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A cross-sectional study for evaluation of Retinal Nerve Fiber Layer thickness and Macular Volume in patients of Schizophrenia using Optical Coherence Tomography at a tertiary healthcare center in South Gujarat.

Dr. Priti Kapadia Gupta[1] Dr. Shinjini Sahay[2]
1. Professor and Head of Department, Ophthalmology, GMC Surat
2. Resident, Ophthalmology, GMC Surat

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ABSTRACT
AIM: The study was performed to evaluate the Retinal Nerve Fiber Layer (RNFL) Thickness and Macular Volume in patients of Schizophrenia using Spectral- Domain Optical Coherence Tomography (SD-OCT) to establish an association of the findings with severity and duration of Schizophrenia.
SETTINGS AND DESIGN: Cross- Sectional Study.
METHODS AND MATERIAL: A total of 45 patients of Schizophrenia were assessed for severity of illness using the Positive And Negative Symptom Scale (PANSS) and for duration of disease. Stable patients with a PANSS score of less than 75 were recruited for the study. The RNFL thickness and Macular Volume was obtained using SD-OCT and the data was statistically analyzed.
STATISTICAL ANALYSIS USED: Correlation test and ANOVA for finding an association between quantitative variables.
RESULTS: The mean age of the 45 patients included in this study was 34.11 ± 10.5 years, mean duration of disease was 6.54 years and the mean PANSS score was 35.6±2.9. Overall RNFL thickness was in 107.8 ± 9.6 in right eye and 107.3 ± 9.6 in left eye, Mean Macular Volume in right eye was 7.50 ± 0.44 and 7.52 ± 0.4 in the left eye. The overall RNFL thickness was reduced in relation to PANSS score in both eyes but the result was not statistically significant (RE p=0.046, LE p=0.849). Macular Volume was within the normal range in both eyes in relation to PANSS score. Overall RNFL thickness (RE p= 0.066, LE p=0.247) and Macular Volume (RE p=0.468, LE p=0.441) was lower in the chronic phase of illness but the results were not statistically significant.
CONCLUSION: The findings of this study suggest that the RNFL thickness and Macular Volume are reduced in patients of Schizophrenia and correlated with the severity and duration of illness. Although the results were not found to be statistically significant, it does emphasize the use of OCT in patients with Schizophrenia to identify a neurodegenerative process that may be an underlying pathological mechanism and thereby making it a useful screening tool to monitor the disease progression and its severity.
KEYWORDS: Schizophrenia, SD-OCT, neurodegeneration.

I. INTRODUCTION

Schizophrenia is a chronic debilitating psychiatric condition that ranks among the leading causes of global disease-related disability.[1] It is a progressive, chronic and disabling mental disorder characterized by positive, negative, and cognitive symptoms that affect almost all aspects of mental activity, including perception, attention, memory, and emotion.[2] Its clinical presentation is wide-ranging and reliable investigations are generally lacking. Different neuroimaging and neuropathological methods have been frequently used by researchers to identify specific abnormalities which support a neurodegenerative hypothesis in Schizophrenia.[3] Structural brain abnormalities in patients of Schizophrenia based on several neuroimaging studies have included ventricular enlargement (particularly lateral ventricles), total brain volume deficits, and reductions in the volumes of thalamus, hippocampus, anterior cingulate cortex, and in the area of the corpus callosum. However, there is still uncertainty about the key areas involved in the pathogenesis of this condition.[4]

Schizophrenia has been associated with deficits in visual perception and processing as evidenced by previous studies.[5] It has been postulated that this could be due to dopamine dysregulation.[6] Studies have established that dopamine is a major neurotransmitter and modulator in the retina. Lack of retinal dopamine is

believed to alter visual processing by modification of receptive field properties of ganglion cells.[6] Researchers have shown in an animal model that retina with dopaminergic deficiency loses a subset of retinal amacrine cells. It also remains to be determined whether dopamine dysregulation actually causes any structural defects of the optic nerve and retinal layers in schizophrenic patients.[7]

Optical coherence tomography (OCT) is a relatively new non-invasive imaging technique that can assess the thickness of retinal nerve fiber layer (RNFL), macular thickness and volume, and is used in various ophthalmologic disorders including glaucoma and macular diseases.[8] A decreased thickness can correspond to neuronal death and axonal loss in RNFL. Using OCT, a significant reduction in the peripapillary RNFL thickness has been reported in patients with various neurologic diseases such as multiple sclerosis, Alzheimer´s disease and Parkinson´s disease, suggesting that this technology might also prove useful in other neurodegenerative disorders.[9]

