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Original Article

Anterior segment parameters and tear functions in patients with thalassemia major

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Abstract

Aim: To determine whether the biomicroscopic, topographic and biomechanical properties of the anterior segment and the tear function have changed in Thalassemia Major (TM) patients.
Material and Methods: Eighty-eight eyes of patients with TM and 102 eyes of healthy controls paired with age, gender, and spherical equivalent were included in this cross- sectional case-control study. Biomicroscopic, topographic and biomechanical findings of anterior segment and Schirmer test measurements were compared between the two groups.
Results: The mean age was found to be 15.11±6.01years in TM group, and 13.83±4.92 years in the control group (p=0.17). In 34 (38.63%) patients with TM, minor peripheral lens opacities were detected. Visual acuity was 20/20 in all patients with lens opacity. The mean iridocorneal angle (ICA) was 44.67±5.86 and the topographic anterior chamber depth (ACD) was 3.65±0.28 mm in the TM patients. Mean ICA was 48.78 ± 6.51 and topographic ACD was 3.76±0.30 mm in the control group (p<0.001 and P=0.02 respectively). The mean Schirmer test result was 14.06±4.13 mm in patients with TM and 16.2±3.75 mm in the control group (p=0.001).
Conclusion: In contrast to previous literature, we did not found any vision decreasing complications in the TM group. Although peripheral lenticular opacities were detected in some of the patients with TM, none of the patients had an anterior segment finding that could reduce visual acuity. Intraocular lens calculation formulas and surgical technique may be affected due to decreased ICA and ACD values in patients with TM.

Keywords: Thalassemia major; anterior segment; cornea; topography.

INTRODUCTION

Thalassemia Major is a syndrome characterized by erythrocyte dysplasia and destruction due to a defect in beta globuline chain in erythrocytes. Hypochromic microcytic anemia, reticulocytosis and high serum ferritin levels are common hematological findings. The disease begins in the infantile period. It is aimed to meliorate anemia via blood transfusions and reduce iron accumulation in the body via chelation therapy (1-3). Iron accumulation is treated by subcutaneous deferoxamine (DFO), orally deferiprone and orally deferasirox treatments (4). The course of TM is determined by severity of hypochromic microcytic anemia due to disease, complications due to blood transfusions and side effects of chelation treatments (5). Long bone deformities and typical craniofacial changes may proceed despite the adequate transfusion therapy (6-8). The dominant malar hill, depression of the bridge of the nose, mongoloid eye structure and maxillary hypertrophy are the basic craniofacial changes (9).

Ocular development is closely related to growth of adjacent bony orbit. Therefore, it has been showed that abnormal development of orbital bone causes changes in ocular biometric and refractive parameters (9). Ocular findings in patients with TM are related with disease itself, excessive iron accumulation and the side effects of chelating agents (10). Numerous blood transfusions and high serum ferritin levels may trigger changes in tear film parameters and lens opacities (11,12).

In our study, we aimed to investigate whether the biomicroscopic, topographic and biomechanical

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parameters of the anterior segment were affected in patients with TM. Additionally, we planned to investigate the correlation between markers of lacrimal functions, serum ferritin levels and radiologic markers of cardiac and hepatic iron load.

MATERIAL and METHODS

Cross sectional study was conducted in the Ophthalmology Department and Pediatric Hematology Department of Saglık Bilimleri University Kanuni Sultan Suleyman Training and Research Hospital. Eighty-eight eyes of 44 patients with TM and 102 eyes of 51 participants without systemic disease were included in the study. Two groups had paired with age and sex. The study was conducted in accordance with the approval of the ethics committee of Saglık Bilimleri University Kanuni Sultan Suleyman Training and Research Hospital and Helsinki Declaration. Written informed consent was obtained from all patients, healthy controls and their legal guardians.

All participants underwent complete ophthalmologic examination including visual acuity and biomicroscopic examination. Refraction measurements were made with KR-800 (Topcon, Tokyo, Japan) autorefractometer device. Intraocular pressure (IOP) measurements were made with NT510 (Nidek, Aichi, JAPAN) non-contact tonometer device. Topographic measurements of anterior segment were performed by using Sirius (Costruzione Strumenti Ophthalmologist, Florence, Italy) topography device where placido-disc and Scheimpflug camera technologies were used together. Corneal hysteresis (CH), corneal resistance factor (CRF) and cornea correlated IOP (IOPcc) and Goldmann-correlated IOP (IOPg) were measured with Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, NY, USA) device. Axial length (AL) and anterior chamber depth (ACD) were measured with Nidek AL-Scan (Nidek, Aichi, Japan) device.

