CASE SERIES

Ocular manifestations in patients with transfusion-dependent β-thalassemia

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Abstract

Background: Ocular involvement in patients with transfusion-dependent β-thalassemia is quite common, and its frequency differs among studies. This case series aimed to describe the ocular abnormalities occurring in β-thalassemia patients who need regular blood transfusions and receive iron chelation therapy.

Case Series: This is a case series prospectively studied 32 β-thalassemia patients from Northern Greece receiving regular blood transfusions and iron-chelating therapy. Patients' average age was 35.5 years. Eighteen patients with major phenotypes and fourteen patients with intermedia type underwent comprehensive ophthalmic examination at the time of enrolment, including visual acuity evaluation, refraction and color vision tests, Amsler grid test, slit-lamp, and dilated-pupil fundus examination. Additionally, we performed visual field testing and optical coherence tomography in all patients and fluorescein angiography only in selected cases. After six months, patients' complete ophthalmic examination was repeated for any new ocular findings due to the disease process and iron chelation therapy.

Ocular involvement was detected in 46.87 % of the patients. Lesions were most frequently seen in elderly patients with thalassemia major. Lens opacities were present in 21.8 %, and degeneration of the retinal pigment epithelium was described in 15.6 % of the patients, representing the commonest fundus alteration observed, followed by fundus atrophy. The most severe and vision-threatening condition described in this study was the presence of angioid streaks with choroidal neovascularisation. Six months follow-up of patients did not reveal any new ocular findings.

Conclusion: Early detection of severe ocular abnormalities is important in patients with thalassemia; thus, an ophthalmologic examination should be included at regular check-ups. An annual examination is currently indicated for asymptomatic patients, while in symptomatic and complicated cases, patients should be closely followed-up. HIPPOKRATIA 2021, 25 (2):79-82.

Keywords: Eye manifestations, beta-Thalassemia, transfusion, iron, chelation therapy

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Introduction

Thalassemia is a hereditary blood disorder characterized by a quantitative defect in hemoglobin synthesis. Clinical manifestations are highly variable, ranging from clinically asymptomatic individuals to severe anemia[1]. Beta thalassemia (β-thalassemia) is the commonest form of thalassemia characterized by defective β-chain production leading to ineffective erythropoiesis, reduced red blood cell survival, and subsequent anemia, which is the main feature of the disease[2]. The highest prevalence of β-thalassemia is in the Mediterranean countries, the Middle East, and Central Asia[1]. In Greece, the prevalence of heterozygous carriers is approximately 7.5 %[3] in the general population. β-thalassemia, depending on genetics and the severity of symptoms, is classified into thalassemia major (TM), which is the most severe form, thalassemia intermedia (TI), and thalassemia minor/trait. TI defines a heterogeneous group ranging in severity from mild symptoms to the severe transfusion-dependent type, with severe manifestations of TM[4]. Treatment of TM and severe TI comprises frequent red blood cells (RBC) transfusions, folic acid supplements, and iron chelation. In some cases, splenectomy may be required. Currently, the only definitive treatment available is bone marrow transplantation, while researchers are presently working on genetic therapy with very promising results[1,5].

Ocular involvement is quite common, and its frequency differs among studies, from 41.3 % reported by Jafari et al[6] to 85 % reported by Abdel-Malak et al[7]. Ocular findings could be both structural and functional, varying significantly in severity. Ocular disorders range from completely asymptomatic to severe conditions like optic neuropathy, angioid streaks with choroidal neovascularization (CNV) and Desferrioxamine (DFO) retinopathy. The most common ocular findings include cataract, visual acuity changes, thinning and tortuosity of retinal

vessels, pigmentary retinopathy, and visual field defects[8].

This case series aimed to identify the spectrum of ocular complications of β-thalassemia, both functional and structural, related to the disease and the chelation therapy. We also underline the importance of appropriate multimodal imaging techniques.

Case Series

A total of 32 patients (64 eyes) from Northern Greece, aged 25-61 years (mean age 35.5 years) with an established diagnosis of β-thalassemia, 14 with TI and 18 with TM, were prospectively enrolled in this study. Seventeen patients were female and fifteen male. All recruited patients received scheduled blood transfusions along with oral iron-chelating agents. We excluded from the study subjects with minor β-thalassemia, other hemoglobinopathies, and anemias due to other causes. We also excluded patients with decreased visual acuity or retinopathy due to any other cause. The study was performed following relevant guidelines and regulations, was approved by the Ethics Committee of the Aristotle University of Thessaloniki (No 3.478), and informed consent was obtained from all the patients who participated in the study.