The retina is a good model for the study of these neurodegenerative diseases, since it lacks myelin. This means that any changes in the RNFL will reflect axonal damage, thus providing us a window to the brain. Brain atrophy had been well established in multiple sclerosis and Alzheimer's disease and the OCT findings of significant RNFL thinning in these diseases correlated with the neurologic changes.[10] With evidences of visual processing and grey matter volume deficits in schizophrenia, evaluations of structural RNFL with OCT may establish tissue loss, which can explain the abnormalities mentioned above. The aim of this study was to evaluate the RNFL thickness in schizophrenic patients using Spectral Domain OCT (SD-OCT) and to study the peripapillary RNFL thickness and Macular Volume in schizophrenic patients and also to assess whether a correlation exists between the RNFL thickness and macular volume with the clinical severity and duration of the disease.

II. SUBJECTS AND METHOD

The study was conducted at a tertiary care hospital in South Gujarat from January 2020 to June 2021. Systematic Random Sampling, every 10th stable patient of Schizophrenia diagnosed as per the DSM 5 criteria between the age group of 18 to 60 years attending routine Psychiatry OPD clinics was evaluated by a pair of Consultant and Resident doctor. The patients were assessed for duration of illness and its severity from the records and thereby assigned a symptom score as per the PANSS score sheet. Those patients with a PANSS score of less than 75 were recruited to the Ophthalmology Department for further evaluation. Written informed consent of the patients and their respective guardian for participation in the study was taken. Participants considered in this study had no ocular or systemic diseases that are known to influence the retina (Example: Glaucoma, Age Related Macular Degeneration, High Myopia, Diabetes Mellitus, Hypertension, Alzheimer's disease, Parkinsonism, Multiple Sclerosis). Complete ophthalmologic evaluation, including visual acuity using illuminating Snellen's chart, subjective testing for Refractive Error, slit lamp examination for Anterior Segment evaluation, fundus examination by indirect ophthalmoscopy to evaluate Posterior Segment and Intra Ocular Pressure measurement on Non- Contact Tonometer was done to rule out any preexisting ocular pathology that may hinder the outcome of the study. 0.8% tropicamide and 5% phenylephrine eyedrops were used to dilate pupils. Spectral Domain Optical Coherence Tomography (SD-OCT) using TOPCON 3D OCT-1 Maestro was performed on these subjects after detailed history and ophthalmic evaluation. Circum-papillary RNFL thickness over temporal-superior-nasal-inferior-temporal circle placed automatically over the optic disc centre was recorded in 4 quadrants and 12 clock-hour sectors around the TSINT circle. Macular 3D scans (6x6mm- 512x128) were obtained and the Macular Volume was recorded.

The data was analyzed with Epi info version 7.1 and appropriate statistical tests were applied (Correlation test, ANOVA) for finding an association between OCT readings and PANSS Score. Other quantitative variables were analyzed using mean, median, mode and standard deviation and other related statistical tests were applied. The p value was determined to finally evaluate the levels of significance. $P<0.05$ was considered as significant. Waiver of consent was sought since research was based on data collected through standard health check-up procedures.

III. RESULT

The present study was conducted at a tertiary care hospital in South Gujarat. A total of 45 clinically stable cases of Schizophrenia with a PANSS score of less than 75 attending Psychiatry OPD were included in this study. The mean age of the patients was 34.11 ± 10.5 years and majority of patients were between 18 to 45 years (84.4%) age group. Male: female ratio was 1.3:1, 57.8% being males and rest 42.2% being females. The mean duration of disease among patients was 6.54 years. Duration of disease among majority of patients

(44.4%) was less than five years followed by 6 to 10 years (35.6%) and more than 10 years (13.3%). The mean PANSS score in the study population was 35.56±2.9. Overall RNFL thickness was in 107.8 ± 9.6 in right eye and 107.3 ± 9.6 in left eye.
RNFL thickness according to Retinal quadrants in both eyes were as follows:
In Superior 133.56 ± 13.02 in right eye and 134.38 ± 10.07 in left eye, in Inferior 140.9 ± 12.8 in right eye and 140.7 ± 14.1 in left eye, in nasal 82.8 ± 11.6 in right eye and 83.2 ± 14.5 in left eye and in temporal 70.3 ± 6.8 in right eye and 71.1 ± 6.5 in left eye.
Mean Macular volume was found within normal range in both right eye (7.50 ± 0.44) and left eye (7.52 ± 0.4).

