

Retinal Nerve Fiber Layer Thickness Measurement by Spectral-Domain Optical Coherence Tomography in Patients with Major Depressive Disorder

Majör Depresif Bozukluk Hastalarında Optik Koherens Tomografi ile Retinal Sinir Lifi Tabakası Kalınlığı Ölçümü

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ABSTRACT

Introduction: In recent years, an increasing number of studies have researched retinal nerve fiber layer (RNFL) changes in neurodegenerative disorders. In this study, our aim was to determine structural RNFL changes in patients with major depressive disorder.

Methods: A total of 30 patients with major depressive disorder and 30 age- and sex-matched controls were recruited. Using optical coherence tomography (OCT), the peripapillary RNFL thickness in major depressive disorder patients and control subjects was measured and compared at each location.

Results: Patients with major depressive disorder did not show a statistically significant reduction in overall peripapillary RNFL thickness.

Conclusion: Our study showed that RNFL thickness is not reduced in major depressive disorder patients and that OCT is not a useful tool for diagnosing and monitoring the progression of major depressive disorder. This study suggests that the pathophysiology of unipolar depression is different than in neurodegenerative disorders, pervasive developmental disorders, schizophrenia, and bipolar disorder.

Keywords: Depression, retina, magnocellular pathway

ÖZ

Amaç: Son yıllarda, nörodejeneratif hastalıklarda retinal sinir lifi tabakasındaki (RSLT) değişiklikleri araştıran çalışmalar artmaktadır. Bu çalışmada, bizim amacımız majör depresif bozukluğu olan hastalarda retinal sinir lifi tabakasındaki yapısal değişiklikleri saptamaktır.

Yöntem: Structured Clinical Interview for DSM (SCID) görüşmesi sonucunda majör depresif bozukluk tanısı konan 30 hasta ve yaş, cinsiyet açısından hastalarla eşleştirilen 30 sağlıklı birey kontrol grubu olarak çalışmaya dahil edilmiştir. Optik Koherens Tomografi (OKT) kullanılarak, majör depresif bozukluk hastalarında ve kontrol grubunda, retinal sinir lif tabakası (RSLT) kalınlığı her lokasyonda ölçülüp karşılaştırılmıştır.

Bulgular: Majör depresif bozukluk tanılı hastaların RSLT kalınlığında, istatistiksel olarak anlamlı bir azalma görülmemiştir.

Sonuç: Çalışmamız, majör depresif bozukluk hastalarında RSLT kalınlığının azalmadığını ve majör depresif bozukluk tanısında ve hastalığın gidişini izlemede OKT kullanımının uygun araç olmadığını göstermiştir. Bu çalışma unipolar depresyon patofizyolojisinin, nörodejeneratif hastalıklar, yaygın gelişimsel bozukluklar, şizofreni ve bipolar bozuklukta farklı olabileceğini göstermektedir.

Anahtar kelimeler: Depresyon, retina, magnoselluler yolak

INTRODUCTION

Major depressive disorder is a highly prevalent, etiologically multifactorial, and clinically heterogeneous disorder (1). In vivo structural and functional imaging studies, as well as postmortem investigations of adults, suggest that the frontal-striatal-thalamic and limbic-thalamic-frontal neural circuits have an important role in the pathogenesis of depression (2). The hypothesis that stress, via activation of the neuroendocrine system, neurotransmitter changes, and pro-inflammatory cytokines can induce neurodegeneration and contribute to the pathology of depression led to the development of the cytokine hypothesis of depression, which has been consistently tested since the 1990s (3). Applying this model, one might speculate that the microstructural abnormalities in projections that transfer signals from the orbitofrontal cortex to the thalamus may disturb functioning of the frontothalamic pathways; specifically, cognitive and emotional processing (4). Medial frontal cortex (MFC) and orbitofrontal cortex (OFC) are anatomically defined as the prefrontal cortex regions that receive robust projections from the magnocellular nucleus; medial nucleus of the mediodorsal thalamus. The OFC and MFC are regions where functional changes could cause neuropsychological disturbances in decision-making, problem solving and affect modulation (5). The thalamus receives strong dopaminergic projections and plays a critical role in the mood-related neural networks. Previous research has shown that functional and histological abnormalities in the thalamus are involved in the pathophysiology of depression (6).

Visual processing research in human and nonhuman primates has identified two separate but interacting visual subsystems. The magnocellular pathway, which is primarily responsible for processing information about location and motion, and the parvocellular pathway, which is pri-



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marily responsible for processing information about detail and color (7).

