Original Research Article

EVALUATION OF RETINAL NERVE FIBERS LAYER THICKNESS AND MACULAR VOLUME BY OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH SCHIZOPHRENIA

ABSTRACT

Aim: To understand the potential of evaluating the thickness of the retinal nerve fiber layer (RNFL) and macular volume in patients with schizophrenia, using Optical Coherence Tomography (OCT), and its possible application to monitor this disorder.

Study Design and participants: Cross-sectional study that included two groups, one with 20 patients diagnosed with schizophrenia and a control group with 20 healthy volunteers. Patients with schizophrenia were divided into two subgroups, one with less than 5 years of of illness duration and the other with more than 5 years. Both groups underwent OCT. The study was conducted between April 2014 and July 2014, with the collaboration of the Ophthalmology and Psychiatry departments.

Results: Schizophrenic patients showed a significant decrease in all measurements of the macula, volume and thickness, when compared to the control group ($p<0.05$). No differences were found between groups regarding RNFL thickness, although there was a correlation between disease duration and decreased overall RNFL thickness ($r=-0.338$; $p=0.033$). Comparison between the group with schizophrenia for less than five years and the group with more than 5 years, revealed statistically significant differences in volume ($p=0.021$) and thickness ($p=0.018$) of the temporal outer ring of the macula.

Conclusion: Results suggest that there are differences in the retina in patients with schizophrenia. These data support the hypothesis of a neurodegenerative component of the disorder. OCT is a noninvasive exam that, although non-specific, can be useful either to diagnose or monitor disease progression.

Keywords: Schizophrenia, OCT, macula, RNFL

1.INTRODUCTION

Schizophrenia is a complex clinical entity that affects around 24 million people worldwide.[1] It is a chronic mental disorder. It is mainly defined according to current classifications, as a function of the psychotic symptoms. However, this syndrome is also defined as a function of various other dimensions, including cognitive, emotional and volitional, all responsible for most of the functional impairment of these patients.

Schizophrenia has been intensely studied over the past century, remaining however poorly understood with regard to its etiology and pathophysiology. One of the lines of research has focused on the existence of changes in the central nervous system. Several neuro-imaging studies have shown structural changes, such as ventricular enlargement and reduced total brain volume, mainly due to loss of gray matter.[2,3]These changes are already present at the first psychotic episode and even during the prodromal period, and tend to worsen with disease progression. Although available evidence suggests that the pathological process starts during neurodevelopment, the extension of the relative contribution of a neurodegenerative process is still unclear.[4]

The effect of antipsychotics on the structure of the central nervous system is not consensual, and there are studies with positive and negative results regarding their ability to alter brain volume, and some studies even suggest a differential effect of typical and atypical antipsychotics. A recent meta-analysis concluded that there appears to be a longitudinal decrease in gray matter in patients with schizophrenia, which correlates with a higher cumulative exposure to antipsychotics, but this is not the only factor involved in this process.[5]

It is increasingly important to find new noninvasive methods to study the brain and its function, so that the patient may be more comfortably monitored.

In this context, it is important to understand the potential of evaluating the thickness of the retinal nerve fiber layer (RNFL) by Optical Coherence Tomography (OCT) in patients with neurological and/or psychiatric disorders, such as schizophrenia. OCT allows to access non-myelinated cells *in vivo*, without the need for other more invasive and costly neuro-imaging studies neuro-imaging studies, with exposure to radiation.

OCT allows a non-invasive assessment and monitoring of various eye pathologies, such as glaucoma and retinal disorders. Its use has been increasingly extended to other areas of medicine, as a useful tool to access retinal ganglion cells. In other neurological disorders, such as Alzheimer's disease and Parkinson's disease, the relationship between the decrease in RNFL thickness and the atrophy of brain tissue has been studied, with positive and promising results. Therefore, the aim of this study was to ascertain if OCT can also be useful in schizophrenia, and if OCT measurements correlate with disease progression, so that, in the future, these

patients have a non-invasive, harmless and convenient method for monitoring/staging.

Retina is thus a possible "window to the brain" that remains to be opened. This study provides a step further in discovering the potential of this neurological tissue for the evaluation of pathologies other than strictly ophthalmological.

