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Changes of the Retinal Nerve Fiber Layer in Patients with Mild Cognitive Impairment and Alzheimer's Disease

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Abstract: ***Background**: Alzheimer's disease (AD) is the most common type of dementia and are often associated with visual disorders. Mild cognitive impairment (MCI) is characterized by an impaired memory when compared with people of similar age and education level which indicates an earlier on set of AD. The aim of this study is to measure the retinal nerve fiber layer (RNFL) thickness of AD and MCI patients comparing with the normal age controls. Methods: The retinal nerve fiber layer (RNFL) thickness was assessed with optical coherence tomography (OCT) in patients with MCI, AD (mild, moderate and severe) and also in the corresponding age matched controls. **Results**: The thicknesses of RNFL are gradually and significantly decreased from MCI to severe AD in the superior quadrant and total mean values when compared to that in the controls. It is also observed that there is a significant reduction of the retinal nerve fiber layer thickness in the inferior quadrant in severe AD patients. **Conclusions**: Our data shows that the retinal nerve fiber layer degeneration occurs in parallel with progression of dementia. Owing to its cost effective and non - invasive nature, monitoring RNFL thickness is essential in assessing progression of disease and the efficacy of management.*

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

1. Introduction

Alzheimer's disease (AD) is a common type of dementia characterized by cognitive deficits including progressive memory disturbances, apraxia, aphasia, andagnosia. AD patients also presents with visual defects affecting visual acuity [1], colour vision, spatial contrast sensitivity, stereopsis, and ocular motility [2]. The pathological changes described in AD are neurofibrillary tangles and senile plaquesin the central nervous system (CNS). Mild cognitive impairment (MCI) is described as only impairment in cognitive function with otherwise normal activities of daily life [3]. Amnesic MCI patients show early transitional stage development of Alzheimer's and may have memory impairment, but not associated with dementia [4].10% - 15% MCI patients per year are likely to progress to AD, whereas 1% to 2% of healthy population are at risk of developing AD [5, 6].

Optical coherence tomography (OCT) is a non - invasive investigation tool that assess the thickness of retinal nerve fiber layer (RNFL) and is essential in various ocular diseases such as glaucoma, optic neuropathy, ocular hypertension, and multiple sclerosis [7]. Previous studies have demonstrated a likely degeneration of the RNFL in AD [8 - 15]. For example, a study by Hilton et al. in postmortem patients, demonstrated wide spread degeneration of axons in the optic nerves in 8 out of 10 AD patients [16]. Sadun's work also demonstrated that the ganglion cells degeneration are mainly observed in large M - cell axons [8]. However, other studies didn't support those findings [17, 18], possibly methodological differences might be responsible for the differences but this needs further study. The aim of the our study is to determine whether the thickness of the RNFL is reduced in parallel from MCI patients to severe AD patients in comparison with the age – matched healthy controls using sophisticated OCT method.

2. Methods

After getting approval from Ethics committee of Sree Balaji Medical College and Hospital, Chromepet, Chennai, India and written informed consent from patients, 25 MCI, 25mild AD patients, 23 moderate AD patients, 20 severe AD patients and 40 age - matched controls were enrolled. All patients as well as the controls were examined for refractive error, intraocular pressure (IOP), visual acuity, dilated fundus examination, anterior and posterior segment biomicroscopy.

All AD patients were diagnosed by the neurologists in the department of Neurology, Sree Balaji Medical College and Hospital according to the Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS - ADRDA) [19] and the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria [20].

Each MCI patients were diagnosed by atleast three neurologists in the department of Neurology, Sree Balaji Medical College and Hospital, according to Petersen criteria [21]. The criteria for age matched controls were: (1) no complaints regarding memory (2) MMSE scores above 28. Criteria for all study subjects are: (1) Diopters: spherical −3.00DS ~ +3.00DS, cylinder −3.00 DC ~ + 3.00 DC, anisometropia ≤ 2D; (2) IOP measured three times should be < 21 mmHg. The exclusion criteria includes: glaucoma, optic neuropathy, ocular trauma or surgery, retinal detachment, retinal artery occlusion, cerebral infarction and other diseases which may affect RNFL thickness and also diabetes mellitus, hypertension,

OCT examinations were done according to standard protocol using a SD OCT (Heidelberg). Two dimensional images of the retina was obtained. RNFL thickness was measured circularly around the papilla (optic disc: 3.4 mm) and it is also repeated thrice per quadrant (superior, inferior, nasal and temporal) and the average of all the 12 values were used

for each eye in µm. Data are tabulated as mean ± SD and statistical analysis was done with SPSS 16.0 The differences about gender among cases and controls were compared with chi - square test. The differences in age, RNFL thickness, and IOP among five groups were done with one - way ANOVA to test the data between groups. A $p < 0.05$ was considered to be of statistical significance.

