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Original Article

Evaluation of Optical Coherence Tomography Findings and Choroidal Thickness in Beta-Thalassemia Major Patients Using Chelation Therapy

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Abstract

Objectives: This study aims to analyze the posterior segment of the eye in children with thalassemia major (TM) treated with chelation therapy.

Methods: Forty-four patients diagnosed with TM and 44 age- and gender-matched participants without systemic diseases were included in this cross-sectional comparative study. A complete ophthalmologic examination, including visual acuity and fundus examination, was performed on all participants. The study and control groups' optic coherence tomography (OCT) evaluation was performed with a spectral domain featured OCT device. Central macular thickness (CMT), macular volume, ganglion cell complex (GCC) thickness, retinal nerve fiber layer (RNFL) thickness, subfoveal choroidal thickness (CT), CT at 1 mm temporal to the fovea, CT at 1 mm nasal to the fovea, CT at the 1 mm temporal to the optic nerve head, and CT at the 1 mm nasal to the optic nerve head were compared between the study and control groups.

Results: The mean ages for the study group and for the control group were 15.2±6.2 and 14.2±4.9 years, respectively. The mean subfoveal CT was 287.73±47.04 µm in the TM group and 312.66±39.95 µm in the control group (p=0.014). CT at the nasal to the fovea and temporal to the optic nerve head was thinner in the TM group than in the healthy group. The mean CMT, macular volume, GCC thickness, and RNFL thickness of the study and the control groups were similar. No significant difference was found between the patients with and without deferoxamine therapy concerning macular thickness, GCC thickness, and macular and peripapillary CT.

Conclusion: Our results suggested that subfoveal, perifoveal, and peripapillary CTs were significantly thinner in children with TM than the control group. The use of deferoxamine did not cause a further reduction in CT.

Keywords: Choroidal thickness, deferoxamine, optical coherence tomography, thalassemia major

Introduction

Thalassemia major (TM) is a crucial public health problem in Mediterranean countries. It is a genetic disease with reduced hemoglobin production and erythrocyte destruction accompanied by hypochromic microcytic anemia. It is a disease whose effect begins in the infantile period. The need for lifelong blood transfusion causes iron accumulation in the tissues. Subcutaneous deferoxamine injections, oral de-

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feriprone, and oral deferasirox chelation drugs are required to prevent iron accumulation in tissues. In patients with TM, both excessive iron accumulation in the tissues and the use of drugs preventing iron accumulation may cause ocular changes (1).

Ocular findings related to deferoxamine toxicity are cataract, optic neuropathy, and macular and equatorial pigmentary degeneration (2). Deferoxamine-associated retinopathy has been investigated for many years. Electron microscopy findings, including patchy retinal pigment epithelium depigmentation, abnormally thickened Bruch's membrane, and normal photoreceptor layer, have been described (3). Wu et al. (1) have shown that toxicity mainly affects the retinal pigment epithelium-Bruch membrane-photoreceptor complex. It has been well described by multimodal imaging techniques that deferoxamine usage for more than 10 years has resulted in a very high rate of vision-threatening pattern dystrophy-like changes in the macula (4).

In a recent study, it has been shown that there has been a decrease in choroidal thickness (CT) circulation due to chronic anemia in patients with TM, which is more prominent in patients using deferoxamine (5). A decrease in choroidal circulation may cause hypoperfusion of outer retinal layers, given that it provides the essential metabolic support of photoreceptor cells with high metabolic activity (6). Whether the use of deferoxamine along with chronic anemia causes changes in peripapillary CT and ganglion cell complex (GCC) thickness in patients with TM is not yet clearly known.

The present study aims to investigate whether the macular, peripapillary CT, and GCC changes in patients with TM and patients using deferoxamine as a subgroup.

Methods

Study Population and Design

This study was conducted at the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, Ophthalmology and Pediatrics Hematology-Oncology Departments between April 1, 2018, and May 1, 2018. Written informed consent was obtained from the legal guardians of all patients included in the study and the healthy control group. This study was conducted in accordance with the Helsinki protocol and with the approval of the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital ethics committee (KAEK/2018.3.4). Forty-four patients diagnosed with TM and 44 age- and gender-matched participants without systemic diseases were included in the study. One eye of each participant was included in the study. Patients with myopia and hyperopia more than 4 diopters, patients with axial length (AL) shorter than 21 mm and AL longer than 25 mm, and patients who had a history of intraocular surgery and amblyopia were excluded from the study. Participants with additional systemic diseases other than TM in the study group and those with systemic disease in the control group were not included in the study.

