The cup/disc ratio, retinal nerve layer, and macular thickness in children with B-thalassemia major

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Purpose We aimed to measure cup/disc ratio (C/D), peripapillary retinal nerve fiber layer (P-RNFL) thickness, and central macular thickness (CMT) in children with thalassemia major and healthy children as a control group.

Patients and methods A total of 25 children with thalassemia major were selected from the pediatric outpatient clinics and were compared with 25 apparent healthy children serving as a control group. Complete eye examination was conducted, and intraocular pressure measurements were obtained; after that optical coherence tomography with the NIDEK RS-3000 retinal scan was performed to obtain C/D ratio, P-RNFL, and CMT.

Results CMT (total, superior, and inferior) and P-RNFL (total, superior, inferior, nasal, and temporal) were thinner in children with thalassemia, with *P* value = 0.000. C/D ratios (vertical and horizontal) were larger in children with thalassemia compared with their healthy controls (*P*=0.000). Negative correlations of the serum ferritin level with CMT (superior and inferior) and P-RNFL in all quadrants of the left eye. A positive correlation of the serum ferritin level with C/D (horizontal and vertical) of the left eye was found.

Conclusion Children with thalassemia major have thinner P-RNFL in all quadrants and CMT and large C/D ratio.

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Introduction

β-thalassemia is an autosomal recessive blood disorder caused by a defect in β-globin production, and regular blood transfusion is required in severe form of the disease [1].

Regular blood transfusion therapy helps to prolong patients? lives, but iron cannot be actively excreted. So, toxic accumulation of iron in various organs occurs. These organs include the spleen, liver, myocardium, endocrine organs, and potentially the eye. Fortunately, iron chelating agents can control this overload by binding iron and promoting its excretion. Different iron chelators are used, including desferrioxamine (delivered by subcutaneous or intravenous infusion) and two oral iron chelators, deferiprone and deferasirox [1].

The clinical picture of this disease includes intensive chronic anemia, growth retardation, hepato-splenomegaly, and bone disorders (mainly abnormalities of facial and head bones) [2].

β-thalassemia major affects the eye as many other organs; angioid streaks, peau d'orange, retinal venous tortuosity, the retina pigment epithelium (RPE) degeneration, RPE mottling, retinal edema, retinal hemorrhages, macular scarring, optic disc drusen, and pseudopapillitis are some of the ocular manifestations. β-thalassemia minor rarely causes ocular complications [3].

Aim of the study

The aim of this study was to detect optical coherence tomography (OCT) findings in children with thalassemia major including cup/disc ratio (C/D), peripapillary retinal nerve fiber layer (P-RNFL) thickness, and central macular thickness (CMT), and their correlation with the mean hemoglobin and serum ferritin level.

Patients and methods

Participants

A total of 50 children of both sexes were enrolled in this study and divided into two groups.

Study group included 25 children with β-thalassemia major (TM group) based on clinical and laboratory data, on regular blood transfusion, who were randomly selected from the outpatient pediatric clinic.
Control group included 25 apparently healthy children.

The study was carried out in Pediatric, Clinical Pathology, and Ophthalmology departments I Alzhraa University Hospital, Faculty of Medicine for Girls, Al Azhar University, Cairo, Egypt.

Design

Participants were evaluated during a hospital visit to determine family history, medical history, and full ocular and systemic history reporting. Each children height and weight were measured after overnight fasting. The body weight was measured using Seca scale closest to 0.1 kg in barefoot and light dress, after emptying the urinary and gastrointestinal apparatuses (Seca Model 770; Seca, Hamburg, Germany). *Z* score for weight/age and height/age was calculated [4]. The presence of other hemoglobinopathies, anemia owing to other causes, congenital ocular anomalies, media opacity, intraocular pressure more than 21 mmHg, high myopia, pre-existing ocular trauma, surgery or infections any retinal disease, and autoimmune diseases such as Behcet's disease or systemic lupus erythematosus or systemic disease such as diabetes or hypertension were excluded from the study.

Sampling

(1) Two milliliters was drawn and placed in a vacutainer tube containing EDTA for complete blood picture using automated cell counter model Sysmex KxN21.
(2) Three milliliters was drawn and placed in a plain tube and centrifuged within 30 min of collection, and the serum was separated for serum ferritin at the same day using enzyme-linked immunosorbent assay.

