Analysis of retinal nerve fiber layer thickness in cognitive impairment

Praveen Kumar K V[1,*], Sharad Nivrutti Gomase[2], Chiranjeevi P[3]

[1]Assistant Professor, Dept. of Ophthalmology, Narayana Medical College, Nellore, Andhra Pradesh, [2]Ex-Junior Resident, Armed Forces Medical College, [3]Junior Resident, Dept. of Ophthalmology, Narayana Medical College, Nellore, Andhra Pradesh, India

*Corresponding Author:
Email: praveenkumarafmc@gmail.com

Abstract

Introduction: Cognitive impairment may be present at birth or can occur later in adulthood. Few studies have shown correlation of cognition with retinal nerve fiber layer thickness (RNFL). The present study was planned to analyse RNFL thickness in disorders of cognition.

Materials and Methods: 60 eyes of cognitive impairment were included. All patients underwent RNFL thickness measurement by OCT at initial visit and after 3 months. Statistical analysis was done with a p value less than 0.05 to be significant.

Results: 60 eyes of cases of cognitive impairment were included. 16 (53%) cases had cognitive impairment following traumatic brain injury and 14 (47%) cases were secondary to Alzheimer's disease. The mean RNFL thickness in the superior quadrant was 105.92 μm ±28.343μm at initial visit and at 3 months follow up was 105.72 μm±27.916 μm, in the nasal quadrant was 69.17 μm ± 13.199μm at initial visit and at 3 months follow up was 68.97 μm± 13.119 μm, in the inferior quadrant RNFL thickness was 111.03 μm±22.558 μmat initial visit and at 3 months follow up was 110.92 μm±22.372 μm, in the temporal quadrant was 59.35 μm ±11.333 μm at initial visit and at 3 months follow up was 59.18 μm ±11.247 μm but the difference was not statistically significant. Subgroup analysis of cases also did not show any statistically significant difference in RNFL thickness.

Conclusion: RNFL thickness remains unaffected in cognitive disorders. However studies on a large sample of patients with a longer follow up are needed.

Keywords: Cognitive impairment, RNFL thickness, Optical coherence tomography.

Introduction

Cognitive development involves process of perception, action, attention, problem solving, memory and mental imagery. Cognitive functioning refers to the ability to attend to complex external or internal stimuli, to identify their relevant features, and to make appropriate responses to them.[1] Cognitive impairment is a broad term to describe a wide variety of impaired brain function relating to the ability of a person to think, concentrate, react to emotions, formulate ideas, solve problems, reason and remember. Cognitive impairment may be present at birth or can occur later in adulthood as a result of various conditions like side effects of cancer therapy, malnutrition, heavy metal poisoning, autism (abnormal development of communication and social skills), metabolic conditions. With age, other conditions such as stroke, dementia, delirium, brain tumors, chronic alcohol use or abuse, substance abuse, some vitamin deficiencies, and some chronic diseases may cause cognitive impairment. Head injury and infection of the brain and meninges can also cause cognitive impairment.

The retina and the areas of the brain involved in cognitive functioning share a common origin from the embryonic prosencephalon. The optic nerve is a cranial nerve that can be visualised directly and thus provides us anindirect estimate of the health of the central nervous system. Studies describing increased prevalence of glaucoma in patients with Alzheimers disease (AD) infers the involvement of retina in cognitive functioning.[2,3]

Few studies have shown correlation of cognition with retinal nerve fiber layer thickness. Reduction in RNFL thickness in AD was reported in a few studies.[4,5] A study by Iseri et al also showed a correlation between cognitive impairment and total macular volume.[6] Retinal ganglion cell loss in postmortem studies of patients of AD was also reported by few authors.[7]

The thickness of RNFL can be measured by various techniques like Optical coherence tomography (OCT) and scanning laser polarimetry. OCT is a non invasive and non contact diagnostic imaging technology that utilizes interferometry and low coherence light in the near infrared range to achieve high resolution cross sectional images of the eye. It allows identification of different layers of the retina individually similar to histopathological examination and provides significant clinical information in various retinal conditions.[8,9] OCT is also useful in neuro-ophthalmological disorders like optic neuritis and optic chaismal lesions, as these disorder affect the optic nerve and thereby the thickness of RNFL.The role of OCT in cognitive disorders is presently in the nascent stage. There is paucity particularly in Indian literature on the role of OCT in cognitive disorders. The present study was thus planned to analyse the features of RNFL in disorders of cognition.

