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REVIEW ARTICLE

Ophthalmological Complications in Beta Thalassemia Major Patients: A Narrative Review

Mervat Atfy [1], Ashraf Bor'i [2], Marwa Elsayed[1], Diana Hanna[1]

Pediatric Hematology and Oncology unit, Pediatric Department, Faculty of Medicine, Zagazig University, Egypt[1]. Ophthalmology Department, Faculty of Medicine, Zagazig University, Egypt[2]

Corresponding author:
Marwa Elsayed

Email:
marwaelsayedelsharkawy@gmail.com

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Abstract

Background: A mutation in the β globin chain gene causes beta thalassemia major, an inherited blood condition. Patients with β-thalassemia are increasingly experiencing ocular problems, which negatively impact their health-related quality of life. Ocular abnormalities have been the subject of several research, most of which have concentrated on the posterior ocular segment; however, little is known about the anterior segment components. Ocular complications might develop due to numerous mechanisms, as microvascular disruption, longstanding anemia, iron accumulation, the toxicities of the iron chelators, as well as the abnormal growth of the orbit due to unusual craniofacial growth. **Aim:** This review aimed to highlight the acquired knowledge regarding ocular impairment in beta-thalassemia major patients. **Conclusion:** Complications such as retinopathy, crystalline lens opacification, color vision deficiency, nyctalopia, depressed visual field, reduced visual acuity, have all been reported in β-thalassemia patients undergoing chelation therapy. It is crucial to do routine ophthalmological assessment to early detect and prevent permanent damage.

Keywords: Ophthalmological Complication, Beta Thalassemia Major, Iron chelators.

INTRODUCTION

Globally, thalassemia is the most prevalent single gene disorder [1]. Mutations in the beta globin gene cause multi-system affection and inefficient erythropoiesis in β-thalassemia [2]. The gold standard for treating β-thalassemia is routine blood transfusion therapy [3]. Although life expectancy has increased dramatically due to advancements in iron chelating therapy, a number of negative side effects have emerged [4]. Thalassemia and its therapy approaches can cause a variety of visual problems. Multiple studies have demonstrated that various eye problems can arise from a range of underlying factors, such as

chelation therapy, iron overload, anemia, and expansion of the orbital bone marrow [5]. Patients with beta-thalassemia major who underwent chelation therapy encountered various eye-related issues including changes in electrophysiological test findings, Color vision impairment, retinopathy, crystalline lens opacification, nyctalopia, reduced visual field, diminished visual acuity, and diminished contrast sensitivity [6]. This review aimed to highlight the current knowledge and recent findings regarding the ophthalmological abnormalities of β-thalassemia major (β-TM) patients to aid in the prompt diagnosis and prudent treatment of such issues.

Anterior ocular segment changes:

Lens opacities make up the majority of anterior segment abnormalities. Many studies have reported lens opacities in β-TM patients with a prevalence of 9.3% up to 44% [7-12]. The published studies have conflicting results regarding the alterations in anterior chamber in

patients with β-TM. Furthermore, there is debate on the connection between the disease and the alterations in the anterior chamber caused by the use of iron chelators [13]. Lens opacities are considered a major risk factor for the reduced visual acuity in β-TM patients especially if they are located near the visual axis [7,8]. In β-TM patients, Taneja et al. found a strong association between high serum ferritin levels, serum iron levels, and the amount of blood transfusions and lens opacities [8]. Lens opacities in β-TM patients may be caused by oxidative damage to the lens caused by iron overload or oxidant/antioxidant imbalance [8,14]. It is important to note that the most recent cataract grading system is the Lens Opacities Classification System III (LOCS III), which divides cataracts into three categories: posterior sub-capsular, cortical, and nuclear [15]. Cataracts and their complications can be prevented by early screening and detection throughout the disease course [16].

Significant general and ocular growth retardation (lower BMI and shorter AXL) is observed in children with β-TM. Changes in ocular growth most likely led to compensatory biometric adjustments (thicker lenses and steeper corneas) in order to achieve emmetropization, which exacerbated the reaction and caused a myopic shift. However, alterations in biometric parameters, myopic shift, or ocular growth modifications are not directly linked to growth retardation [17]. Children with β-TM did not vary from controls in terms of biometrics or anterior segment morphology, but they did have a large occipitofrontal circumference and substantial growth retardation. The findings indicated a negative correlation between body mass index and pupil diameter in children with ferritin levels over 1000 ng/mL, and a positive correlation between occipitofrontal circumference and mean keratometry value in children with ferritin levels below 1000 ng/mL [18]. The biometric globe parameters, intra ocular pressure

(IOP), and anterior chamber angle (ACA) are all impacted by thalassemia. Those with thalassemia had higher IOP and narrower temporal angle of anterior chamber (T-ACA). Reports of shorter axial length (AL), vitreous chamber depth (VCD), and anterior chamber depth (ACD) were made. Furthermore, bigger lenses and steeper corneal curvature were discovered. Both the control group and the thalassemia patients had the same central corneal thickness (CCT) and relative lens location. [19]

Hanna et al. used the Pentacam HR (high-resolution) to measure corneal and lens densitometry in children and adolescents with transfusion-dependent β-thalassemia major. They found that patients with β-thalassemia major had significantly different corneal and lens densitometry parameters than controls. They came to the conclusion that these results might offer fresh hope for the subclinical diagnosis of corneal and lens anomalies in these patients using Pentacam as a quick, accurate, and non-invasive technique [20].

