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CHARACTERISTICS AND TOPOGRAPHICAL DISTRIBUTION OF RETINAL THINNING ON OPTICAL COHERENCE TOMOGRAPHY IN SCHIZOPHRENICS AND HEALTHY: A COMPARATIVE STUDY

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Abstract

***Introduction**: To compare results of spectral-domain optical coherence tomography (SD-OCT) like retinal nerve fiber layer (RNFL) and macular thickness (MT) in Schizophrenic patients and healthy individuals.*

***Method:** Cross-sectional study. Forty schizophrenic patients and age-gender matched 40 healthy individuals were included in the study. Using SD-OCT, peripapillary RNFL thickness, MT, neuro-retinal rim area (NRR) and mean cup-to-disc ratio (CDR) were measured and compared in 4 quadrants.*

***Results**: Mean age of schizophrenic patients was 30.9±7.57years and healthy individuals was 29.65±5.53years (p>0.05). Mean duration of illness was 4.63±2.75 years. Schizophrenic patients showed a significant reduction in overall RNFL thickness (patients: 87.75±8.49µm in the right eye [RE] and 88.42±10.51µm in the left eye [LE]; healthy: 97.75±8.74µm RE and 98±8.744µm LE; p=0.0001 both eyes); except in temporal quadrant. Average MT (patients: 251.92±19.55µm RE and 249.37±22.24µm LE; healthy: 262.07±24.55µm RE and 260.92±23.37µm LE; p=0.044 RE and p=0.026 LE). However, there was no significant difference in central MT (p=0.52 RE, p=0.37 LE), NRR area (p=0.45 RE, p=0.11 LE) and mean CDR (p=0.26 RE, p=0.19 LE) between schizophrenics and healthy.*

***Conclusion**: RNFL and macular thickness reduces in schizophrenics when compared to normal, particularly in the superior, inferior and nasal quadrants.*

Keywords: Schizophrenia, SD-OCT, Retinal nerve fiber layer, macular thickness

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INTRODUCTION

Schizophrenia is the most severe, chronic psychiatric health illnesses with unknown underlying neurobiology.[1] It is characterized by many cognitive symptoms that distress mental activities like perception, emotion, devotion and recollection. [2-3]

Neuroimaging studies in schizophrenics exhibit deficits in gray-matter volume, abnormalities in white-matter and widening of ventricles which relatively support the neuro-developmental hypothesis of this disorder. [4-12]

The retina is, anatomically and developmentally, an extension of the central nervous system (CNS) and it is coupled to brain via optic nerve.[4] The retina behaves as a study model for neurodegenerative diseases in view of its unmyelinated fibers [13-14] and mimics cellular processes of a healthy brain. It mirrors various pathophysiological changes in neurodegenerative disorders like Alzheimer's and Parkinson's. The limited published data in neuroimaging encouraged investigators to harness retina as a "window-to-the-brain". Hence, accurate and reliable measurement of RNFL thickness is of clinical importance.

RNFL thickness can be measured in-vivo with spectral-domain optical coherence tomography (SD-OCT), which is a noninvasive, contactless, reproducible and high-resolution imaging technique. It can quantify the neurodegenerative processes of the retina, providing an objective tool to identify axonal impairment. [14] Imaging with OCT has been successfully used to measure RNFL thickness in several neurologic diseases, as in multiple sclerosis, Alzheimer's disease and Parkinson's disease. [15-22]

The aim of our study was to analyze and compare RNFL thickness, macular thickness, neuro-retinal rim area and cup-to-disc ratio changes using SD-OCT between schizophrenics and healthy individuals.

METHODS

This comparative cross-sectional study was conducted at a tertiary eye-care hospital in Western Maharashtra, India from July 2019 to July 2020. It was approved by Institutional Ethics Committee and has been conducted in accordance with the 'Declaration of Helsinki'. A written informed consent was taken from all the study subjects.

Individuals >18 years of age diagnosed with Schizophrenia by the psychiatry department were taken as study group. Healthy individuals of age >18 years among the volunteers were taken as comparison group; recruited via online advertisements, flyers, and personal referrals.

Exclusion criteria included any pre-existing ocular pathologies that might affect the RNFL thickness such as glaucoma, optic neuropathies, ocular trauma, recent ocular surgeries within last 3 months, a concurrent clinical CNS disorder, pregnancy, refractive error >±2.0 diopters of spherical equivalence and significant media opacities that could impede OCT examination.

Subjects included in the study underwent complete ophthalmologic evaluation including best corrected visual acuity (BCVA) and retinoscopy, slit-lamp biomicroscopy, intraocular pressure measurement and fundus examination. Before OCT, pupils were pharmacologically dilated with 0.5% tropicamide eye drops. OCT scans (Spectralis OCT, Heidelberg Engineering, Germany) for both eyes were performed for measurement of RNFL thickness, macular thickness, neuro-retinal rim area and cup-to-disc ratio by an experienced technician. In order to avoid any diurnal variation, all OCT scans were performed between 1:00 pm to 2:00 pm.

