sciendo

10.2478/AMB-2024-0048

ORIGINAL ARTICLE

OCULAR INVOLVEMENT IN CHILDREN WITH BETA-THALASSEMIA MAJOR

B. Lubis[1], S. M. Lubis[2], B. D. Sulistyowati[3]

[1]Division of Pediatric Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara – Medan, Indonesia
[2]Division of Pediatric Endocrinology, Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara – Medan, Indonesia
[3]Pediatric Ophthalmology Department, SMEC Eye Hospital – Medan, Indonesia

Abstract. Aim: *Thalassemia is a severe genetic blood disorder, and several organs, including eyes, can be affected. The mechanism of ocular abnormalities in thalassemia is multifactorial; one of them is regular blood transfusion, which can cause iron overload. Ocular abnormalities can also occur because of the side effects of iron chelators. This study evaluated ocular involvement in children with Beta-thalassemia major and its association with serum ferritin levels.* ***Methods:*** *A cross-sectional study was undertaken at the Thalassemia daycare center in a tertiary referral hospital in Medan. All patients' hemoglobin was measured before transfusion, and serum ferritin levels were measured at six-month intervals. A Pediatric Ophthalmologist carried out the ophthalmological assessment, which included a detailed history of visual problems and visual acuity testing. Fisher's Exact test and Spearman test were used for statistical calculation.* ***Results:*** *Thirty-seven beta-thalassemia major children ranging from three to 18 years old. Visual acuity, anterior segment, fundus, and retina were evaluated. Ophthalmologic examinations showed that ocular involvement increased with age. Visual acuity was reduced in 16.2% of the subjects. Papilledema was the most common ocular finding among the subjects (13.5%), followed by cataracts (8.1%) and optic atrophy (8.1%). A significant correlation between blood transfusion volume and serum ferritin levels was found.* ***Conclusion:*** *Ocular involvement was found in more than half of the subjects in this study. However, regular ophthalmologic evaluations by serum ferritin examination were required to detect early alterations in their visual system for a better quality of life.*

Key words: *beta-thalassemia, children, ocular abnormalities, ferritin*

Corresponding author: *Siska Mayasari Lubis, Child Health Department, Faculty of Medicine, Universitas Sumatera Utara, Jl. Dr. Mansur No. 5, Kampus USU, Medan, Sumatera Utara, 20155, Indonesia, tel: +628116143959, e-mail: siska@usu.ac.id*

INTRODUCTION

Thalassemia is a severe genetic blood disorder caused by a mutation in the globin gene. Abnormal globin chains cause excessive destruction of red blood cells [1]. One of the most common hemoglobinopathies is Beta-thalassemia major. The therapy for beta-thalassemia major is regular blood transfusions throughout life. Although transfusions can decrease mortality, accumulation of iron from a repeated blood transfusion and increased intestinal iron absorption due to ineffective erythropoiesis can lead to organ damage such as the liver, heart, and endocrine gland [2].

The mechanism of ocular manifestation in thalassemia is multifactorial. One of them is regular blood transfusion therapy, which causes iron overload. To overcome iron overload, an iron chelating agent is given. The Thalassemia International Federation (TIF) guidelines recommend starting iron chelation therapy when serum ferritin levels are greater than 1000 ng/ml or after receiving 10-20 times pack red cell transfusions [3, 4]. However, iron-chelating agents also chelate other essential metals for normal eye function, such as copper and zinc, increasing the risk of ocular abnormalities. Nyctalopia, visual field defect, cataract formation, damage to retinal pigment epithelium (RPE), optic neuropathy, and decreased visual acuity are some ocular abnormalities that can occur due to iron deposition in the eye or as side effects of iron chelators [3, 5, 6].

This study aimed to assess the prevalence of ocular involvement in multi-transfused beta-thalassemia children and determine their correlation with serum ferritin levels.

MATERIALS AND METHODS

The ethics committee approved this study. Written consent has been given by all individuals (children and their guardians) who participated in this study. A cross-sectional study was conducted at the Thalassemia daycare center in a tertiary referral hospital in Medan. The inclusion criteria for this study were children with Beta-thalassemia major, aged 18 years old, and who had undergone two years' worth of blood transfusion. This study also included subjects who received a dose of 15 ml/kg BW packed red cells to maintain hemoglobin concentrations after transfusion above 11 g/dL for at least two years. This study excluded subjects with a history of corneal disease, contact lens use, prior ocular surgery, ocular trauma, and topical eye medication use. Thirty-seven children with beta-thalassemia major participated in this study. All patients' hemoglobin was measured before transfusion, and serum ferritin levels were measured at six-month intervals. All records were kept in the thalassemia daycare center. A Pediatric Ophthalmologist carried out the ophthalmological assessment, which included a detailed history of visual problems and visual acuity testing. To test visual acuity, a teller acuity card was used for children under two years old, Cardiff for children aged two until preschool, and a Snellen chart for children older than five. The anterior segment was examined using a slit lamp. Indirect retinoscopy, fundus photo, and optical coherence tomography (OCT) were used to evaluate the posterior segment. From the OCT examination, a defect on nervus opticus (edema or atrophy) could be seen. This finding could also be used to determine whether the patient had a visual acuity loss even though there was no complaint from the patient.

