Ocular Manifestations in Children with B Thalassemia Major and Visual Toxicity of Iron Chelating Agents

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Abstract: Objectives: This study was planned to determine the prevalence of ocular manifestations in multiple transfused β Thalassemia major patients and to determine the association of these manifestations with 2 types of iron chelating agents. **Materials and methods:** Cross sectional study included 80 β Thalassemia major patients, these patients were divided into 3 groups based on Thalassemia treatment regimens received at time of presentation. Full medical history, thorough physical examinations were done to all patients groups, and ophthalmological examination to determine the prevalence of ocular manifestations for all patient groups and to correlate these manifestations or changes with iron chelating agents. **Results:** In eighty patients (46males, 34 females) with age ranging between 6 to 16 years, ocular involvements were detected in 85% of cases in the form of lens opacity (10%) (more in patients receiving Desferrioxamine), decreased visual acuity(45%), retinal pigment epithelium (RPE) mottling (25%), disc hyperemia(12.5%) and increased cup/disc ratio (37.5%) and these involvements were observed to be more in younger age. **Conclusion:** Most of the ocular changes of beta Thalassemia are attributed to the course and severity of the disease. Reduction in serum iron and serum Ferritin levels by iron- chelating agents and regular ocular examination to look for side-effects of such agents can aid in preventing or delaying ocular complications.
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1. Introduction

Thalassemia is the most common single gene disorder worldwide (1). Mutations involving the beta globin gene in β Thalassemia cause disruption in red cell maturation leading to ineffective erythropoiesis and multi-system involvement (2).

Blood transfusions therapy on continuing bases represent the primary treatment for β Thalassemia (3). Although these treatments alleviates anemia, they lead to massive tissue deposition of iron and may eventually results in multi organ dysfunction. With advances in chelating iron the life expectancy has improved significantly but several side effects have emerged (4).

Adverse ocular changes resulting of the disease itself or as side effects of the iron chelating agents include: Cataract, pigmentary retinopathy, optic neuropathy, thinning and tortuosity of retinal vessels and vitroretinal hemorrhages (5).

Iron chelating agents such as Desferrioxamine and Deferriprone which are used to avoid systemic complications of siderosis may cause chelating of other metals such as Copper, Zinc,

Nickel and Cobalt which are essential for normal retinal function thus causing several ocular abnormalities (6).

This study was conducted to access the prevalence of ocular manifestations in β Thalassemic Egyptian children on regular blood transfusion and to access the ocular side effects of iron chelating agents.

2. Materials and Methods

This study was conducted in the Hematology clinic in Beni-Sueif University Hospital and the Pediatric outpatient clinic in National Institute of Laser Enhanced Sciences (NILES). Eighty children diagnosed as β Thalassemia major patients were enrolled in the study. All children enrolled have been receiving treatment in the form of packed red cell transfusion at a dose of 10 ml/kg b.wt./transfusion in order to maintain their hemoglobin concentration between 9 – 11 gm/dl and iron chelating agents were started if the serum Ferritin level was above 1000 ug/dl. An informed consent for participation was obtained.

Patients with Hemoglobin disorders other than β Thalassemia major were excluded, also patients with any congenital ocular abnormalities were excluded.

The patients were divided into 3 groups based on Thalassemia treatment regimens received at time of presentation. *Group A*: received blood transfusion but no iron chelating therapy. *Group B:* A combination regimen of blood transfusion and Desferrioxamine. *Group C:* combination regimen of blood transfusion and oral Deferriprone.

All the patients in this study were subjected to the following:

1- Full medical history including onset and duration of the disease, Frequency of blood transfusions, Splenectomy: whether it was done or not, Iron chelating agents: type, dose, duration and compliance and Family history: positive consanguinity and similar condition.
2-Thorough physical examination: The pediatrician investigators performed systemic examination, especially for presence of Pallor, Icterus, Hepatosplenomegaly, Frontal bossing, prominent maxilla, growth failure and Skin hyper pigmentation. The ophthalmological investigator, performed ocular examination. Ocular examination included: Near and distance visual acuity assessment with and without glasses using Snellen's charts, external examination with diffuse illumination, Slit-lamp examination, Direct and indirect ophthalmoscopy , Fundus fluorescein angiography (FFA) , Optical Coherence tomography (OCT), and Visual Field (VF)test were done for all patients.
3- Laboratory investigations:
Complete blood counts, Serum Ferritin, Iron level, Hb electrophoresis and Reticulocytosis.

