		2132		
	Control group	20	55.4		1108		
	Total	80					
Test stastics[a]							
					RNFL overall		
Mann-Whitney U					302		
Wilcoxin W					2132		
Z					-3.312		
Asymp. Sig.(2-tailed)					0.001		

Significance: *:This is a lower bound of the true significance; a: Lilliefors significance correction; a: Grouping variable: Patient

Table 2: RNFL temporal thickness of patients group compared to control group.

Patient		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
RNFL temporal	Patient	60	100%	0	0%	60	100%
	Control group	20	100%	0	0%	20	100%
Descriptives							
	Patient			Stastic		Std. Error	
RNFL temporal	Patient	Mean		74.1129		1.321273	
		95% confidence interval for Mean	upper bound	71.17404			
			lower bound	77.05176			
		5% trimmed Mean		73.90324			
		Median		73.167			
		Variance		129.425			
		Std. Deviation		11.37651			
		Minimum		43.667			
		Maximum		105.333			
		Range		61.666			
		Interquartrile range		13.5			
		Skewness		0.395	0.309		
		Kurtosis		0.915	0.608		
	Control group	Mean		82.14335	1.793041		
		95% confidence interval for Mean	upper bound	78.39047			
			lower bound	85.89623			

		5% trimmed Mean		82.25928			
		Median		80.1335			
		Variance		64.3			
		Std. Deviation		8.018721			
		Minimum		65.6			
		Maximum		96.6			
		Range		31			
		Interquartrile Range		14.325			
		Skewness		0.14		0.512	
		Kurtosis		-451		0.992	
Tests of normality							
Patient		**Kolmogorov-Smirnova**			**Shapiro-Wilk**		
		statistic	**df**	**sig.**	**stastistic**	**df**	**sig.**
RNFL temporal	Patient	0.91	60	0.2*	0.971	60	0.156
	Control group	0.168	20	0.142	0.942	20	0.264
Npar tests Mann-Whitney test							
Ranks							
Patient		**N**	**Mean rank**		**Sum of ranks**		
RNFL temporal	Patient	60	35.63		2137.5		
	Control group	20	55.13		1102.5		
	Total	80					
Test stasticsa							
					RNFL overall		
Mann-Whitney U					307		
Wilcoxin W					2132.5		
Z					-3.25		
Asymp. Sig.(2-tailed)					0.001		

Significance: *:This is a lower bound of the true significance; a: Lilliefors significance correction; a: Grouping variable: Patient

Table 3: Macular GCC FVL% of patient group compared to control group.

Patient		**Cases**					
		Valid		**Missing**		**Total**	
		N	**Percent**	**N**	**Percent**	**N**	**Percent**
GCC FVL%	Patient	60	100%	0	0%	60	100%
	Control group	20	100%	0	0%	20	100%
Descriptives							
Patient				**Stastic**		**Std. Error**	
GCC FVL%	Patient	Mean		0.93128		0.151708	
		95% confidence interval for Mean	upper bound	0.62772			
			lower bound	1.23485			
		5% trimmed Mean		0.77452			
		Median		0.587			
		Variance		1.381			

		Std. Deviation		1.175126		
		Minimum		0.003		
		Maximum		8.277		
		Range		8.274		
		Interquartrile range		0.93		
		Skewness		4.442	0.309	
		Kurtosis		25.979	0.608	
	Control group	Mean		0.20295	0.030759	
		95% confidence interval for Mean	upper bound	0.13857		
			lower bound	0.26733		
		5% trimmed Mean		0.19628		
		Median		0.1815		
		Variance		0.019		
		Std. Deviation		0.137557		
		Minimum		0.027		
		Maximum		0.499		
		Range		0.472		
		Interquartrile Range		0.178		
		Skewness		0.777	0.512	
		Kurtosis		0.391	0.992	

Tests of normality

Patient		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		statistic	df	sig.	stastistic	df	sig.
GCC FVL%	Patient	0.215	60	0	0.587	60	0
	Control group	0.132	20	0.200*	0.916	20	0.082

Npar tests Mann-Whitney test

Ranks

Patient		N	Mean rank	Sum of ranks
GCC FVL%	Patient	60	47.5	2850
	Control group	20	19.5	390
	Total	80		

Test stastics[a]

	GCC FVL%
Mann-Whitney U	180
Wilcoxin W	390
Z	-4.667
Asymp. Sig.(2-tailed)	0

Significance: *:This is a lower bound of the true significance; a: Lilliefors significance correction; a: Grouping variable: Patient

Table 4: MMSE of patient group compared to control group.