The parameters evaluated were mean RNFL thickness using circular scans of 3.4mm diameter at the center of the optic disc by "optic disc cube 200x200 scan". RNFL thickness at 4 quadrants [nasal (N), temporal (T), superior (S), inferior (I) and global (G)] were automatically calculated by the OCT device; central macular thickness using "macular cube 512x128 scan"**;** mean neuro-retinal rim area and cup-to-disc ratio using "optic disc cube 200x200 scan" determined by the instrument's software within an elliptical ring around the fovea with an inner diameter of 1mm vertically and 1.2mm horizontally and outer diameters of 4mm and 4.8mm. Only well-centered, high-quality images with a signal strength >15 dB was included in the study.

Data was collected as per Data Collection Protocol. Microsoft excel was used for making graphs and tables. SPSS-version-20.0 was used to compute the results. Qualitative data variables were expressed as frequency and percentage; while quantitative data variables expressed as mean, standard deviation (SD) and median. Unpaired t-test was used to calculate p-value for comparison between the means. Chi-square test was used to calculate p-value for comparison between patient representations in both the groups. $p<0.05$ was considered significant.

RESULT

A total of 80 subjects were included in the study; out of which 40 were patients of schizophrenia and rest 40 were age and sex matched healthy individuals. Mean age of schizophrenic patients was 30.9±7.57 years (range:19-60 years; median:31 years). Mean age of healthy individuals was 29.65±5.53 years (range:19-45 years; median:29 years). There was no statistically significant difference between two groups with respect to age (p=0.40).

The mean duration of schizophrenic illness was 4.63±2.75 years. 27 schizophrenic patients belonged to age group between 25 to 36 years (Figure 1).

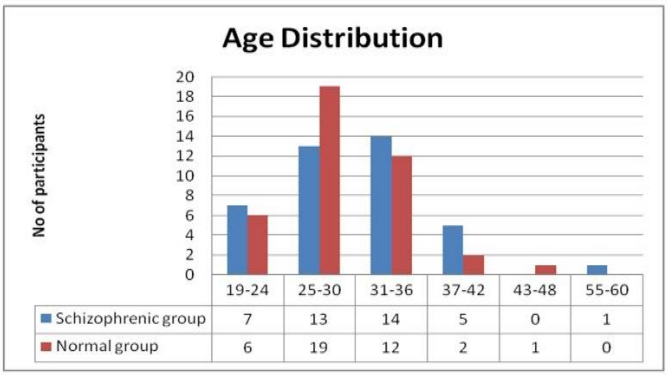

Figure1: **Distribution of schizophrenic patients and healthy individuals based on age intervals.**

There were 29 males (72.5%) in the schizophrenic group which was almost similar to 30 males (75%) in the group of healthy individuals. There was no significant difference in gender representation between the two groups with p=0.799.

The mean intraocular pressure in the schizophrenic group was 16.6±2.4 mmHg in the right eye (RE) and 16.8±2.63 mmHg in the left eye (LE). Similarly, mean IOP in the healthy group was 16.35±2.21 mmHg RE and 16.05±2.28 mmHg LE. There was no significant difference in means of IOP between two groups (p=0.63 RE and p=0.17 LE).

The peripapillary RNFL thickness was significantly lesser in schizophrenic group in respect to overall thickness (p=0.00) as well as in the superior (p=0.00), nasal (p=0.00) and inferior quadrants (p=0.00) (except the temporal), when compared to healthy individuals (Table1). Though the means were lesser in temporal area, the difference was non-significant (p=0.37 RE, p=0.39 LE).

Table 1: **Comparison of peripapillary retinal nerve fiber layer thickness between patients with schizophrenia and healthy individuals**

Quadrant	Eye	RNFL thickness in Schizophrenia group (n=40) (Mean±SD)	RNFL thickness in Healthy group (n=40) (Mean±SD)	p-value
Overall	RE	87.75±8.49	97.75±8.74	**0.00**
	LE	88.42±10.51	98±8.744	**0.00**
Superior	RE	108.88±13.31	119.45±16.19	**0.00**
	LE	110.88±17.86	121.25±16.09	**0.01**
Inferior	RE	111.5±15.53	128.12±15.63	**0.00**
	LE	112.35±16.88	128.42±16.39	**0.00**
Nasal	RE	63.37±13.83	74.25±7.8	**0.00**
	LE	64.72±14.23	74.67±8.49	**0.00**
Temporal	RE	67.27±10.76	69.17±8.22	0.37
	LE	65.75±11.12	67.65±8.65	0.39

The macular average thickness in the schizophrenic group was found to be significantly less than the healthy individuals as depicted in Table 2. However, the difference between the central macular thickness between the two groups was not significant.