Tear film breakup time (TBUT) was recorded in seconds as the time of disintegration fluorescein paper staining of the eye by the tears. The time interval between the last complete blink and the appearance of the first tear film break-up was measured three times and recorded as second unit. The mean value of three separate measurements was used for statistical analysis. For Schirmer test, after a topical 0.05% Proparacaine hydrochloride (Alcaine, Alcon, Puurs, Belgium) drop instillation standardized Whatman filter Schirmer test paper was placed on the lateral 1/3 of the lower lid. Baseline secretion was measured in mm as the wet line measured 5 minute after test paper application.

Serum hemoglobin and ferritin levels, previously administered chelation treatment and duration and current chelation treatment patients with TM were recorded. Liver and heart T2 * and R2 * values, which are indicative of iron accumulation in the body, were recorded.

Cardiac and liver T2*, R2* values were determined with magnetic resonance imaging (MRI) device as described in previously reports (13). In previous studies it has been shown that cardiac and hepatic T2*-R2* values detected with MRI is an important indicator of cardiac and liver iron load (13-15). Cardiac and liver iron levels vary inversely with cardiac and liver T2* values. R2* value is calculated as shown in this equation (1000/T2*) (16).

Patients with history of intraocular surgery were not included in the control group.

Statistical analysis of the comparisons was done by using SPSS 18.00 (SPSS for Windows, SPSS, Chicago, USA) program. In both groups, parameters have normal distribution according to the Kolmogorov-Smirnov test were compared by independent t-test and the parameters that did not comply with normal distribution were compared with the Mann-Whitney U test. Categorical variables were compared with chi-square test.

RESULTS

The mean age was 15.18±6.24 years in the TM group and 14.23±4.88 years in the control group (p=0.23). Male gender ratio was 47.72% in TM group and 45.09% in control group (p=0.77). Body mass index was found to be 18.83±3.25 in the TM group and 21.10±5.30 in the control group (p=0.078). Spherical equivalent was -0.39 ±1.00 diopters (D) in the TM group patients and -0.18±1.07 D (p=0.055) in the control group.

The mean hemoglobin value was 8.41±0.97 mg / dl and the ferritin level was 1805.13±1565.69 ng/ mL in patients with TM. It has been detected that 2 patients were using deferiprone, 39 patients were using deferasirox, 2 patients were using deferasirox with DFO, and one patient was using deferiprone with deferasirox during last examination. Treatment had been started by subcutaneous DFO and later continued with deferiprone or deferasirox treatment in twenty-eight patients. The mean duration of DFO treatment was 7.48±4.62 years. Deferiprone treatment was applied in eleven patients during the follow-up; mean duration of treatment was 5.54±3.93 years. Deferasirox treatment had been applied in 42 patients with TM and mean duration of treatment was 6.72±2.37 years.

Cardiac T2 and R2 values were 29.11±10.42 and 68.26±153.37, respectively, liver T2 and R2 values were noted as 13.53±12.34 and 135.96±143.00 respectively in patients with TM.

Visual acuity was less than 20/20 only in two patients with TM. One of these patients had anisometropic amblyopia due to hypermetropia and one had strabismic amblyopia. Peripheral minor lenticular opacities were detected in 34 (38.63%) of the patients with TM. None of these lens opacities were large or central to reduce visual acuity (Fig 1). There was no significant difference in serum ferritin levels between the patients with lens opacity and patients without lens opacity (p=0.79).

According to Schirmer test, tear secretion was 14.06 ± 4.13 mm in patients with TM, and 16.21 ± 3.75 mm in control group. The mean tear breakup time (TBUT) was

noted as 10.05±1.93 seconds in patients with TM and 11.20±1.67 seconds in control group. The differences between the groups for both tests were significant (p=0.001). There was a significant (p<0.05) and positive correlation between Schirmer test and TBUT (r=0.504). Serum ferritin levels, cardiac T2 and Liver T2 values were not significantly correlated with Schirmer test (p=0.132, p=0.301, and p=0.437 respectively).