Examination techniques

All children were subjected to detailed ophthalmic examination, including evaluation of visual acuity, pupillary function, ocular motility, as well as anterior and posterior segment evaluations. Spectral domain OCT was done with the NIDEK RS-3000 retinal scan (NIDEK, Japan).

OCT was done for both CMT and P-RNFL. CMT was done by macular map analysis (6 mm×6 mm). It gave us the total, superior, and inferior CMT. RNFL thickness was done by disc map (6 mm×6 mm). It gave us the total, superior, inferior, nasal, and temporal RNFL. Disc map also gave us C/D either vertical or horizontal.

So, our OCT parameters were CMT, total CMT, superior CMT, inferior CMT, total RNFL, superior RNFL, inferior RNFL, nasal RNFL, temporal RNFL, C/D ratio vertical, and C/D ratio horizontal.

Ethical consideration

The study protocol was approved by local Ethics Committee, and all procedures were in accordance with the Helsinki Declaration. The research was fully explained to all the participants' families, and an informed consent was obtained from each participant families. *Z* score (or SD score) = (observed value−median value of the reference population)/SD value of reference population.

Statistical analysis

Data were collected, revised, coded, and entered into the statistical package for social science (IBM SPSS), version 20. Spearman's correlation coefficients were used to assess the relation between two studied parameters in the same group. Receiver operating characteristic curve was used to assess the best cutoff point with sensitivity and specificity.

Results

The mean age of children with thalassemia was 15.16 ±2.1 years. There were 14 female and 11 male. There is a significant decrease in their weight and height and hemoglobin level and an increase in serum ferritin in children with thalassemia in comparison with their healthy controls (Table 1).

In the present study, the age of onset of blood transfusion, duration of transfusion, and frequency of transfusion ranged from 6 to 11 months, 3 to 14 years, and one to four times/month, respectively.

The use of deferiprone was 60%, whereas the use of desferrioxamine was 40% of the chelation therapy in the patient group (Table 2).

Regarding the ocular finding, CMT (total, superior, and inferior) and P-RNFL (total, superior, inferior, nasal, and temporal) were thinner in patients with thalassemia in both eyes. C/D ratios (vertical and horizontal) were larger in the thalassemia group in comparison with their healthy controls (Table 3).

In our study, there were negative correlations of the serum ferritin level with CMT (superior and inferior) and P-RNFL in all quadrants of the left eye. A positive correlation of the serum ferritin level with C/D (horizontal and vertical) of the left eye was found. Moreover, there was a positive correlation of the hemoglobin level with CMT (superior and inferior) and P-RNFL in all quadrants of the left eye. A negative correlation of the hemoglobin level with C/D (horizontal and vertical) of the left eye was detected (Fig. 1 and Table 4).

Table 1 Demographic and laboratory data of the two studied groups

	Control group (*N*=25)	Patients group (*N*=25)	χ^2/t/*Z*	*P* value
Sex [*n* (%)]				
Females	13 (52.0)	14 (56.0)	0.081	0.777
Males	12 (48.0)	11 (44.0)		
Age (years)				
Mean±SD	14.6±1.98	15.16±2.1	0.972	0.336
Z score (weight/age)				
Median (IQR)	0.219 (–0.521–1.698)	–0.521 (–1.366–0.430)	–2.039	0.041
Z score (height/age)				
Median (IQR)	0.373 (–0.451–1.059)	–0.039 (–0.657–0.373)	–2.222	0.026
Ferritin level (ng/ml)				
Median (IQR)	24 (22–30)	700 (630–820)	–6.094	0.000
Hemoglobin				
Mean±SD	12.3±0.53	6.89±0.59	–34.123	0.000

χ^2, χ^2 test; IQR, interquartile range; *t*, independent *t* test; *Z*, Mann–Whitney test. *P* value more than 0.05, nonsignificant. *P* value less than 0.05, significant. *P* value less than 0.01, highly significant.

Table 2 Transfusion and chelation history of the patient group

Variables	Range	Mean±SD
Onset of transfusion (months)	6–11	8.24±1.22
Duration of blood transfusion (years)	11–17	
Frequency of blood transfusion (month)	1–4	1.8±0.72
Chelation therapy	*n* (%)	
Deferiprone	15 (60)	
Desferal (desferrioxamine)	10 (40)	

In the present work, there was a negative correlation between chelation therapy and nasal RNFL of the right eye, and also total CMT of both eyes was negatively correlated with chelation therapy (Table 5).

