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Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: A short report

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ABSTRACT – *Background and Objectives:* Our study aims to assess retinal nerve fiber layer (RNFL) thickness in patients affected by schizophrenia.

Methods: Ten schizophrenic patients (mean age 39 +/- 13 years, best corrected visual acuity ≥ 20/20, refractive error between +/-2 diopters, and intraocular pressure <18 mmHg) were enrolled. They were compared with 10 age-matched controls. In all subjects, optic nerve head (ONH) measurements, peripapillary RNFL thickness, macular thickness and volume were measured by optical coherence tomography (OCT).

Results: Schizophrenic patients showed an statistically significant reduction of the overall RNFL thickness (95+/-13 μm, range: 53-110) compared with those values observed in control eyes (103+/-8 μm, range: 88-119) (p = 0.047, Mann-Whitney U test). We also observed reduced peripapillary RNFL thickness in nasal quadrant in schizophrenic patients (75+/-17 μm, range: 41-111) when compared with controls (84+/-10 μm, range: 67-105) (p = 0.048, Mann-Whitney U test). The remaining peripapillary RNFL quadrants, macular thickness and volume did not reveal differences between both groups. No statisti-

cally significant differences were observed between the control group and schizophrenia patients with regard to ONH measurements, macular thickness and volume.

Conclusions: Schizophrenia patients had a reduction of peripapillary RNFL thickness evaluated by OCT. To our knowledge, neither reduced RNFL thickness nor macular thickness and volume have been previously documented in patients diagnosed with schizophrenia. These findings suggest that neuronal degeneration could be present in the retina of schizophrenic patients as previously observed in neurodegenerative disorders.

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Introduction

Schizophrenia is a disabling mental condition that affects over 2 million people in the USA alone, but its etiology remains poorly understood[1,2]. Researchers for the past 30 years have looked for specific brain structural abnormalities in this disease[3]. Firstly, the disorder was studied by examining pathological brain tissue samples, often derived from patients who had died after a prolonged period of illness. In recent years, with the advent of brain imaging methods such as magnetic resonance imaging (MRI), it has become possible to study brain structure in individuals during their first episode of psychosis. Findings of 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[4-14]. However, there is still uncertainty about the key areas involved in the pathogenesis of this condition[15].

Optical coherence tomography (OCT) is a relatively new noninvasive 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[16] and macular diseases[17]. A decreased thickness can correspond to neuronal death and axonal loss in RNFL. In earlier reports, RNFL thickness was assessed in normal individuals and the results showed that gender has no effect on the evaluation, whereas aging can be associated with a reduction of RNFL thickness[18-20]. Using OCT, a significant reduction in the peripapillary RNFL thickness has been reported in patients with various neurologic diseases[21], such as multiple sclerosis[22-33], Alzheimer´s disease[34-37] and Parkinson´s disease, suggesting that this technology might also prove useful in other neurodegenerative disorders[38-40].

The goals of this study were to determine by OCT the differences in the peripapillary RNFL thickness, macular thickness and volume, between schizophrenic patients and control subjects, and to assess whether a correlation exists between the RNFL thickness and the clinical severity of the disease.

Material and methods

We compared 20 eyes of ten patients (8 males and 2 females) with schizophrenia to 20 eyes from ten age-matched healthy control subjects (8 males and 2 females). The

schizophrenic patients were consecutively obtained from the Department of Psychiatry at the *Hospital Clínico Universitario* in Zaragoza, Spain. The patients underwent a detailed psychiatric examination including a semi structured clinical interview following the SCID outline and all them fulfilled the inclusion and exclusion DSM-IV-TR criteria of schizophrenia. They were also assessed by means of the PANSS interview. The control subjects were recruited from the Department of Ophthalmology of the same hospital. After appropriate information, written informed consent of all subjects was obtained. The research followed the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics committee. The control subjects also underwent a detailed neurological examination. All schizophrenic patients and control subjects underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity, ocular motility, pupillary reflexes, slit lamp biomicroscopy, intraocular pressure (IOP) measurement, and dilated fundus examination. The examiners were not masked to the diagnosis. All participants had a corrected visual acuity of 20/20 or better with a refractive error between ± 2 spheric diopters, and IOP less than 18 mmHg. Eyes with posterior pole pathology such as macular degeneration or diabetic retinopathy, glaucoma suspect, or patients with media opacification such as cataract or vitreous hemorrhage that prevented ocular and OCT examination were excluded.