Materials and Methods

The study was a prospective non interventional study conducted at a tertiary eye care centre in India. The study was conducted over a period of two years. A

total of 30 cases of cognitive impairment diagnosed by mental status examination and cognitive deficit assessed by Mini mental state examination by a qualified psychiatrist were included in the study. Institutional ethical clearance was obtained for the study. A written informed consent was taken from all the patients. Patients with any other psychiatric disorder other than cognitive impairment, patients unable to undergo OCT, patients with associated optic nerve disorders including glaucoma, patients with any other macular disorders were excluded from the study. All patients meeting the inclusion and exclusion criteria, who presented to the department of psychiatry, were included in the study. All patients underwent a comprehensive ocular examination consisting of best corrected visual acuity, slit lamp biomicroscopic evaluation of the anterior segment and intraocular pressure measurement. Dilated fundus examination was done and particularly the disc was evaluated to rule out glaucoma. All patients underwent RNFL thickness measurement by optical coherence tomography (Cirrus High Definition Spectral Domain (HD SD) OCT Model 4000 (Carl Zeiss–Meditec, Dublin, California, USA) and the measurements were noted. RNFL measurements were obtained using the Optic Disc Cube 200 × 200 protocol. The Cirrus OCT Optic Disc Protocol Cube 200 × 200 images 6 × 6 mm2, and samples 200 × 200 data points in less than 1.5 seconds. The scanning laser images were then focused. Using the

iris and fundus viewports, the alignment was properly positioned to the optic nerve head in the centre of the scan. A Cirrus software algorithm automatically detects the centre of the optic disc and positions a 3.46 mm diameter calculation circle over this point. In each series of scans, average Retinal Nerve Fibre Layer thickness (RNFL) and RNFL thickness in each quadrant (superior, inferior, temporal and nasal) were analysed. The patients were followed up after 3 months. Repeat ocular examination was done along with measurement of RNFL thickness using the same protocol. All scans were performed by the same individual. All the data was tabulated and statistically analysed with p less than 0.05 to be significant.

Results

The study included 60 eyes of diagnosed cases of cognitive impairment. The age of the patients ranged from 32 to 83 years with mean age of 57.43 years. Out of 30 cases of cognitive impairment patient in the study, 27 (90%) were males (90%) and 3 (10%) were females. Out of 30 cases, 16 (53%) cases had cognitive impairment following traumatic brain injury (TBI) and 14 (47%) cases were secondary to Alzheimer's disease (AD).

RNFL thickness of all cases [Table 1]

Table 1: Table showing RNFL thickness of cases at 0 and 3 months follow up

RNFL	Months	No. of eyes	Mean (µm)	Std. Deviation	Paired t	P
Avg RNFL	0	60	86.35	14.025	1.211	0.231 NS
	3	60	86.22	14.012		
Superior RNFL	0	60	105.92	28.343	1.079	0.285 NS
	3	60	105.72	27.916		
Nasal RNFL	0	60	69.17	13.199	1.492	0.141 NS
	3	60	68.97	13.119		
Inferior RNFL	0	60	111.03	22.558	0.532	0.597 NS
	3	60	110.92	22.372		
Temporal RNFL	0	60	59.35	11.333	1.645	0.105 NS
	3	60	59.18	11.247		

At presentation, mean average RNFL thickness was 86.35 µm ± 14.025µmwhereas at 3 months follow up, mean average RNFL thickness was 86.22 µm± 14.012µm. The change in average RNFL thickness was not statistically significant (p=0.23).

Themean RNFL thickness in the superior quadrant was 105.92 µm ±28.343 µm at initial visit and at 3 months follow up RNFL thickness was 105.72 µm±27.916µm and this was not statistically significant (p=0.28).

The mean RNFL thickness in the nasal quadrant was 69.17 µm ± 13.199 µm at initial visit and at 3

months follow up was 68.97 µm±13.119µm and was not statistically significant. (p=0.14).