Being a part of the central nervous system, the retina contains a high density of neuronal cells with a laminar structure outside the brain (8). Age related neuronal cell loss, inflammatory responses and other pathological events that occur in the retina are similar to those that occur in the brain (9). Since the anatomical structure of the retina is far simpler than that of the brain, one can use the retina to investigate degenerative processes, signaling mechanisms, and even neuroprotective agents (8).

In vivo visualization of the retinal nerve fiber layer (RNFL) can be achieved by optical coherence tomography (OCT), a non-invasive, fast imaging technique used to monitor retinal changes in glaucoma (10). The retinal tissue imaging with OCT facilitates the use of the retina as a surrogate for many neurodegenerative diseases. In the studies that have investigated the relationship between depression and neurodegenerative processes in recent years, it has been reported that there are anomalies in neurochemical metabolites like N-acetyl-aspartate and choline (11). In a study where first episode, drug-naïve depression patients who had at least moderate symptom severity was examined, it was concluded that neurodegeneration was evident in early phases of depression (12). Postmortem studies of brains of depressed patients indicate a decrease in the density of glial cells in cortical regions, especially in the prefrontal and cingulate areas (13). The increase in the level of S100B protein, a marker of glial degeneration in the blood serum of patients, correlated with exacerbation of depressive symptoms and was inhibited by antidepressants (14). The mammalian retina provides an excellent opportunity to study glia–neuron interactions and the interactions of glia with blood vessels. Three main types of glial cells are found in the mammalian retina, which serve to maintain retinal homeostasis: astrocytes, Müller cells and resident microglia. Astrocytes are mostly located in the RNFL (15).

This imaging technology has recently been applied to the study of neurological conditions with diffuse and progressive brain pathology. RNFL thinning has been shown in patients with mild cognitive impairment without dementia (16). A correlation between RNFL thinning and the severity of cognitive impairment in patients with Alzheimer's disease has been reported (17,18). Altıntaş et al. (19) reported that RNFL thinning is present in patients with Parkinson's disease. In these patients there is a loss of dopaminergic neurons not only in the cortex and basal ganglia but also in the retinal ganglion cells. The mammalian retina contains dopaminergic neurons that regulate the receptive field of ganglionic cells providing contrast sensitivity and color vision (19,20).

Previous studies have demonstrated that the expansion of dopamine in retinal cells is lower in patients with degenerative diseases (21). Dementia, a degenerative disease, and depression have similar symptoms, such as cognitive impairment and memory loss. Similarly, it has been shown that changes that are detected in the magnocellular pathway can be associated with the negative symptoms of schizophrenia (22). On the basis of the similarities between the symptoms of depression and the negative symptoms of schizophrenia, it may be assumed that the magnocellular pathway could also be impaired in depression. In this study, we aimed to compare RNFL thickness in a group of patients with major depressive disorder with a control group of healthy age- and sex-matched subjects.

METHODS

Thirty patients with a major depressive disorder diagnosis according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) were consecutively enrolled in the study (23,24). Voluntary hospital staff were also included in the study as a control group.

The following exclusion criteria were applied: neurological disorder; psychiatric disorders other than major depressive disorder; history of malignancy, head trauma or stroke, drug abuse or addiction, metabolic or endocrine abnormalities, diabetes mellitus (even in the absence of retinopathy), intraocular pressure (IOP) >21 mmHg (even in the absence of glaucoma, presence of glaucoma), congenital color vision disorders, congenital optic nerve head anomalies, best corrected visual acuity (BCVA) <0.6, high ametropia (sphere dpt >4 and cylinder dpt >2), optic media opacities that could bias functional or structural retinal testing such as cataract (nuclear sclerosis > Grade 2), central corneal opacities and OCT tests performed unreliably.

Both groups underwent full ophthalmological examinations by an ophthalmologist. This examination consisted of BCVA, Snellen chart, slit lamp examination, IOP measurement (Goldman applanation tonometer), angle, and fundus examination (Goldman 3-mirror lens), Humphrey 30-2 threshold visual fields test and color vision testing (Ishihara color test).