The mean AL was 23.17 ± 0.78 mm in the TM group and 23.29±0.9 mm in the control group (p=0.33). The comparisons of topographic and biometric anterior segment parameters between two groups were listed on table 1.

There were no significant differences between the two groups in terms of IOP, IOPcc, IOPg, CH, and CRF. The measurements were detailed in table 2.

Iridocorneal angle (ICA), topographic ACD and biometric ACD measurements were found to be significantly lower in TM patients (p = 0.00; p = 0.02; p = 0.003, respectively).

Table 1.Comparison of topographic and biometric anterior segment parameters between Thalassemia Major and Control group

	Thalassemia Major	Control group	p value*
CCT [1](μm)	560.23±42.51	559.14±36.06	0.85
K1 (D)	43.10±1.34	42.92±1.49	0.40
K2 (D)	43.78±1.39	43.92±1.47	0.73
Iris Diameter (mm)	12.22±0.37	12.28±0.41	0.28
Anterior Chamber Depth[1] (mm)	3.65±0.28	3.76±0.30	0.02
Anterior Chamber Volume (mm^3)	159.88±22.18	163.72±28.70	0.34
Iridocorneal Angle	44.67±5.86	48.78±6.51	0.00
CCT [2](μm)	551.43±41.15	551.18±28.71	0.96
Anterior Chamber Depth[2] (mm)	3.56±0.26	3.70±0.29	0.003

[1] Measurement taken with Sirius Topography Device; [2]Measurement taken with Nidek Al-Scan Biometry Device; μm=micrometer; D= Dioptre; CCT=Central Corneal Thickness; * 0.05 considered statistically significant

Table 2.Comparison of intraocular pressure and biomechanic parameters of cornea between Thalassemia Major and control group

	Thalassemia Major	control group	p value*
IOP	17.98±3.40	17.38±3.75	0.27
IOPcc	16.77±3.42	16.88±4.70	0.86
IOPg	17.54±3.71	17.74±4.51	0.75
CH	11.28±2.05	11.37±2.12	0.76
CRF	11.81±2.36	11.93±2.23	0.73

IOP=Intraocular pressure; IOPcc= corneal-compensated IOP; IOPg =Goldmann-correlated IOP; CH=corneal hysteresis; CRF=corneal resistance factor

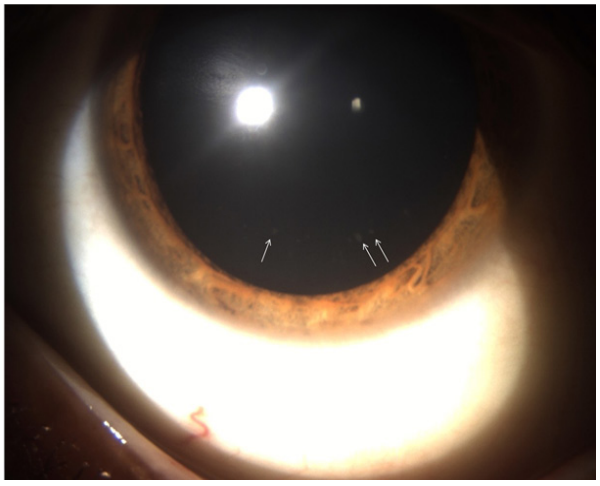

Figure 1. Peripheral small lenticular opacities (arrows)

DISCUSSION

TM is a hereditary disease that is commonly encountered in the Mediterranean region, which is increasing in prevalence with consanguineous marriages (2). Recurrent blood transfusions, the use of chelating agents and the differences in regional treatments affect the course of the disease (1). The frequency of ocular involvement in TM patients varies between studies.