At presentation, mean inferior quadrant RNFL thickness was 111.03 µm ±22.558 µm whereas at 3 month mean inferior quadrant RNFL thickness was 110.92 µm± 22.372µm but the difference was not statistically significant (p=0.59).

At presentation, mean temporal quadrant RNFL thickness was 59.35 µm ±11.333 µm whereas at 3 month mean temporal quadrant RNFL thickness was 59.18 µm±11.247µm but the difference was not statistically significant (p=0.10) [Fig. 1]
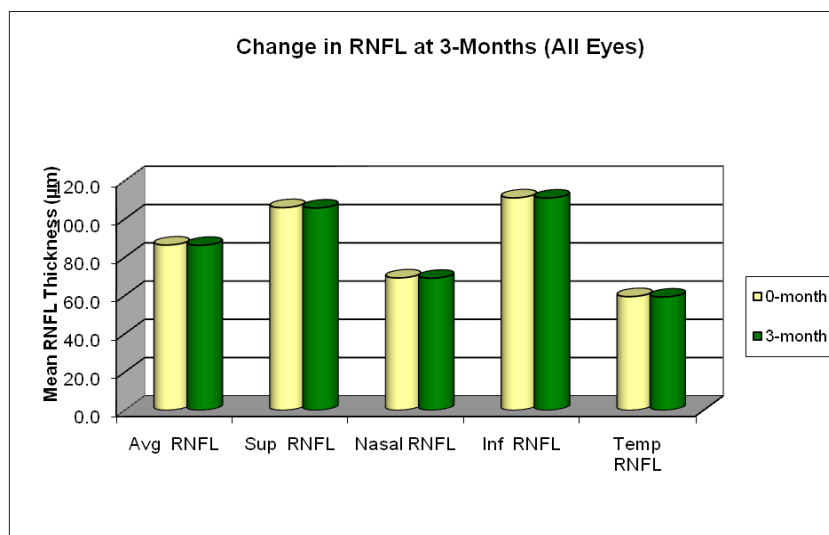
Fig. 1: Bar chart showing change in RNFL thickness in cases at presentation and at 3 months follow up

RNFL thickness in cases of Alzheimers Disease [Table 2]

Table 2:.Table showing RNFL thickness analysis of cases of cognitive impairment due to alzheimer's disease at 0 and 3 months follow up

RNFL	Months	No. of eyes	Mean (μm)	Std. Deviation	Paired t	P
Average RNFL	0	28	79.75	14.107	0.238	0.813 NS
	3	28	79.79	14.201		
Superior RNFL	0	28	93.46	29.804	1.030	0.312 NS
	3	28	93.68	29.508		
Nasal RNFL	0	28	65.25	11.108	1.536	0.136 NS
	3	28	65.04	11.302		
Inferior RNFL	0	28	103.71	25.908	1.560	0.130 NS
	3	28	104.04	25.841		
Temporal RNFL	0	28	56.61	10.521	1.0	0.326 NS
	3	28	56.46	10.560		

28 eyes of cognitive impairment due to Alzheimer's disease were analysed. At presentation (0 month) mean average RNFL thickness was 79.75 μm ± 14.107 μm whereas at 3 months, it was 79.79 μm ±14.201 μm. The change in average RNFL thickness was statistically not significant (p=0.813).

The mean RNFL thickness in superior quadrant was 93.46 μm ± 29.804 μm whereas at 3 month follow up was 93.68 μm ± 29.508 μm and was not statistically significant (p=0.312).

The mean RNFL thickness in nasal quadrant at initial visit was 65.25 μm ±11.108 μm whereas at 3 month was 65.04 μm ±11.302 μm and was not statistically significant (p=0.136).

The mean RNFL thickness in inferior quadrant was 103.71 μm ±25.908 μm whereas at 3 month follow up was 104.04 μm ±25.841 μm and was not statistically significant (p=0.130).