Figures 2–4 show examples for the OCT finding for a child with thalassemia major and other healthy control child.

The total CMT in the right eye (OD), the total CMT in the left eye (OS), the inferior CMT (OS) in the left eye, and the nasal RNFL in right eye (OD).

Discussion

The serum iron level increases in individuals with thalassemia major. The excessive free radicals caused by iron overload lead to elevated oxidative status. The damage of P-RNFL and other tissues may occur as a result of this oxidative stress in addition to anemic hypoxia [5].

Children with β-thalassemia major are liable to impairments in the retinal microvasculature. This is owing to acquired diffuse elastic tissue defect associated with thalassemia, which leads to vaso-occlusive impairments in the retinal microvasculature [6].

The chronic iron overload in patients with thalassemia major is treated with desferrioxamine mesylate, which is an iron chelating agent [7]. The ocular toxicity of desferrioxamine is well documented [8]. Simon *et al.* [9] reported that significant ocular toxicity occurred in using desferrioxamine and advised regular ophthalmic examination. Viola *et al.* [10] reported that progressive retinal and RPE pathologies occurred during long-term use of desferrioxamine, which resulted in visual loss.

In the current study, the prevalence of ocular involvement was higher than some previous studies. It was detected in 100% of the patients. Different percentages of ocular abnormalities were reported in previous studies, Jafari *et al.* [11] reported that 68.5% of their patients had ocular abnormalities, whereas Dewan *et al.* [12] reported changes in 36% of their patients, and the study by Gartaganis *et al.* [13] reported that 41.3% had ocular involvement. However, Taneja *et al.* [2] reported ocular involvement in 58% of patients, and Gaba *et al.* [14] reported ocular involvement in 71.4% of patients. The increased percentage in our study may result from giving blood transfusion at a lower hemoglobin level or may be owing to different age range of their participants.

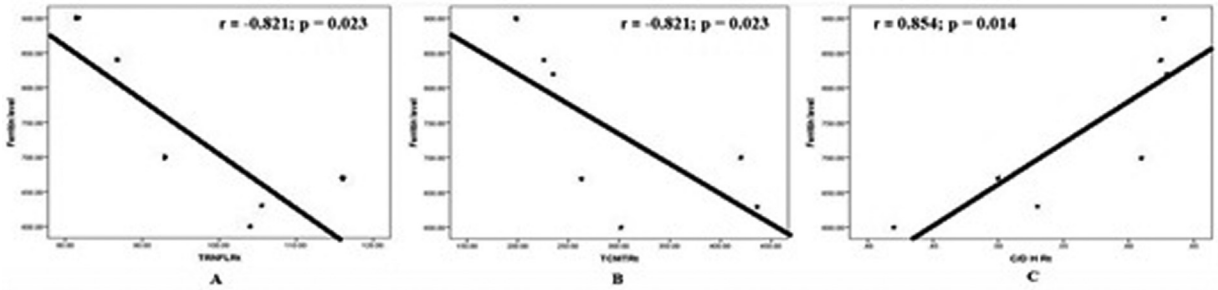
In the present study, there was a significant decrease in the best-corrected visual acuity in children with thalassemia compared with their healthy controls. These findings agree with Saif *et al.* [15], Taher *et al.* [16], Aksoy *et al.* [17], and Kumble *et al.* [18] who found a decrease in visual acuity in patients with

Table 3 Comparison between patient group and the controls regarding ocular finding of the right and left eyes

