

## Optical Coherence Tomography Findings In Patients Of Alzheimer's Disease - An Indian Perspective

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**Abstract: Background:** Alzheimer's disease (AD) is the most common cause of dementia and its incidence is increasing worldwide along with population aging. Previous clinical and histologic studies suggest that the neurodegenerative process, which affects the brain, may also affect the retina of AD patients. **Objective:** The objective of the current study was to determine the thickness changes of retina nerve fibers with optical coherence tomography (OCT) in AD patients. **Material & Methods:** The OCT was used to assess the thickness of retinal nerve fiber layer (RNFL) and macular volume from 21 AD patients and 50 healthy age-matched controls. **Results:** Compared with healthy age-matched controls, the RNFL thickness of AD patients were much thinner ( $p < 0.05$ ) in all retinal quadrants. Similarly, macular volumes were diminished in both perifoveal and outer macular regions in all sectors ( $p < 0.05$ ). The degree of tissue loss corroborated with the severity of dementia as objectively assessed by dementia rating scales. **Conclusion:** There is generalized retinal nerve degeneration in patients of Alzheimer's disease and the degree of loss correlated with the severity of disease.

**Keywords:** Alzheimer's disease, macular volume, OCT, RNFL

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### I. Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and its incidence is increasing associated with population aging.<sup>1</sup> AD is characterized by progressive cognitive impairment, such as memory deficits, decline in learning and executive functions, aphasia, apraxia, agnosia and visual abnormalities, most common being impairment of spatial contrast sensitivity, motion perception, color discrimination and visual loss. In the past these were attributed to lesions affecting the primary visual cortex and associated areas.<sup>2-5</sup> However, histological studies have also shown depletion in retinal ganglion cells (RGC) and their axons of AD patients.<sup>6</sup> Toxic amino acids, such as fibrillar tau and A $\beta$  aggregates were accumulated within the retina and its microvasculature, and signs of neuroinflammation were present in the retina.<sup>7-11</sup> Therefore, according to several clinical and histological studies there is strong evidence of anterior visual pathway impairment in AD patients, with predominant involvement of RGC and their fibers.<sup>12-14</sup>

Optical coherence tomography (OCT) is a non-invasive technology, which acquires cross-sectional images of retinal structures allowing neural fundus integrity assessment and quantifying structural axonal damage by measuring OCT peripapillary retinal nerve fiber layer (RNFL) that allows an indirect estimation of RGC layer impairment or directly by estimating macular thickness measurements, since 30–35 % of the retina thickness in macular area is composed by the RGCs and their fibers.<sup>15-17</sup> The purpose of this cross sectional study was to evaluate the OCT findings in an Indian cohort of AD patients and try to corroborate patterns of RNFL thinning or macular volume loss as demonstrated in previous studies from other parts of the world as well as to form a baseline yardstick upon which future longitudinal studies can be carried out.

### II. Material And Methods

A cross sectional, observational case control study was conducted over a period of 1 ½ years from Jan 2012-June 2013 in the Department of Neurology at Medical College Hospital, Kolkata after obtaining Institutional Ethical Clearance. Patients were selected from the Neurology OPD at MCH and suitable age matched, healthy consenting controls were included from among accompanying friends and relatives. Patients with primary complaint of memory impairment or other cognitive domain affection were screened by applying Folstein's Mini-mental State Examination (MMSE) and if found appropriate were included in the study subject to the inclusion and exclusion criteria mentioned below.

#### Inclusion criteria

1. Age between 40-80 years
2. Ability to understand the instructions given.
3. Only those providing written informed consent.

4. Diagnosis of dementia as per DSM-IV-TR criteria
5. Diagnosis of Alzheimer's disease as per NINCDS-ADRDA criteria.

#### **Exclusion criteria**

1. Presence of diabetes mellitus
2. Glaucoma, IOP>21mm of Hg, H/O surgery for glaucoma or patients on anti-glaucoma treatment.
3. History of optic neuritis or H/O sudden loss of vision in either eye.
4. History of multiple sclerosis or other demyelinating CNS disease.
5. History of stroke, serious head injury, meningitis or encephalitis.
6. History of HIV infection.