Patient		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
MMSE	Patient	60	100%	0	0%	60	100%
	Control group	20	100%	0	0%	20	100%
Descriptives							
	Patient			Stastic		Std. Error	
MMSE	Patient	Mean		27.3		0.225	
		95% confidence interval for Mean	upper bound	27.75			
			lower bound	26.85			
		5% trimmed Mean		27.37			
		Median		28			
		Variance		3.027			
		Std. Deviation		1.74			
		Minimum		23			
		Maximum		30			
		Range		7			
		Interquartrile range		3			
		Skewness		-0.68		0.309	
		Kurtosis		-0.218		0.608	
	Control group	Mean		29.65		0.109	
		95% confidence interval for Mean	upper bound	29.42			
			lower bound	29.88			
		5% trimmed Mean		29.67			
		Median		30			
		Variance		0.239			
		Std. Deviation		0.489			
		Minimum		29			
		Maximum		30			
		Range		1			
		Interquartrile range		1			
		Skewness		-0.681		0.512	
		Kurtosis		-0.1719		0.992	
Tests of normality							
Patient		Kolmogorov-Smirnova				Total	
		statistic	df	sig.	stastistic	df	sig.
MMSE	Patient	0.19	60	0	0.918	60	0.001
	Control group	0.413	20	0	0.608	20	0

Npar tests Mann-Whitney test				
Ranks				
Patient		N	Mean rank	Sum of ranks
MMSE	Patient	60	31.99	1919.5
	Control group	20	66.03	1320.5
	Total	80		
Test stastics[a]				
			MMSE	
	Mann-Whitney U		89.5	
	Wilcoxin W		1919.5	
	Z		-5.78	
	Asymp. Sig.(2-tailed)		0	

Significance: a: Lilliefors significance correction; a: Grouping variable: Patient

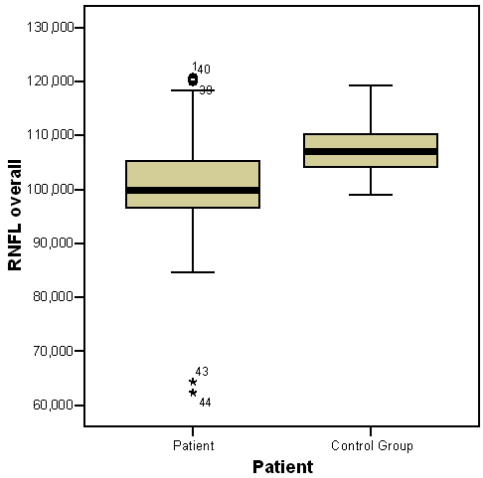

Figure 1: There is statistically significant difference of RNFL overall thickness between MCI patients and controls. MCI patients present decreased median compared to controls, p: 0.001.

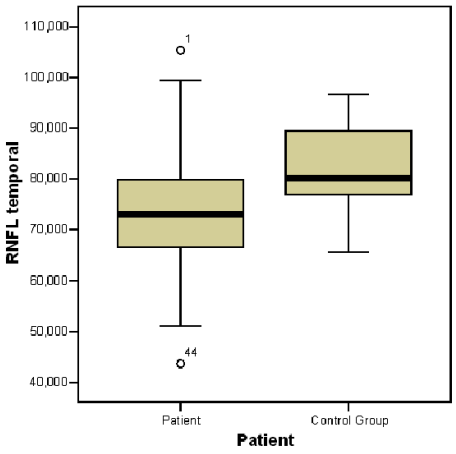

Figure 2: There is statistically significant difference of RNFL temporal thickness between MCI patients and controls. MCI patients present decreased median compared to controls, p: 0.0013.

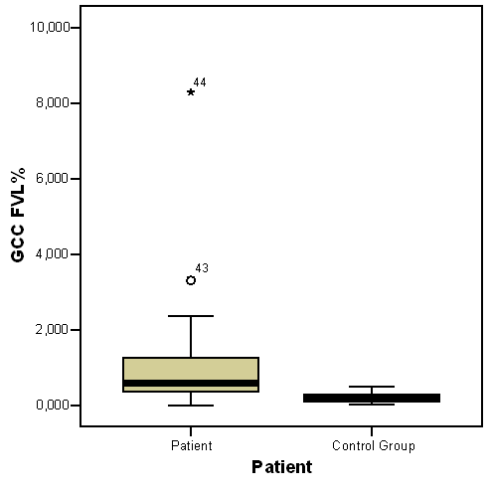

Figure 3: There is statistically significant difference of Ganglion Cell Focal Volume Loss% (GCC FVL%) between MCI patients and controls. MCI patients present increased GCC FVL% compared to controls, p: 0.001.