	Control group (*N*=50)	Patients group (*N*=50)	Independent *t* test		Control group (*N*=50)	Patients group (*N*=50)	Independent *t* test	
			t	*P* value			*t*	*P* value
	Right eye				Left eye			
VA	0.02±0.07	0.12±0.12	3.73	0.001	0.09±0.1	0.09±0.1	0	1.000
IOP	14.23±1.9	14.02±1.4	0	1.000	14.5±2.8	14.9±3.5	0	1.000
T-CMT (μm)	245.8±6.01	210.2±11.92	−13.332	0.000	244.56±7.42	207.68±7.44	−17.55	0.000
S-CMT (μm)	116.44±3.48	93.44±9.22	−11.666	0.000	118.44±4.05	95.76±8.28	−12.304	0.000
I-CMT (μm)	116.68±2.51	92.56±11.49	−10.254	0.000	117.68±4.13	92.08±12.96	−9.412	0.000
T-RNFL (μm)	139.88±2.45	99.88±8.25	−23.241	0.000	142.2±4.05	98.96±6.53	−28.137	0.000
S-RNFL (μm)	134.44±7.15	113.72±10.41	−8.202	0.000	136.48±4.9	115.52±9.17	−10.083	0.000
I-RNFL (μm)	153.6±9.65	124.28±9.66	−10.736	0.000	154±7.08	125.08±4.6	−17.132	0.000
N-RNFL (μm)	85.92±5.42	79.12±6.53	−4.006	0.000	87.64±5.08	74.96±6.46	−7.71	0.000
T-RNFL (μm)	80.48±3.79	61±6.09	−13.582	0.000	80.72±6.09	62.04±2.65	−14.054	0.000
C/D H	0.34±0.02	0.61±0.13	10.535	0.000	0.34±0.04	0.65±0.13	11.727	0.000
C/D V	0.29±0.03	0.52±0.14	7.878	0.000	0.29±0.04	0.57±0.09	14.893	0.000

CMT, central macular thickness; C/D H, cup/disc ratio horizontal; C/D V, cup/disc ratio vertical; I-CMT, inferior central macular thickness; I-RNFL, inferior retinal nerve fiber layer; IOP, intraocular pressure; N-RNFL, nasal retinal nerve fiber layer; RNFL, retinal nerve fiber layer; S-CMT, superior central macular thickness; S-RNFL, superior retinal nerve fiber layer; T-CMT, total central macular thickness; T-RNFL, total retinal nerve fiber layer; VA, visual acuity.

Figure 1



(a) Negative correlation between serum ferritin level and total retinal nerve fiber layer of right eye. (b) Negative correlation between serum ferritin level and total central macular thickness of right eye. (c) Positive correlation between serum ferritin level and cup/disc ratio horizontal of the right eye.

thalassemia. This decrease in best-corrected visual acuity may be owing to the retinal changes resulting from hypoxia, high serum ferritin, or chelating agents.

The OCT has a high level of sensitivity in measuring P-RNFL, CMT, and C/D ratio (vertical and horizontal). This provides important clinical information for diagnosis of variant retinal and optic nerve affections [18].

In the present study, we demonstrated that the average P-RNFL of the thalassemia major group was thinner in all quadrants versus the control. This agrees with Aksoy *et al.* [17], who found thinner P-RNFL in thalassemia major in all quadrants, but in iron-deficiency anemia, only the inferior quadrant was thinned. Thinning of the P-RNLF correlated with ferritin level and hemoglobin value but not with visual acuity and number of blood transfusions.

Turkyilmaz *et al.* [19] used OCT in measuring P-RNFL in children with iron-deficiency anemia. The average RNFL and the superior and inferior quadrant RNFLs were found to be significantly thinner in the iron-deficiency anemia group than in the control group. They supposed that RNFL thinning might be a result of deficiency of iron element or anemic hypoxia or both.

Table 4 Correlation between serum ferritin, hemoglobin level, and the ocular finding of the right and left eyes in the patients group

	Right eye				Left eye			
	Ferritin level		Hb		Ferritin level		Hb	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
VA	–0.460*	0.021	–0.585**	0.002	0.316	0.124	0.553**	0.004
T-CMT	–0.821*	0.023	0.857*	0.014	–0.893**	0.007	0.857*	0.014
S-CMT	–0.929**	0.003	0.955**	0.001	–0.841*	0.018	0.473*	0.017
I-CMT	–0.811*	0.027	0.802*	0.03	–0.857*	0.014	0.821*	0.023
T-RNFL	–0.821*	0.023	0.659**	0	–0.857*	0.014	0.581**	0.002
S-RNFL	–0.929**	0.001	0.752**	0	–0.929**	0.003	0.470*	0.018
I-RNFL	–0.768*	0.036	0.550**	0.004	–0.786*	0.036	0.814**	0
N-RNFL	–0.879**	0.009	0.414*	0.04	–0.458*	0.021	0.857*	0.014
T-RNFL	–0.893**	0.007	0.461*	0.02	–0.955**	0.001	0.991**	0
C/D H	0.854*	0.014	–0.870*	0.011	0.821*	0.023	–0.786*	0.036
C/D V	0.786*	0.036	–0.823*	0.023	0.920**	0.003	–0.839*	0.018