Patients who fulfilled the primary screening MMSE for dementia were further subjected to the NINCDS-ADRDA criteria to diagnose "dementia of the Alzheimer's type" (in addition to fulfilling the DSM-IV-TR criteria). The Kolkata Cognitive Screening Battery (KCSB) validated by Das et al<sup>18</sup> was used to evaluate the cognitive functions of the Alzheimer's patients since most of our patients were of limited literacy which precluded the application of standardized Western test batteries written in English like Addenbrooke's Cognitive Examination-Revised (ACE-R) or Montreal Cognitive Assessment (MOCA). This test battery has already been used and validated by Ganguli and her colleagues in a rural Ballabgarh population in north India.<sup>19</sup> This cognitive test battery differed from Ganguli's in one particular domain, which was the information related to places according to existing local norms. In this battery, questions on post office, district, village and block were replaced with questions on locality (road name), city, state and country. This partially modified Hindi cognitive screening battery was translated into Bengali and again back translated to Hindi by independent bilingual professional translators in order to ensure the integrity of the translation. The translated test battery was named the Kolkata Cognitive Screening Battery (Appendix).

Different cognitive domains were tested such as verbal fluency (VF), object naming (ON), Mental state examination (MSE), calculation, immediate recall, memory delayed, memory recognition and visuo-construction. As shown in the table, the domains were further refined as "memory" being calculated as the total score of immediate recall, memory delayed and memory recognition wherein the difference of the memory recognition and delayed recall was taken as the "cue effect". Similarly, "language" was taken as the sum of the VF and ON scores while "non-language" was taken as the sum of MSE, calculation, memory and visuo-construction scores. Some further parameters such as Language:Memory, Language:MSE and VF:ON ratios were also calculated from the basic data.

Relevant radiological and biochemical investigations were done to match the inclusion and exclusion criteria as well as for assessment of disease. The radiological workup consisted of at least one non-contrast MRI of brain. Biochemical workup included at least evaluation of the fasting and 2hrs post-prandial blood glucose (FBS and PPBS), Serum electrolytes, urea and creatinine, thyroid function test and Serum Vit B12 levels.

Patients who passed the radiological and biochemical screen in view of the inclusion/exclusion criteria were subjected to ophthalmological examination including clinical ophthalmoscopy, applanation tonometry (for IOP measurement) and Visual Evoked Potential (VEP) measurement to rule out exclusion criteria as well as collect data pertaining to the eyes. After this, all the participants underwent OCT scanning of both eyes. Spectral domain OCT was performed using Heidelberg Engineering Spectralis HRA+OCT Rev 1.5.2.0 machine at the Regional Institute of Ophthalmology (RIO), Kolkata. The OCT machine obtained separate reflexes of the polarized single mode light from various layers of the retina starting from the inner limiting membrane to the retinal pigment epithelial layer, analysis of which gave the thickness of the different retinal layers. The standard definition of the inner and outer retinal layers which has been clearly stated by Hajee et al and is clearly delineated by the standard color coding in any modern OCT machine was used for this study. This study focused on the inner retinal layer which reflected the nerve fiber changes which are of interest.

The peripapillary retinal nerve fiber layer (PRNFL) thickness was studied in the temporal superior (TS), nasal superior (NS), temporal (T), nasal (N), temporal inferior (TI) and nasal inferior (NI) quadrants. The average global thickness (G) was extrapolated from the formula  $G = (TS + NS + 2T + 2N + TI + NI) / 8$ . This data was compared with similar parameters recorded from the eyes of age matched healthy controls.

The macular thickness was also studied in 3 concentric circles of 1mm (central macula), 3mm and 6mm. The outer 2 circles were further divided into 4 sectors (Superior (S), Inferior (I), Temporal (T) and Nasal (N)) by diagonal lines. The volume of each of these parts was calculated by multiplying the sectoral area with the average macular thickness in that sector. Total macular volume was also determined as the sum total of all such measurements.

The clinical and OCT data was then compared among cases and controls to look for any predictable patterns and also any definite relationship with disease stage or severity. The numerical data (parametric and non-parametric) were subjected to appropriate statistical analysis using MedCalc, a standard statistical software

accepted for biomedical research. For each statistical analysis, as per convention, the result was considered statistically significant only if a p-value less than 0.05 ( $p < 0.05$ ) was obtained. The central tendencies mean and median, along with variance, standard deviation and standard error of the mean were calculated for various parameters under study for each group. These data were compared among groups using the F-test, independent sample t-test or Mann-Whitney test as statistically appropriate. One way ANOVA was used to study the influence of categories on a continuous variable while Pearson's rank correlation and Kruskal-Wallis were used to test the correlation between clinical and OCT findings for nominal and ordinal data respectively.

### III. Result

Of a total of 225 patients with primary complain of loss of memory, 44 were eventually found to fit into the criteria for Alzheimer's disease. Among them 23 were excluded from the final study based on our exclusion criteria and a final of 21 patients or 42 eyes were included for clinical and OCT analysis. 50 out of 139 screened controls were also similarly examined giving us 100 age matched "control" eyes. The baseline demographic data is presented in Table 1.