All enrolled patients underwent a comprehensive ophthalmic examination, including visual acuity (VA) evaluation, refraction and color vision tests, Amsler grid test, slit-lamp and dilated-pupil fundus examination. Additionally, we performed visual field testing and optical coherence tomography in all patients and fluorescein angiography only in selected cases. Patients were followed up for six months, and patients' complete ophthalmic examination was repeated at the follow-up visit, and new ocular findings, if any, were also documented. Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA) software.

Ocular involvement was detected in 46.87 % of patients in our series. Lesions were most frequently seen in elderly patients with TM. Lens opacities were present in 21.8 %, and retinal pigment epithelium (RPE) degeneration was described in 15.6 % of patients, representing the most frequent fundus alteration observed, followed by fundus atrophy. The most severe and vision-threatening condition described in this study was the presence of angioid streaks with CNV. Other findings described were the yellowish color of the conjunctiva, epiretinal membrane (ERM) with or without vitreoretinal traction.

The mean VA of the right and left eye was 9.125/10 and 9.25/10, respectively. Two male patients presented with decreased ability to distinguish red and green colors. In both cases, family history was positive for daltonism. Three patients complained about distorted vision.

Slit-lamp examination of the anterior segment revealed yellowish coloration of the conjunctiva in three patients (9.37 %). Lens cortical opacities were observed in 14 (21.8 %) patients with TM. In eight cases, cataract was dense and in the visual axis, affecting visual acuity. Lens opacities were the most common finding in our series. The mean age of patients with relevant lens opacification was 53.5 years. More specifically, in our series, 26.6 % of males with a mean age of 52 years and 17.6 % of females with a mean age of 54 years presented with lens opacification affecting their vision.

Fundus examination revealed mottling of RPE in 15.6 % of patients, and this was the most common finding of the posterior pole examination in our series. In six eyes (9.37 %), significant fundus atrophy was described. Two male patients aged 56 and 58 years with TM had angioid streaks. Macular involvement was bilateral in one patient and unilateral in the other, with diffuse retinal edema and cystic regions. In five eyes (7.81 %), ERM was found, and in one of these patients Amsler grid test was positive as the ERM caused significant vitreoretinal traction (Table 1).

Visual field examination revealed no scotomas or alterations related to β-thalassemia. In eight cases (12.5 %), diffuse and homogeneous reduction of light sensitivity was described due to lens opacities. In all these cases, repetition of the examination was recommended after cataract surgery. In two cases, the results were not valid as there was a high percentage of false-positive responses. The examination was repeated three times without significant improvement of the tests' validity, and for this reason, these two cases were excluded from the study.

Table 1: Posterior segment ocular findings in this series of 32 patients (64 eyes) with beta-thalassemia thoroughly examined and followed up for six months.

		Number of eyes	
Fundus lesion	**%**	**TM**	**TI**
RPE changes	15.6 %	6	4
Fundus atrophy	9.3 %	4	2
Epiretinal membrane	7.8 %	3	2
Angioid streaks	4.6 %	3	-
Macular edema	3.1 %	2	-

TM: Thalassemia major, TI: Thalassemia intermedia, RPE: retinal pigment epithelium.

The mean value of the Central retinal Thickness (CRT) of the right and left eye was 221.87 and 224.87 μm, respectively. In five eyes of this series, there was a significant increase of the central foveal thickness associated with macular edema due to angioid streaks with CNV (three eyes, in two patients) and the presence of vitreoretinal traction (VRT) due to ERM (both eyes of a single case). Fluorescein angiography (FA) was performed only in two male patients with angioid streaks and clinical suspicion of CNV. In fact, in both cases, FA confirmed the presence of type 2/classic CNV.

A six-month follow-up of patients did not reveal any change in ocular findings. In cases with CNV anti-vascular endothelial growth factor (antiVEGF) treatment was scheduled.

Discussion

Ocular changes and complications could vary significantly among patients with β-thalassemia. There are various symptoms described; ocular manifestations range from completely asymptomatic to decreased visual acuity, visual field defects, color vision anomalies, cataract, nyctalopia, retinopathy, and optic neuropathy. Ocular involvement depends on the disease itself, the accumulation of iron in the ocular tissues, and the lack of minerals such as iron, copper, zinc, cobalt, and nickel, all essential for the proper retinal function and the chelation therapy[9]. The discrepancy among patients regarding life span and occurrence of systemic and ocular symptoms is highly correlated to socioeconomic and environmental factors[8]. Lesions were most frequently seen in elderly patients with TM because of the longer duration of the disease itself and the higher number of blood transfusions received. In our series, ocular involvement was found in 46.87 % of patients, and lesions were most frequently seen in patients with TM.