3. Results

In this study, there were 46 male patients (57.5%) and 34 females (42.5%) as shown in table 1. Their age ranged from six to sixteen years, 40 patients of them were between (6-10 years) and 40 between (11-16years) with a mean age of 10.49±2.9years.

Patients were assigned in to three groups according to treatment regimens suggested as shown in table 1 into:

Group A: include 34 patients (42.5%), received only blood transfusion but no iron chelating agents.
Group B: includes 10 patients (12.5%), a combination regimen of blood transfusions and subcutaneous Desferrioxamine.in a dose 20 – 40 mg/kg/day SC 3 to 6 days every week.
Group C: include 36 patients (45%), received blood transfusions and Deferriprone.75 – 100 mg/kg/day

Also table (1) shows males preponderance observed over females in different patients groups

Ocular involvement was observed in 68 patients having Thalassemia (85%). whereas 12 patients (15%) showed no ocular abnormalities.

Ocular changes according to age within the patients are shown in table 2:

The table (2) shows that decreased visual acuity, RPE mottling, disc hyperemia and increased cup/disc ratio (C/D ratio) were observed to be more common in younger age, whereas RPE degeneration was observed to be more with increasing age. This may be related to late diagnosis of Retinal Pigment Epithelium (RPE) degeneration and neglected treatment of ocular problems.

Table (3) shows ocular involvement in different groups of Thalassemic patients 68/80 (85%) had ocular involvement. *P* value 0.001 is considered significant. Ocular involvement was in the form of:

1-36/80 (45%) decreased visual acuity in patients groups (*P*=0.001 is significant).
2-8/80 (10%) lens opacities in patients groups (*P* =0.004 is significant).
3-14/80 (17.5%) RPE degeneration in patients groups (*P* =0.006 is significant).
4-20/80 (25%) RPE mottling in patients groups (*P* =0.001 is significant).
5-34/80 (42.5%) venous tortuosity in patients groups (*P* =0.001 is significant).
6-10/80 (12.5%) disc hyperemia in patients groups (*P* =0.02 is significant).
7-30/80 (37.5%) increase cup/disc ratio in patients groups (*P* =0.003 is significant).

In table (4) of the 10 patients who received Desferrioxamine therapy, 4 (40%) had lenticular opacities. However only 4 (11.5%) patients who were not on Desferrioxamine had lenticular opacities as shown in table (5). Thus, lens opacities were significantly more in patients receiving Desferrioxamine ($p \leq 0.05$). Prolonged exposure to Desferrioxamine therapy was shown to lead to occurrence and density of lens opacities.

Of the 36 patients who received Deferriprone therapy, 2 (5.6%) had lenticular opacities, thus no significant correlation was found between lens opacities and Deferriprone therapy

In table (5) Regarding RPE degeneration, RPE mottling and retinal vessel tortuosity, all were found to be less in patients receiving Desferrioxamine therapy, and the opposite was found in those receiving Deferriprone therapy.

The decreased visual acuity in patients receiving Desferrioxamine therapy and Deferriprone were not statistically significant. Thus, the type of iron-chelating agents used had shown to be of no influence on decreased visual acuity.

Table (6) shows a significant correlation between serum ferritin and venous tortuosity (*P* =0.03), also significant relation between serum Ferritin and increased cup/disc ratio (*P* =0.02).

Table (7) shows a significant correlation between serum iron and venous tortuosity *(P=0.03)* also significant relation between serum iron and increased cup/disc ratio *(P=0.01)*.

The cup disc ratio for all patients is shown in table (8) where a cup disc ratio of 0.5 or more was reported as increased cup disc ratio.

