Evaluation of Inner Retinal Layers and Choroid with Spectral Domain Optical Coherence Tomography in Thalassemia Major Patients

Talasemi Major Hastalarında Spektral Domain Optik Koherens Tomografi ile Koroid ve Retina İç Katlarının Değerlendirilmesi

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ABSTRACT

Purpose: Hypoxic or ischemic diseases can cause a deterioration in the structure of the retina and choroid. The aim of the study was to evaluate whether there are differences in subfoveal choroidal thickness (SCT), central foveal thickness (CFT), peripapillary retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness of patients with beta thalassemia major (β-TM) receiving deferasirox treatment.

Materials and Methods: The study included 35 patients with β-TM and 35 age and sex matched healthy children as a control group. The age interval for both groups was 6-18 years. SCT, CFT, RNFL and GCC thickness were measured by spectral domain optical coherence tomography (SD-OCT) compared with control group. Serum iron (Fe), ferritin and hemoglobin (Hb) levels were recorded.

Results: There was no statistically significant difference in age, visual acuity, refraction error, the intraocular pressure between the groups. The mean superior GCC value was 99,1±2,26 µm, inferior GCC was 102,87±3,06 µm in the thalassemia group. In the control group, it was 132,77±4,22 µm and 130,03±3,61 µm respectively (p<0,001). The mean SCT and peripapillary RNFL thickness were significantly lower in patients with β-TM than in the healthy controls (p<0,001) (p<0,05).

Conclusion: In patients with thalassemia major, there is a decrease in GCC thickness in addition to SCT and RNFL thickness. This result may have occurred as a result of the disease itself, or the side effect of deferasirox. Presence of severe anemia, hypoxia and excessive iron in β-TM can disrupt the structure of the RNFL and GCC layer that leads to neurodegeneration.

Key Words: Ganglion cell complex thickness, iron overload; peripapillary retinal nerve fiber layer, subfoveal choroidal thickness, thalassemia major.

ÖZ

Amaç: Hipoksik ve iskemik hastalıklar retina ve koroidin yapısında bozulmalara neden olabilir. Bu çalışmada amacımız, deferasiroks tedavisi uygulanan beta talasemi majör (β-TM) hastalarında subfoveal koroid kalınlığı (SKK), santral fovea kalınlığı (SFK), peripapiller retinal sinir lifi kalınlığı (RSLK) ve gangliyon hücre kompleks kalınlığında (GHKK) farklılık olup olmadığını araştırmaktır.

Gereç ve Yöntem: Çalışma 35 β-TM hastası ile yaş ve cinsiyet açısından benzer 35 sağlıklı çocuktan oluşan kontrol grubu içermektedir. Yaş aralığı her iki grup için 6-18 yaş idi. SKK, SFK, RSLK ve GHKK spektral domain optik koherens tomografi (SD-OKT) cihazı ile ölçüldü ve sonuçlar kontrol grubu ile karşılaştırıldı. Serum demir, ferritin, hemoglobin düzeyleri kaydedildi.

Bulgular: Gruplar arasında yaş, görme keskinliği, refraksiyon kusuru, göz içi basınç değerleri arasında istatistiksel olarak anlamlı farklılık saptanmadı. Talasemi grubunda; superior GHKK değeri ortalama 99,1±2,26 µm, inferior GHKK 102,87±3,06 µm iken, kontrol grubunda değerler sırasıyla 132,77±4,22 µm ve 130,03±3,61 µm idi (p<0,001). Ortalama SKK ve peripapiller RSLK değeri talasemi grubunda kontrol grubuna göre anlamlı oranda düşük saptandı (p<0,001) (p<0,05).

Sonuç: Talasemi majör hastalarında SKK ve peripapiller RSLK değerlerinde azalmanın yanısıra GHK kalınlığında da azalma olmaktadır. Bu durum hastalığın doğal seyrinin bir sonucu olabilmekle birlikte, deferasiroksun yan etkisi olarak ta gelişebilir. Talasemi major hastalığında ciddi anemi, hipoksi ve aşırı demir yükünün varlığı RSLK ve GHK tabakasında hasara neden olarak nörodejenerasyona sebep olabilir.