Posterior ocular segment and fundus abnormalities:

Several studies have reported retinal abnormalities in β-TM patients, fundus changes were found to be frequent, age-related, and similar to symptoms of pseudoxanthoma elasticum (PXE) condition in the eyes [5]. Patients with β-TM who have retinal abnormalities are divided into two categories: PXE-like syndrome and non-PXE-like syndrome. PXE-like syndrome describes vascular, dermal and ophthalmological changes that develop due to genetic disorder caused by a mutation in the ABCC6 gene on chromosome 16 or other disorders including beta-thalassemia [21]. Peau d'orange has been found to be the most occurring abnormality, then central pattern dystrophy-like changes and angioid streaks that don't go beyond peau d'orange [22]. Barteselli et al. [22] discovered that 70 out of 255 patients (27.5%) had at least one PXE-related retinal change, 19.6% had Peau d'orange, 12.9% had angioid streaks, 7.5% had changes resembling pattern dystrophy, and 2% had optic disc drusen.

On the other hand, the non-PXE-like changes have reported especially in elderly patients with TM and increased vascular tortuosity was linked to chronic anemia [23].

Numerous investigations involving individuals with B thalassemia have documented retinal hemorrhage, retinal edema, cup-to-disc ratio expansion, peripheral and central retinal thinning, venous tortuosity and engorgement, retinal pigment epithelium (RPE) degeneration and

mottling, and macular scarring[7]. Children with β-TM were found to have considerably thinner subfoveal, perifoveal, and peripapillary CT scans than the control group. There was no additional decrease in CT as a result of using deferoxamine. [24].

Most studies reported the influence of iron overload in the development of retinal alterations, however, there is a conflict regarding the relationship between iron chelator type and fundus alterations among β-TM patients. Researches' findings showed high discrepancy, some found that Deferoxamine (DFO) was a protective factor for RPE degeneration, while others reported that DFO acted as a major contributor to retinal complications, particularly if used in high dose and intravenous route administration [25-30].

Refractive error and ocular biometric components:

A change in the craniofacial anatomy may result in aberrant orbital growth since ocular growth is dependent on the expansion of the nearby bony orbit, which in turn may alter the biometric characteristics of the eye and, ultimately, ocular refraction [31].

Research has indicated that the growth hormone shortage in β-TM patients typically results in poor weight and height. In compared to the normal population, people with growth hormone insufficiency had larger crystalline lenses, steeper corneas, and shorter axial lengths, according to many studies [32].

According to Elkitkat et al., myopia was the most common refractive error among the β-TM group when compared to controls [17]. Conversely, Heydarian et al. could not discover any discernible variation in refractive errors between the two groups [33]. Merchant et al. revealed that 23% of the study group had errors of refraction; however, no significant correlation between these findings and several β-TM patient parameters was found [34].

Ocular surface disease:

Changes in tear function parameters (shortened BUT, increased Rose Bengal staining, and lower Schirmer test findings) have been associated with ocular surface illness, which is characterized by goblet cell loss and squamous metaplasia of the conjunctiva. Possible causes include deficiencies in trace elements and vitamins, peroxidative damage brought on by a vitamin E deficiency, or exposure to environmental ultra violet (UV) radiation. When epithelial cells are cultured, UV radiation causes intracellular peroxide to develop. Patients with thalassemia appear to be more susceptible to UV radiation-induced peroxidative tissue damage due to secondary iron overload brought on by ongoing blood transfusions. Vitamin E is considered one of the most effective antioxidants. The oxidant/antioxidant balance may also be impacted by beta-thalassemia patients' low vitamin E plasma levels, which may make the ocular surface [19].

Visual field defects:

Perimetry measures the central and peripheral (superior, inferior, nasal, and temporal) components of the visual field (VF) [35].

In individuals with β-thalassemia disorders, visual field defects are prevalent, between 33.7 and 74%. General depression is the most common type of visual field impairment among these patients [36].

Researchers have found a substantial correlation between the dose of chelating agents and visual field loss, leading them to hypothesize that chelating agent toxic effects may be the cause of visual field defect. Studies have demonstrated that individuals using chelators at doses more than 40–50 mg/kg/d had visual field defects as well as IV administration routes of DFO [26, 37].

Dry eye:

A variety of approaches have been used in studies on dry eye in people with β-thalassemia. According to studies that used the Tear Break-Up Time Test (TBUT) to analyze the quality of the tear film, the tear break-up time was less than 10 seconds in 13.3%, 33%, and 46.15% of β-thalassemic patients [12]. According to Gartaganis et al., in 20% of β-thalassemic patients, rose bengal staining was abnormal, and in 56.73% of patients, the wet area in the Schirmer strip was smaller than 10 mm within 5 minutes. Additionally, they used a cytobrush to do conjunctival cytology in order to identify the contributing causes to ocular surface problems. The results of their research included squamous

metaplasia and goblet cell loss, which are typical findings in dry eye patients. It follows that fewer goblet cells [38].

CONCLUSION

Patients with β-thalassemia major are susceptible to ocular problems as a result of orbital bone abnormalities, iron excess, persistent anemia, and iron chelating treatment.

Therefore, it is important for these individuals to have regular eye exams. If any of these difficulties arise, the patient should be sent to a hematologist for further considerations and chelation treatment adjustment to suppress or avoid future side effects.

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