Table 1: Age and Gender wise distribution of patients

Age (years)	Male		Female		Total	
	N	%	N	%	N	%
18 to 30	10	38.5	10	52.6	20	44.4
31 to 45	12	46.2	6	31.6	18	40.0
46 to 60	4	15.4	3	15.8	7	15.6
Total	26	100.0	19	100.0	45	100.0

Table 2: Average RNFL Thickness according to Retinal quadrants

RNFL Thickness		Mean ± SD
Superior	**Right Eye**	133.56 ± 13.02
	Left Eye	134.38 ± 10.07
Inferior	**Right Eye**	140.93 ± 12.8
	Left Eye	140.76 ± 14.15
Nasal	**Right Eye**	82.84 ± 11.67
	Left Eye	83.27 ± 14.54
Temporal	**Right Eye**	70.31 ± 6.85
	Left Eye	71.16 ± 6.55
Overall	**Right Eye**	107.80 ± 9.62
	Left Eye	107.38 ± 9.61

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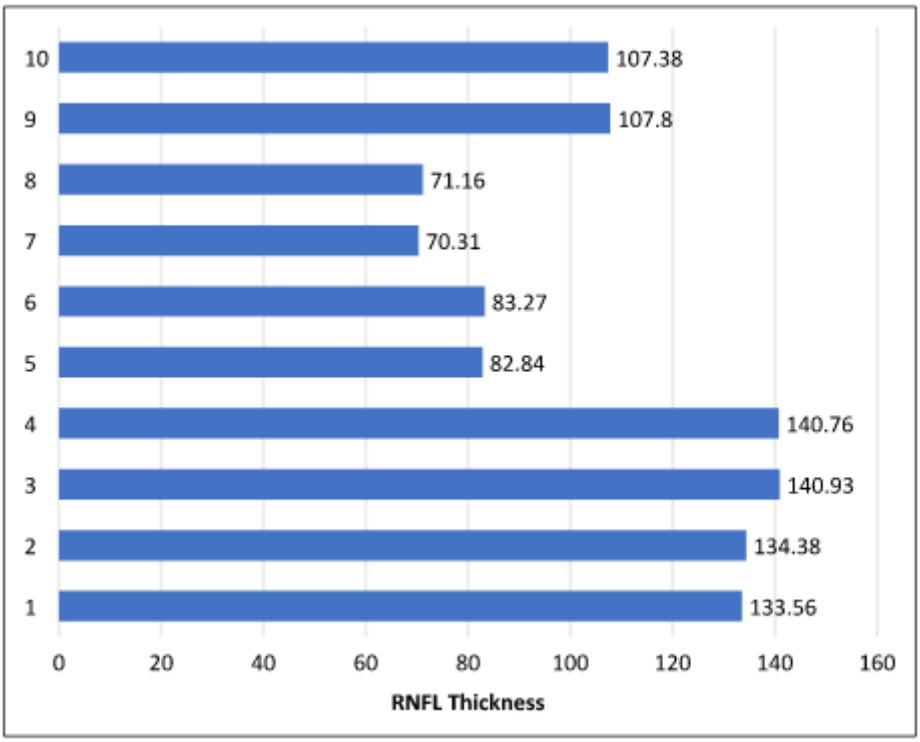

Chart 1: Average RNFL thickness according to Retinal quadrants

Table 3: Distribution of mean Macular Volume in study population

Macular Volume	Mean	SD
Right Eye	7.5	± 0.44
Left Eye	7.52	± 0.4

Table 4: Correlation of PANSS with retinal quadrant wise RNFL Thickness

PANSS	1	P value
Superior RE	0.151	0.322
Superior LE	0.103	0.502
Inferior RE	-0.106	0.487
Inferior LE	-0.018	0.909
Nasal RE	0.157	0.302
Nasal LE	0.123	0.422

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Temporal RE	0.146	0.337
Temporal LE	-0.039	0.799
Overall RE	0.111	0.467
Overall LE	-0.029	0.849