The Shapiro-Wilk test was used to analyze the normality of quantitative variables. Descriptive data were represented as frequency, percentage, mean ± standard deviation (SD), and median (min-max). The relationship between ocular involvement and serum ferritin levels was analyzed using the Chi-Square test or Fisherman's Exact Test (if the cell expected count was less than five). The Spearman test determined the correlation between serum ferritin levels with frequency and transfusion volume. A P-value of < 0.05 was considered statistically significant for the statistical calculation using the Statistical Package for Social Science (SPSS) version 24.0 with a 95% confidence interval.

RESULTS

Thirty-seven patients with thalassemia aged 3-18 were enrolled in this study. Twenty subjects (51.3%) were male, and 17 (48.7%) were females. Table 1 shows the baseline characteristics of all subjects. The predominant ethnicity in this study was Javanese (59.8%). All patients received regular blood transfusions, but only 31 patients (83.8%) received iron chelation therapy. Twelve patients (32.4%) were on deferasirox, and 19 (51.4%) were on deferiprone. Serum ferritin level was less than 1000 ng/ml in four subjects (10.8%), 1000-5000 ng/ml in 21 subjects (56.8%), 5000-10.000 ng/ml in eight subjects (21.6%), more than 10.000 ng/ml in four subjects (10.8%). The median serum ferritin level was 2892 ng/ml, the mean transfusion volume was 186.5 ± 88.7, and the mean transfusion frequency was 18.3 ± 9.4 times. Table 2 describes the age distributions of subjects with ocular involvement. The prevalence of ocular involvement in patients under five and 5-10

years old was 60%, while in patients above 10 years old, it was 83.3%.

Table 3 describes the ocular involvement found in the subjects, while the relationship between serum ferritin levels and ocular involvement is shown in Table 4. Of the 37 subjects, ocular involvement was found in 25 (67.6%) subjects. Among subjects, patients with serum ferritin levels between 1000 and 5000 ng/ml had the most hyperpigmentation of the bulbar conjunctiva and anterior chamber, 63.6% and 50%, respectively. Fifty percent of subjects with serum ferritin levels of 5000-10 000 ng/ml had reduced visual acuity.

This study found five (13.5%) subjects with papilledema, three (8.1%) subjects with cataracts, and three (8.1%) subjects with optic atrophy. Papilledema was identified in 60% with serum ferritin levels of 1000-5000 ng/ml. There was 33.3% ocular atrophy in each group of subjects with serum ferritin levels of more than 1000 ng/ml. Cataracts were observed in 66.7% of the subjects with serum ferritin levels between 1000 to 5000 ng/ml. However, there was no significant association between serum ferritin levels and bulbar conjunctival hyperpigmentation, anterior chamber hyperpigmentation, visual acuity, and ocular abnormalities.

Table 1. Baseline characteristics of subjects

Characteristic	n (%)
Age, year	
< 5	5 (13.5)
5-10	20 (54.1)
> 10	12 (32.4)
Gender	
Male	20 (51.3)
Female	17 (48.7)
Ethnicity	
Acehnese	2 (5.4)
Javanese	22 (59.5)
Karonese	3 (8)
Melayunese	2 (5.4)
Padangnese	6 (16.2)
Sundanese	1 (2.7)
Chinese	1 (2.7)
Mean body weight, kg (mean ± SD)	24.5 ± 8.8
Mean body height, cm (mean ± SD)	123.6 ± 18.9
Mean BMI, kg/m^2 (mean ± SD)	15.4 ± 2.2
Median age at diagnosis, month (min-max)	30.0 (3.0-180.0)
Iron chelating agent	
Deferasirox	12 (32.4)
Deferiprone	19 (51.4)
None	6 (16.2)
Serum ferritin level	
< 1000 ng/ml	4 (10.8)
1000-5000 ng/ml	21 (56.8)
5000-10000 ng/ml	8 (21.6)
> 10.000 ng/ml	4 (10.8)
Median serum ferritin level, ng/ml (min-max	2892 (430-31285)
Mean transfusion volume, ml (mean ± SD)	186.5 ± 88.7
Mean transfusion frequency, time (mean ± SD)	18.3 ± 9.4

