

# Ophthalmologic Changes in Thalassemia Patients

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## Abstract

**Background:** Ocular abnormalities in patients with  $\beta$ -thalassemia major who are on frequent lifelong blood transfusion are under estimated in Iraqi community despite a lot of published articles with this regard.

**Aim:** to study ophthalmological changes among patients with  $\beta$ -thalassemia major and their correlation with clinical variables including age and gender of the patient, rate of blood transfusion, serum ferritin and disease duration.

**Patients and methods:** this study involved 68 patients 38 male and 30 female, their age between 12-43 years all were examined at thalassemia center of Al- Diwaniyah maternity and children teaching Hospital and Al-Diwaniyah teaching hospital, ophthalmology unit, assessment of medical conditions and classification of disease category by pediatrician and then finding a specific ophthalmological sings correlate with the disease severity, duration and type of chelating agents used in addition to patient's different criteria.

**Results:** Data collected showed that predominant findings were vascular torsouasity, Segment changes revealed that posterior segment changes in form of engorgement and pigmentation more frequently and earlier than anterior changes

**Conclusion:** most ophthalmological changes we found involve the epithelium in form of degeneration with a very mild or no ischemic changes as thalassemia consider a condition of well oxygenated status.

**Key words:** Thalassemia, ophthalmologic changes

## INTRODUCTION

"Thalassemia is an inherited autosomal recessive disorder of haemoglobin synthesis characterized by absence of equilibrium between the  $\alpha$ -globin and  $\beta$ -globin chain production leads to either a complete absence of  $\beta$ - globin chain production ( $\beta^0$  - thalassemia), or a partial reduction ( $\beta^+$  thalassemia). while in  $\alpha$ -thalassemia,  $\alpha$  globin gene production is either absent or partially reduced [1].

The diagnosis of  $\beta$ -thalassemia is usually delayed till the forth up to sixth month of life following replacement of fetal hemoglobin (HbF) by adult forms since HbF containing red blood corpuscles (RBC) are resistant to hemolysis and the diagnosis is suspected when usual clinical features such as fatigue, lethargy, and pallor are present [2].

$\beta$ -thalassemia major patients are in need for frequent lifelong blood transfusion every 2-5 weeks aiming at maintaining adequate hemoglobin levels "the pre-transfusion Hb-level above 9-10.5 gm/dl & post transfusion Hb should not be more than 14-15 gm/dl", getting natural development and growth and reducing the hyperplasia of erythroid tissue and deformities of skeleton [3]. To avoid febrile transfusion reactions associated with unnecessary iv administration of white blood cells (WBC) and plasma proteins, blood products which are Rh antigens phenotypically matched and leukoreduced are preferred [4].

Iron overload is attributable to two reasons, repeated blood transfusion is the first reason and enhanced iron absorption by gastro-intestinal tract is the second reason [5]. Following 20 to 30 blood transfusions " 500 mg iron/Kg" body stores for iron are going to be saturated and further iron will be deposited in a variety of tissues and organs with subsequent pathological events [6]. Iron deposition in eye can lead to several ocular abnormalities such as conjunctival blanching, isolated cataractous changes in the lens, Xerosis/Bitot's spot, Heterochromia and other abnormalities [7].

Patients complaining of  $\beta$  - thalassemia major with repeated blood transfusion are also in need for iron

chelation therapy such as "desferrioxamine (Desferal, DFO)" that is given either through iv infusion or sc infusion via a portable pump device at "a dose of 30-60 mg/kg/day over 8-12 hr., for 5-6 days/week". Hundred mg of desferrioxamine can approximately bind 8 mg of iron [8]. Adverse effects of desferrioxamine are usually irritation at injection sites and fever; some dangerous side effect include infection with "*Yersinia enterocolitica*" and severe mucormycosis [9]. Long term complications of prolonged desferrioxamineuse include ocular toxicity and ototoxicity [10]. Another iron chelating agent is "Deferasirox (Exjade, DFX)" that is given orally at "dose of 20 – 40 mg / kg once daily" before the morning meal. Adverse effects of Deferasirox are usually in form of gastrointestinal upset, increased hepatic enzymes and increased creatinine [11]. Anther orally iron chelating agent is Deferiprone which is also given orally at " dose of 75mg/kg divided into three sub doses, each given one hour before food". Adverse effects of deferiprone include arthropathy and agranulocytosis that make discontinuation of the treatment necessary [12]. Gastrointestinal upset, liver enzymes alteration and zinc deficiency are other adverse effects [12]. The Purpose of chelation therapy is to maintain level of body iron on safe side at all time (serum ferritin is 500-1000 microgram /liter, or linear iron concentration between 4 -7.5 mg/gm dry weight) [13].