The cytological analysis of the conjunctival epithelium revealed goblet cell loss and ocular surface disturbance caused by conjunctival squamous metaplasia (11). Environmental ultraviolet (UV) radiation causes perioxidative damage in epithelial cells. It is thought to be that patients with TM became more sensitive to UV rays related with the iron overload secondary to long-term blood transfusion (17). Furthermore, limbal and

scleral hyperpigmentation, deletion in iris pattern, venous dilatation and irregularity of the conjunctival veins have been reported in the literature (18). In animal experiments performed with iron loading, hemosiderin accumulation has been reported in extracellular area of choroidal connective tissue, ciliary body, iris, sclera and especially in connective tissue macrophages in the lacrimal gland (19). Gartaganis et al. (11) reported decreased scores in both Schirmer's test and TBUT whereas, Aksoy et al. (4) reported a decrease only in Schirmer test score. In our study, TBUT and Schirmer test scores had been significantly decreased in TM patients. However, the TBUT and Schirmer test scores did not correlate with the parameters that indicate serum ferritin level and heart-liver iron accumulation.

Ocular complications in TM patients are not only due to iron accumulation. Ocular disturbances are also reported due to the chelating agent used. DFO is the main chelator agent that has been used for many years to prevent iron accumulation. Decreased visual acuity due to retinal pathologies has been reported in the use of deferiprone whereas lens opacification has been more frequently reported in patients treated with DFO (20). Contrary to these findings, different studies have reported the development of choroidal neovascular membrane due to DFO and development of cataract due to deferiprone (21,22). Although there may be ocular complications mentioned above due to the chelator treatments, there is a better clinical course in terms of major organ involvement and morbidity in patients using chelators (20). In our study, we detected that patients who were under 11 years of age on last examination used never DFO in their life and patients who were above 11 years of age on last examination, was used deferasirox after DFO. The fact that, patients could not be randomized according to chelation type and duration, statistical analysis could not be done according to chelating agents. Although the average duration of DFO use was 7.48±4.62 years in our study, there was not any dense and large lens opacity to reduce visual acuity.

Studies showed that there was no difference in terms of spherical equivalent and refractive astigmatism in TM patients (9,23,24). In addition, astigmatism against the rule was more common in patients with TM whereas astigmatism compatible with the rule more common in control group (9,23). It is reported that in another study, there was no significant difference between the two groups in SE values despite the lower AL in the TM group. This condition could have been explained by the being of the vertical meridian is steeper in patients with TM (23). According to our study, there was no significant difference in terms ofspherical equivalent (SE) in patients with TM. The lack of comparison of the cylindrical values was the limitation of our study.

Lens opacities and lenticular astigmatism secondary to lens opacities have been advocated as one of the most important causes of decreased visual acuity in patients with TM (12,25,26). It has been reported that there was a significant correlation between lens opacities and serum iron, ferritin levels and the number of blood transfusions (12). It has been advocated that oxidative damage related with increased iron load may lead to lens opacification (25). Taneja et al. (12) reported higher ocular involvement (58%) than Aksoy et al. (4). Aksoy et al. (4) attributed the cause of this reported different rates, to difference in the mean ferritin levels of the patients included in the studies (2341.98ng / ml to 1430 ng / ml). In contrast to these report, there was no significant difference in serum ferritin levels between the group with lens opacification and the group without lens opacification in our study.

In studies reporting that AL is shorter than healthy individuals, it is argued that this decrease in AL may be the result of craniofacial bone structure change due to bone marrow enlargement (9,27,28). The affection of eye development due to the abnormal effect of craniofacial changes on the orbital bones in patients with TM may be the reason of ICA and ACD in TM patients were found to be lower in our study. For all that, there was not any change in AL in patients with TM in both our study and the other study conducted in the close region to our study (4). In the aforementioned study, there was no difference in terms of refractive state, IOP and central corneal thickness between TM patients and control group (4).

CONCLUSION

In contrast to previous literature, we did not found any vision decreasing complication in the TM group such as dense cataract. Although peripheral lenticular opacities were detected in a part of TM patients, none of the patients had an anterior segment finding that could reduce visual acuity. Considering that the mean age of TM patients was 15.18±6.24 years in our study, it can be thought that the ocular findings that may cause a decrease the visual acuity may be seen at a later age. Decrease of ICA and ACD may affect the intraocular lens calculation formulas and the surgical technique during cataract surgery. Therefore, the decrease of these values in TM patients may be clinically significant. Related with the low tear secretion in patients with TM, symptoms and signs of dry eye may increase in the following years. Thus it is recommended that patients should be followed for dry eye.

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