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Research paper

Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity

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ABSTRACT

Background: Previous research has consistently detected inflammation in the etiology of depression and neuroimaging studies have demonstrated gray matter abnormalities implying a neurodegenerative process in depression. The aim of this study was to compare ganglion cell layer (GCL), and inner plexiform layer (IPL) volumes and retinal nerve fiber layer (RNFL) thickness between first episode and recurrent major depressive disorder (MDD) patients and controls using optic coherence tomography (OCT) in order to detect findings supporting a degenerative process. Also choroid thicknesses of the same groups were compared to examine effects of inflammation on MDD.

Methods: This study included 50 recurrent MDD patients, 50 first episode MDD patients and 50 controls. OCT measurements were performed by a spectral OCT device. GCL and IPL volumes and RNFL and choroid thicknesses were measured automatically by the device.

Results: GCL and IPL volumes were significantly smaller in recurrent depression patients than first episode patients and in all MDD patients than controls. Also there were significant negative correlations between their volumes and disease severity parameters such as Ham-D and CGI scores, and disease duration. RNFL thicknesses were also lower in recurrent MDD patients than first episode patients and all MDD patients than controls but statistical significance was achieved only for global RNFL and temporal superior RNFL. Mean choroid thickness was higher in MDD patients than controls and in first episode MDD patients than recurrent MDD patients.

Limitations: Cross-sectional design of our study limits conclusions about progressive degeneration during the course of MDD. Lack of a control neuroimaging method like magnetic resonance imaging makes it hard to draw firm conclusions from our results.

Conclusions: OCT finding of decreased GCL and IPL volumes supports previous research suggesting degeneration in MDD. OCT may be an important tool to track neurodegeneration in patients with major depression. Considering RNFL to be the latest layer that will be affected during course of degeneration, GCL and IPL volumes appear to be better parameters to follow. In addition, choroid may be an important structure to detect acute attack period and to follow inflammatory process in MDD like in systemic inflammatory diseases.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder that affects nearly 1 in every 5 people in their lifetime (Bromet et al., 2011). Also depression is the leading cause for morbidity worldwide and it is responsible from nearly 8.2% of total years lived with disability (Ferrari et al., 2013). Pathophysiology and brain imaging findings of such a prevalent and disabling disorder has received great research interest especially during recent years.

Research in recent years suggests a multidimensional and reciprocal relation between inflammation and depression. Sickness behavior, which was first described by Hart (1988) is induced by acute infection or tissue injury and is characterized by symptoms such as fatigue, anhedonia, loss of appetite, psychomotor impairment, impaired cognitive functioning, and depressed mood. Similarity of this syndrome with MDD increased research interest on this topic. 'The macrophage theory of depression' defined by Smith (1991) proposed that cytokines including IL1-β and TNF-α which were secreted by macrophages led to some cases of MDD. Maes et al. (1991, 1992) extended this hypothesis by identifying

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increased inflammatory biomarkers including cytokines and acute phase reactants such as C-reactive protein (CRP) in peripheral blood of depressed patients. Many later studies expanded scientific knowledge about the relation between depression and inflammation.

A degenerative process in MDD has also been suggested by previous neuroimaging studies. Particularly, magnetic resonance imaging (MRI) has been used to identify brain regions implicated in the pathophysiology of MDD and structural and functional abnormalities have been found especially in cingulate cortex, dorsomedial frontal cortex, amygdala, basal ganglia, and dorsolateral prefrontal cortex (Campbell and MacQueen, 2006; Shah et al., 1998; Sheline 2003). A meta analysis of voxel based morphometry studies in MDD demonstrated significant gray matter reductions in anterior cingulate cortex, dorsolateral and dorsomedial prefrontal cortex, amygdala and parahippocampal gyrus (Bora et al., 2012). The authors suggested more severe reductions in patients who had multiple previous depressive episodes. Postmortem studies have also reported decreased synapse number and neuron density in prefrontal cortex of subjects with major depressive disorder (Kang et al., 2012).

Optic coherence tomography is a relatively new, non-invasive, contactless, and radiation-free imaging method which measures the peripapillary retina with a high spatial resolution (Fujimoto, 2003). OCT used first in the field of ophthalmology (Izatt et al., 1994; Schuman et al., 1995). Then, it was used for neurodegenerative diseases like multiple sclerosis, Alzheimer's disease, and Parkinson's disease (Schönfeldt-Lecuona et al., 2014). In these studies, degeneration in retina parallel to disease severity was detected (Armarcegui et al., 2010; Inzelberg et al., 2004). Correlation between retinal atrophy detected by OCT and neuronal atrophy in cerebral cortex was also demonstrated (Lamirel et al., 2009).

