·Clinical Research·

Ocular findings in children with thalassemia major in Eastern Mediterranean

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Abstract

• AIM: To investigate ophthalmologic findings in children with thalassemia major (TM) and compare the findings with healthy controls.

• METHODS: In a cross-sectional study, 43 children with thalassemia major from pediatric hematology outpatient clinics from two university hospitals and age/sex matched 47 healthy children were included in the study. After a complete ophthalmic examination, tear function tests including the Schirmer test, fluorescein tear break-up time (BUT), ultrasound pachymetry, and axial length measurement were performed. Obtained data was recorded for statistical analysis and the values of right eyes were compared between groups.

• RESULTS: The mean best corrected visual acuity was 1.34±0.75 in TM and 1.08±0.28 in controls. It was found lower than 0.1 logMAR unit in 10 (23.2%) children with TM and 2 (4.2%) in controls, and the difference was statistically significant(P<0.05). The mean central corneal thickness was 540±26.95 in children with TM and 536.98±20.45μm in controls (P>0.05). The mean axial length was 22.53±0.50 in TM and 22.57±0.43mm in the control group. The mean Schirmer test score was 19.94±6.91 in TM and 24.22±3.95mm in the control group (P <0.01). The mean BUT score was 9.62 ±1.28 in TM and 9.73 ±0.6s in the control group (P >0.05).

• CONCLUSION: In TM, while corneal thickness, axial length, and BUT are close to controls, the Schirmer scores are less than normal. The study revealed that TM may be affected by the tear function and visual acuity.

• **KEYWORDS:** thalassemia major; ocular findings; tear function test; central corneal thickness; axial length

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INTRODUCTION

Thalassemia major (TM) is a genetic disorder that commonly manifests during early infancy and requires lifelong blood transfusion due to the deficiency of red blood cells. It leads to decreased hemoglobin production and hypochromic microcytic anemia associated with erythrocyte dysplasia and destruction. As chronic anemia adversely affects the growth and development of the children, iron accumulation in the tissues due to destruction of the red blood cells, excessive blood transfusion, and use of iron chelators create a negative impact on the organs functions[1-4]. Thalassemia major is a serious medical, social, and psychological problem. The course of illness depends on the availability of adequate blood transfusion and other therapeutic facilities. Their life expectancy is lower than in the normal population, but many patients in developed countries survive to the fifth decade of life. The association of TM and certain systemic diseases such as growth retardation, delayed development of sexual maturity, thyroid, parathyroid and sex hormone deficiencies, diabetes, and liver and heart function disorders have been reported. The cause of systemic disorders in children with TM is multifactorial and includes chronic anemia and hypoxia, iron overload, low somatomedin activity, endocrinopathies, low socioeconomic status, and racial factors[2-5].

One of the tissues affected by TM is eyes'. In studies on the ophthalmic findings, it has been reported that various changes in patients with thalassemia major were seen. It was determined that ocular surface disorder of these patients was characterized by goblet cell loss and conjunctival squamous metaplasia. Additionally, shorter axial length, thicker lens, steeper corneal curvature, more against-the-rule pattern astigmatism, toxic retinal pigmentary degeneration, and presumed optic neuropathy have been reported in the aforementioned studies[5-12].

We aimed to investigate any possible changes in the ophthalmic findings of children with thalassemia major compared to healthy children.

SUBJECTS AND METHODS

The study was performed on 43 patients who applied to Sutcu Imam University Hospital for ophthalmic examination by two regional thalessemia centers. Ethical approval for the study was obtained from the Research Committee of Sutcuimam University of Medical Faculty, and informed consent was obtained from the all participants and their parents. Declaration of Helsinki principles were followed.

Eighty-six eyes of 43 children with TM between two and 18 years of age were included in the present study. Thalassemia major was diagnosed with a) having a deep (Hb <6g/dL) microcytic anemia of patients at diagnosis; b) low levels of HbA and high HbF (>50%) in hemoglobin electrophoresis; and c) family history. However, genetic mutations for thalassemia major were not studied. As well as enrolling criterion was those who had been diagnosed with thalassemia for at least two years. Ninety-four eyes of 47 age and sex-matched healthy primary school children were recruited as a control group to compare the results. Children, who used of contact lenses, had previous ocular trauma, prior ocular surgery, or taking topical medications were excluded from the study.

All participants underwent a complete ophthalmologic examination which included best corrected visual acuity (VA) according to logMAR unit, slitlamp biomicroscopic examination, tear function tests including the Schirmer test, break-up time (BUT), ultrasound pachymetry, axial length measurement, and fundoscopy. Autorefractometer (Topcon R-50) was used for detecting refractive errors in the participants.