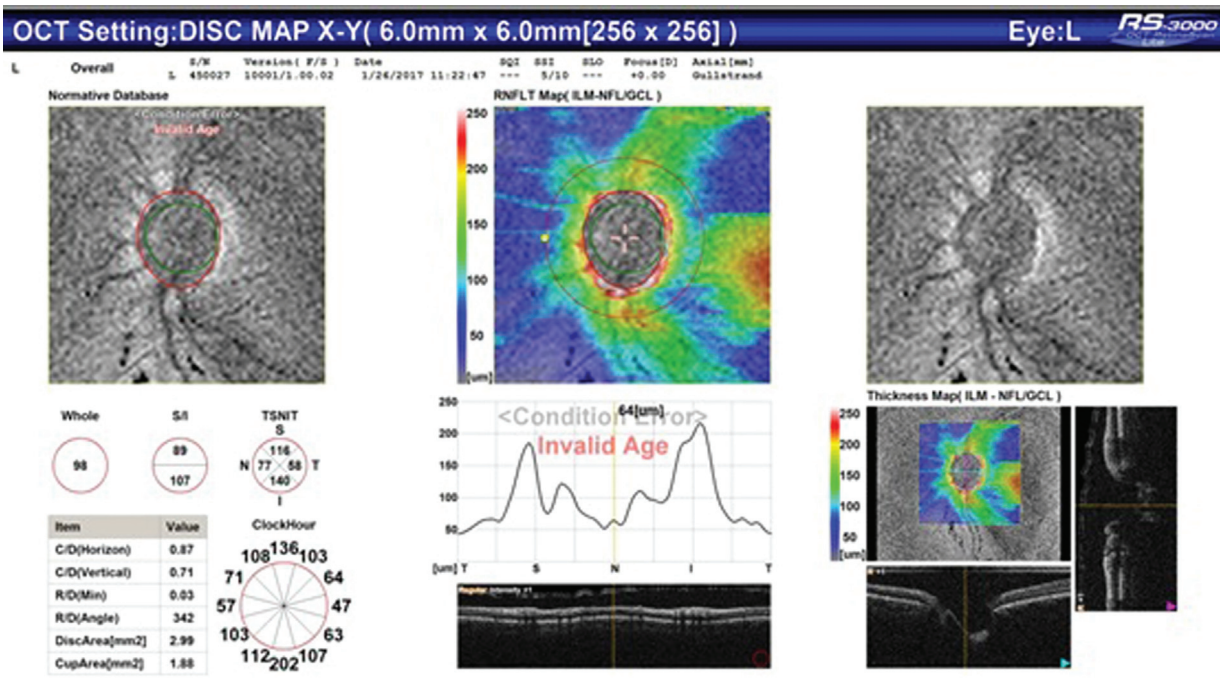
C/D H, cup/disc ratio horizontal; C/D V, cup/disc ratio vertical; I-CMT, inferior central macular thickness; I-RNFL, inferior retinal nerve fiber layer; N-RNFL, nasal retinal nerve fiber layer; S-CMT, superior central macular thickness; S-RNFL, superior retinal nerve fiber layer; T-CMT, total central macular thickness; T-RNFL, the total retinal nerve fiber layer; VA, visual acuity. *significant **highly significant.

Table 5 Correlations between chelation therapy and the ocular finding in the patient group

	Deferiprone (mean±SD)	Desferal (mean±SD)	Independent *t* test	
			t	*P* value
T-CMT (OD)	206.07±11.77	216.40±9.61	–2.306	0.030
T-CMT (OS)	205.20±7.38	211.40±6.10	–2.199	0.038
I-CMT (OS)	96.60±10.75	85.30±13.52	2.324	0.029
N-RNFL (OD)	76.40±5.18	83.20±6.41	–2.926	0.008