Table 2: **Comparison of macular thickness between patients with schizophrenia and healthy individuals**

Macular thickness	Eye	Schizophrenics (n=40) (Mean±SD)	Healthy group (n=40) (Mean±SD)	p-value
Macula average thickness	RE	251.92±19.55	262.07±24.55	**0.044**
	LE	249.37±22.24	260.92±23.37	**0.026**
Macula central thickness	RE	226.8±19.15	229.87±23.25	0.52
	LE	226.52±19.51	230.75±23.02	0.37

The mean neuro retinal rim area was found to be 1.52±0.101 mm^2 RE and 1.52±0.088 mm^2 LE in the schizophrenic group; whereas, it was 1.54±0.119 mm^2 in RE and 1.55±0.098 mm^2 in LE in healthy individuals with insignificant difference between the two groups (Table 3).

Table 3: **Comparison of neuro-retinal rim area between patients with schizophrenia and healthy individuals**

	Right eye		Left eye	
Neuro retinal rim area (mm^2)	Schizophrenic group (n=40)	Healthy group (n=40)	Schizophrenic group (n=40)	Healthy group (n=40)
Mean	1.52	1.54	1.52	1.55
SD	0.101	0.119	0.088	0.098
p-value	0.446		0.111	

Table 4 depicts mean cup-to-disc ratio measurements between the two groups. The mean cup to disc ratio was found to be 0.397±0.081 in the right eye and 0.401±0.073 in the left eye in the schizophrenic group whereas, it was found to be 0.375±0.090 in the right eye and 0.379±0.080 in the left eye in the normal group. Hence, there was no significant difference of cup to disc ratio between the two groups with p value of 0.258 and 0.198 in the right and left eyes respectively.

Table 4: **Comparison of average cup-to-disc ratio between patients with schizophrenia and healthy individuals**.

	Right eye		Left eye	
Average cup-to-disc ratio	Schizophrenic group (n=40)	Healthy group (n=40)	Schizophrenic group (n=40)	Healthy group (n=40)
Mean	0.397	0.375	0.401	0.379
SD	0.081	0.090	0.073	0.080
p-value	0.258		0.198	

DISCUSSION

Schizophrenia is a multifaceted neurocognitive disorder with early visual processing shortfalls. As previously known that the main abnormalities in schizophrenic patients are grey-matter volume reduction and ventricular volume increment, the knowledge hails from structural and functional neuroimaging. Neuroimaging provides an unprecedented view of neuro-anatomical structures in vivo. Yet, it is not devoid of many hitches in measuring brain volumes of patients with schizophrenia, as the volumetric loss in these patients is <4% per year, which maybe close to the limit of MRI detection and also less information regarding effects of anti-psychotic preparations on entire brain volume.[9]

Whereas, OCT measurements are of particular interest in neurologic diseases like multiple sclerosis, Alzheimer ś and Parkinson ś, in which there is axonal damage and evidence of RNFL thinning which suggest that OCT might also show usefulness in other neurodegenerative disorders like Schizophrenia.

In our study, it was found that peripapillary RNFL and macula thickness was significantly reduced in schizophrenic patients when compared to healthy individuals. On studying each quadrant of RNFL between the two groups, thinning was more pronounced in inferior, nasal, and superior quadrants.

As RNFL includes retinal ganglion neurons with their axons, the loss of retinal ganglion cells and their fibers observed in schizophrenic patients might be attributed to a neurodegenerative process and measurable in the retina. Though, an age-related reduction in RNFL thickness has been reported among normal subjects, this reduction observed in our schizophrenic patients was significantly greater than that observed in the age-matched controls, therefore, it cannot be solely credited to aging.[23]

Ascaso et al described a significant reduction in RNFL thickness in the overall and in nasal quadrant alone in his 10 schizophrenic patients compared with healthy individuals.[9] This contradicted with our findings of peripapillary RNFL thinning in all the quadrants except temporal area. This could be due to the small sample size and use of Stratus-OCT in the former study compared to Cirrus-OCT used in our study. Cirrus-OCT is the recent introduction in OCT imaging that uses spectral-domain technology, which expands data procurement due to a higher scanning speed and axial resolution permitting high-resolution. Cirrus-OCT also has a higher reproducibility rate compared to Stratus-OCT which make measurements more consistent. [23-24]

A larger study by Lee et al found significant RNFL thinning in the superior, temporal and inferior quadrants, except the nasal part, which was much more significant in patients with longer disease duration.[13] However, our study did not compare the retinal thickness with the duration of illness as specific cell layers (ganglion cell layer, inner plexiform layer) and volumes were not included in our study.