For all patients with cup/disc ratio more than 0.5 a visual field and OCT were done. Visual field results showed that all patients had within average changes of the mean deviation with no significant visual field

pattern changes. For the OCT changes were within normal thickness of the retinal nerve fiber layer.

The visual acuity for the patients in the study was reported in table (9).

The decrease in visual acuity was reported as decrease of lines than the baseline measurement and reported in table (10).

Table (1): Group-wise baseline characteristics according to age and sex

	Group A (no iron chelating) (%)	Group B (Desferrioxamine) (%)	Group C (Deferriprone) (%)	Total (%)
Total subjects	34 (42.5)	10 (12.5)	36 (45)	80(100)
Age Group (years)				
6-10	24	2	14	40 (50)
11-16	10	8	22	40 (50)
Sex				
Males	20	6	20	46(57.5)
Females	14	4	16	34(42.5)

Table (2): Ocular changes according to age

Age (year)	6-10	11-16	*Total (%)*
Number of subjects (%)	40(50%)	40(50%)	*80(100%)*
Ocular Involvement (%)	34 (85%)	34 (85%)	*68 (85%)*
Decreased Visual acuity (%)	22 (55%)	14 (35%)	*36 (45%)*
Lens opacities (%)	4 (10%)	4 (10%)	*8 (10%)*
RPE* degeneration (%)	4 (10%)	10 (25%)	*14 (17.5%)*
RPE* mottling (%)	14 (35%)	6 (15%)	*20 (25%)*
Disc hyperemia (%)	6 (15%)	4 (10%)	*10 (12.5%)*
Increase cup/disc ratio (%)	16 (40%)	14 (35%)	*30(37.5%)*

*RPE: Retinal Pigment Epithelium

Table (3): Ocular involvement in different groups of β-Thalassemia patients

	Group A (no iron chelating)	*Group B (with Desferrioxamine)*	*Group C (with Deferriprone)*	*P value*
1-Ocular involvement				
Present	26	8	34	0.001
Absent	8	2	2	
2-Visual Acuity				
Normal	18	6	20	0.01
Decreased	16	4	16	
3-Lens opacities				
Present	2	4	2	0.04
Absent	32	6	34	
4-Fundus changes				
RPE* degeneration	4	0	10	0.006
RPE mottling	8	0	12	0.001
Venous tortuosity	14	4	16	0.001
Disc hyperemia	4	2	4	0.02
Increased cup/disc ratio	16	0	14	0.003

*RPE: Retinal Pigment Epithelium

Table (4): Lens opacity among the patient group

Groups	*Lens opacity*		*Total*
	No	Yes	
Group A	32	2	34
% within group	94.1%	5.9%	100%
Group B	6	4	10
% within group	60%	40%	100%
Group C	34	2	36
% within group	94.4%	5.6%	100%
Total	72	8	80
% within group	90%	10%	100%

P= 0.05 sig.

Table (5): Fundus and visual acuity changes in Desferrioxamine and Deferriprone groups

	Desferrioxamine therapy (Group B)	Deferriprone therapy (Group C)
Number of subjects	10	36
RPE* degeneration		
Present	0 (0%)	10 (27.8%)
Absent	10 (100%)	26 (72.2%)
RPE mottling		
Present	0 (0%)	12 (33.3%)
Absent	10 (100%)	24 (66.7%)
Retinal vessels tortuosity		
Present	4 (40%)	16 (44.4%)
Absent	6 (60%)	20 (55.6%)
Visual acuity		
Normal	6 (60%)	20 (55.6%)
Decreased	4 (40%)	16 (44.4%)

*Retinal pigment epithelium. % within group

Table (6): Relation of mean serum Ferritin and different ocular manifestation among different patient group

Ocular manifestations	*Number of subjects*	*Mean serum ferritin (ng/d) ±SD*	*P value*
Ocular involvement			
Yes	68	679.38±278.62	0.07
No	12	450.4±291.89	
Visual acuity			
Decreased	36	642.28±211.82	0.09
Normal	44	647.28±344.49	
Lens opacity			
Present	8	599.25±82.76	0.7
Absent	72	650.12±303.56	
RPE degeneration			
Present	14	796.63±495.47	0.1
Absent	66	612.87±222.71	
RPE mottling			
Present	20	705.7±235.65	0.4
Absent	60	624.81±305.48	
Venous tortuosity			
Present	34	757.4±303.44	0.03*
Absent	46	561.97±253.03	
Disc hyperemia			
Present	10	656.46±123.63	0.9
Absent	70	643.4±306.46	
Increased cup/disc ratio			
Present	30	772.03±345.29	0.02*

Absent	50	568.83±233.50	

*P value less than 0.05 is considered significant.