Anahtar Sözcükler: gangliyon hücre kompleks kalınlığı, demir aşırı yükleme peripapiller retinal sinir lifi, subfoveal koroidal kalınlık, talasemi major.

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INTRODUCTION

Beta thalassemia major (β-TM) is one of the most common genetic diseases characterized by hematologic abnormalities. The serum iron level of individuals with thalassemia major increases, due to blood transfusion and excessive destruction of blood cells, resulting in an accumulation of iron in the tissues.[1] Patients with thalassemia major usually come to medical attention within the first two years of life. These patients require lifelong blood transfusions at regular intervals. Iron chelation treatment, to reduce iron store in the body and improve the long-term survival rate of patients with β-TM is considered a mandatory adjuvant therapy.

Chelating agents are widely used in managing patients with chronic iron overload. Previous studies discovered that both iron overload and iron-chelating agents may be mutually confounding factors in the causation of ocular changes of thalassemia.[1-2] Deferoxamine is the most used iron-chelating drug to treat hemosiderosis secondary to transfusions. Numerous significant drug-related toxicities such as night blindness, centrocaecal scotoma, constricted peripheral visual field, pigmentary retinopathy, optic neuropathy have been reported in the literature. [3,4]

New iron-chelating therapies (deferasirox and deferiprone) are available. But their long-term ocular safety has not been comprehensively investigated.

In this study, we used spectral domain optical coherence tomography (SD-OCT) to investigate central foveal thickness (CFT), subfoveal choroidal thickness (SCT), peripapillary retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness of patients with β-TM using deferasirox treatment by comparing them to those of healthy age and gender-matched controls.

MATERIALS AND METHODS

This prospective study was conducted between February-May 2017 in the Department of Ophthalmology and the Department of Pediatric Hematology. All patients were selected from those attending the Pediatric Hematology Clinic of the hospital.

The study protocol was approved by the local Ethics Committee. This investigation complied with the Tenets of the Declaration of Helsinki. Informed consent was obtained from the parents of the children.

The study included 35 patients with β-TM and 35 age and sex-matched healthy children as a control group. Individuals without pathology on the anterior segment and fundus examination were included in the study.

All thalassemia patients were receiving regular blood transfusions approximately once a month and oral iron-chelator therapy, deferasirox was (20-40 mg/kg/day) used. Deferasirox treatment was started when ferritin level was above 1000 ng / ml.

Individuals with a history of a corneal disease, contact lens use, ocular trauma, previous ocular surgery or dry eye, glaucoma, uveitis, any kind of retinopathy, any systemic disease other than β-TM, refractive error more than ± 3D were excluded.

All participants underwent acomplete ophthalmic evaluation, including best corrected visual acuity (as measured on a Snellen chart), slit lamp biomicroscopy for an anterior and posterior segment, intraocular pressure (IOP) with Goldmann applanation tonometry, axial length and SD-OCT measurements. All examinations for an individual study participant were performed on the same day. Data from the right eye of each participant were used for the analyses.

Serum iron (Fe), ferritin, hemoglobin (Hb) levels were recorded. Blood test and ophthalmic eye examination were performed on the same day.

CFT, SCT, peripapillary RNFL and GCC thickness were measured by SD-OCT (RS-3000 advance; NIDEK, Gamagori, Japan). All measurements were performed by the same ophthalmologist.

We captured the OCT scans using the macula line 12-mm horizontal scan. The scans consisted of 1,024 A-scans with high definition. Each image consisted of 120 averaged B-scans, with a 4-μm resolution. After capturing the macula line scan for measuring the foveal thickness, which is automatically calculated by the device. The OCT device was approached from the patient's eye until the image was inversed and we got the choroidal mode. SCT was calculated as the perpendicular distance between the hyper reflective outer border of the retinal pigment epithelium and the sclero-choroidal interface, which was manually drawn using the embedded software (NAVIS-EX Image Filing software).