**Table 1** Baseline demographic data of test and control groups

	Sex		Mean Age (years)
	Male	Female	
Study subjects (n=21)	09	12	69.0
Controls (n=50)	23	27	67.3
P-value	0.1755 (t-test)		

No significant age difference was found between the test and control groups as seen from the table. Table 2 shows cognitive performance of AD patients on KCSB

**Table 2** Cognitive performance of AD patients on KCSB compared to controls

Items	Mean Score		p-value
	AD pts	Controls	
Animal naming	4.955	12.800	
Fruit naming	5.159	13.800	
VF	10.114	26.600	
Object naming	9.068	14.900	
MSE	14.614	28.820	
Calculation	1.773	4.600	
Immediate recall	8.227	23.500	
Memory delayed	1.886	6.560	
Memory recog	5.568	19.120	
Visuo const	2.727	12.080	
Total score	53.977	136.180	

Our study subjects showed a rather global involvement of all items covered in KCSB. No significant sex predilection to the performance was found.

Both eyes of our 21 study subjects (42 eyes in total) and 50 control subjects (100 eyes) were subjected to OCT analysis as mentioned in the methodology. The inner retina in the peripapillary area (nerve fiber layer), macula and posterior pole were studied.

Table 3 showed that there was statistically significant global reduction in the PRNFLT in Alzheimer's patients. Significant thinning was found in each of the six sectors of peripapillary retina. The influence of KCSB lower scores (indicating increased severity of dementia) on the global RNFL thickness was compared using ANOVA along with Levene's test for equality of variances and Student Newman Keuls test for all pair wise comparisons (if ANOVA was positive). ANOVA showed F ratio=15.668, p=0.022. Hence the influence was considered statistically significant. Thus the severity of RNFL thinning paralleled the clinical severity of dementia.

Also the RNFL thickness on the temporal side (TI, T and TS combined) was more than that on the nasal side (NI, N and NS combined) in control eyes. The same pattern was maintained in Alzheimer's patient's eyes despite relative thinning in all sectors.

**Table 3** Comparison of RNFL thinning and macular volume loss among AD patients and controls

Sectors	Sector thickness (µm)			Macular volume (ml <sup>3</sup> )			
	Controls	AD Pts	p-value	Macula	Controls	AD Pts	p-value
G	99.017	81.682	<0.0001	M1	0.222	0.198	<0.0001
TS	138.120	100.071	<0.0001	M3-S	0.509	0.353	<0.0001
NS	103.970	88.667	<0.0001	M3-I	0.505	0.338	<0.0001
T	76.580	63.238	<0.0001	M3-T	0.485	0.394	<0.0001
N	73.570	63.667	<0.0001	M3-N	0.523	0.357	<0.0001
TI	143.410	112.429	<0.0001	M6-S	1.566	1.360	<0.0001
NI	106.340	98.476	<0.0001	M6-I	1.554	1.368	<0.0001
				M6-T	1.485	1.332	<0.0001
				M6-N	1.738	1.350	<0.0001
G	Global			M1	Central macula		
TS	Temporal superior			M3-S	Middle macula(1-3mm) Superior quadrant		
NS	Nasal superior			M3-I	Middle macula(1-3mm) Inferior quadrant		
T	Temporal			M3-T	Middle macula(1-3mm) Temporal quadrant		
N	Nasal			M3-N	Middle macula(1-3mm) Nasal quadrant		
TI	Temporal inferior			M6-S	Outer macula(3-6mm) Superior quadrant		
NI	Nasal inferior			M6-I	Outer macula(3-6mm) Inferior quadrant		
				M6-T	Outer macula(13-6m) Temporal quadrant		
				M6-N	Outer macula(3-6mm) Nasal quadrant		

Table 3 also analyzed the macular volumes among our study subjects and controls. There was significant loss of macular volume in all sectors in Alzheimer's patients compared to controls. Furthermore it was found that there was a significant negative correlation between age and total macular volume in patients of Alzheimer's disease but no such significant correlation was found among the age matched controls (r= - 0.4655). This indicated that significant macular thinning with age, resulting in macular volume loss may be a feature of neurodegenerative diseases and not suffered by all people in general.