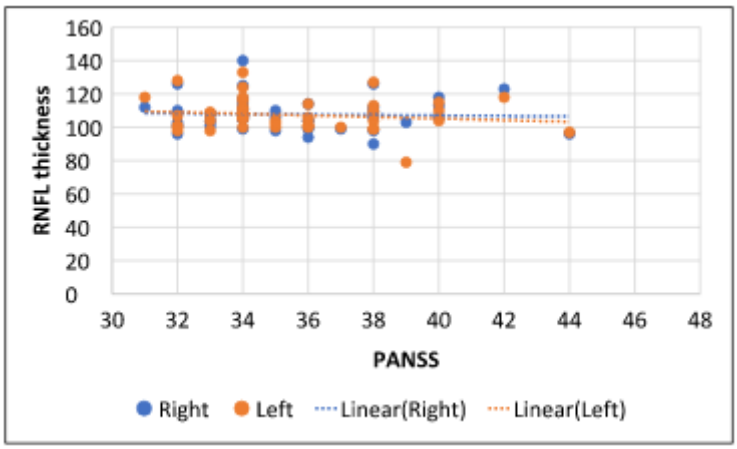

Chart 2: Correlation of PANSS with overall RNFL thickness

Table 5: Correlation of PANSS with Macular Volume

PANSS	1	**P value**
Macular Volume RE	0.265	0.082
Macular Volume LE	0.158	0.3

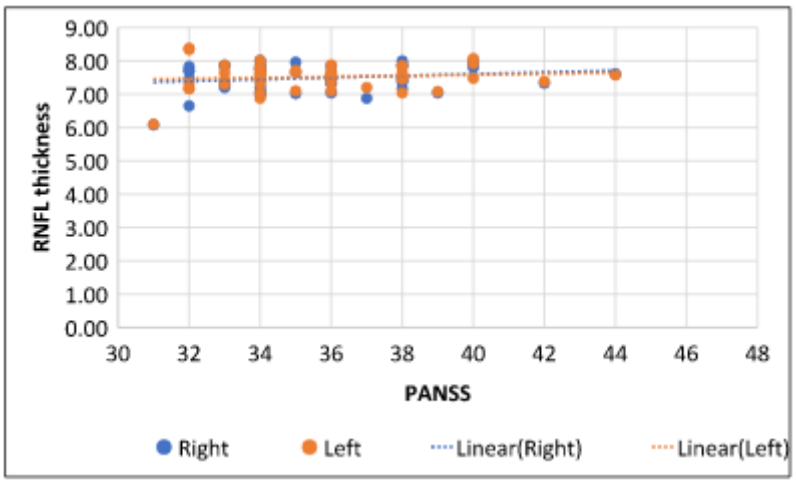

Chart 3: Correlation of PANSS with macular volume

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Table 6:Correlation of Duration of disease with RNFL Thickness

Parameter	Eye	Duration	N	Mean	SD	P value (Anova)
Overall RNFL Thickness	Right	< 5 years	23	110.8	±10.4	0.066
		6 to 10 years	16	105.7	±8.0	
		>10 years	6	101.8	±7.1	
	Left	< 5 years	23	109.7	±10.0	0.247
		6 to 10 years	16	105.6	±9.7	
		>10 years	6	103.5	±6.1	

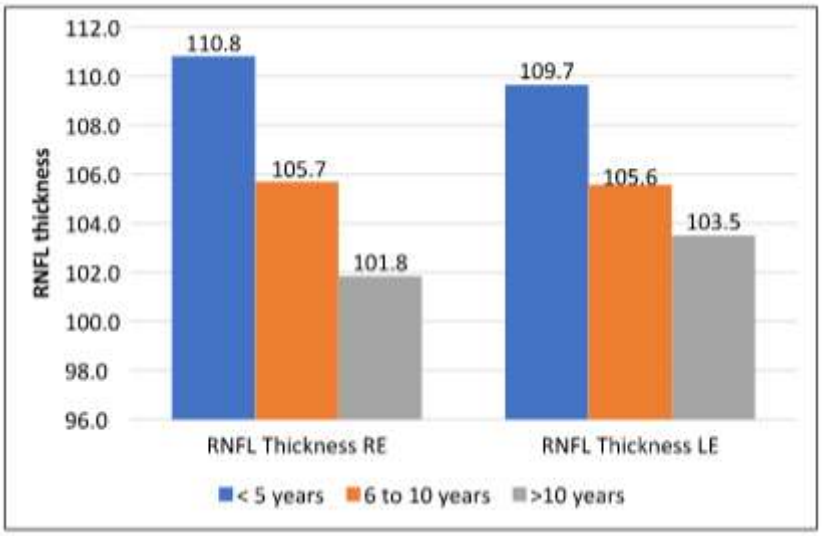

Chart 4: Correlation of Duration of disease with RNFL Thickness

Table 7: Correlation of Duration of disease with Macular Volume

Parameter	Eye	Duration	N	Mean	SD	P value (Anova)
Macular Volume	Right	< 5 years	23	7.5	±0.4	0.468
		6 to 10 years	16	7.4	±0.5	
		>10 years	6	7.3	±0.3	
	Left	< 5 years	23	7.5	±0.3	0.441
		6 to 10 years	16	7.5	±0.5	
		>10 years	6	7.4	±0.4	