3. Results

Data obtained from our study shows that there is no statistically significant difference in age, gender and IOP among study groups ($P > 0.05$) (Table1).

It was found to be a significant difference between the control group and MCI, mild, moderate or severe AD in superior, inferior quadrant and total mean RNFL thickness ($p < 0.05$) but no significant difference in nasal and temporal quadrant ($p > 0.05$). The RNFL thickness of MCI, mild, moderate and severe dementia group were reduced in superior quadrant and total mean RNFL, compared with control group and there was a statistically significant difference ($p<0.05$). Further, the RNFL thicknesses when compared with MCI group, were significantly decreased in moderate and severe AD group ($p <0.05$). There was no significant difference in RNFL thickness among varying severity of AD groups. In the inferior quadrant, there are no significant differences ($p >0.05$) in the MCI group, mild and moderate AD group compared with controls. In the total mean RNFL, compared with that in the normal control group, the RNFL thickness gradually decreases from MCI group, mild AD, moderate AD, severe AD ($p <0.05$) (Table 2) . Further, on plotting these data together, reveals a falling trend with the disease progression (Figure1).

Table 1: Patients with MCI, mild, moderate, severe AD and control groups (mean ± SD)

	MCI	MI AD	MO AD	SE AD	control		*P*
	(n = 25)	(n = 25)	(n = 23)	(n = 20)	(n = 40)		value
Sex M	13	10	11	11	19	$X^2 = 0.362$	>0.05
F	12	15	12	9	21		
Age (y)	69.2 ± 5.5	70.5 ± 4.2	71.8 ± 4.1	73.1 ± 4.9	70.7 ± 6.8	F = 1.231	>0.05
IOP (mmHg)	15.2 ± 1.1	16.1 ± 1.9	15.5 ± 1.4	14.9 ± 1.3	15.7 ± 1.0	F = 2.126	>0.05
VA (logMAR)	0.15 ± 0.09	0.22 ± 0.11	0.31 ± 0.20	0.34 ± 0.23	0.07 ± 0.08	F = 3.491	<0.05

n: patients; MI: mild; MO: moderate. SE: severe; M: male; F: female; MCI: Mild cognitive impairment; AD: Alzheimer's disease; IOP: intraocular pressure; VA: visual acuity.

Table 2: RNFL thickness (µm) in patients with MCI, mild, moderate, severe AD and controls (mean ± SD)

	MCI	mild AD	moderate AD	severe AD	control	*F*value
S	114.24 ±14.21▲	112.68 ±10.47▲	107.69 ± 11.32▲■	101.26 ± 18.22▲■	120.10 ± 14.34	2.212*
I	121.23 ± 17.12	114.99 ± 11.02	113.12 ± 15.11	112.24 ± 10.22▲■	124.96 ± 10.13	5.456**
N	74.23 ± 11.86	70.02 ± 11.22	63.92 ± 16.02	60.94 ± 17.22	80.12 ± 12.24	1.029
T	64.17 ± 12.84	60.89 ± 11.93	60.27 ± 10.65	60.38 ± 10.67	67.12 ± 14.36	1.237
M	94.97 ± 16.94▲	91.42 ± 11.12▲	91.57 ± 11.27▲■	86.97 ± 16.95▲▲■	100.91 ± 14.96	7.649**

S: superior of Peripapillary RNFL thickness; I: inferior of Peripapillary RNFL thickness; N: nasal of Peripapillary RNFL thickness; T: temporal of Peripapillary RNFL thickness; M: total mean of RNFL thickness; Compared with the control group: ▲*P*<0.05, ▲▲*P*<0.01; comparison to MCI: ■*P*<0.05Ftest: *p<0.05, **p<0.001.