Proliferative type retinopathy is limited to sickle cell disease whereas, thalassemia is mainly accompanied by non-proliferative pigmented retinopathy and this pigmentary alteration is thought to be the result of free iron liberation that is caused by as RBCs hemolysis or probably a side effect of chelating agents toxicity [14]. The surface of the eye is also liable for pathologic alterations caused by goblet cells loss as well as squamous metaplasia and the possible explanation is attributable to trace elements and vitamins deficiency. Oxidative damage related to lack of vitamin E or environmental UV radiation is blamed; thalassemic patients are more liable to UV harmful effect

via oxidative tissue damage due to secondary iron over load [14].

Eye involvement in  $\beta$ -thalassemia major involve anterior and posterior segment and it is attributed chiefly to the accumulation of iron in the tissues following RBCs lysis a state named "siderosis", any of ocular signs do not progress to cause significant ocular abnormality in most situation and this what we want to explain in on this ongoing study, as a disease  $\beta$ -thalassemia major don't reach to state of ischemia only rarely and it associated with high iron over load and then high level of oxygen saturation and as we know the eye in general and the retina specially is just like brain tissue can't withstand hypoxia for long period of time [14].

#### PATIENTS AND METHODS

A cross-sectional study design was adopted on 68 patients (38 males and 30 females) diagnosed with  $\beta$ -thalassemia major (homozygous thalassemia) on the basis of the blood investigations (peripheral blood counts and hemoglobin electrophoresis); their age ranged from 12 - 43 years. All patients were treated with various transfusion regimens depending on hemoglobin's level and chelating agent in daily doses adjusted according to serum ferritin level. The study was conducted in Thalassemia center of Diwanayah maternity and children teaching hospital and ophthalmological unit at Al-Diwanayah teaching hospital in Al- Diwanayah Governorate, Republic of Iraq. From September 2016 – September 2017.

#### The questionnaire and data collection

- 1 The information was taken from the patients or their families (mother, father) and the card visit. Data include: age, sex, address, age at diagnosis of thalassemia, age of starting blood transfusion, frequency of blood transfusion per year and chelating agent.
- 2 Measurements such as height was measured using an age appropriate stadiometer and weight was measured by weight scale.
- 3 Laboratory Investigation: Blood samples were obtained from all patients and sent for serum ferritin test inside Thalassemia center of Diwanayah maternity and children teaching hospital in Al- Diwanayah Governorate,
- 4 Ophthalmological examinations: visual acuity, intraocular pressure measurement, slit lamp examination of anterior segment and funduscopy done at ophthalmology unit, AL-Diwanayah teaching hospital, in addition to CT-scan examination of orbit and histopathological examination of tissue sample (conjunctiva) for three patients found incidentally to have conjunctival retention cyst and pterigium.

#### Serum ferritin measurement

Patients' serum Ferritin was measured by ELISA device (ACC U-BIND ELIZA MICROWELLS) depended on ng/mL.

#### Ophthalmological examination

Ophthalmological examination by slit lamp and funduscopy using 90 D Volk lens.

#### Statistical analysis

Statistical analysis was analyzed by using SPSS (statistical package for social sciences) version (21) computer software and Microsoft Excel 2016. A level less than 0.05 was considered as statistically significant.