Table (7): Relation of mean serum iron level and ocular manifestations in different patient groups

Ocular manifestations	*Number of subjects*	*Mean serum iron (µg/dl)±SD*	*P value*
Ocular involvement			
Yes	68	341.97	0.1
No	12	254.17	
Visual acuity			
Decreased	36	332.72	0.8
Normal	44	325.59	
Lens opacity			
Present	8	351.50	0.7
Absent	72	326.28	
RPE degeneration			
Present	14	399.57	0.8
Absent	66	326.52	
RPE mottling			
Present	20	393.00	0.09
Absent	60	307.40	
Venous tortuosity			
Present	34	382.71	0.03*
Absent	46	288.98	
Disc hyperemia			
Present	10	328	0.9
Absent	70	328.91	
Increased cup/disc ratio			
Present	30	396.67	0.01*
absent	50	288.08	

*P value is considered significant at< 0.05.

Table (8): Cup disc ratio for all patients groups

	0.2	0.3	0.4	0.5	0.6	0.7	0.8	Grand Total
female	12	8	2	0	10	0	2	34
male	4	14	10	8	4	2	4	46
Grand Total	16	22	12	8	14	2	6	80

Table (9): Visual acuity examination for patients included in this study

	No
female	34
6/12	6
6/18	2
6/6	18
6/9	8
Male	46
6/12	6
6/18	2
6/6	12
6/9	26
Grand Total	80

Table (10): Number of line decreased of Best Corrected visual acuity (BCVA) than the baseline for patients included in this study.

	female	male	Grand Total
-2	4	2	6
6/12	2		2
6/18	2	2	4
-1	6	24	30
6/12		6	6
6/6	2	2	4
6/9	4	16	20
0	24	20	44
6/12	4		4
6/6	16	10	26
6/9	4	10	14
Grand Total	34	46	80

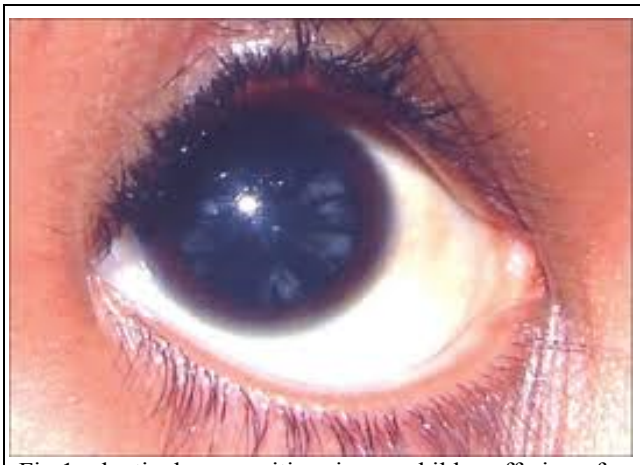

Fig.1: lenticular opacities in a child suffering from Thalassemia major.