Peripapillary RNFL thickness map of the 3.45 mm diameter ring and parameters describing optic disk features are provided. The map provides the average RNFL thickness in the temporal, superior, nasal and inferior quadrants and global average.

GCC thickness is defined by the distance from the internal limiting membrane to outer inner plexiform layer. The OCT images are processed automatically to provide a thickness map of the GCC. Superior and inferior GCC parameters were evaluated.

Statistical Analysis: Statistical analyses were performed by SPSS 20.0 (IBM Inc., Chicago, IL, USA). The normality of continuous data was assessed by the Kolmogorov-Smirnov test. All measurements were distributed normally except for GCC and SCT. Independent sample Student t-test and

Mann-Whitney U test, if necessary, were used to compare the parameters of the study and the control group. The relationship between clinical measurements was evaluated by Spearman's correlation test. Nominal data were analyzed by Pearson's Chi-Square test. $p<0.05$ was considered as a statistically significant result.

RESULTS

The mean age of the children was 11,77±0,69 years (range: 6-18 years) in the β-TM group, 10,91±0,55 years (range:7-18 years) in the control group. (p=0.358) The gender and refractive status of the groups were similar, there were no statistically significant differences (p>0.05). Clinical characteristics of the patients are given in Table 1 and Table 2.

Table 1. *Demographic and ocular findings of the groups*

	β-TM Group	Control group	P value
Gender (male/female)	19/16	21/14	0,591
Age (year)	11,77±0,69	10,91±0,55	0,358
Visual Acuity	1,15±0,75	1,19±0,26	0,225
IOP (mmHg)	12,5±1,92	13,2±1,42	0,340
Axial lenght (mm)	21,8±0,9	21,9±0,7	0,645
B-TM: β thalassemia major, IOP: Intraocular pressure			

Table 2. *Mean values of laboratory tests of the groups*

	β-TM Group	Control Group	P value
Hb (gr/dl)	8,85±0,27	12,54±1,4	<0,001
Hct (%)	27,01±0,76	36,45±1,3	<0,001
Serum Fe (mcg/dl)	216,2±21,81	92,40±6,5	<0,001
Serum Ferritin (ng/ml)	2998±428,81	22,3±4,7	<0,001
β-TM: β thalassemia major, Hb: Hemoglobin, Hct: Hematocyrit, Fe:Iron			

The mean duration of thalassemia was 8,5 years (range: 6,3-15). The patients have been receiving iron chelation therapy for a mean duration of 7,6 years (5-12 years).The best corrected visual acuity according to Snellen was similar in both groups (range 20/25- 20/20).

Superior andinferior GCC thickness values were significantly different between the groups. The mean superior GCC value was 99,1±2,26 µm, inferior GCC was 102,87±3,06 µm in the thalassemia group. In the control group, it was 132,77±4,22 µm and 130,03±3,61 µm respectively (p<0,001). The mean SCT and peripapillary RNFL thickness values were significantly lower in patients with β-TM than in the healthy controls (p<0,001). No statistically significant difference surfaced between the groups in terms of CFT. The mean of CFT, SCT, RNFL and GCC thickness of both groups are shown inTable 3.

Patients were divided into 2 groups according to the amount of drug they received (<1500 mg and >1500 mg). Received drug dosage was lower than 1500 mg in 17 patients and more than 1500 mg in 18 patients. Correlation analysis was performed to assess whether there was a relationship between the ocular measurements and drug dosage. Negative and moderate correlation (R=42.6%) (p=0.019) between drug dosage and inferior GCC thickness was determined. There was no significant correlation with sup GCC, SCT and RNFL thickness.

There was no correlation between Fe and Ferritin levels with RNFL and GCC thickness. Within the β-TM group neither RNFL nor GCC thickness was correlated with the serum ferritin and Hb levels (p>0,05).

DISCUSSION

In this study, we found that a decrease in GCC thickness in addition to RNFL and SCT thickness in patients with β-TM.