The mean RNFL thickness in the temporal quadrant at initial visit was 56.61 μm ±10.521 μm whereas at 3 month mean temporal quadrant RNFL thickness was 56.46 μm ±10.560 μm and was statistically not significant (p=0.326) [Fig. 2].
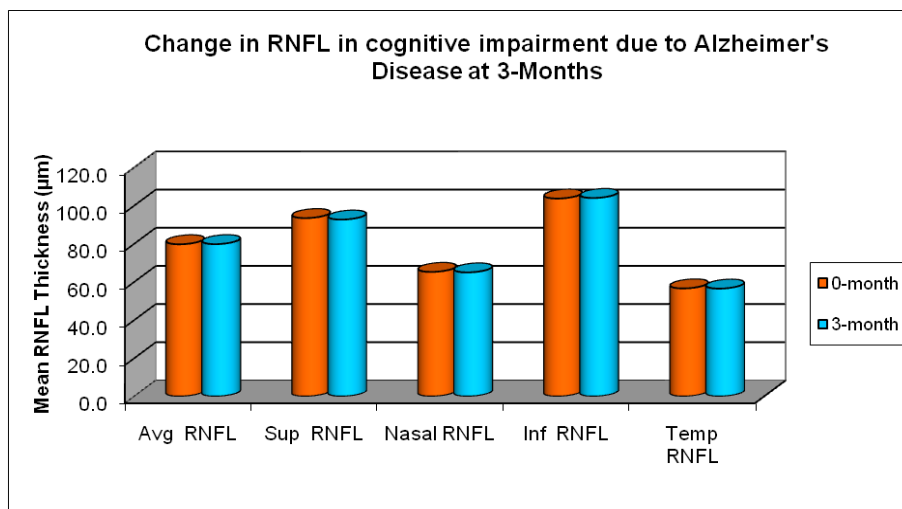
Fig. 2: Bar chart showing change in RNFL thickness in cases of Alzheimers disease at presentation and 3 months follow up

RNFL thickness in cases of cognitive impairment secondary to traumatic brain injury [Table 3]

Table 3: Table showing RNFL thickness of cases of cognitive impairment due to traumatic brain injury (TBI) at 0 and 3 months follow up

RNFL	Months	No. of eyes	Mean (µm)	Std. Deviation	Paired t	P
Avg RNFL	0	32	92.13	11.282	1.791	0.083NS
	3	32	91.84	11.314		
Sup RNFL	0	32	116.81	22.196	1.982	0.056 NS
	3	32	116.25	21.894		
Nasal RNFL	0	32	72.59	14.076	0.845	0.405 NS
	3	32	72.41	13.788		
Inf RNFL	0	32	117.44	17.120	1.392	0.174 NS
	3	32	116.94	17.052		
Temp RNFL	0	32	61.75	11.631	1.293	0.206 NS
	3	32	61.56	11.450		

32 eyes of cognitive impairment due to traumatic brain injury were analysed. At presentation, mean average RNFL thickness was 92.13 µm±11.282µmwhereas at 3 month mean average RNFL thickness was 91.84 µm±11.314µm. The change in average RNFL thickness was statistically not significant (p=0.083).

The mean RNFL thickness in superior quadrant at presentation was 116.81 µm ±22.196 µmwhereas at 3 months followup, it was 116.25 µm±. 21.894 µmand was statistically not significant (p=0.056).

The mean RNFL thickness in the nasal quadrant was 72.59 µm ±14.076µm at presentation,whereas at 3 months follow up it was 72.41 µm. ±13.788 µm and was not statistically significant (p=0.405).

The mean inferior quadrant RNFL thickness at presentation was 117.44 µm ±17.120 µmwhereas at 3 month follow up it was 116.94 µm. ±17.052µm and was not statistically significant (p=0.174).

The mean temporal quadrant RNFL thickness at initial visit was 61.75 µm ±11.631 µm whereas at 3