## RESULTS

Data collected show that predominant findings were vascular tortuosity involving mainly retinal vasculature followed by smooth iris surface, as below classification of patients under different criteria as follow:

**Table 1:** Ophthalmological findings

Ophthalmological findings	n	%
Vascular tortuosity	47	35%
Retinal pigmentary changes	32	24%
Nasalization of optic vessels	4	3%
Iris smooth surface	50	37%
Limbal girdle of Vogt (in young patients)	3	2.2
Total	68(136 eyes)	

Segment changes reveal that posterior segment changes in form of engorgement and pigmentation more frequently and earlier than anterior changes, as follow

**Table 2:** Classification of findings according to predominant segment involved

Anatomical location	n	%
Anterior segment	53	39%
Posterior segment	83	61.02%
Both	93	68.4%
Total	136	

Thalassemic patients have increased osteoblast activity which don't lead to any pressure related problems like orbital apex syndrome or optic nerve stnosis as describe below:

**\*CTscan finding** ; orbital diameter 33 \*37\*30\*31,thickness of bony wall 12mm no signs of stenosis. And as we explained above frequent blood transfusion in thalassmea lead to increase blood volume which result in vascular engorgement especially in the retina, but degenerative changes assume to hit only the epithelium (cornea and conjunctiva) with changes resemble to those occur in aging and a condition of malnutrition, as below: Conjunctival biopsy reveal degenerative changes represented by epithelial thinning and decrease thickness of lamina propria

**Table 3:** Visual acuity results

Affected visual acuity	n	%	Causes
Positive	17	25	*Refractive error 12 Cataract 5
Negative	51	75	----
Total	68		17

\*Two patients had old trauma excluded from this table

Causes of impaired acuity mainly due to refractive error which varied from myopia to hypermetropia, myopic astigmatism and hypermetropic astigmatism; the degree ranges from 0.5 – 1.75 no direct correlation found between this refractive error and thalassemia.

## DISCUSSION

Thalassemia is a haemoglobinopathy that lead to formation of an abnormal heamoglobin which could under certain physical conditions aggregate in the blood vessels And form thrombus with their spectrum of consequences according to severity of thalassemia and the predisposing factors, here we discuss the ophthalmological findings that we diagnosed in studied group; most common signs was iris washed appearance that could be due to degenerative changes occurring in the epithelium and even affect crypts [14] to be well formed other common findings presented by vascular toruosity of the retina caused by accumulation of abnormal hemoglobin [1,4] but not to a state of closure or "ischemia " a matter we want to discuss here, our theory is : degenerative changes that affect regenerating tissues like epithelium and smooth muscles increase capacity of blood vessels to be more realistic and expanding in size in response to volume increment[15]. Among the studied group only two patients were had mild decrease in visual acuity while the other had normal acuity exam as we explained above the frequent blood transfusion with high heamoglobin level lead to high oxygen level which is very important for tissue metabolic activity especially in case of retina as process of dawn and dusk adaptation repeatedly occur throughout the day and consume such high level of oxygen .tow patients among studied group were found to have conjunctival pathologies one in the form of ptergium and the other inclusion cyst after we did surgical removal for both (excisional biopsy with 2 mm pathology free margin) and sent for histopathological examination the result was degenerative epithelial changes and thinning of lamina propria these findings explain how thalassemia associated with epithelial degeneration mostly because of decreasing blood level of vitamin E which is attributed to its increased consumption pursuant to the oxidative stress; chronic hepatic iron overload , while causing a substantial reduction of serum lipid can lead to concurrent reduction of serum vitamin E ,some studies have reported a serum zinc deficiency resulted from the release of Zn from hemolyzed red blood cells[3,16].

Underlying mechanism of endothelial dysfunction in B-thalassemia is thought to be due to NO(nitric oxide) bioavailability which lead to structural arterial alterations and consequently potential changes in mechanical properties this will associated with increase luminal diameter in response to increase intraluminal pressure as compared with sickle disease in which the sickling of red blood cells which adhere to both vascular endothelium and white blood cells also vascular endothelium is activated with up regulation of adhesion molecules[17,18].

## CONCLUSION:

Most ophthalmological changes we found involve the epithelium in form of degeneration with a very mild or no ischemic changes as thalassemia consider a condition of well oxygenated status.

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