After proparacaine hydrochloride instillation, axial length was measured with contact (non-immersion) ultrasonic biometry (CineScan, Quantel Medical, MT, USA). Ultrasonic pachymetry measurements were performed by using Sirius topography (CSO, Firenze, Italy) in both groups.

The tear film BUT test was performed by instilling one drop of fluorescein solution into the conjunctival sac without using topical anesthetic. Tear film was observed with a cobalt blue filter under wide lighting. The interval between last blink and the appearance of corneal dry spot in the stained tear film was measured. This procedure was repeated three times and their average value was used. Less than 10s was considered abnormal.

The basal Schirmer test was performed after one drop topical anesthetic instillation (Alcain, Alcon-Couvreur, Puurs, Belgium). Standardized Whatmann filter paper was secured the lateral cantus away from the cornea and left in place for 5min. The amount of wetting was measured in millimeters. The less than 10mm measurements were considered as insufficient secretion.

Table 1 Distribution of the mean right eyes' values and laboratory results in groups

Parameters	Children with TM	Control group	*P*
VA[1] (logMAR)	1.34±0.75	1.08±0.28	<0.05
IOP[2] (mmHg)	14.51±1.92	14.41±1.49	>0.05
CCT[3] (μm)	540±26.95	536.98±20.45	>0.05
Axial length (mm)	22.53±0.50	22.57±0.43	>0.05
Schirmer test (mm)	19.94±6.91	24.22±3.95	<0.05
BUT[4] (s)	9.62±1,28	9.73±0.64	>0.05
Blood ferritine (ng/mL)	1430±923.36	17.37±2.23	<0.005
Hemoglobin (g/dL)	6.57±0.77	14.97±0.78	<0.005

Fisher's exact Chi-square test. [1]Best corrected visual acuity; [2]Intraocular pressure; [3]Central corneal thickness; [4]Flouresein break-up time.

The mean age at the onset of blood transfusion of children with TM was within the first few months. We obtained information from the personal file that they had received chelation therapy since two years of age.

The data of right eyes in participants were used for statistical analysis. SPSS (Statistical package for social sciences) for Windows 10.0 program was performed. The data of groups were compared by using Fisher's exact Chi-square test. Results were given in 95% confidence interval and P<0.05 were showed significance level.

RESULTS

Mean age was 9.31±3.89 years (range 2-17) in children with the TM and 8.05 ±2.19 years (range 4-11) in the control group. There was no statistically significant difference between the groups (P > 0.05).

The mean VA of the right eye was 1.34 ±0.75 in TM and 1.08±0.28 in controls. VA was found lower than 0.1 logMAR unit in 10 (23.2%) children with TM and 2 (4.2%) control subjects, and the difference was statistically significant (P< 0.05).

Lens opacity was observed in 4 (9.3%) children with TM. It was not completely closed optical axis, but VA was minimally affected. Hence cataract surgery was not recommended. However, lens opacity was not observed in the control group. There was a significant difference between the groups in terms of lens opacities. (P< 0.05). The fundus examination revealed the mottling of retina pigment epithelium (RPE) in 3 children and optic disc pallor in one child with TM. In the control group, fundus examination was normal. There was a statistically significant difference between groups in terms of the distribution of these findings (ρ < 0.05 Fisher exact Chi-square). The distribution of ophthalmic findings values are presented in Table 1.

DISCUSSION

Thalassemia major is a hereditary disease especially affects those living in the Mediterranean region, which has a high frequency of the consanguineous marriages [1,2]. The disease requires lifelong follow-up and treatment and creates a social and economic problem. The patient's environmental and

socioeconomic situation affects life span and the emergence of systemic symptoms [2]. Therefore, the symptoms may vary due to differences by regions. The course of the disease in patients with TM, repeated blood transfusions, and the use of chelating agents may affect the condition of systemic symptoms [3]. In a study reported from New Delhi, 33% of children with TM had decreased visual acuity while in another study visual acuity was not affected [5,12]. In another article, partially reversible visual disturbances have been reported associated with the use of desferrioxamine (DFO)[13]. In the present study, the average visual acuity of children with TM was reduced compared to control group, and children with decreased visual acuity was 23%. Our finding was lower than those studied in New Delhi, but higher than in others[5,12,13]. It may be related to receiving regular treatment or regional differences of disease or patients.

One of the most important factors for the reduced visual acuity in children with TM was lens opacity [5, 9,12,13]. The percentage of children with lens opacities was 9.3% in our study. In previous studies, this ratio was reported as 44%, 41%, and 11%[5,9,12]. In the above-mentioned studies, direct correlation was observed between the lens opacities and the decrease in visual acuity. In addition, the presence of retinal pathology is another important cause of reduced visual acuity in children with TM[5,8,9,]. In our study, 4 (9.3%) children with TM were identified retinal pathologies. Taher *et al*[7] identified RPE changes in 21 (25%) of 84 patients, while Dennerlein *et al* [9] in 6 (35%), Gartaganis *et al* [8] in 5 (17.2%). Sultanov *et al*[11] detected retinal angioid streak and Gartaganis *et al* [8] reported leopard skin appearance in 15% of patients.