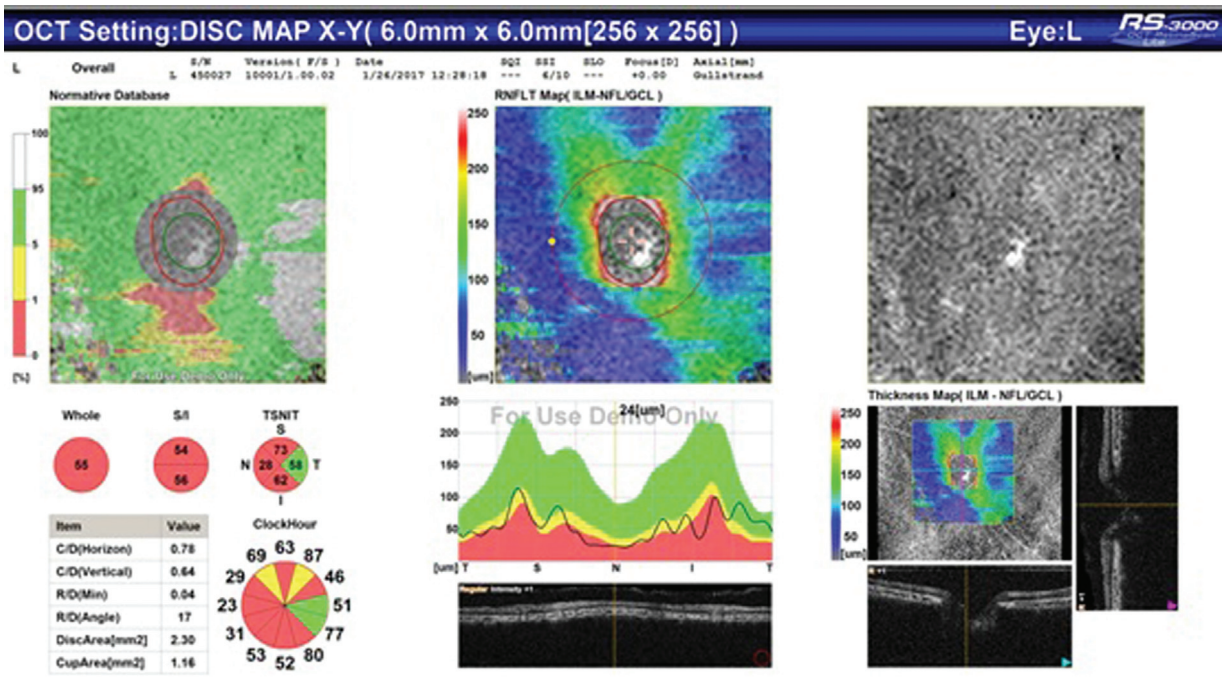
CMT, central macular thickness; I-CMT, inferior central macular thickness; N-RNFL, nasal retinal nerve fiber layer; T-CMT, total central macular thickness.

Figure 2



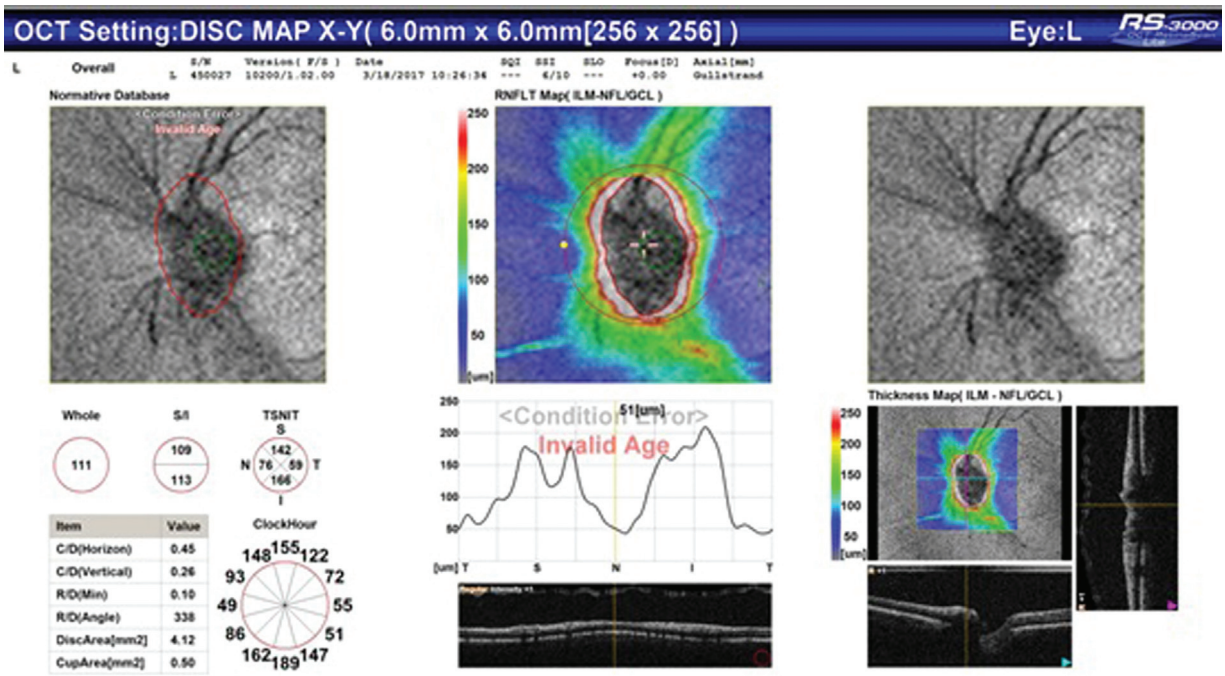
A patient with thalassemia with total RNFL 98 μm, C/D vertical 0.7, and C/D horizontal 0.8. C/D, cup/disc ratio; RNFL, retinal nerve fiber layer.