More recently OCT was used to detect neuronal degeneration in psychiatric disorders. Using time domain OCT Cabezon et al. (2012) reported a significant reduction in the overall and superior quadrant retinal nerve fiber layer (RNFL) thickness in schizophrenia patients compared with controls. Spatial resolution of OCT devices increased with new spectral domain OCT and this enabled separation of other retinal sublayers such as ganglion cell layer (GCL) and inner plexiform layer. GCL and IPL was shown to have better structure-function correlation in neurodegenerative diseases such as multiple sclerosis then RNFL (Saidha et al., 2011). Our group recently demonstrated reduced GCL and IPL volumes in schizophrenia patients compared with controls using spectral OCT (Celik et al., 2016). We also detected significant negative correlations between disease severity parameters and GCL and IPL volumes.

Retinal abnormalities in mood disorders, especially in major depressive disorder is a relatively new research area. Abnormalities in retinal contrast processing s were shown during depression which improved with treatment (Bubl et al., 2010, 2012). An electrooculography study demonstrated the presence of a correlation between electrophysiological abnormalities and psychometric assessments (Fountoulakis et al., 2005). Abnormalities in serotonin and dopamine, which are known to be very important in the pathophysiology of major depressive disorder, have also shown to be involved in retinal processes (Schwitzer et al., 2015).

Recently Yildiz et al. (2016) used time domain OCT to compare major depressive patients with controls. They could not find a significant difference in OCT parameters between groups. Resolution of time domain OCT is lower than spectral OCT and therefore it generally gives reliable information only about differences in RNFL. RNFL is believed to reflect axons of ganglion cells, GCL is believed to reflect ganglion cell bodies, and IPL is believed to reflect dendritic arborizations of ganglion cells (Gabriele et al., 2011). Previous studies by our group showed that GCL and IPL volumes obtained by spectral OCT differentiate patients and controls better and they have stronger correlations with disease severity parameters (Celik et al., 2016; Kalenderoglu et al., 2016). Therefore, one can expect to find significant differences with spectral OCT between major depression patients and controls.

Aim of this study was to detect changes suggesting inflammation and neurodegeneration in retinal sub-layers of patients with MDD, both first episode and recurrent, by measuring RNFL and choroid thicknesses, and GCL and IPL volumes with spectral-OCT.

2. Method

2.1. Study design

This study included first episode (n=50; 16 males and 34 females) and recurrent (n=50; 15 males and 35 females) MDD patients who were diagnosed according to DSM IV criteria in psychiatry department of Adiyaman University Medical School. Approval for this study was obtained from local ethics committee. Sociodemographic data form was filled for all study group, and Hamilton Depression Rating Scale (Ham-D), and Clinical Global Impression Scale (CGI) were applied to depressive patients.

2.2. Inclusion/Exclusion criteria

Patients who had comorbid first axis diagnoses, severe neurological, immunological or systemic diseases, and primary ophthalmological diseases (glaucoma or retinal diseases) were excluded. Patients with refraction errors ≥ 1 prism diopter were also excluded. Both the patient and the control groups were examined in ophthalmology clinic and best corrected visual acuity (BCVA), intraocular pressure, slit lamb bio-microscopy, and fundus examination by eye dilatation were measured. Patients and controls with normal eye findings were included.

To eliminate effects of age and sex on retinal thickness groups were matched according to these parameters. Therefore, first episode depression patients and controls that match with recurrent depression patients were selected.

2.3. OCT measurements

OCT measurements were performed in Ophthalmology Department of Adiyaman University Medical School by the same author (ASK) using spectral OCT (Spectralis™ OCT, Version 6.0, Heidelberg Engineering, Germany). Choroid measurements were performed at 3 regions and mean of these 3 measurements was calculated. Thickness of RNFL was measured at 7 regions (temporal (T), nasal (N), temporal superior (TS), temporal inferior (TI), and global for each eye (Fig. 1). But because calculations for these 7 regions were highly correlated we used results for only global RNFL measurement in the analyses. Segmentation of retinal sublayers and RNFL thickness, GCL, and IPL volumes calculations were performed automatically by the OCT device (Fig. 2). Choroid thickness was measured manually. At subfoveal region a perpendicular line was drawn from outer edge of the retinal pigment epithelium to the choroid-sclera junction. Additional two lines were drawn at the nasal and temporal sides at 500 μm intervals from the first line. The mean value of these 3 measurements were taken as the choroidal thickness (Fig. 3).

2.4. Statistical methods

Statistical analyses were performed using SPSS 21.0 package