4. Discussion

Our data shows that the thickness of RNFL gradually decreases in the superior quadrant and total mean RNFL with the disease progression from MCI to severe AD. Thickness of the retinal nerve fiber layer in inferior quadrant is also seen to be decreased in severe AD.

Similar to our data, a previous study showed a significant thinning in RNFL at the superior quadrant in patients with AD by measuring peri - papillary RNFL in AD using OCT. It is also observed that no significant differences in the RNFL thickness at inferior, temporal or nasal quadrants between the study groups [22]. In one of the previous study it was found that there was thinning of nerve fiber layer in the AD patients compared with controls at the superior and inferior quadrants measured by OCT [23]. Other reports [24, 25]demonstrated a clear thinning of RNFL, involving all four quadrants in AD and MCI patients. Our present study demonstrates a thinning in retinal nerve fiber layer at superior quadrant selectively in early AD patients. With progression of AD, the degeneration of the retinal nerve fiber layer is observed also in inferior quadrant. The reason associated with selective thinning RNFL in the superior quadrant is unknown. Based on anatomy the axons from superior aspect of retina project through the parietal lobe portion of optic radiation to the cuneus of primary visual cortex, whereas axons from the inferior aspect of retina project to lingual gyrus. In a histo - pathology study about the cortical damage in AD showed that a greater density of senile plaques and neuro fibrillary tangles is seen incuneus than in lingual gyrus, and suggested that this may explain the predominant thinning of RNFL in superior quadrant in AD [26]. Several previous reports show that degeneration of nerve fibers in the primary visual cortex were attributed to visual problems in AD [27 - 29]. However, there is increasing evidence that the primary visual pathway degeneration also contribute to the visual disorders. For example, there are few studies suggesting optic nerve and retinal degeneration in patients with AD [5, 7 - 9, 16]. With progression of AD, the degeneration of the RNFL is seen not only in superior quadrant, but also involving the inferior quadrant. However, few literatures did not support this. A previous study showed defects in visual function that are known to occur in Alzheimer's dementia are not related to

optic nerve head structural anomalies, especially at early stage [30]. Kergoat et al. in his study analyzed fundus images, imaged by scanning laser polarimetry, and they observed no differences in the RNFL thickness between AD and controls [30]. Hence, it necessitates further study to identify the best possible cause of visual disorders in AD and also to illustrate whether its attributed to disorders of visual cortex or primary visual pathways.

Amyloid - beta (Aβ) plaques have been reported in postmortem retinal tissue from AD patients [31 - 33]. We found that degree of degeneration of the retinal nerve fiber layer deteriorated gradually along with progression of severity and duration of AD which can be attributed to the loss of retinal Ganglion Cells (RGC) [2]. It is observed in a study that the amyloid protein has also been associated with the degeneration of RGC in a mouse model of glaucoma [34]. Hence, amyloid accumulation in the retina of AD patients may lead to degeneration of RGC paralleling with amyloid - related neuro degeneration in cerebral parenchyma.

MCI is a risk factor for development of AD. The RNFL thickness seen in MCI patients in our study is striking although this needs further studies. If significant association is demonstrated it would be very essential for patients to have ocular screening with OCT to support diagnosis for detecting earlier onset of MCI. Our data shows that RNFL thickness is reduced in MCI indicating MCI progression in patients while a follow - up study is needed to investigate the degree and duration of the RNFL in relation to the progression from MCI to AD. However, cautions must be taken due to the following reasons: 1) This study is a observational cohort study and it is not a clinical trial. Large sample size is necessary to further validate our present findings; 2) Petersen criteria was used to define MCI without using any further bio - markers or even PET imaging; 3) A spectral domain OCT was used so lower resolution images can be an issue for data accuracy. Our data reported here may help neurologists to consider OCT as an additional tool for better diagnosis and management as well as monitoring of dementia patients. However its plausible to use it for the severity of dementia.

5. Conclusions

OCT is a safe and non - invasive method used to assess the degeneration of retina in various ophthalmologic and neurological disorders. From our data reported here, it is suggested that OCT can be used to improve diagnosis of MCI in individuals with subtle memory disturbances and also to monitor the progression of Alzheimer's disease and evaluate effectiveness of management.

6. Abbreviations

AD: Alzheimer's disease
MCI: Mild cognitive impairment
RNFL: Retinal nerve fiber layer thickness
OCT: Optical coherence tomography
CNS: Central nervous system.

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