Although the iron is essential for normal function of the retina, excess of the iron can be toxic. As a potent free

Table 3. *Comparisons of the thickness measurements in the study and control groups*

	β-TM Group	**Control Group**	**P value**
CFT (µm)	268,07±6,25	273,37±4,05	0,209
SCT (µm)	228,67±7,92	298,63±1,14	<0,001
GCC superior (µm)	99,1±2,26	132,77±4,22	<0,001
GCC inferior (µm)	102,87±3,06	130,03±3,61	<0,001
RNFL superior (µm)	126,63±3,94	159,51±3,36	<0,05
RNFL inferior (µm)	135,9±5,29	163,89±4,54	<0,05
RNFL temporal (µm)	79,9±4,22	149,03±2,34	<0,05
RNFL nasal (µm)	99,37±4,41	172,8±3,14	<0,05
RNFL average (µm)	103,57±2,99	150,86±2,29	<0,05
CFT: Central foveal thickness, SCT: Subfoveal choroidal thickness, GCC:Ganglion cell complex, RNFL: Retinal nerve fiber layer			

radical creator, iron generates hydroxyl radicals leading to significant oxidative stress.[5]

The disruption of iron and ferritin has been characterized in the adult rat retina. Proton-induced X-ray emission identified the largest amounts of iron in the inner segments of photoreceptors, the retina pigment epithelium, the choroid, the inner nuclear layer and the ganglion cell layer (GCL). [6]

An increase in the level of iron has been shown to cause oxidative injury to the retina.[7] In the literature, there are few studies evaluating RNFL thickness in the children with β-TM. Simsek et al [8] observed that the RNFL was thinner in all quadrants in the children with β-TM and RNFL thickness was positively correlated with hemoglobin levels and was negatively correlated with serum ferritin levels. In another study; Uzun et al [9] observed average, nasal, inferior and temporal RNFL thickness was thinner with β-TM patients and thinning of RNFL did not correlate with Hb and ferritin levels. Aksoy et al reported that RNFLs were thinner in β-TM patients. They speculated that the RNFL thinning may have occured as a result of the hypoxic process or side effects of iron chelators.[10]

Similarly; in our study, we found a significant change in RNFL values measured from all quadrants compared to the control group. However, we did not obtain any correlation between serum Ferritin and Hb levels with RNFL thickness.

The macula region contains over 50% of all retinal ganglion cells and is probably the ideal region to detect early cell loss and changes over time because of the high density of cells. The function and structure of the GCC encompass three layers in the inner retina: RNFL, which is made up of the ganglion cell axons; GCL, which is composed of the cell bodies; and the inner-plexiform layer (IPL), which is made up of the ganglion cell dendrites.

A few recent studies have shown that measurement of macular GCC thickness has the same glaucoma diagnostic performance as RNFL thickness.[11-13]

There is increasing evidence that assessment of macular GCC by SD-OCT algorithms is useful for early detection of retinal ganglion cell (RGC) damage in progressive and potentially blinding ophthalmic diseases. Several studies on macular GCC parameters, comprising RNFL, GCL, and IPL have shown good glaucoma diagnostic ability[14-16] and detected a presence of neurodegeneration in early vascular diabetic retinopathy. [17-18]

Reduction of the macular retinal GCC, composed by the RGC layer and the IPL, may be an early, initial manifestation of RGC loss. Indeed, the RGCs are densest in the macula and form a stratified multi-cellular layer within the central area of the visual field. Loss of axons and/or RGC bodies in this region will result in thinning of the macular RGC layer, visible on HD-OCT. Thus, it has been suggested that thickness of the macula OCT and GCC complex could provide a better structural indicator of neuronal and/or axonal loss compared to the peripapillary RNFL scan in certain optic neuropathies.[19] Macular GCC measures may be better at detecting macular damage, while peripapillary RNFL measures would identify damage outside the macula.[20] In this study we found that GCC thickness both superior and inferior quadrants was decreased.

When we evaluate the relationship between the drug dosage and the thickness measurements, we detected negative and moderate correlation between drug dosage and inferior GCC thickness.