month follow up it was 61.56 µm± 11.450 µm and was not statistically significant (p=0.206) [Fig. 3].
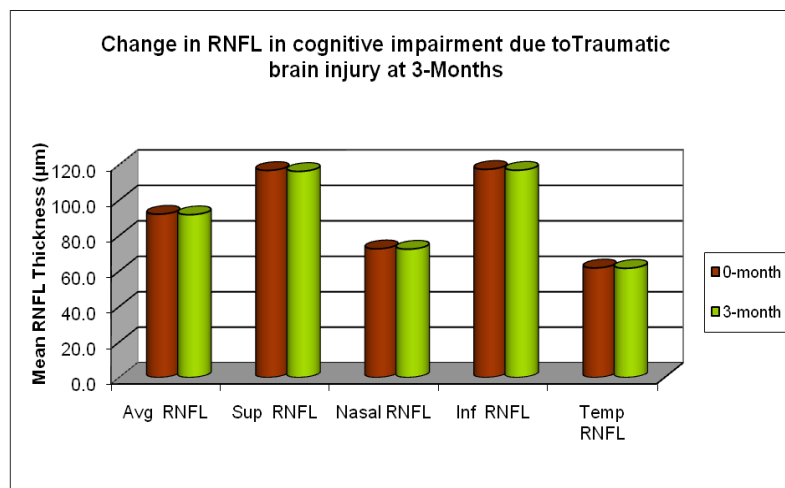
Fig. 3: Bar chart showing change in RNFL thickness in cases of traumatic brain injury at presentation and 3 months follow up

Discussion

The present study assessed the retinal nerve fibre layer thickness in patients with cognitive impairment and evaluated the efficacy of the same in diagnosis of those disorders. Various studies previously have highlighted the importance of OCT in measurement of RNFL thickness in different neurological disorders.[4,10-12]

In an OCT, detection of the reference and sample beams is based on time domain or spectral-domain protocol. Stratus OCT (Carl Zeiss Meditec, Dublin, California) can acquire 400 A-scans per second with an image resolution of about 10 micrometer (µm). The new spectral domain OCT (SD-OCT) systems can acquire about 26,000 A-scans per second. This increase is achieved by replacing the original moving reference arm with a stationary one and by calculating the fourier transform to simultaneously measure the light reflectance from different depths of the retina. The 3-D scanning protocol of the SD-OCT machines can acquire more than 100 images in 3-4 seconds, revealing defects that may have been missed on the stratus OCT protocols. These images are also used to reconstruct fundus images to which individual OCTs are registered. The registration provides the origin of the scan on the retina and ensures the same location is monitored on each visit. Derived volumetric measurements may allow accurate quantification of the amount of fluid or size of the lesion rather than just providing a data-limited, single cross-sectional image. The increase in image definition may better resolve retinal borders and provide more accurate quantitative data.[13,14]

In spite of its enormous utility and ease of use, inaccurate results are common with OCT if the clinician himself is not aware of the basic software functioning and algorithms. Artefacts are commonly encountered in OCT imaging.[15,16]

There are two types of OCT- Stratus and Spectral domain OCT. The Stratus OCT software incorrectly identifies the outer retinal boundary, as it draws this boundary at the inner highly reflective line that corresponds to the junction of the outer and inner segments of the photoreceptors rather than the outer highly reflective line.[17,18] The SD OCT uses outer RPE as the outer retinal boundary. Thus, the Stratus OCT underestimates the true retinal thickness, by nearly 50 microns, and may fail to detect retinal thickness changes between the photoreceptor outer segment and the RPE.[19] The presence of vitreoretinal traction may cause a failure in the localization of the internal limiting membrane with misplacement of the inner boundary on the zone of vitreous traction. Spectral domain OCT (SD-OCT) has faster acquisition time and thus reduces errors produced by patient or operator factors, thus allowing better focussing on area of interest.[13] Despite the introduction of spectral-domain OCT into clinical practice over the past years, many retina practitioners throughout the world continue to rely on the Stratus OCT because of cost issues and hence the same has been used in the present study. For the posterior segment, in addition to obtaining cross-sectional images of the retina, the instruments may have built-in algorithms to automatically measure retinal thickness, peripapillary retinal nerve fiber layer thickness (RNFL), and quantify optic nerve head (ONH) morphology (e.g. disc size and cup-disc ratio).

The age of study population ranged from 32 to 83 years with mean age of 57.34 years. This pattern of age distribution must have been due to the inclusion of cases from hospital based population. Cognitive impairment due to traumatic brain injury and Alzheimer's disease were only included in the study due to nature of patients seen in psychiatry OPD of the hospital. 16 cases (53%) were due to traumatic brain injury (TBI) and 14 (47%) cases were due to Alzheimer's disease (AD). The present study had male preponderance, 90% cases being the male. This could behave been due to clientele of the service hospital.