Table 2. Association between the age and ocular involvement

Age (years)	Ocular Involvement		P-value*
	No (%)	Yes (%)	
< 5	2 (40.0%)	3 (60.0%)	0.431
5-10	8 (40.0%)	12 (60.0%)	
> 10	2 (16.7%)	10 (83.3%)	

*Fisher's Exact test

Table 3. Ocular involvement findings

	n (%)
Characteristics of bulbar conjunctiva	
Normal	26 (70.3)
Hyperpigmentation	11 (29.7)
Characteristics of the anterior chamber	
Normal	31 (83.8)
Hyperpigmentation	6 (16.2)
Visual acuity	
Normal	31 (83.8)
Decrease	6 (16.2)
Ocular abnormalities	
None	26 (70.2)
Papilledema	5 (13.5)
Complicated cataract	3 (8.1)
Optic atrophy	3 (8.1)

Table 4. Association between ocular involvement and serum ferritin level

Serum ferritin level category	Bulbar conjunctiva				P-value*
	Normal (%)		Hyperpigmentation (%)		
< 1000	2 (7.7)		2 (18.2)		0.485
1000-5000	14 (53.8)		7 (63.6)		
5000-10 000	6 (23.1)		2 (18.2)		
> 10 000	4 (15.4)		0 (0.0)		
	Anterior chamber				
	Normal (%)		Hyperpigmentation (%)		
< 1000	3 (9.7)		1 (16.7)		0.835
1000-5000	18 (58.1)		3 (50.0)		
5000-10 000	7 (22.6)		1 (16.7)		
> 10 000	3 (9.7)		1 (16.7)		
	Visual acuity				
	Normal (%)		Decreased (%)		
< 1000	3 (9.7)		1 (16.7)		0.230
1000-5000	19 (61.3)		2 (33.3)		
5000-10 000	5 (16.1)		3 (50.0)		
> 10 000	4 (12.9)		0 (0.0)		
	Ocular abnormalities				
	None (%)	Papilledema (%)	Complicated cataract (%)	Optic atrophy (%)	
< 1000	3 (11.5)	1 (20.0)	0 (0.0)	0 (0.0)	0.835
1000-5000	15 (57.7)	3 (60.0)	2 (66.7)	1 (33.3)	
5000-10 000	6 (23.1)	0 (0.0)	1 (33.3)	1 (33.3)	
> 10 000	2 (7.7)	1 (20.0)	0 (0.0)	1 (33.3)	

*Fisher's exact test

The correlation between frequency and transfusion volume with serum ferritin level is shown in Table 5. The blood volume of transfusion was significantly associated with serum ferritin levels (P-value < 0.05). However, the transfusion frequency did not show a significant relationship.

Table 5. Correlation between frequency and volume of transfusion with serum ferritin level

	Mean	P-value*
Frequency of transfusion, time	18.35	0.389
Serum ferritin level, ng/ml	5122.83	
The volume of blood transfusion, ml	186.5	0.014
Serum ferritin level, ng/ml	5122.83	

*Spearman test

DISCUSSION

Patients with thalassemia are required to undergo a lifelong blood transfusion. Therefore, siderosis and adverse ocular changes can occur as a result of the disease or due to iron overload and chelation therapy. Patients with thalassemia can exhibit various ocular abnormalities, such as color vision anomalies, decreased visual acuity, papilledema, and other abnormalities. Due to the liberation of free iron from hemolysis, thalassemia major may also be associated with non-proliferative pigmentary retinopathy.

This study was conducted to find various ocular changes in patients with thalassemia on regular transfusion. In 37 thalassemia children, we found 25 subjects (67.6%) with ocular involvement. All subjects had no complaints. Previous studies reported the prevalence of ocular involvement in 68.5%, 41.3%, and 57.8% of their subjects [6, 9, 10]. It is difficult to make an accurate comparison because different results of ocular abnormalities reported in previous studies may happen because of the different parameters used to evaluate them.

Visual acuity was affected in 16.2% of the subjects in this study, whereas a study in India reported 26% [11]. We also found pigmentation of the conjunctiva in 29.7% of the individuals. It was higher than the

previous study, which reported only 7.6% [12]. This study found the most prevalent ocular abnormality was papilledema (13.5%). Both complicated cataracts and optic atrophy were found in three subjects (8.1%).

From our findings, subjects aged > 10 years had a higher frequency of ocular involvement (83.3%), while the younger subjects had 60% frequencies in both groups. This shows that the longer the disease duration, the more eye changes. This result was supported by Gartaganis S. et al. and Gosai D. et al., who reported similar findings [6, 11].