The aim of this study is to understand the potential of evaluating the thickness of the retinal nerve fiber layer (RNFL) and macular volume and thickness in schizophrenic patients, using OCT, and its possible application to monitor this pathology.

2.MATERIALS AND METHODS

Cross-sectional, observational study, conducted at Hospital Prof. Dr. Fernando da Fonseca (HFF), between April 2014 and July 2014.

The population sample consisted of 20 patients with the diagnosis of schizophrenia based on the criteria of the *International Classification of Diseases 10th Revision Procedure Classification System* (ICD 10), clinically stable, with regular follow-up in the Psychiatric Department of HFF.

Schizophrenic patients were divided into 2 groups, depending on the duration of illness. One group with less than 5 years duration of illness (10 patients) and one group with more than 5 years duration of illness (10 patients).

Patients were evaluated in Psychiatry consultation, taking into account: duration of illness; age of onset; therapy with typical or atypical antipsychotics; compliance to therapy - Scale "Medication Adherence Rating Scale" (MARS); and degree of positive or negative symptomatology, and general psychopathology - Scale "Positive and Negative Syndrome Scale" (PANSS). Cognitive functioning was also assessed using the following cognitive tests: "Standardized Cognitive Assessment Conde de Ferreira" (SCACF, Prof. Marques Teixeira), comprising: STROOP Test, Wisconsin Card Sorting Test, HVLT-R (Hopkins Verbal Learning Test - Revised), TMT (Trail Making Test) and WMS-III (Wechsler Memory Scale). In this evaluation results were provided as a function of different cognitive domains, such as attention and focus, learning and memory, executive function and processing speed.

The control group consisted of 20 gender- and age-matched healthy individuals.

Both groups were given a General Health Questionnaire, were generally assessed at an Ophthalmology consultation, and underwent OCT, with software to study the macula (volume and thickness) and the optical disc (RNFL thickness).

2.1 Inclusion criteria

Men and women over 18 years of age, diagnosed with schizophrenia, based on the criteria of ICD 10, with the ability to provide informed consent.

2.2 Exclusion criteria

All participants that, in the General Health Questionnaire, were found to have other

degenerative or neurological diseases, general systemic diseases that could affect the eye, such as autoimmune or infectious diseases, and history of traumatic brain injury associated with loss of consciousness. During the evaluation in Psychiatry consultation, participants who presented episodes of acute decompensation, with current history of prominent addictive behaviors (alcohol or other illegal drugs), with personal history of macrostructural lesions of the central nervous system, and other relevant co-morbid psychiatric disorders, particularly mental retardation or dementia, were also excluded. Ophthalmological exclusion criteria were: refractive error ≥ -6.00 D; BCVA < 8/10; intraocular pressure (IOP) ≥ 22 mmHg; opacification of transparent media of the eye; change of excavation/upper disc > 0.4; and pathology of the retinal posterior pole, such as diabetic retinopathy, hypertension or another.

2.3 Optical Coherence Tomography (OCT)

The OCT SPECTRALIS® (Heidelberg Engineering GmbH) was used for the study of the macula and optical disc. This device uses confocal laser scanning for image acquisition, through focus of the laser beam on the retina. Two different beams of light (infrared, IR) are used simultaneously, in order to obtain 3D volume scans. These beams are periodically deflected through oscillating mirrors, thus allowing a sequential scan of the retina. Being linked to a normative database, it is possible to compare thickness and volume of the various layers of the retina, by comparing the values obtained from an individual with the database of normal individuals. Thus, it is possible to obtain high resolution spatial images, with a scanning proximity of 11 µm. This device incorporates the active tracking system of eye movement (TruTrack) and fovea-disc alignment technology (FoDi), allowing to capture two images in the exact same position, compensating for the eye and head movement of the patient.

Macula assessments were conducted using the macular assessment protocol *"fastHR",* and the 9 sectors defined by the *"Early Treatment Diabetic Retinopathy Study* (ETDRS) were obtained, having been evaluated 3 circles of 1, 3 and 6 mm centered on the fovea. A 20x20º scan, with 25 scans per section, was performed. The two outer circles (inner and outer macular ring) were subdivided into four quadrants (nasal, temporal, superior, inferior). The center circle is the fovea. All images obtained had a quality of more than 15.