Chu et al found no difference in RNFL thickness and macular volume between the two groups.[20] and suggested that unmyelinated axons in schizophrenic patients remained unaffected by the disease process. However, Chu et al also used the Stratus-OCT machine with less resolution that may be insufficient to perceive subtle aberrations. Another study in 2017 by Silverstein et al carried out for the similar purpose, blamed comorbidity with diabetes mellitus and hypertension as the causes for RNFL thinning. A likely clarification for this discrepancy of findings could be the variability of OCT technologies used.[25]

Cabezon et al showed significant overall and superior peripapillary RNFL thinning without any statistically significant thinning in the macula region in his 30 schizophrenic patients.[22] This contradicted our findings of significant overall peripapillary RNFL thinning with corresponding macula fiber thinning, supporting a generalized structural RNFL loss in schizophrenic patients. Our recognition rate is higher because of use of advanced technology Cirrus-OCT as opposed to Stratus-OCT.

Several studies also support our finding of reduction in the average macular thickness in patients with schizophrenia. Lee et al showed significant thinning of overall macula thickness and macular volume in the schizophrenic patients compared to healthy individuals.[13] Yilmaz et al found no significant difference in central foveal thickness between the two groups, supporting our findings.[26]

As there are no alike studies in the literature comparing mean neuro-retinal rim area and average cup-to-disc ratio of patients with schizophrenia with that of healthy individuals, larger sample size studies might help in creating correlations between these parameters. This study highlights the thinning of RNFL and macula in patients with Schizophrenia like

previous studies carried out in neurodegenerative diseases like Parkinson's and Alzheimer's disease. [17-19] Based on these findings and results of previous studies evaluating retina using OCT and Neuro-imaging in patients with schizophrenia, a neurodegenerative mechanism may be labelled as a primary cause for the disorder.

The role of the dopaminergic system in visual performance has been well recognized. Visual functions controlled partially by dopamine like contrast sensitivity (CS) and color vision deficits (CVD), have been detected in dopaminergic pathologies such as Parkinson's disease. [27-28] The RNFL has been recognized in this group of patients to be thinner when compared to controls. Hence the role of dopamine has been postulated to be involved not only in the functional, but also the structural deficits. CS and CVD also have been observed in schizophrenia patients. [27, 29] Therefore, the RNFL thinning observed in our study could be attributed to the dopamine dysregulation.

Shuwairi et al even proposed that dopamine-excess may yield general dysfunction in color discrimination, while dopamine-deficiency may produce hue-deficit. [29] Degree of dopaminergic degeneration is not clearly established. However, the retina with dopamine-deficiency has been revealed to lose few amacrine cells. Thus, dysregulated dopamine input to ganglion cells may cause abnormal production of glutamate and alter the efficacy of the neurochemical systems contributing to atrophy of these fibers. Therefore, the RNFL thinning detected in our study could be an outcome of neurodegeneration or neurochemical dysregulation.

Thus, our study provides more evidence for RNFL and macula changes and suggests that a better understanding of these changes could deliver additional piece of the puzzle for understanding the pathophysiology of Schizophrenia and that easy-to-perform SD-OCT embraces great potential for claim in future research in this psychiatric disorder.

To the best of our knowledge, this is a novel study in schizophrenic patients that showed statistically significant peripapillary RNFL thinning in all the quadrants (except temporal one), macula thinning, neuro-retinal rim area and cup-to-disc ratio measurements compared to healthy individuals. Schizophrenia has been associated with deficits in visual perception and processing as evidenced by the previous studies done, but the structural abnormalities have not been documented. Our study has shown significant structural thinning of RNFL in schizophrenics that could explain the deficits in visual perception and processing in these patients. Additionally, results of our study could be statistically more reliable compared to the previous studies in view of use of advance Cirrus SD-OCT technology.

Nevertheless, we recognized several limitations to our study. This study involves small sample size. Hence, our results cannot be simply generalized to the entire population. All the schizophrenic patients were taking antipsychotic medication at the time of our study. Hence, it is impossible to exclude the probable effect of the drugs on our findings. Also, the possibility of bias from age-gender matching was not ruled out in this study. Further studies are needed to establish the relationship between pathological mechanisms for schizophrenia and the reduction in peripapillary RNFL thickness that we observed.

CONCLUSION

Schizophrenia patients have a substantial amount of reduction in the overall RNFL thickness and more pronounced in the inferior, superior and nasal quadrant when compared with healthy individuals; signifying axonal degeneration measurable by SD-OCT. Though, neuroimaging has been an important established method to measure

volumetric brain volume drop and its progression, our results highlight the future perspective of SD-OCT in screening, diagnosing as well as in sensing deterioration of neuronal degeneration via RNFL and macular thickness measurements in Schizophrenia.

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