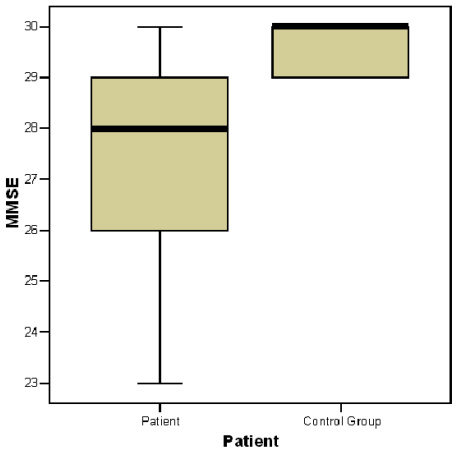

Figure 4: There is statistically significant difference of MMSE score between MCI patients and controls. MCI patients present decreased MMSE score compared to controls, p: 0.001.

Statistical analysis

A database was created with the use of the Statistical Program for Social Sciences (SPSS® ver12). Descriptive Statistics were utilized to find means, medians, standard deviations and interquantile ranges. Statistical significance was set to 95%. Independent t-tests were used to compare means between patients and control group when variables reached normal distribution. Mann-Whitney U test was used to compare medians between patients and control group when variables did not reach normal distribution.

DISCUSSION

Recent research reflects an increased effort to identify visual biomarkers that can be used to diagnose MCI patients early in the disease process and then to follow up the disease process. OCT studies have focused on RNFL and GCIPL (defined as the sum of ganglion cell and inner plexiform layers) thickness measurement in order to find a reliable visual biomarker for early MCI diagnosis.

Variable studies showed statistically significant decrease of peripapillary RNFL and macular GCIPL thickness in MCI patients compared to controls. However there are some studies which found no statistically significant difference in the thickness of RNFL and GCIPL between MCI patients and controls. Lad et al. [32] demonstrated that regional thicknesses of RNFL or GCIPL on macular or nerve OCT did not differ between MCI and controls. They identified areas of thickening of GCIPL and RNFL in the macula adjacent to areas of thinning suggesting that RNFL and GCIPL may undergo dynamic changes during AD

progression. The retinal thickening in MCI was attributed to gliosis (and transient thickening) preceding neuronal loss and atrophy of the axonal projections in the RNFL (33). Knoll et al. [33] found no significant difference in RNFL and macular thickness between MCI and controls. They also reported an inverse relationship between cognitive testing and RNFL thickness suggesting that retinal involvement may include paradoxically increased thickness of the RNFL probably due to gliotic reactive changes. In support of this hypothesis, histopathology studies suggest that gliosis precedes human AD pathology in the brain [34,35]. Kwon et al. [36] found that average RNFL thickness was slightly increased in the MCI group compared to the healthy cohort. Snyder et al. [37] reported an increase of Inner Plexiform Layer (IPL) volume in MCI patients and this increase could be a result of beta-amyloid protein (Aβ) deposition occupying space within IPL. Furthermore, Ascaso et al. [38] showed that MCI patients had the greatest macular volume, followed by controls and then AD patients. Ferrari et al. [39] demonstrated a significant global RNFL thinning in moderate AD but not in mild AD patients as compared to controls suggesting that thinning of the RNFL may not occur until the severe stages of AD. Pillai et al. [40] also found no difference in RNFL thickness, GCIPL thickness and macular volume in MCI patients compared to controls. Shen et al. [41] did not find significant differences in RNFL thickness between MCI and cognitively normal controls. Jiang et al. [42] studying the macular microvascular network in MCI patients found lower density in deep vascular plexus in the superior nasal quadrant but found no significant differences of macular thickness between MCI and controls. Gilbert et al. [43] found reduced retinal blood speed and flow in MCI patients compared to normals but did not find significant difference in RNFL thickness in these groups. One hypothesis about increased thickness of inner retinal layers in MCI patients is gliosis and subsequent thickening followed in later stages by thinning [32]. Another hypothesis about increased thickness is that neuronal ischemia and swelling of ganglion cells would lead to hypertrophy and subsequent apoptosis [44].

On the contrary, other studies found decreased RNFL thickness in MCI patients. A number of clinical studies [45-52] have demonstrated quadrant-specific retinal RNFL abnormalities in MCI patients. However, the region of the RNFL affected varies substantially between these studies. Our study showed a statistically significant decrease in overall RNFL peripapillary thickness (Mann-Whitney test, p: 0.009) and a statistically significant decrease in temporal RNFL thickness (T-test, p: 0.013). Wu et al. [45] and Gao et al. [46] also have found decrease in temporal RNFL thickness. Ascaso et al. [38] have found thinning of RNFL in all quadrants surrounding the optic nerve except nasal, Coppola et al. [47] have found RNFL thinning in all quadrants except superior, Liou et al. [48] have found RNFL thinning in the superior quadrant and Kesler et al. [49] have found RNFL thinning in the inferior quadrant of the optic nerve head.