For evaluation of the optical disc, RNFL thickness was assessed using the protocol of glaucoma for the evaluation of "RNFL", with a scan pattern of 12° centered on the head of the optical disc. The default pattern position is 2.6° nasal and 2.1° superior from the fovea and only one scanning per section is performed. The global thickness and six areas of the peripapillary region (temporal-T, inferior-temporal-IT, inferior-nasal-IN, nasal-N, superior-nasal-SN and superior-temporal-ST) were analysed using a STINT pattern. Three images were always used, with a quality of more than 15

and "ART 100 frames" of 100%. The last acquisition was always chosen.

2.4 Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) Version 22 (SPSS, Inc., Chicago, IL, USA). Differences between groups were analyzed using the independent samples t-test. To establish correlations, the Pearson's correlation was used. Tests were considered significant for a significance level of α=0.05.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Demographic Data

The population sample consisted of 40 individuals, 20 with a diagnosis of schizophrenia and 20 healthy individuals as the control group.

The two groups were age-matched (control 33.4±11.2; schizophrenic 32.9±11.9). The group of patients with schizophrenia with more than 5 years of disease duration was on average older (42.0±3.9) than the group with less years (23.8±9.9), p<0.001. Regarding gender, there were more males in both groups that was balanced between groups (Table 1). Both eyes were evaluated separately, thus each group consists of 20 individuals and 40 eyes.

Table 1. Demographic Data

	Men	Women
Control	16 (80%)	4 (20%)
Schizophrenic	17 (85%)	3 (15%)

Table 2. Comparison of RNFL thickness (µm) between schizophrenic patients and control group.

	n	Mean	SD
Overall RNFL			
Control	40	101,2	9,101
Schizophrenic	40	101,05	7,338
< 5 years	20	102,6	5,698
≥ 5 years	20	99,5	8,544
ST RNFL			
Control	40	145,8	16,034
Schizophrenic	40	135,7	17,297
< 5 years	20	135,55	17,887
≥ 5 years	20	135,85	17,15
SN RNFL			
Control	40	112,5	16,954
Schizophrenic	40	120,575	23,894
< 5 years	20	124,7	25,826
≥ 5 years	20	116,45	21,659
IT RNFL			
Control	40	143,75	16,089
Schizophrenic	40	144,475	15,509
< 5 years	20	144,65	14,996
≥ 5 years	20	144,3	16,381
IN RNFL			
Control	40	112,5	11,908
Schizophrenic	40	114,475	19,931
< 5 years	20	116,95	20,516
≥ 5 years	20	112	19,534
N RNFL			
Control	40	74,9	16,445
Schizophrenic	40	76,875	10,743
< 5 years	20	79,15	11,86
≥ 5 years	20	74,8	9,288
T RNFL			
Control	40	73,3	11,305
Schizophrenic	40	69,325	7,833
< 5 years	20	69,45	7,316
≥ 5 years	20	69,2	8,508

3.1.2 Statistical analysis of OCT data

Comparison of RNFL thickness in its different quadrants showed no statistically significant differences neither between the control group and the group of patients with schizophrenia, nor between the two subgroups with schizophrenia (Table 2). However, there was a negative correlation between the duration of illness and decrease of global RNFL thickness, with r=-0.338 and p=0.033 (Figure 1).

All macular measurements, volumes and thickness, showed a statistically significant decrease between the group with schizophrenia and the control group (Table 3). Patients with schizophrenia showed a particularly statistically significant decrease, with p<0.001, of the following parameters: global macular volume, temporal macular outer ring volume, superior macular inner ring thickness and temporal macular outer ring thickness.

Comparison between the group with schizophrenia for less than five years and the group with more than 5 years, showed statistically significant differences in volume (p=0.021) and thickness (p=0.018) of the temporal macular outer ring (Table 4).

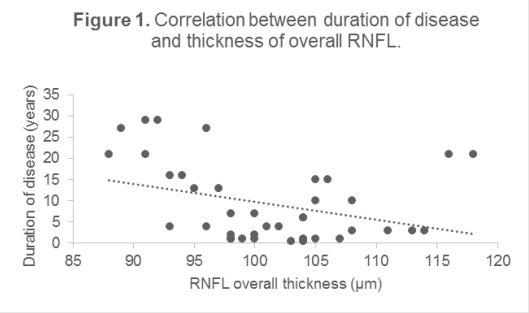

Figure 1. Correlation between duration of disease and thickness of overall RNFL.