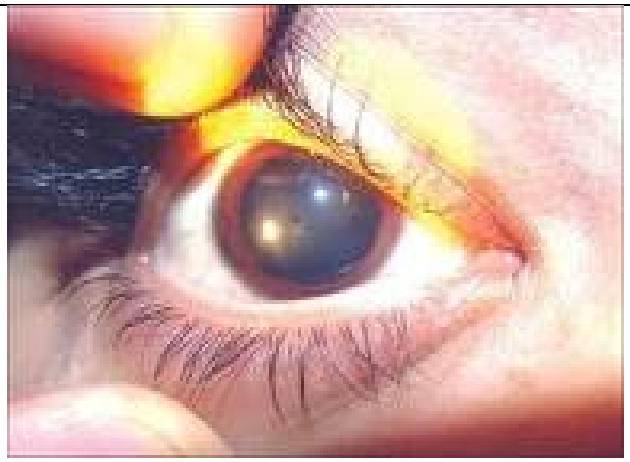

Fig. 2: Loss of iris pattern in a child suffering from Thalassemia major

4. Discussion

Patients suffering from Thalassemia present with varied ocular and systemic manifestations. Ocular findings range from decreased visual acuity, color vision anomalies and night blindness, to cataract, visual field defects and optic neuropathy. Iron-chelating agents like Desferrioxamine and Deferriprone are reported to cause many of these ocular changes. In our study, we studied the various ocular manifestations of β-Thalassemia and also the effects of various iron-chelating agents on the

eyes. The results of this study were based on data obtained from 80 Thalassemia cases, at the Pediatric Hematology clinic at the Beni-Sueif university hospital and NILES. Ocular examinations and investigations were done at the Ophthalmic Department at Beni-Sueif University Hospital and NILES. In our study, patients belonged to age group six to sixteen years. However similar studies in the western world had also been performed in patients of up to 45years of age. This age disparity can be attributed to lower survival rates among Thalassemic in Egypt; reasons for this seem to be poor compliance with therapy, difficulty in obtaining regular blood transfusions and high cost of iron chelation therapy. The literature provides no clue as to whether Thalassemia is more preponderant in a particular sex. In our study, a slight male preponderance (1.35:1) was observed over female. This is consistent with studies of **Gartaganis *et al.,* 2000** (7) and **Gaba *et al.,* 1998** (8) where ratios of 1.07:1 and 1.33:1, respectively, were observed. Frequency of ocular involvement in our study was 85%. **Gartagantis *et al.,*** *2000* reported figures of 41.3%, **Taneja *et al.,* 2010** reported figures of 58% while *Gaba et al*, *1998* reported ocular involvement in 71.4% of subjects in their respective studies. In study done by **Pooja Dewan** *and his colleagues,* **2011** it was found that 36% of patient group had ocular involvement. Eight out of 80 subjects (10%) in our study had lenticular opacities. **Gartaganis *et al.,* 2000 and Gaba *et al.,* 1998** in their studies, found lens opacities in 13.85% and 45.7% of subjects. In our study, Lens opacities were not correlated significantly with higher average serum iron levels and serum Ferritin levels but significantly more with the use of Desferrioxamine as an iron chelating (40%) as compared to patients not receiving iron chelation (5.9%), Whereas no significant correlation was found in our study between the occurrence of lens opacity and Deferriprone therapy. We didn't find any relation between cataract and raised serum Ferritin. This is in contrast with studies **Gartaganis *et al.,* 2000** whose study found no correlation between the occurrence of lens opacity and raised serum Ferritin.

Pooja Dewan and his colleagues, 2011 found that 20% of patients had cataract that associated with raised serum Ferritin levels. It is unlikely that DFO alone was responsible for the cataractous changes, so we need to ascertain the role of raised serum Ferritin and the toxic effects of the labile iron pool in causing ocular abnormalities. Patients with Thalassemia have been found have a higher labile iron pool, and it has been proposed that this mediates cellular damage. Iron causes oxidative damage to proteins, lipids and DNA through the generation of free radicals in the Fenton reaction, and it has been shown to disrupt the blood-retinal barrier. Iron is potentially related to several ocular diseases, including glaucoma, cataract, age related macular degeneration and intra-ocular hemorrhage. Raised serum Ferritin is surrogate marker of transfusion hemosiderosis, which may predispose Thalassemic patients to the toxic effects of iron. The specific role of iron in ocular injury in Thalassemia needs to be studied.

In our study unaided visual acuity was found normal in 44 (55%) patients while in **Gaba** *et al.,* **1998** study, the figure was 62.9%and **Taneja** *et al.,* **2010** study, this figure was 67%.