Figure 3



A patient with thalassemia with total RNFL 55 μm, C/D vertical 0.5, and C/D horizontal 0.7. C/D, cup/disc ratio; RNFL, retinal nerve fiber layer.

Figure 4



A normal healthy child with total RNFL 111 μm, C/D vertical 0.2, and C/D horizontal 0.4. C/D, cup/disc ratio; RNFL, retinal nerve fiber layer.

In our study, there was a negative correlation between RNFL thickness and serum ferritin and a positive correlation with hemoglobin level. This agrees with Aksoy *et al.* [20], who found that RNFL thickness was highly correlated with hemoglobin and the average RNFL thickness was highly negatively correlated with mean ferritin level.

In the present study, CMT (total, superior, and inferior) was thinner in patients with thalassemia, in contrast to their healthy control with negative correlations between CMT (superior and inferior) and serum ferritin level.

This comes in agreement with El-Shazly *et al.* [21] who observed that patients with β-thalassemia major treated

with chelating agents (e.g. desferoxamine and deferasirox) had lower foveal thicknesses. They suggested that a significant foveal thickness decrease could be owing to chelation therapy, although they did not examine the retina and choroid before chelation therapy, meaning that no data are available regarding the treatment-native patients with thalassemia.Moreover, Arifoglu *et al.* [22] found there is a decrease in superior and inferior macular thickness in patients with thalassemia minor but normal foveal thickness. This different result in central thickness may be owing to the difference in the type of thalassemia (our patients have thalassemia major, whereas the patients of Saif *et al.* [14] had thalassemia minor.

C/D ratio (vertical or horizontal) has not been measured before by OCT in any study, but Saif *et al.* [15] examined C/D ratio clinically, and they found larger C/D ratio in patients with thalassemia. Moreover, a large C/D ratio was also reported by Saif *et al.* [23] in patients with anemia.

In our study, the larger C/D ratio was significantly correlated with serum ferritin and hemoglobin level. This agrees with Saif *et al.* [15] and Taneja *et al.* [2] who showed a positive correlation between the larger C/D ratio and serum ferritin levels.

Taneja *et al.* [2] have also described the relationship between ophthalmic findings in patients with thalassemia major and serum ferritin levels. They showed that ocular changes increased with the increase of serum iron, serum ferritin levels, and the number of blood transfusions received. Moreover, RPE degeneration correlated positively with the use of deferiprone and desferrioxamine.

The present study has some limitations. One of them was the small number of children with thalassemia. The second one was the inability to establish the definite cause of these changes, whether they were related to hypoxia, iron overload, or iron chelation therapy.

In conclusion, the patient with thalassemia major should be regularly followed up. The hemoglobin level should be kept high, the serum ferritin should be kept low, and iron chelating agent should be given cautiously.

Recommendations

A study on a larger scale involving children with thalassemia should be conducted.

Experimental studies should be done to know the exact cause of these changes

There should be frequent assessment of eye in children with thalassemia for detection of early retinal changes.

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Conflicts of interest

There are no conflicts of interest.

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