According to several studies, children with TM compared to controls, have significant growth retardation in general (smaller Body Mass Index) and ocular growth (shorter axial length and smaller vitreous chamber depth). However, a direct correlation between growth retardation and variations in ocular growth and biometric parameters has not been proven. Ocular growth changes presumably led to compensatory biometric adaptations, like thicker lenses and steeper corneas, to overcome the refractive disadvantage of shorter axial length, smaller vitreous chamber depth, and reach emmetropia. Thus, refractive status and visual acuity differences between healthy controls and TM patients are not consistent among studies, and no significant difference was recorded between the mean of spherical equivalent among the two groups[10].

Regarding color perception, in our series, two male patients presented with decreased ability to distinguish red and green colors. This is a hereditary condition, and in fact, in both cases, family history was positive for daltonism. Other researchers also concluded that there is no evident connection between thalassemia and any form of color blindness[6,11].

The ocular surface disorder is a common finding in β-thalassemia, and it may correlate to goblet cell loss and squamous metaplasia of the conjunctiva[6]. Age, trace elements, vitamin deficiencies, and iron overload could be involved in their pathogenesis[12], while Jethani et al absolve chelating therapy of causing ocular surface disorders[13].

Anterior segment abnormalities in thalassemic patients mainly consist of lens opacities. According to pertinent literature, lens opacities were found in 9.3-44 % of patients[8,14] and represented one of the critical factor for decreased visual acuity in these patients[14]. This is in accordance with the findings in our series, as lens opacities were affecting vision in 21.8 % of patients, and this was the most common finding. Lens opacities are highly correlated to the number of blood transfusions received and the elevated serum iron and ferritin levels[14]. Iron overload and the consequent oxidative damage of the lens, the disturbance of oxidant/antioxidant balance, and iron-chelating agents may also be causative factors for lens opacities in patients with β-thalassemia[7,14].

In patients with β-thalassemia, excessive damage of red blood cells may cause hemolytic anemia and consequent jaundice. Conjunctiva changes its color first of all tissues as bilirubin levels rise. Indeed, in our series, conjunctival icterus was present in three patients (9.37 %).

Fundus changes in patients with β-thalassemia are rather common, age-related, and could be correlated with iron overload, treatment with iron-chelating agents, and previous splenectomy. Lesions are similar to those of pseudoxanthoma elasticum (PXE), with an exception for the retinal vascular tortuosity[8], and most frequently include RPE degeneration, RPE mottling, "salt and pepper" appearance denoting degeneration of the macula, angioid streaks, pigmentation in the peripheral retina, retinal vessel tortuosity, vitreoretinal hemorrhages, retinal/macular edema, pseudo-papillitis, and macular scarring[15]. The most severe and sight-threatening complications include CNV and DFO retinopathy. In our series, 15.6 % of patients had lesions at the RPE level and two patients presented with angioid streaks that affect their visual acuity due to CNV formation.

PXE-like syndrome consists of peau d'orange in the periphery, the earliest retinal sign, angioid streaks, and optic disc drusen[15]. Patients with angioid streaks are usually asymptomatic, while visual disturbances may occur if the lesion extends towards the fovea, resulting in subretinal hemorrhages and the development of CNV that can cause severe loss of visual acuity[8]. Angioid streaks occurred in 12.9-20 % in different studies, and their presence increased with age, chelation therapy, and splenectomy[16]. Optic disc drusen is a frequent finding in patients with β-thalassemia that contain a high amount of calcium and might be caused by ectopic calcification[16].

In our series, the mean value of the CRT of the right and left eye was 221.87 and 224.87 μm, respectively. This result is consistent with the findings of other studies[17], which also concluded that there was no significant difference between thalassemic patients and healthy individuals regarding CRT.

Further and more extended research is needed as this series has few limitations due to the small size of the sample and the short period of patients' follow-up.

Conclusion

Ocular involvement in β-thalassemia is relatively common, and it could be correlated both to the primary condition and the treatment modalities required. Early identification of severe ocular abnormalities, such as angioid streaks with CNV and retinal hemorrhages, is pivotal for vision preservation. Thus, ophthalmic check-ups should be part of a regular follow-up of all thalassemic patients. Currently, an annual examination is indicated for asymptomatic patients, while in symptomatic and

complicated cases or high-risk patients, like those on high intravenous DFO dose, patients should be followed up closely[8].

Conflict of interest

Authors declare no conflicts of interest.

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The last two authors (Kozobolis V and Labiris G) share equal senior authorship.

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