Iron is an important component of many metabolic processes. On the other hand, iron may play a role in the pathogenesis of eye diseases as a source of oxidative damage. Iron causes oxidative damage to lipids, proteins, and DNA by creating free radicals in the Fenton reaction, and it has been shown to disrupt the blood-retinal barrier [13]. Most ocular abnormalities were found in subjects with serum ferritin levels of 1000-5000 ng/ml; 60% with papilledema, and 66.7% with complicated cataracts. Three subjects with optic atrophy were divided into each group of subjects with serum ferritin levels greater than 1000 ng/ml. However, no significant correlation was found between serum ferritin levels and ocular abnormalities. This finding was consistent with Jafari R et al., who found no correlation between ocular abnormalities and mean serum ferritin level [9]. This result could be because this study used serum ferritin level as a marker for iron overload instead of more accurate tests such as liver iron concentration measurement or MRI [14]. Nevertheless, appropriate regulation of iron is necessary to prevent iron toxicity and ocular abnormalities in children with Beta-thalassemia.

This study found no significant correlation between transfusion frequency and serum ferritin level. On the other hand, a study by Susanah S et al. reported a positive correlation between serum ferritin levels and the amount of transfusion in their patients [15]. This difference could occur because our study has fewer subjects, and some of the subjects had already received iron chelation therapy during this study. However, we found a significant relationship between blood transfusion volume and serum ferritin levels ($P < 0.05$).

This study has limitations. Not all the patients use iron chelating therapy due to their low socioeconomic level; thus, we could not evaluate the effect of chelation therapy on the ocular abnormality. We also did not compare ocular abnormalities with the frequency and volume of blood transfusion therapy for patients with thalassemia, nor did we compare differences between iron chelation regimens. There is also a possibility that their ocular abnormalities could have occurred before their first blood transfusion treatment. Therefore, further prospective investigations with a large sample of patients with thalassemia are suggested.

CONCLUSIONS

Ocular involvement was found in more than half of the subjects in this study. Regular ophthalmologic evaluations by serum ferritin examination were required to detect early alterations in the Thalassemia children's visual system to maintain their quality of life.

REFERENCES

1. Vichinsky EP. Changing patterns of thalassemia worldwide. In: Ann N Y Acad Sci. 1054.; 2005:18-24.
2. Taher AT, Saliba AN. Iron overload in thalassemia: Different organs at different rates. Hematology. 2017; 2017(1):265-271.
3. Taher A, Bashshur Z, Shamseddeen WA, et al. Ocular findings among thalassemia patients. Am J Ophthalmol. 2006;142(4):704-705.
4. Thalassaemia International Federation. Guidelines for the Management of Transfusion Dependent Thalassemia (TDT); 2014.
5. Thuangtong A, Wiriyaudomchart S, Rungsiri K. Incidence of ocular toxicity from iron chelating agents at Siriraj Hospital. Siriraj Med J. 2020; 72(3):209-213.
6. Gartaganis S, Ismiridis K, Papageorgiou O, et al. Ocular abnormalities in patients with β thalassemia. Am J Ophthalmol. 1989; 108(6):699-703.
7. Wong RW, Richa DC, Hahn P, et al. Iron toxicity as a potential factor in AMD. Retina. 2007; 27(8):997-1003.
8. Merchant RH, Punde H, Thacker N, et al. Ophthalmic Evaluation in Beta-Thalassemia. Indian J Pediatr. 2017;84(7):509-514.
9. Jafari R, Heydarian S, Karami H, et al. Ocular abnormalities in multi-transfused beta-thalassemia patients. Indian J Ophthalmol. 2015;63(9):710-715.
10. Taneja R, Malik P, Sharma M, et al. Multiple transfused thalassemia major: Ocular manifestations in a hospital-based population. Indian J Ophthalmol. 2010; 58(2):125-130.
11. Gosai D, Mehariya K, Gosai J. Study of ocular manifestations in children of thalassemia. Int J Res Med Sci. 2014; 2(2):695-698.
12. Haghpanah S, Zekavat OR, Bordbar M, et al. Ocular findings in patients with transfusion-dependent β-thalassemia in southern Iran. BMC Ophthalmol. 2020; 20(1):376.
13. Loh A, Hadziahmetovic M, Dunaief JL. Iron homeostasis and eye disease. Biochim Biophys Acta - Gen Subj. 2009; 1790(7):637-649.
14. Wood JC. Diagnosis and management of transfusion iron overload: The role of imaging. Am J Hematol. 82.; 2007:1132-1135.
15. Susanah S, Idjradinata PS, Sari NM, et al. Time to Start Delivering Iron Chelation Therapy in Newly Diagnosed Severe β-Thalassemia. Sadikot R, ed. Biomed Res Int. 2020; 2020:8185016.