#### IV. Discussion

The OCT studies showed significant reduction of peripapillary retinal nerve fiber layer thickness in AD patients compared to age matched healthy controls. The thinning was significant in all sectors analysed. This finding was in concordance with the studies of Parisi et al, Paquet et al and Berisha et al.<sup>14, 20-21</sup> Paquet et al included both MCI and early AD while Berisha et al included early AD only. Berisha et al showed statistically significant loss of RNFL thickness in the superior quadrant while Paquet found pan retinal loss of thickness like us. Studies by Kirbas et al, Lu et al and Marziani et al also found RNFL thinning in all quadrants.<sup>22-24</sup> However, Kergoat et al used scanning laser polarimetry to measure the RNFL and found no significant association between AD and reduction of RNFL thickness.<sup>25</sup> The presence of some disagreement, despite the majority of studies showing functional, electrophysiological and/or OCT abnormalities in the retino-optic pathway led He et al to do a meta-analysis of all available published data till 2012. He concluded that the published data suggest an association between RNFL thinning and AD and that there was significant RNFL thickness reduction in all quadrants compared with healthy controls.<sup>26</sup> Similarly, Gao et al. evaluated 25 patients with AD and found a significant reduction of macular volume in these patients.<sup>27</sup> Salobar-Garcia et al. also demonstrated a preferential reduction of macular parameters in mild-AD patients. In this study, the peripapillary

RNFL thickness was thinner, but did not reach a significant difference compared with age-matched controls, suggesting a preferential involvement of the macula in early stages of the disease.<sup>28</sup>

Alzheimer's disease being a neurodegenerative disease that involves a significantly large portion of the brain in course of time is expected to involve the eye which is developmentally a part of the CNS and cause degeneration of the retinal cells, many of which are in fact neurons. This degeneration can be seen on OCT as inner retinal thinning. These OCT findings correlate well with the histopathological findings in autopsy studies showing nerve cell degeneration in the retina of patients who had features of AD in the histopathological study of the brain.

We also studied the relation of the OCT findings with the clinical parameters of the patients. Since the clinical scores were discrete, in whole numbers, and basically arbitrary, we considered the scores as categories, rather than variables. So, we used ANOVA in addition to Spearman's rank correlation to study the influence of the scores on OCT findings and considered a relation as significant only when both ANOVA and Spearman's coefficient were both significant. When the relations of clinical scores to the OCT findings were studied in the patients, some significant differences were found in the study of the peripapillary and the macular regions. The total KCSB scores had significant influence on thinning of the peripapillary RNFL ( $p=0.022$ ). However, the relation of the total KCSB score with macular volume loss was not significant ( $p=0.139$ ). On subgroup analysis, however, it was interesting to note that macular volume loss was significantly associated with total non-language item scores ( $p=0.001$ ) and MSE scores ( $p<0.001$ ) while not being significantly related to the memory items total score ( $p=0.084$ ). This discrepancy is a bit difficult to explain and the relevance of such small differences may also be questionable. Nevertheless, it raises the possibility that though loss of memory is considered to be the hallmark of AD, it may not be the most consistent reflection of neurodegeneration, at least in the retina. Further studies involving larger cohorts from different geographic areas are required to validate this finding.

Age was associated with significantly greater macular volume loss in AD patients and not in controls. The possible explanation of this finding could be either a simple averaging of the differential macular volume loss in patients with ageing which was seen among the controls suggesting that the higher volume loss in our study group compared to controls could mean that the presence of a neurodegenerative disorder in a patient may add to the process of age related macular thinning. This finding could also reflect a spurious association, reflecting an increased burden of AD among elderly patients. A possibility of genetic, epigenetic, proteomic or other biological processes underlying the neurodegenerative process may accelerate the process of ageing itself. Further studies are warranted.

This study had a number of limitations. Being conducted on patients living in and around the Kolkata metropolis, who were mostly Bengali speaking, there was a lack of ethnic diversity. The number of patients included, though larger than previously published studies, still leaves room for larger multicenter studies. Also we could not include patients in very early or pre-symptomatic stages of disease owing to the inherent design of our study. Though our findings can be statistically extrapolated backwards, yet good scientific evidence about the OCT changes in presymptomatic or early symptomatic stages of AD is not available from this study. The study design being cross-sectional also leaves room for improvement. A longitudinal study using repeated OCT on the same patients will provide better information on the course of the disease. We also could not use ERG due to its non availability and hence could not parallelly assess the functional impairment in visual processing along with OCT changes in cases and controls.

Nevertheless, we have included a significant number of patients, provided important data for Indian patients and found out significant associations which can be used for further research and clinical work.

## V. Conclusion

There is generalized retinal nerve degeneration in patients of Alzheimer's disease and the degree of loss correlated with the severity of disease.

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