There was no significant correlation between the deferasirox dosage and superior GCC, SCT and RNFL thickness.

There are few studies investigated that the effects of iron chelating agents on the retina with electrophysiological tests. [21-23]

Walia et al report a case with reversible retinopathy associated oral deferasirox theraphy. They found electrophysiological depression without anatomic or vascular abnormality. They reported that when deferasirox treatment was discontinued electrophysiological abnormalities improved. [21]

As opposed to these studies, Sakamoto et al showed that iron-chelating agents have neuroprotective affects against retinal injury induced by intravitreal N-methyl-D-aspartate (NMDA) via their anti-oxidative activity. [24] Previously it was demonstrated that intravitreal NMDA caused oxidative stress [25] and Ophir et al suggested that oxidative stree that was associated with iron may cause retinal ischemia-reperfusion injury. [26]

The choroid is more sensitive to the effects of hypoxic or ischemic diseases than other ocular components. Any structural or functional changes in the choroidal blood flow such as systemic hypertension, diabetes mellitus or hypoxia can cause a deterioration in the structure or function of the retina.[27-28] Because the choroid consists of a vascular structure and provides oxygen and nutrients to the outer retina and it maintains the highly metabolically active photoreceptor cells.[29]

Choroidal thickness is usually measured on the subfoveal area where the choroid is thickest.[30] SCT measurements were correlated with ocular perfusion pressure in the healthy individuals because of the highly vascular structure of choroid.[31]

Simsek et al[8] demonstrated that patients with β-TM had a significantly thinner choroidal thickness than that of the healthy children. And they suggest that β-TM, a cause of severe anemia and hypoxia, can disrupt the structure of the choroid that allows blood flow to the eye and that this disruption may cause disorders in other ocular components.

In our study, we found a similar result, SCT was significantly thinner in the β-TM group.

El-Shazly et al [32] concluded that thalassemia patients can develop a significant decrease in CFT. They suggested that foveal thickness is independently affected by the type of chelator. Deferoxamine affected foveal thickness more significantly than the oral chelator deferasirox. Also, they observed that SCT was lower among thalassemia groups and compared with that in controls. In our study, there was no significant difference in foveal thickness between the groups.

Study Limitations

The number of patients was low due to poor cooperation in the pediatric group during OCT screening. GCC thinning may have occurred as a result of the disease itself, or a side effect of deferasirox. Further prospective studies with larger sample sizes and longer follow up time are required in order to find an explanation. The most important limitation of our study is absence of a control group that including thalassemia patients not receiving treatment. If it was possible, the effect of the chelating treatment can be evaluated better. Assessment of regression of findings by discontinuing the drug when abnormal findings were detected could also be a guide in determining relevant changes.

Our study results could also be supported by electrophysiological tests.

CONCLUSION

There was a significant decrease in GCC and RNFL thickness in our study. Iron is crucial for normal functioning of the neuronal cells but iron accumulation may accelerate ganglion cell death. Thinning of the RNFL and GCC thickness may be related to oxidative stress and cellular death through apoptosis due to iron accumulation. In the literature, there is no study evaluating GCC, in addition to studies evaluating RNFL. As mentioned above, we have found a decrease in GCC thickness as a finding of early damage in ganglion cells. When we evaluated whether there was a relationship between drug dosage and decreased thickness measurements, we found that superior GCC, RNFL values were not related to drug dosage. We also found that the reduction in inferior GCC values was negatively correlated with drug dosage. GCC thickness may be the good option for showing neurodegeneration in patients with TM. According to these results; it is possible to say that there is a neurodegeneration in the natural course of the thalassemia major and that the inferior GCC is the first to be affected by the treatment of chelation. But it can not be said precisely whether the decrease in GCC, RNFL and SCT thickness is a natural course of the disease or deferasirox side effect. The nature of the disease or the treatment of the chelator agents can be caused ocular side effects, therefore, it is very important that directing patients to the eye disease clinic for regular ophthalmic examination.

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