Retinal nerve fiber layer and macular thickness in patients with schizophrenia: Influence of recent illness episodes

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ABSTRACT

Optical coherence tomography (OCT) has been recently used to investigate neuropsychiatric disorders. We aimed to study retinal OCT measures of patients with schizophrenia with respect to healthy controls, and to evaluate possible differences between recent illness episode (RIE) and non-recent illness episode (NRIE) patients. Thirty schizophrenia patients were classified as RIE ($n=10$) or NRIE ($n=20$), and compared with 30 matched controls. Statistical analyses included linear mixed-effects models to study the association between OCT measures and group membership. Multivariate models were used to control for potential confounders. In the adjusted linear mixed-effects regression model, patients had a significantly thinner retinal nerve fiber layer (RNFL) in overall measurements, and in the nasal, superior and inferior quadrants. Macular inner ring thickness and macular volume were also significantly smaller in patients than controls. Compared with controls, in the adjusted model only NRIE (but not RIE) patients had significantly reduced RNFL overall measures, superior RNFL, nasal RNFL, macular volume, and macular inner ring thickness. No significant correlation was found between illness duration and retinal measurements after controlling for age. In conclusion, retinal parameters observed using OCT in schizophrenia patients could be related to clinical status and merit attention as potential state biomarkers of the disorder.

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1. Introduction

Schizophrenia is one of the most severe mental disorders and a serious public health problem. The diagnosis of schizophrenia relies primarily on identifying the characteristic symptoms of the disorder through a clinical interview. Nevertheless, in view of the variety of clinical presentations of schizophrenia among different patients, and the symptom overlap with other disorders (Demirci and Calhoun, 2009), objective markers for diagnosing schizophrenia and related conditions are currently being sought (Zarogianni et al., 2013). The interest of biomarkers in schizophrenia has been emphasized in recent reports (Kasper, 2013), especially those based on neuroimaging methods. Neuroimaging techniques have been extensively studied over the past years, and there is now a considerable number of studies including structural and functional magnetic resonance imaging that aim to develop new diagnostic markers for schizophrenia. Relevant findings of neuroimaging studies in patients with schizophrenia include gray (Glahn et al., 2008) and white (Takayanagi et al., 2013; Bracht et al., 2014) matter abnormalities. Nevertheless, at the present moment it is difficult to draw firm conclusions regarding the

precise nature of the underlying neuropathology of the disorder (Fornito et al., 2009). In this context, optical coherence tomography (OCT), a non-invasive imaging technique, provides reproducible, high-resolution cross-sectional imaging of the retinal nerve fiber layer (RNFL) and optic nerve head topography, providing an objective tool to diagnose axonal damage and thus constituting a *"window into the brain"* (London et al., 2013). A significant reduction in peripapillary RNFL thickness has been reported in patients with various neurological disorders such as multiple sclerosis (Sergott et al., 2007; Thrower, 2007), Alzheimer's disease (Parisi et al., 2001; Berisha et al., 2007; Marziani et al., 2013; Larrosa et al., 2014; Ascaso et al., 2014) or Parkinson's disease (Inzelberg et al., 2004; Hajee et al., 2009; Garcia-Martin et al., 2014; Jimenez et al., 2014), suggesting that this technique may also prove to be useful in other neuropsychiatric disorders.

Together with these neuroimaging findings, the impaired functioning of the visual system and the retinal alterations found in patients with schizophrenia support the use of OCT to investigate this disorder (Meier et al., 2013). In the first study reported in the literature, our group found a decreased RNFL thickness as measured with OCT in patients with schizophrenia (Ascaso et al., 2010). Similar results have been later reported by Lee et al. (2013), who additionally found a relationship between abnormal OCT parameters and illness duration, but not by Chu et al. (2012), who did not find significant differences in retinal parameters between patients in the early stages of illness and controls.

Thus, the goal of our study was to confirm in a larger sample of patients with schizophrenia the findings described in our first report, testing the hypothesis that a significant thinning of peripapillary RNFL and macular thickness would be found in schizophrenia patients when compared with controls. In addition, on the basis of the contradictory findings reported in the literature, we explored the hypothesis that abnormal OCT parameters would be observed in patients with non-recent illness episodes (NRIE) of schizophrenia, but not in patients with a recent illness episode (RIE). Finally, we studied the correlation between abnormal OCT parameters and illness duration.