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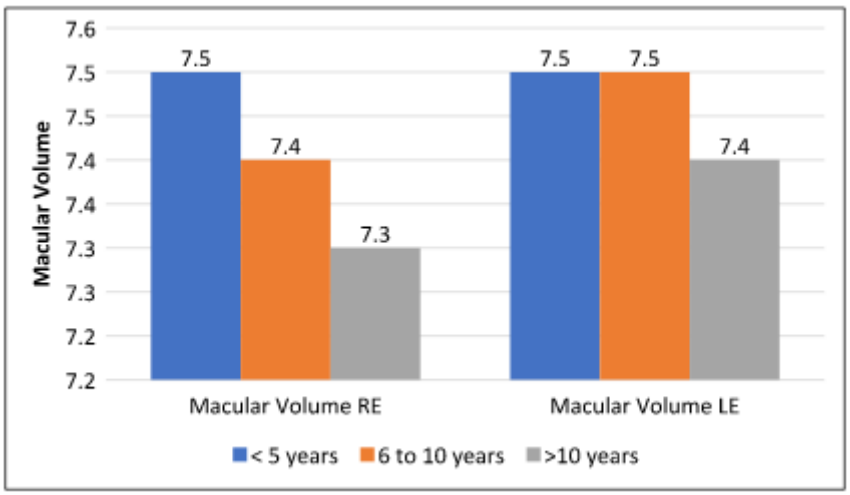

Chart 5: Correlation of Duration of disease with Macular Volume

IV. DISCUSSION

Above tables and graphs show correlation of PANSS score with RNFL Thickness in different quadrants and PANSS score with Macular Volume. Our findings suggest that RNFL thickness is reduced and Macular Volume is within normal range in schizophrenic patients but showed no significant correlation between PANSS score and RNFL Thickness in all the quadrants and whole retina (RE p= 0.467, LE p= 0.849). No significant correlation was found between PANSS score and macular volume (RE p=0.082, LE p= 0.30). Our findings are in line with an earlier study who have reported RNFL thinning in schizophrenia. The earliest study investigating the retinal changes in schizophrenia was a short report on 10 patients and found that overall RNFL thickness and nasal RNFL thickness were reduced in the patient group.[11] A larger study by Lee WW at al.[12] have shown that overall peripapillary RNFL thickness, superior, temporal, and inferior RNFL thickness were significantly reduced in schizophrenia. Yilmaz et al.,[13] reported reduced overall and nasal RNFL thickness as well as reduced macular thickness in schizophrenia patients. The thinning in RNFL was also confirmed by Liu et al.[14] and Celik et al.[15]. Miller et al.,[16] showed decreased macular volume but no change in RNFL thickness in Schizophrenia patients, when compared with controls.

In the present study, as depicted above, the overall RNFL thickness and Macular Volume was lower in the chronic phase of the disease compared to early phase. Reduction in RNFL thickness (RE p=0.066, LE p=0.247) and macular volume(RE p=,0.468 LE p=0.411) was correlated with increased duration of illness, difference being insignificant. (Lesser number of study population in the chronic phase of disease.) Lee WW et al.,[17] found significant reduction in overall peripapillary RNFL thickness, macula thickness and macular volume, particularly in the chronic phase of the disease and correlated with increased duration of illness. Schonfeldt-Leucona et al.,[18] also found correlation between the duration of illness and RNFL abnormalities.

According to the available literature, this is a unique study done at a tertiary healthcare center in South Gujarat on patients of Schizophrenia. Dissemination of results of this study will help the clinician objectively confirm neurodegeneration in patients of schizophrenia. Thus, findings of OCT can be used as a screening tool to assess neurodegeneration in relation to severity and duration of illness.

V. LIMITATIONS

The present study had a small sample size to provide a generalized result owing to the Covid 19 pandemic and it was also difficult to convince patients of schizophrenia to undergo an ophthalmic evaluation and explaining the importance of an OCT for their underlying psychiatric condition. Patients were uncooperative and apprehensive about undergoing an OCT scan. Most of our patients also were receiving antipsychotic medications at the time of data collection which can be a confounding factor for the study.

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