Recent studies conducted by **Taher** *et al.,* **2006** have found normal visual acuity in 80.6%of the subjects. In our study we found that decreased visual acuity was found in 36 patients (45%) of our study groups. 4/10 (40%) of patients receiving Desferrioxamine had decreased visual acuity and 16/36 (44.4%) of patients receiving Deferriprone had decreased visual acuity. 16/36 (47%) of patients not receiving iron chelation had decreased visual acuity(11). Thus, the type of iron chelation used show minimal statistical difference regarding decreased visual acuity. This observation is consistent with findings of **Taneja** *et al.,* **2010 and Taher** *et al.,* **2006** also found that the type of iron-chelating agent used had no influence on decrease in visual acuity.

Regarding the fundus changes of the thalassemia patients in our study, RPE degeneration was detected in (17.5%) of the patients (P=0.006). RPE mottling was detected in (25%) of the patients (P=0.001) and (12.5%) of the patients showed disc hypermia (P=0.02). (37.5%) of the patients showed increased cup/disc ratio (P=0.003). When comparing retinal changes among different group, we found that RPE degenerations in 27.8% of the patients receiving Deferriprone therapy.

RPE mottling was detected in (33.3%) of the patients receiving Deferriprone therapy. Whereas no changes in patients receiving Desferrioxamine therapy. This result was found to be consistent with **Taneja** *et al.,* **2010** study that postulated that their patients with RPE changes had received lesser doses of Desferrioxamine and larger doses of Deferriprone thus indicating that Desferrioxamine may be protective while Deferriprone use may be contributory to occurrence of RPE degeneration. Correlation of serum iron levels and serum Ferritin levels with RPE degeneration or RPE mottling were not statistically significant.

Chen H and his colleagues, 2009, did not find retinal pigmentary degeneration in any of their patients receiving Desferrioxamine.

Also these findings are consistent with those of **Taher *et al.,* 2006 w**ho found that patients on Deferriprone to be four times more likely to have RPE degenerations as compared to patients on Desferrioxamine.

Retinal venous tortuosity was observed in 34 patients of 80 (42.5%). This incidence is more when compared by the incidence reported by Gaba et a, 1998

(17.14%) and Taher *et al., 2006*, (17.9%) and Taneja *et al., 2010* (11%).

Retinal venous tortuosity was found in 4 out of 10 patients receiving Desferrioxamine therapy (40%), and 16 out of 36 patients on Deferriprone (44.4%) were with no significant difference regarding type of iron chelation. Correlation of serum Ferritin levels and serum iron levels with retinal venous tortuosity was statistically significant (P=0.03). This is in consistent with **Taneja** *et al.,* **2010** who found that tortuosity was more in patients with higher serum iron and serum Ferritin levels. **Gaba** *et al.,* **1998** have also reported similar observations.

Increased cup/ disc ratio was observed in 30 patients of 80 (37.5%) that was more in patients with higher serum iron and Ferritin levels. This is in consistent with **Taneja *et al.,*** *2010* who found 2 patients of 45 (4%) had increased cup disc ratio and its correlation with serum Ferritin and serum iron levels were statistically significant. We found a larger number of Thalassemic children to have ocular abnormalities despite only moderate doses of Desferrioxamine and Deferriprone and in the presences of high serum Ferritin levels, which implicate a role of iron in ocular pathology in Thalassemia. We recommend a larger study to evaluate the role of iron in ocular abnormalities in these patients. The reversibility of ocular changes should also be studied by changing the chelating agent or altering its dose.

A limitation of the present study is that it cannot conclusively establish whether ocular changes are a result of the disease or due to iron- chelating agents. This requires stoppage of chelation therapy. It may be kept in mind though that iron overload and iron chelating agents both may be mutually confounding factors in the causation of ocular changes of Thalassemia.

In conclusion, Most of the ocular changes of beta Thalassemia are attributed to the course and severity of the disease. Reduction in serum iron and serum Ferritin levels by iron- chelating agents and regular ocular examination to look for side-effects of such agents can aid in preventing or delaying ocular complications.

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