During OCT, a cross-sectional image of the retina is produced by measuring the echo time delay of back-scattered infra-red light after it has passed into the eye and is bounced back using a low coherence light source and interferometer. OCT was performed by an ophthalmologist trained and experienced in using the Spectralis device and software (Heidelberg Engineering GmbH.; Heidelberg, Germany) at Near East University Department of Ophthalmology. RNFL images were acquired for each eye by taking a circumpapillary scan of 3.4 mm diameter to effectively intercept all nerve fibers converging toward the optic disc while avoiding inaccurate measurements resulting from peripapillary atrophy (25). The thickness of the RNFL quadrants were temporal (T), nasal (N), inferonasal (IN), superotemporal (ST), superonasal (SN), inferotemporal (IT) and calculated by the OCT device software and represented by a line graph indicating RNFL thickness at all sections of the scanning circle. With the Fast RNFL protocol, the mean of three circular 3.4 mm diameter scans, centered on the optic disc, was used to express RNFL thickness.

Ethical approval was granted by the Joint Ethics committee of the Near East University School of Medicine, and this study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). After providing a description of the study, written informed consent was obtained from all participating subjects.

Statistical Analysis

A total of 54 individuals (27 diseased and 27 healthy controls) were included in the study based on previous reports and a power analysis, which was carried out with G*Power (Version 3.1.7) software. In order to prevent any possible loss of statistical power, the number of patients was set to 60 (30 in each group). The chi-square test was used to compare numeric data and Student's t-test was used to compare continuous data. The level of statistical significance was set at $p < 0.05$.

Data were analyzed using IBM Statistical Package for the Social Sciences for Macintosh, (Demo Version 22.0, Armonk, NY, USA). The level of statistical significance was set at $\alpha = 0.05$.

RESULTS

Thirty patients with a diagnosis of major depressive disorder and thirty healthy controls were included in our study. In comparisons of patient and control groups, no significant differences between mean age ($p = 0.682$) or sex ($p = 1.000$) were found (Table 1).

The mean age at onset of the major depressive disorder was 28.83 ± 8.75 years; the mean duration of the disorder was 5.70 ± 7.31 years; and the mean number of episodes was 2.17 ± 1.51 . Seven of the patients (23.3%) had mild depression levels, while 15 had moderate (50%) and 8 had severe (26.7%) depression levels. All patients were receiving antidepressant medication. In patients, the mean visual acuities were right = 0.004 ± 0.11 , left = 0.004 ± 0.12 and in controls right = -0.029 ± 0.10 and left = -0.029 ± 0.11 . Intraocular pressures were within the normal range and there was no evidence of optic disc cupping in any of our subjects.

There were no statistically significant differences between the measurement values of RNFL thickness for right (r) and left (l) eyes of patient and control groups (superotemporal: r: $t = -0.601$ $p = 0.55$, l: $t = -0.107$ $p = 0.91$; superonasal: r: $t = 0.007$ $p = 0.99$ l: $t = 0.428$ $p = 0.67$; nasal: r: $t = -0.689$ $p = 0.49$ l: $t = -1.521$ $p = 0.13$; inferonasal: r: $t = -0.045$ $p = 0.96$ l: $t = -1.403$ $p = 0.16$; inferotemporal: r: $t = -0.645$ $p = 0.52$ l: $t = 0.577$ $p = 0.56$; temporal: r: $t = -1.532$ $p = 0.13$ l: $t = 0.318$ $p = 0.75$; global: r: $t = -1.104$ $p = 0.27$ l: $t = -0.411$ $p = 0.68$, respectively) (Table 2).

DISCUSSION

Depression commonly occurs in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Lewy body disease, and Huntington's disease, but it has been suggested that depression itself, particularly in later life, may be an indication of latent neurodegeneration (26,27,28,29,30). Additionally, human imaging studies showing cellular loss in key brain regions (e.g., the prefrontal cortex and amygdala) of patients with mood disorders link reductions in brain volume to depression (31). Depending on the region, the cause for this reduction may be due to either neurodegeneration or reduced neurogenesis (32). Animal models of depression support human findings, reporting loss of hippocampal volume, or neurodegeneration in certain brain areas (33).

Impairment of the visual system has been reported for neurodegenerative disorders, schizophrenia, pervasive developmental disorder, and bipolar disorder (21,34,35,36,37). To our knowledge, this study is the first to investigate the relationship between major depressive disorder and RNFL with the use of OCT.

Optical coherence tomography is known to be effective for detecting early functional impairment in the magnocellular pathway (38). The subcortical system is rooted in the magnocellular pathway and projects to the amygdala.