Besides decreased RNFL thickness, many studies [53-55] found decreased macular volume and thickness in MCI patients. Our study showed a statistically significant increased macular Ganglion Cell Complex Focal Volume Loss (FVL%)(Mann-Whitney test, p: 0.001) compared to the control group. As mentioned above, FVL% measures the amount of focal (isolated) loss over the entire GCC map while GLV% measures the average amount of GCC loss over the entire GCC map. FLV% assesses and quantifies the localized depressions while GLV% assesses and quantifies the general depressions in the thickness GCC map. Eraslan et al. [56] studying AD patients found increased GVL% in the macula. We found increased FVL% in MCI patients. Probably, initially the loss of ganglion cells in MCI patients is isolated and as result we observe increase in FVL% and after, when dementia progresses, the loss of ganglion cells becomes diffuse and the depression of macular thickness map is not focal anymore but general and consequently increased GVL% is observed.

Cheung et al. [55] found significantly reduced GCIPL thickness in MCI compared to controls probably due to loss of thickness in ganglion cell layer (GCL). More than half of the retinal ganglion cells are located in the macula within the Ganglion Cell Layer (GCL). The body of a retinal ganglion cell ranges from 10 to 20 times the diameter of its axons [57]. Consequently, loss of macular ganglion cells is more pronounced than RNFL loss. For this reason Cheung et al. support that GCIPL neuronal loss is more strongly related to MCI, compared to RNFL axonal loss, suggesting that GCIPL thickness is a more sensitive marker than RNFL thickness for assessing neurodegenerative pathology in MCI and can discriminate better between MCI and controls than RNFL thickness can do. Choi et al. found that reduced temporal RNFL thickness and reduced macular GCIPL thickness as well as reduced macular cube thickness and volume at baseline could predict the disease progression from MCI to AD over a 2 year follow up period. They also conclude that GCIPL parameters seem to be more predictive of the conversion to AD dementia from MCI compared to RNFL parameters.

Our study did not find any correlation between RNFL thickness, macular thickness and volume, mGCC thickness, FVL% or GVL% with cognitive function in MCI patients. Similary, Gao et al. did not establish any correlation between MMSE scores and any OCT parameter in MCI patients as well. Knoll et al. reported an inverse relationship between cognitive testing and RNFL thickness suggesting that retinal involvement may include paradoxically increased thickness of the RNFL. By contrast Choi et al. reported that reduced GCIPL thickness was associated with memory decline in MCI patients. Domingo et al. found that in MCI patients the reduction of macular thickness is more severe as the cognitive impairment worsens. Octem et al. [51] found siginficant correlation between RNFL thickness and cognitive function in MCI patients. Shen et al. setting out a prospective clinical investigation to determine the potential association between the attenuation of RNFL thickness and the deterioration of cognitive function over a period of 25 months found that less reduction in the inferior quadrant of RNFL thickness might indicate a higher risk for the patients to develop cognitive deterioration.

Other than retinal structural changes Bulut et al. [58] observed with OCT reduced macular choroidal thickness in MCI patients and identified a positive correlation between thickness and cognitive score.

Questions about why does the retina reflect brain pathology in AD patients still remain. Considering the common embryological origin of the retina and the brain one possibility is that the retina is vulnerable to the same neuroinflammatory injury that causes neurodegenerative disease in the brain. Another possibility is that the brain damage and dysfunction in AD may lead to nerve loss in the retina [59-61].

The major limitations of this study include the relatively small number of subjects involved and the lack of follow-up in order to visualize within-subjects changes in retinal biomarkers associated with disease progression.

Based on available literature OCT cannot yet be applied as a diagnostic biomarker for AD in clinical practice [62]. It has long been recognized that glaucoma, a chronic neurodegenerative disease, causes RNFL thinning. Prevalence of glaucoma in AD patients is increased (25.9%) compared to the normal population (1-5.2%) [63-65]. RNFL thickness and macular thickness are significantly decreased in AD patients compared to controls, however, glaucoma, a potential confounder in AD patients, possibly overestimated the effect of AD on retinal thickness described in previous studies [62]. OCT measurements in AD patients with and without glaucoma would inform us about the real grade of retinal thickness loss caused by dementia. Also, the pattern of RNFL and GCIPL thickness as the disease progresses has not been determined yet.

CONCLUSION

Future longitudinal follow up studies on RNFL and GGIPL thickness measurement of the same individual as the disease progresses could give new insight in OCT measurements as biomarker of neurodegeneration. Segmentation of individual retinal layers and correlation of OCT measurements with other biomarkers of neuronal injury could be very useful. Ocular biomarkers could be a useful screening tool to distinguish individuals at risk for developing AD and identify candidates for secondary prevention trials designed to intervene earlier in the disease progression by slowing the aggregation of Aβ in the brain.

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