Table 3. Comparison between macular thickness (µm) and volume (mm3 between patients whit schizophrenia (1) and control group (0).

	Goups	n	Mean	SD	p
Overall thickness	0	40	271,3	22,735	0,019
	1	40	258,73	24,231	
Central volume	0	40	0,214	0,018	0,012
	1	40	0,203	0,019	
Thickness - Fovea	0	40	229,33	27,639	0,005
	1	40	213,63	20,3	
Overall volume	0	40	8,844	0,281	<0,001
	1	40	8,59	0,325	
Thickness - Superior inner ring	0	40	352,05	11,556	<0,001
	1	40	340,9	15,047	
Thickness - Inferior inner ring	0	40	344,83	12,588	0,013
	1	40	336,75	15,656	
Thickness - Nasal inner ring	0	40	348,58	13,179	0,018
	1	40	340,3	17,288	
Thickness - Temporal inner ring	0	40	334,75	12,002	0,029
	1	40	327,63	16,248	
Thickness - Superior outer ring	0	40	305,38	11,308	0,002
	1	40	297,35	11,412	
Thickness - Inferior outer ring	0	40	293,45	10,617	0,006
	1	40	286,78	10,289	
Thickness - Nasal outer ring	0	40	322,78	11,272	0,005
	1	40	314,33	14,57	
Thickness - Temporal outer ring	0	40	294	9,394	<0,001
	1	40	284,85	12,247	
Volume - Superior inner ring	0	40	0,553	0,018	0,001
	1	40	0,536	0,024	
Volume - Inferior inner ring	0	40	0,542	0,02	0,015
	1	40	0,529	0,025	
Volume - Nasal inner ring	0	40	0,547	0,02	0,03
	1	40	0,535	0,027	
Volume - Temporal inner ring	0	40	0,526	0,019	0,025
	1	40	0,514	0,026	
Volume - Superior outer ring	0	40	1,619	0,061	0,003
	1	40	1,577	0,061	
Volume - Inferior outer ring	0	40	1,556	0,056	0,006
	1	40	1,521	0,055	
Volume - Nasal outer ring	0	40	1,711	0,06	0,005
	1	40	1,666	0,077	
Volume - Temporal outer ring	0	40	1,559	0,052	<0,001
	1	40	1,51	0,066	

Table 4. Comparison of volume and thickness in temporal macular outer ring between schizophrenic with <5 years (0) and ≥5 years of disease progression (1).

	Groups	n	Mean	SD	p
Thickness - Temporal outer ring	0	20	289,35	12,287	0,018
	1	20	280,35	10,688	
Volume - Temporal outer ring	0	20	1,534	0,067	0,021
	1	20	1,486	0,057	

3.2 Discussion

Schizophrenia is a complex disease, whose pathophysiological is still being unveiled. Currently, the neuroprogressive nature of this disorder has an increasing number of supporters.[2,3,6] Therefore, imaging diagnostic methods are increasingly requested for a better understanding of the

neurodegenerative component of the disease. It is in this context that OCT, being a non-invasive imaging technique that does not use radiation, becomes an attractive tool for the study of the nervous tissue.

In this study, the groups were not balanced in terms of gender, with male predominance in both groups, and the average age was higher in the subgroup of patients with schizophrenia for more than 5 years. However, these changes were expected given that schizophrenia is more prevalent in males and, as the duration of illness increases, it is also expected that patients become older.[7] Nevertheless, the schizophrenic patients group and the control group were gender- and age-matched.