Examination Protocol and Study Measurements

A complete ophthalmologic examination, including visual acuity and fundus examination, was performed on all participants. Detailed anterior segment comparison of the same patient group was presented in detail in our previous study (7).

Auto-refractometer measurements were taken using KR-800 (Topcon, Tokyo, Japan), AL measurements were taken with Nidek AL-Scan (Nidek, Aichi, Japan) device.

The study and control groups' optic coherence tomography (OCT) evaluation was performed with a spectral domain featured Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Inc., Dublin, CA, USA) device. Scanning was performed in three different modes: Macular cube, optical disk cube, and HD 5-line raster scanning mode. All measurements taken from the eye with higher signal quality in macular cube scanning mode were included in the study.

Central macular thickness (CMT), macular volume, and GCC thickness were measured with 512 horizontal B-scan in an area of 6 × 6 mm and a 512 × 128 macular cube protocol, which has the ability to measure 128 A-scans in each section. CMT, macular volume, and GCC thickness were automatically calculated by the Cirrus HD-OKT 4000 device. The retinal nerve fiber layer (RNFL) thickness was calculated automatically by the device after the optic nerve head measurement was made.

CT was calculated with the HD 5-line raster scan mode. Choroidal imaging was performed with the 4096 A-scan feature using a 6 mm line. The Cirrus-OCT 4000 device creates a choroidal image by analyzing the image at the vitreoretinal interface with the zero delay technique. The technical details of the evaluation method have been clearly described in the previous studies (8,9). Using the software of the Cirrus HD-4000 device, the subfoveal, 1000 µm temporal of the fovea, 1000 µm nasal of the fovea, 1000 µm temporal of the optic disk head, and 1000 µm nasal of the optic disk were manually determined by the experienced physician (SEB). CT was calculated by manual measurement of the distance between the inner surface of the sclera and the hyperreflective band at the outer edge of the RPE (9).

The age, gender, and body mass index (BMI) of all participants were recorded. Hemoglobin, ferritin values of the study group at the last examination, current chelator therapy they are using were recorded. The total duration of deferoxamine, deferiprone, and deferasirox treatments that the patients received before the study was recorded. Patients with TM were divided into two groups according to whether they used deferoxamine or not.

Central macular thickness, macular volume, GCC thickness, RNFL thickness, subfoveal CT, CT at 1 mm temporal to the fovea, CT at 1 mm nasal to the fovea, CT at the 1 mm temporal to the optic nerve head, and CT at the 1 mm nasal to the optic nerve head were compared between the study and control groups, and among TM patients who received and did not receive deferoxamine treatment.

Statistical Analysis

SPSS 18.00 (SPSS for Windows, SPSS, Chicago, USA) program was used for statistical analysis. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to examine the normal distribution analysis of the parameters compared between both groups. Independent t-test was used for parameters with a normal distribution of data, and the Mann–Whitney U-test was used for parameters that were not normally distributed. Correlations between the mean level of CT and mean level of the other ocular and systemic factors were evaluated by Pearson's correlation.

Results

Demographic and clinical characteristics of the study and control groups are presented in Table 1. In both groups, 48% of the subjects were male.

Visual acuity was 20/20, according to Snellen, in all TM and control participants. In fundus examination, three patients with TM (6.81%) had changes in RPE, and it was found that this change did not reduce visual acuity.

Comparison of macular thickness, ganglion cell layer thickness, RNFL thickness, and CT between the TM and control groups are presented in Table 2. The subfoveal CT, CT at nasal to the fovea, and CT at temporal to the optic nerve head were thinner in the TM group.

In the TM group, the mean hemoglobin value was 8.4±1.0 mg/dl and the mean ferritin level was 1805±1565 ng/mL. At the time of this cross-sectional study, 41 patients were using deferasirox (two patients with deferoxamine combination) and three patients were using deferiprone (one patient with deferoxamine combination). The mean duration of treatment was 7.5±4.6 years in 28 patients treated with deferoxamine, 5.5±3.9 years in 11 patients treated with deferiprone, and 6.7±2.4 years in 42 patients treated with deferasirox. Twenty-eight TM patients who were recently taking deferiprone or deferasirox treatment started treatment with deferoxamine. The findings showed that a significant portion of the patients currently taking deferasirox treatment had used deferoxamine and deferiprone in the past.

Table 1. Demographic and clinical characteristics of the study and control groups

Parameters	Thalassemia major group (n=44)	Control group (n=44)	p[t]
Age (Y)	15.18±6.24	14.23±4.88	0.23
Spherical equivalent (D)	-0.42±0.96	-0.15±1.08	0.23
Axial length (mm)	23.21±0.77	23.20±0.72	0.98
Body mass index	18.83±3.29	21.14±5.76	0.10

Y: Year; D: Diopters; t: Independent t-test.