2. Methods

2.1. Subjects

Thirty-seven patients diagnosed with schizophrenia and fulfilling DSM-IV criteria were consecutively recruited among patients presenting to the outpatient clinic of the Department of Psychiatry at Hospital Clínico Universitario of Zaragoza, Spain from May 2010 to January 2011. Five patients refused participation and two were excluded for clinical reasons. Therefore, the final sample included 30 Caucasian patients with schizophrenia (23 males; mean age 45.1 years, SD=10.4; mean illness duration 16.3 years, SD=11.2). The control group included 30 Caucasian healthy volunteers (22 males; mean age 44.5 years, SD=10.9), who were matched with patients for age ($t=0.20$, df=58, $p=0.839$) and gender ($\chi^2=0.09$, df=1, $p=0.766$). We had estimated that at least 28 pairs of patients and controls would be required to achieve an 80% probability of detecting a mean between-group difference in RNFL thickness of 9 μm with a standard deviation of ± 12 μm, and a standardized difference of 0.75 at a 5% significance level. The 9 μm difference in RNFL thickness was considered based on the results of Lee et al. (2013).

This research followed the tenets of the Declaration of Helsinki, written informed consent was obtained from all subjects prior to their inclusion in the study, and the local ethics committee approved the protocol.

Exclusion criteria for all subjects were as follows: (a) previous or concurrent systemic disease that may affect the eyes, (b) a history of ophthalmological or neurological disease known to affect the visual pathway (e.g. glaucoma, age-related macular degeneration, diabetic retinopathy, degenerative myopia), (c) media opacification such as cataract, corneal leukoma, or vitreous hemorrhage that impede ocular and OCT examination, (d) refractive error of over $+2$ spheric diopters for hyperopic defects or -2 spheric diopters for myopic defects, as this may cause an artefactual reduction in RNFL thickness and difficulty in fixation (Wu et al., 2011; Zhao and Jiang, 2013; Öner et al., 2013a, b), (e) a history of head injury with loss of consciousness, and (f) drug or alcohol dependence.

2.2. Psychiatric assessment

Patients were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002). For this study, an illness episode of schizophrenia was defined based on the DSM-IV "A" criterion for the disorder: two or more of the characteristic symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms), lasting one month or more. To explore the differences between patients with recent versus non-recent episodes of illness, the patient sample was divided into two subgroups: patients who had suffered their last episode in the month preceding assessment ("Recent illness episode", RIE, $n=10$) and those who had been clinically stable and free from psychotic episodes in the previous 6 months ("Non-recent illness episode", NRIE, $n=20$). Patients were considered to be clinically stable when the signs of the disturbance were manifested by only negative symptoms, or by two or more symptoms listed in criterion A present in attenuated form. A period of 6 months was chosen following APA guideline recommendations (Lehman et al., 2004). Eight patients in the RIE subgroup had been admitted to the inpatient unit the month prior to their inclusion in the study.

Severity of illness was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), in its validated Spanish version (Peralta and Cuesta, 1994). The PANSS can be administered using a semi-structured interview lasting 30–40 min, and includes 30 items which are rated on a severity scale ranging from 1 (absence of psychopathology) to 7 (extremely severe). The total PANSS score is obtained by adding the individual item scores, and ranges from 30 to 210.

All patients were treated with antipsychotic medication. Antipsychotic doses were converted into chlorpromazine equivalents, following the consensus-based recommendations described by Gardner et al. (2010).

2.3. Optical coherence tomography

OCT and neuropsychological examinations were carried out on the same day. OCT was performed by a trained and experienced ophthalmologist using a time-domain OCT (TD-OCT) system (Stratus OCT, Carl Zeiss Meditec Inc., Dublin, CA, USA) following dilation of the pupils with 1% tropicamide. Only high-quality images (signal strength > 6) were included. All patients underwent scans to measure peripapillary RNFL thickness, macular thickness and macular volume. RNFL images were acquired for each eye by taking three circumpapillary scans of 3.4-mm diameter centered on the optic disc to effectively intercept all nerve fibers converging toward the optic disc (Schuman et al., 1996). The software allows the mapping of the RNFL thickness in all quadrants (temporal, superior, nasal and inferior), which was calculated by the OCT device software and represented by a line graph indicating RNFL thickness at all sections of the scanning circle. We considered the average values of three different measurements per