Neuropsychological examinations and OCT were performed on the same day. OCT was performed with the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) following dilation of the pupils with 1% tropicamide. Only high-quality images (signal strength ≥ 7) were included. Each patient underwent scans to measure RNFL thickness, optic nerve head (ONH) parameters, and macular thickness at the same visit. RNFL thickness was automatically calculated by the fast RNFL algorithm. Three 360º circular scans with a diameter of 3.4 mm centered on the optic disc were performed. The software allows the mapping of the thickness data according to both quadrant-by-quadrant and a clock hour analyses. We considered the average values of three different measurements per quadrant (superior, inferior, nasal and temporal): the overall data obtained in all quadrants were identified as overall RNFL thickness. Optic nerve head (ONH) measurements were obtained by the fast optical disk scanning protocol, which consists of six radial scans in a spoke-like pattern centered on the ONH. ONH parameters were automatically calculated, including cup/disc area ratio, horizontal cup/ disc ratio, and vertical cup/disc ratio. Macular thickness measurements were obtained by the fast macular thickness protocol, which consists of six radial scans (each 6 mm) in a spoke-like pattern centered on the fovea, with each radial scan spaced 30º apart. To fill the gaps between scans, the OCT uses interpolation. Stratus OCT software calculates retinal thickness as the distance between the first signal from the vitreoretinal interface and the signal from the anterior boundary of the retinal pigment epithelium. The map is composed of nine sectorial thickness measurements in three concentric circles with diameters of 1 mm, 3 mm, and 6 mm. The area bounded by the outer (6-mm) and middle (3-mm) circles forms the outer ring, and the area bounded by the middle (3-mm) and inner circles (1-mm) forms the inner ring. The central 1-mm circular region represents the foveal area. Total average macular thickness, average macular thicknesses in the inner (1-3 mm) and outer (3-6 mm) rings, and the central 1-mm fovea thickness were analyzed in the

study. Total macular volume was calculated automatically by the OCT software.

Data analysis was conducted using SPSS software version 15.0 (SPSS, Inc, Chicago, IL, USA). Values were presented as mean ± standard deviation (SD) and expressed in microns (μm) for the peripapillary RNFL thickness and macular retinal thickness, and in mm^3 for macular volume. The two-sample Mann-Whitney U test for nonparametric numbers was used for determining whether the values of a particular variable differ between schizophrenia and control eyes. A p value < 0.05 was considered statistically significant.

Results

Demographic characteristics of control subjects and schizophrenia patients are shown in Table 1. Not statistically significant differences of mean age were observed between groups (p = 0.913, Mann-Whitney U test). In both groups, more men than women were enrolled. Although the difference was statistically significant (p < 0.05; chi-square test), gender has no effect on RNFL evaluation as previously mentioned. Best-corrected visual acuity was similar in both groups. Optic nerve head (ONH) analysis results were also similar in both groups (Table 2). Table 3 shows the mean data and statistical results of peripapillary RNFL thickness in both groups. Overall RNFL thickness was within 88 and 119 μm (mean ± SD: 103 ± 8 μm) in control subjects and within 53 and 110 μm (mean ± SD: 95 ± 13 μm) in schizophrenia patients. The difference was statistically significant (p = 0.047, Mann-Whitney U test). Only the nasal quadrant of peripapillary RNFL showed an statistically significant reduced thickness in schizophrenia patients, compared with that of control subjects. Mean values of macular thickness and volume in control subjects and schizophrenia patiens are shown in Table 4. No statistically significant differences were observed between control group and schizophrenia patients with regard to the average foveal (1-mm) thickness (p = 0.839), average inner ring macular thickness (p = 0.685), average outer macular macular thickness (p = 0.273), or macular volume (p = 0.705) (Mann-Whitney U test).

Table 1
Demographic data in control subjects and schizophrenia patients

	Gender (male/female)	Age (years) Mean ± SD [Range]
Control subjects (n = 10)	8/2	39.5 ± 13.6 [24-64]
Schizophrenia patients (n = 10)	8/2	39.2 ± 13.5 [50-88]
p value	1.000[a]	0.913[b]

[a] chi-square test.

[b] Mann-Whitney U test.

Table 2
Mean values ± standard deviation of optic nerve head parameters in control subjects and schizophrenia patients

	C/D R	C/D H	C/D V
Control eyes (n = 20)	0.29 ± 0.26	0.29 ± 0.20	0.48 ± 0.21
Schizophrenia eyes (n = 20)	0.39 ± 0.33	0.61 ± 0.24	0.54 ± 0.26
*p value	0.291	0.198	0.481

* Mann-Whitney U test.