Table 2. Comparison of OCT parameters between the thalassemia major and control groups

Parameters	Thalassemia major group (n=44)	Control group (n=44)	p[t]
Macular thickness (μm)	235.79±19.22	237.84±22.86	0.663
Macular volume (mm^3)	9.89±0.41	9.99±0.47	0.303
Ganglion cell thickness (μm)	83.23±6.35	84.68±5.30	0.311
RNFL (μm)	96.43±11.01	97.88±7.12	0.474
Subfoveal CT (μm)	287.73±47.04	312.66±39.95	0.014
CT at 1 mm temporal to the fovea (μm)	299.55±51.42	317.53±51.21	0.128
CT at 1 mm nasal to the fovea (μm)	256.47±49.74	279.17±41.52	0.033
CT at 1 mm temporal to the optic nerve head (μm)	211.73±48.94	241.86±62.67	0.029
CT at 1 mm nasal to the optic nerve head (μm)	205.58±45.41	223.80±45.69	0.099

OCT: Optical coherence tomography, CT: Choroidal thickness, RNFL: Retina nerve fiber layer thickness, t: Independent t-test; bold P values represent statistically significant results.

The mean age of 28 patients who started treatment with deferoxamine was 18.2±5.0 years and the mean age of 16 patients who did not get deferoxamine treatment was 9.9±4.7 years (p=0.000). In addition, the mean AL and BMI of the patients who did not get deferoxamine treatment were significantly lower than the patients who underwent deferoxamine treatment (p=0.002 and p=0.007, respectively). Macular thickness, GCC thickness, and macular and peripapillary CT were similar between groups (Table 3).

Subfoveal CT was not correlated with hemoglobin value, ferritin levels, and the duration of deferoxamine treatment (p>0.05).

Discussion

The choroid contains abundant amounts of vascular and pigmentary structures that provide nutrients to the outer retina and aids in maintaining normal retinal function. The choroid is the thickest, often under the fovea. This finding is thought to be related to the high photoreceptor activity in the macular center. This area is not in the feeding area of the central retinal artery. Since the fovea receives all oxygen and nutrient support from the choroid and shows high metabolic activity, the choroid must be of sufficient thickness in the fovea (10).

Because the choroid is one of the most vascular tissues in the body, changes or diseases that may affect the normal hemodynamics of the body may affect CT (11). Exercise, cigarette-coffee use, age, BMI, gender, sympathetic system activity, menstrual cycle, and pregnancy are physiological processes that may affect choroid thickness, while heart failure, preeclampsia, diabetes, hypercholesterolemia, hypertension, iron deficiency anemia in children, obesity, obstructive sleep apnea syndrome, sildenafil use, carotid artery stenosis, and rheumatologic diseases are systemic diseases that may affect CT (6,11-21).

The main ocular factors that may affect CT are increased AL and age-related choroidal atrophy, causing a decrease in CT (22,23). Vogt-Koyanagi-Harada, central serous chorioretinopathy, and polypoidal choroidal vasculopathy are ocular diseases that may cause an increase in CT (24-26).

Studies on CT in patients with TM are quite limited in the literature (5,27-29). In patients with TM, the disease itself may cause retinal or choroidal changes, as well as long-term iron accumulation and chelator drugs used, which may cause retinal and choroidal changes. These three variable situations make it challenging to evaluate study results in patients with TM. Although the use of deferoxamine tends to decrease due to many systemic side effects, it is clinically important to better define the retinal and choroidal effects of deferoxamine before macular pigment changes, as deferoxamine continues to be used due to the high cost of other drugs (30).

In the first study investigating CT in patients with TM, subfoveal choroidal thinning was reported in patients with TM (5). Perifoveal, peripapillary, and GCC comparisons were not reported in that study. It has been reported that chelation therapy, which is inevitably used by patients with thalassemia, may cause a significant reduction in foveal thickness (5). Furthermore, it has been appointed that deferoxamine causes a greater reduction in subfoveal thickness than oral deferasirox. The fact that no difference was found in subfoveal, perifoveal, and peripapillary CT in the deferoxamine group in our study does not support the aforementioned study. In addition, CMT, GCC, and RNFL thickness did not differ in the deferoxamine group.