A total of 60 eyes (30 patients) of cognitive impairment patient were studied.At presentation (0 month) mean average, superior, nasal, inferior, temporal RNFL thickness was 86.35 µm, 105.92 µm, 69.17 µm, 111.03 µm, 59.35 µm respectively. Similarly mean average, superior, nasal, inferior, temporal RNFL thickness measured after 3 months of follow up was 86.22 µm, 105.72 µm, 68.97 µm, 110.92 µm, 59.18 µm respectively. Though the mean RNFL thickness at 3 months follow up was less compared to that at presentation, the decrease was not statistically significant. The difference in RNFL thickness at presentation and after 3 months can be attributed to the variation in repeatability by the OCT machine used, even though the same operator and same machine was used to measure the thickness for all the cases.[15,16] Another explanation must have been because of small sample size, statistical significance would not have been achieved.

Seibold L et al. when comparing RNFL thickness measurement between various OCT machines, also calculated coefficient of variation (CV) for each machine and found that CV for the Cirrus HD-OCT was 3.03%.[20]

Out of 60 eyes (30 cases) of cognitive impairment in this study, 32 eyes (16 cases) were due to traumatic brain injury (TBI). At presentation (0 month) mean average, superior, nasal, inferior, temporal RNFL thickness was 92.13 µm, 116.81 µm, 72.59 µm, 117.44µm, 61.75 µm respectively. Similarly mean average, superior, nasal, inferior, temporal RNFL thickness measured after 3 months was 91.84 µm, 116.25 µm, 72.41 µm, 116.94 µm, 61.56 µm respectively. Though the mean thickness at 3 months were less than at presentation, it was not statistically significant. The reason for the difference between two mean being the same as mentioned above, that is, due to variation in repeatability by the OCT machine used or due to small sample size. On comparing the mean RNFL thickness for traumatic brain injury with that of Seibold et al value, mean RNFL thickness in this group was similar to their values.[20]

Out of 60 eyes (30 cases) of cognitive impairment in this study, 28 eyes (14 cases) were due to Alzheimer's disease (AD). At presentation, mean superior, nasal, inferior, temporal RNFL thickness was 79.75 µm, 93.46 µm, 65.25 µm, 103.71 µm, 56.61 µm respectively. Similarly mean superior, nasal, inferior, temporal RNFL thickness measured after 3 months was 79.79 µm, 93.68 µm, 65.04 µm, 104.04 µm, 56.46 µm respectively. The mean RNFL values for average, superior and inferior at 3 months was more than that at presentation, but that of nasal and temporal at 3 month was less than that at presentation, the difference was not statistically significant. The reason for the difference between two mean being the same as mentioned above, that is, due to variation in repeatability by the OCT machine used or due to limited sample size.

On comparing the mean RNFL thickness for Alzheimer's disease with that of lower values of RNFL thickness in study by Seibold et al as calculated above, the mean RNFL thickness in average, superior and inferior quadrant of this group was lesser than the lower limit whereas nasal and temporal thickness was comparable.[20] These findings are also consistent with those found by Kesler A et al.[21]

Seibold et al showed that the retinal nerve fiber layer (RNFL) thickness measured by different OCT machine such as Stratus, Cirrus, Spectralis, RTVue was different for same individual. The RNFL values obtain by these OCT machines were significantly different from each other and concluded that values cannot be used interchangeably.[20] So the RNFL values of this study could not be compared with the normal Indian population RNFL thickness, as all population based studies were done either with Time- domain stratus OCT or Spectral domain RTVue OCT machine and hence comparision with controls was not done in the present study.[22,23]

Our study has limitations. The major limitation of this study was repeat measurement of RNFL thickness at 3 months interval which is too short for changes to manifest. The other limitation is the absence of controls in this study and a small sample size.

Conclusion

RNFL thickness is not affected in cases of cognitive impairment. However the study had limitations of small sample size and shorter follow up. Hence, further longitudinal case control studies are recommended in which patients with cognitive impairment are included and subsequently followed for longer period for any changes in the retinal nerve fiber layer thickness.

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