C/D R: cup/disc area ratio; C/D H: horizontal cup/disc ratio; C/D V: vertical cup/disc ratio.

Table 3
Comparison of peripapillary RNFL thickness (μm), overall and in the different quadrants, in control eyes and in eyes of schizophrenia patients

	Overall [Range]	Superior [Range]	Inferior [Range]	Nasal [Range]	Temporal [Range]
Control eyes Mean ± SD (n = 20)	103 ± 8 [88-119]	127 ± 12 [106-155]	128 ± 20 [93-171]	84 ± 10 [67-105]	76 ± 10 [61-88]
Schizophrenia eyes Mean ± SD (n = 20)	95 ± 13 [53-110]	119 ± 17 [80-143]	116 ± 21 [40-141]	75 ± 17 [41-111]	70 ± 15 [26-91]
*p value	0.047	0.176	0.137	0.048	0.213

* Mann-Whitney U test.

Table 4
Mean values ± standard deviation of macular thickness and macular volume measurements in control subjects and schizophrenia patients

	Outer ring [Range]	Inner ring [Range]	Foveal [Range]	Macular volume [Range]
Control eyes Mean ± SD (n = 20)	236 ± 13 [218-263]	270 ± 11 [251-299]	199 ± 20 [171-253]	6.9 ± 0.3 [6.4-7.5]
Schizophrenia eyes Mean ± SD (n = 20)	241 ± 18 [201-272]	268 ± 18 [228-299]	197 ± 18 [175-241]	6.9 ± 0.4 [5.9-7.7]
*p value	0.273	0.685	0.839	0.705

* Mann-Whitney U test.

Discussion

Schizophrenia is thought to be a mental disorder caused by the disconnection of brain regions[41,42]. The most evident focal brain abnormalities in schizophrenic patients are those of grey matter volume loss and ventricular volume increase, and these findings might be related[43]. This knowledge comes from critical advances in imaging technology –including structural (CT, MRI), and functional neuroimaging (PET) methods– all of which provide an unprecedented view of neuroanatomical structures, in vivo[41,44,45]. Nevertheless, there are many difficulties in measuring brain volumes of patients with schizophrenia by MRI. An enormous problem is that the volumetric loss in patients is less than 4% per year, which may be close to the limit of detection by MRI, given the precision of volumetric methods[46,47]. Another major problem is that we do not kwow the effects of antipsychotic medications on total brain volume[48-50]. A further difficulty inherent to studying first-episode cases is that some patients may have been symptomatic, but undiagnosed, for a long time. If progressive brain volume changes are rapid in the period surrounding diagnosis, then the duration of undiagnosed illness would be a serious confounder. However, since no consistent relationship has been found between duration of illness and brain volume loss, this may be less likely[51].

OCT measurements are of particular interest in numerous neurologic diseases in which there is axonal loss[21]. Several studies have demonstrated evidence of RNFL thinning in various neurologic disorders, such as multiple sclerosis[22-33,52], Alzheimer´s disease[34-37] and Parkinson´s disease, suggesting that this technology might also prove useful in other neurodegenerative disorders[38-40]. To the best of our knowledge, this is the first report to demonstrate a thinner overall peripapillary RNFL thickness in schizophrenia patients when compared with controls. Moreover, we observed that the thinning of the peripapillary RNFL was most pronounced in the nasal quadrant.

An age-related reduction of RNFL thickness in normal subjects has been reported[53]. However, the reduction in RNFL thickness observed in our schizophrenic patients was significantly greater than that observed in the age-matched controls and, therefore, it cannot be exclusively ascribed to aging.

RNFL includes retinal ganglion neurons and their axons which form the origin of the optic nerve. The loss of retinal ganglion cells and their fibers observed in schizophrenic patients could be ascribed to a neurodegenerative process involving neuroretinal structures. However, more studies are needed to give further explanations about the relationship between the pathological mechanisms underlying schizophrenia and the reduction in peripapillary RNFL thickness we have observed.

It remains to be determined whether schizophrenia is a neurodegenerative process that begins at about the time of symptom onset and manifests as progressive volumetric loss thereafter, or whether it is better characterized as a neurodevelopmental process that results in abnormal brain volume beginning at an early age[54].

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