In a study conducted in a Greek population, TM and thalassemia intermediate patients were evaluated; it was re-

Table 3. Comparison of OCT parameters according to deferoxamine usage

Parameters	Patients who underwent deferoxamine treatment (n=28)	Patients who did not undergo deferoxamine treatment (n=16)	p
RNFL (μm)	95.7±11.00	98.08±11.33	0.540[t]
Macular thickness (μm)	235.92±17.61	235.50±23.31	0.950[t]
Macular volume (mm^3)	9.93±0.39	9.87±0.43	0.343[m]
GCC (μm)	83.20±6.24	83.40±6.96	0.974[t]
Subfoveal CT μm	294.76±48.05	272.50±42.74	0.178[t]
CT at 1 mm temporal to the fovea (μm)	305.34±48.36	287.00±57.69	0.174[m]
CT at 1 mm nasal to the fovea (μm)	261.38±54.48	245.83±37.35	0.378[t]
CT at 1 mm temporal to the ONH (μm)	219.33±51.02	193.50±40.07	0.313[t]
CT at 1 mm nasal to the ONH (μm)	206.83±39.27	202.60±60.04	0.401[m]

OCT: Optical coherence tomography, CT: Choroidal thickness, ONH: Optic nerve head, RNFL: Retina nerve fiber layer thickness, GCC: Ganglion cell complex; t: Independent t test; m: Mann–Whitney U-test.

ported that the submacular and peripapillary choroid were significantly thinned in beta-thalassemia patients and no significant change was found in CMT and RNFL thickness (28).

In a recent study conducted in Türkiye, while a significant decrease in subfoveal CT, GCC thickness, and RNFL thickness was reported in the patients with TM using deferasirox, any information about perifoveal and peripapillary changes were not reported (29). In that study, in correlation analysis made according to the dose of deferasirox used, while the negative and significant correlation was found between inferior GCC and drug dose, no significant correlation was found with superior GCC thickness, subfoveal CT, and RNFL thickness (29). In another study conducted in Türkiye, patients with deferiprone, subfoveal, and perifoveal CT were significantly lower in the TM (27). It was also reported that CMT, RNFL thickness, and GCC thickness did not differ significantly (27). The mentioned study stated that there was no correlation between CMT, CT, RNFL, GCC thickness with ferritin, and hemoglobin values. Similarly, we did not find significant correlation between subfoveal CT with hemoglobin values, ferritin levels, and the duration of chelation therapy.

In our study, subfoveal CT, perifoveal CT, and peripapillary CT were lower in TM patients, similar to the previous studies (5,27-29). While almost complete concordant results have been reported for CT in studies, the results of GCC thickness are controversial. The measurement of the GCC thickness by OCT has been used in several ocular and neurological conditions, particularly glaucoma. To the best of our knowledge, there are three studies in the literature with GCC analysis in TM patients, together with our study. While a significant decrease in GCC thickness was found in patients with deferasirox, no significant change was reported in the thickness of the GCC in patients using deferiprone (27,29). No significant change in the GCC thickness was found in our patient population, almost all of whom were using deferasirox at the time of the study measurements.

Due to the fact that higher age, AL, and BMI have been found in the deferoxamine group in our study, as it may affect CT, is a limitation of our research. Although almost all of the patients with TM in our study were currently using deferasirox, they had used other drugs, such as deferiprone and deferoxamine, in the past, caused heterogeneity in our patient group. Although deferoxamine is a drug with well-defined macular toxicity, as we presumed that the effects of deferoxamine are irreversible, performing subgroups according to usage history of deferoxamine may be controversial.

Conclusion

The results of our study support the decrease in subfoveal, perifoveal, and peripapillary CT in TM patients in accordance with all previous studies. The absence of any significant difference in CMT, RNFL, and GCC thickness is generally consistent with the previous studies. Our study suggests that the use of deferoxamine does not cause a further reduction in CT, but the small number of patients and the different factors that may affect CT between the groups warrant a cautious approach to this finding. Given that TM is generally seen more in certain geography in the world, the number of studies on the subject is very limited, all parameters are not evaluated in each study, measurements are made with different devices in the studies, and differences in drugs used in patient groups, make it difficult to come to a definitive conclusion on controversial issues. Further studies may guide the controversial findings.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Helsinki protocol and with the approval of the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital ethics committee (KAEK/2018.3.4).
Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.E.B., N.S.; Design – S.E.B., N.S.; Supervision – S.E.B., D.Y.E.; Materials – S.E.B., G.A.; Data collection and/or processing – S.E.B., G.A., M.E.; Analysis and/or interpretation – S.E.B., D.Y.E.; Literature search – S.E.B., G.A., N.S.; Writing – S.E.B., N.S.; Critical review – S.E.B., N.S.

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