In this study, refractive status, IOP, central corneal thickness (CCT), and axial length in children with TM were similar to control group. To the best our knowledge, children with TM, IOP, and CCT have not been documented before. In a study conducted in Iran, Nowroozzadeh *et al* [14] reported that the percentage of children with TM was higher in terms of against the rule astigmatism, typically corneal and lenticular astigmatism. However, in this study, there was not a statistically significant difference between children with TM and controls in terms of the axial length, whereas the aforementioned study in Iran reported a shorter axial length.

Ophthalmic changes due to TM in the literature are mainly on tear function and ocular surface changes. Gartaganis *et al*[8] revealed ocular surface disorder, goblet cell loss, and conjunctival squamous metaplasia in the conjunctival epithelial cytological evaluation. Sultanov *et al* [11] reported hyperpigmentation of the limbus and sclera, dystrophic and atrophic changes, and deletion of the iris pattern, and venous dilatation and irregularity of the caliber of conjunctival vessels. In our study, tear functions of children with TM were evaluated by a Schirmer test and BUT. Although the results of Schirmer test were lower than the control group, BUT scores were close between two groups. However, Gartaganis *et al* [8] reported that tear function tests both BUT and Schirmer scores were lower in children with TM than controls. In a study conducted on rats with iron overload, hemosiderin deposits were detected in macrophages mainly in the connective tissue of lacrimal glands [15]. This event may be the reason of primarily impaired Schirmer test is an indicator of the amount of tear production. In addition, smaller amount of accumulation was seen in the interstitial connective tissue of the choroid, in the ciliary body, in the iris and extracellularly in the sclera.

Eye complications of TM are not related to the iron accumulation in tissues alone. Eye involvement has also been reported to be due to the chelating agent used. In a study, lens opacity was mostly observed in patients using DFO as chelating agent while retinal pathologies and decreased visual acuity were predominantly found in those using deferiprone (DF) [10]. Contrary cataracts due to the use DF, and development of choroidal neovascularization on the use of DFO have been also reported [16,17]. However it has been reported in some other studies cataract and choroid neovascular membrane development could be seen with the use of DF and DFO, respectively [17]. The patients using chelating agent have had better clinical situation in terms of organ involvement and morbidity compared to those never used chelating agents although they had above mentioned complications [10]. In a pediatric population, it was reported that chelation with oral deferasirox was safe and effective[18]. In our study, 27 of the subjects had deferasirox while remaining used DF as chelating agent.

Our study confirms that different proportions of ophthalmologic symptoms can be seen children with TM. Through the long duration of the disease, taking regular treatment, the duration and type of using chelator agent, and hemoglobin and ferritin levels affect the ophthalmic symptoms.Taneja *et al* [5] reported that the ocular involvement was 58%, a rate that is higher than our study. We expected that the most significant reason for their observation is that their average ferritin level (2 341.98ng/ml) was higher than our study (1 430ng/ml). Moreover, a close relationship between ophthalmic symptoms and the use of chelation has been reported. Lakhanpal *et al* [19] found that there was no improvement in visual acuity and retinal pigment degenerations did not recovered in 7 patients of 16 although deferoxamine mesylate (Desferal) use was stopped. In a study investigating ocular side effects of the desferrioxamine, Roulez *et al* [20] have shown that this effect of the drug is reversible. Patients treated with deferoxamine, were determined completely heal of ocular damage [21]. Dennerlein

et al[9] mentioned that desferrioxamine caused ocular toxicity in a dose-dependent manner in patients with TM and discontinuation of treatment returned the findings to normal. In the study by Sorcinelli *et al*[12], the ocular findings in TM are the main consequence of abnormality in the iron metabolism. They postulated that the insufficient iron removed effect of desferrioxamine from ocular tissue.

In this study, patients used deferasirox (n =27) and deferiprone (n =16) as chelator agent. Since the mean age in our patient group was younger, the duration for chelator usage was shorter, the number of transfusions was smaller and hence iron (Fe) deposition in the tissues was less. Control examinations of our patients were performed regularly and the chelator agents used were different. Therefore, ferritin levels were less than the other studies. These factors may account for the fewer occurrences of ocular findings in our study.

The present study evaluated visual acuity and tear function tests and found that decreased the Schirmer test score. Cataract and retinal pathologies were considered the most significant reasons of reducing visual acuity. When we compared these rates with other studies, we found variations may be associated with regional differences, regular treatment and cheltaor agent. This study does not confirm previous reports of a significant difference in refractive status and axial length; measurements of IOP and CCT in children with TM were close to normal.

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