The magnocellular pathway is one of the three pathways that go to the brain. The other two pathways are the parvocellular and koniocellular pathways. The amygdala is a structure of the limbic system that is related to emotions (39,40). The magnocellular pathway develops in the early gestational period (41,42). Thus, anomalies in this pathway in the early gestational period may trigger anomalies in related brain regions (36).

In a study investigating white matter lesions and temporal lobe atrophy related to dementia and major depression in 70-year-olds followed over 10 years, it was shown that white matter lesions and temporal lobe atrophy predict dementia and depression independently from each other. It may be that there is one neurodegenerative and one vascular pathway to both dementia and depression in older adults (43).

In recent years, dysfunctions in the magnocellular pathway have been investigated in schizophrenia. Impairment of the magnocellular path-

Table 1. Demographic characteristics of patient and control groups

	Patient (n=30)		Control (n=30)		x ² /t	p
	n/mean	%±sd	n/mean	%±sd		
Sex						
Female	19	63.30	19	63.30	0.000	1.000
Male	11	36.70	11	36.70		
Age (years)	34.57	8.76	35.47	8.18	-0.411	0.682

sd: standard deviation

Table 2. The comparison of retinal nerve fiber layer thickness in patient and control groups

	Patient (n=30)		Control (n=30)		t	p
	Mean	±sd	Mean	±sd		
Superotemporal (µm)						
R	138.07	14.60	140.57	17.50	-0.601	0.55
L	114.00	24.12	114.60	19.13	-0.107	0.91
Superonasal (µm)						
R	102.70	21.08	102.73	15.12	-0.007	0.99
L	137.03	18.27	134.77	22.50	0.428	0.67
Nasal (µm)						
R	72.40	12.54	74.63	12.76	-0.684	0.49
L	66.10	9.63	70.43	12.28	-1.521	0.13
Inferonasal (µm)						
R	108.77	21.00	109.00	19.17	-0.045	0.96
L	149.63	16.99	156.30	19.73	-1.403	0.16
Inferotemporal (µm)						
R	151.67	16.78	154.70	19.54	-0.645	0.52
L	115.30	22.42	112.10	20.46	0.577	0.56
Temporal (µm)						
R	72.47	11.07	77.27	13.12	-1.532	0.13
L	74.97	12.22	73.87	14.46	0.318	0.75
Global (µm)						
R	98.97	8.64	101.40	8.43	-1.104	0.27
L	99.73	8.26	100.73	10.47	-0.411	0.68

R: retinal nerve fiber layer thickness of right eye; L: retinal nerve fiber layer thickness of left eye; µm: micrometers

way is thought to be related with negative symptom severity and cognitive deficits in schizophrenia (22). Negative symptoms observed in schizophrenia share similarities with symptoms of depression. Also, it is required to make a differential diagnosis between dementia that progresses with cognitive deficits and decrement of retinal thickness and depression. Our study was based on the assumption that depression, which has symptoms in common with schizophrenia and dementia, may also have a dysfunctioning magnocellular pathway, but we did not find decrement in retinal thickness of patients with major depressive disorder compared to healthy controls. This finding indicates that depression may not lead to degenerative processes which are evident in dementia. Dementia is known to progress with degeneration while the role of degenerative processes in pathogenesis is still unclear for schizophrenia.

Keri and colleagues examined magnocellular and parvocellular pathways in bipolar patients within the depressive episode and in the recovery period when the depressive symptoms were improved. They showed that patients in the depressive episode had impaired magnocellular and parvocellular pathway functions. As for when the patients were in clinical remission, magnocellular; and parvocellular functions were better (37). The finding that impairment in magnocellular pathway is evident in depressive episode of bipolar disorder but not in unipolar depression may shed light on differences in pathogenesis of these disorders. It may be assumed that the absence of magnocellular pathway impairment in unipolar depression may indicate structural and anatomical differences between unipolar and bipolar depression.

This study suggests that the pathophysiology of unipolar depression is different than in neurodegenerative disorders, pervasive developmental disorders, schizophrenia, and bipolar disorder. Considering the magnocellular pathway develops in the early gestational period, major depression may be caused by anomalies in later periods and psychosocial factors may have a critical role in depression.

The limited number of our patients, the cross-sectional design of our study and patients' being under antidepressant medication are among the limitations of our study. Longitudinal studies with larger patient groups are required to investigate the changes in the magnocellular pathway in mental disorders.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Near East University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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