Contrary to a study by Lee et al., there were no statistically significant differences in the decrease of RNFL thickness between the control group and the group of patients with schizophrenia, in all studied quadrants.[8] In the present study, as the duration of illlness increases, the overall RNFL thickness shows a statistically significant decrease, which is in accordance with Lee et al.[8] These results allow us to agree with a number of studies that have shown the existence of changes in nerve tissue as the disease progresses.[2, 3.9]

Schizophrenic patients showed a significant decrease of macular central ring thickness (control 271.30±22.74 µm; schizophrenic 258.73± 3.83 µm; p=0.019) and overall macular volume (control 0.281±8.844 µm; schizophrenic 8.589±0.325 µm; p<0.001) compared to the control group. All macular measurements, volumes and thickness, showed a statistically significant decrease in the group with schizophrenia compared to the control group (Table 3). In the study of Ascaso et al this was not verified, and may be due to the fact that, in our study, we used an OCT with greater ability of image resolution and spectral domain (OCT SPECTRALIS®, Heidelberg *versus* Stratus® OCT, Carl Zeiss), and our sample being larger.[9]

Comparison between the group with schizophrenia for less than five years and the group with more than 5 years, showed statistically significant differences in volume and thickness of the temporal macular outer ring. The fact that significant results were only found in the temporal quadrant may be explained by this being the macular quadrant with lower thickness, second to the fovea, and therefore small changes in a layer may possibly be better evaluated in this quadrant.[10] However, given the small size of our sample, this result should be interpreted with caution.

The results of this study show a significant decrease in the evaluated macular parameters in patients with schizophrenia, but this is not true for RNFL. It is known that the retina, in the peripapillary area, is mainly composed by NFL, while in the macula this layer corresponds, together with the ganglion cell layer, to around 30% to 35% of retinal thickness.[11.12] Thus, it may be concluded that the decrease in macular thickness and volume in patients with schizophrenia cannot be solely attributed to the decrease of NFL, for a similar or higher decrease of the RNFL thickness would have been observed. Therefore, other

layers of the retina, such as the layer of ganglion cells, may also contribute to the differences observed in the macula between the two studied groups. In addition, the NFL not only comprises axons of the ganglion cells, but also other cell types, such asneuroglia and astrocytes, which may contribute to the loss of ganglion cells, and consequently their axons, has not been significant in the peripapillary zone.[11.12] However, it may be concluded that there is a neurodegenerative component of the disease, due to the observed significant correlation between decreased RNFL and increasing years of illness. In a study with a larger sample, Lee et al. reported a significant decrease of RNFL in patients with schizophrenia. Thus, our results could benefit from a larger population sample.[8]

Chu et al. found no statistically significant differences in macular volume between the group of patients with schizophrenia and the control group.[13] Due to these results, the authors proposed that axonal damage was less important than changes in the myelinated areas of the brain. However, results of the present study, as well as the results obtained by Lee et al., are contrary to this proposal.[8.13] This disparity in results may be due to several factors: the sample including patients with schizophrenia and schizoaffective disorder, and the OCT equipment used (Stratus® OCT, Carl Zeiss) having a lower resolution than the one used in the present study (OCT®SPECTRALIS, Heidelberg) and in the study by Lee et al. (OCT Cirrus®, Carl Zeiss).

Other recent studies on ophthalmological changes in schizophrenia also revealed changes in the visual fields of patients with schizophrenia and their family members (decreased global sensitivity), and microvascular changes in the retina of patients, thus confirming that other ophthalmological changes may exist in schizophrenia.[14.15] Further studies are warranted to understand to what extent these changes can help in monitoring and treatment of the disease.

This study had some limitations, such as the fact that it was not possible to dissociate the potential effects of medication in the evaluated thickness and volumes. However, given medication in these patients is chronic, its withdrawal could also create a bias factor. Another limitation is that OCT is operator-dependent. However, and in order to minimize this influence, the operator was always the same, so bias due to differences between operators was removed.

4. CONCLUSION

It is increasingly recognized that ophthalmology may provide an important contribution to understanding the changes in the Nervous System in several pathologies, such as schizophrenia, but also in other neurological diseases. The eye, beyond a sensorial organ, also provides a privileged path to access nerve tissue *in vivo*, being a true open window into the brain. Thus, there is an urgent need to observe the patient in an increasingly multidisciplinary perspective, in order to

understand the disease as a whole and in all its possible dimensions.

In conclusion, Optical Coherence Tomography may be a useful tool in the evaluation and follow-up of patients with schizophrenia, without exposing them to ionizing radiation, as in other imaging methods. However, further studies are still needed to understand all the possible ophthalmological changes that these patients present, as well as for the design of algorithms, so that OCT can be used both at the time of diagnosis and in monitoring disease progression. The future encompasses the acceptance of the neurodegenerative component of this disease and the development of novel therapies based on this assumption.

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