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Ocular Manifestations of β -Thalassemia Patients with the Use of Oral Iron Chelating Agents

Sandip Sen[1], Anjan Kumar Das[2], Rajat Mohapatra[3]

[1]Associate Professor, Department of Pediatrics, Dr B.C. Roy PGIPS, Kolkata.
[2]Assistant Professor, Department of Pediatrics, Dr B.C. Roy PGIPS, Kolkata.
[3]Postgraduate student, Department of Pediatrics, Dr B.C. Roy PGIPS, Kolkata.

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ABSTRACT

Background: Ocular involvement in β-thalassemia major is very common. Iron chelators like Desferrioxamine and Deferiprone avoid systemic complications but chelate metals in retina. Objectives: 1.To study the relation of oral iron chelator (Deferiprone) on various ocular manifestations in β-thalassemia major patients. 2. To study the relation of serum ferritin with various ocular manifestations. **Methods:** 100β-thalassemia major patients out of those attending our thalassemia clinic were selected for the study as per our inclusion and exclusion criteria. They were divided into two major groups based on whether they were taking oral iron chelator (Deferiprone) or not. Detailed history, examination and investigations were done and recorded. **Results:** The study revealed that 52% of the patients had ocular involvement with 86.5% of them taking Deferiprone ($p<0.0001$), 13% had retinal pigment epithelium (RPE) degeneration with 92.3% of them on Deferiprone ($p=0.003$) and 18% had RPE mottling with 88.8% of them taking Deferiprone ($p=0.001$). Other ocular changes like lens opacity, disc hyperemia, best corrected visual acuity (BCVA) and venous tortuosity showed some difference between the two groups but that was insignificant. Further the study also showed that higher serum ferritin levels were significantly associated with ocular changes like decreased BCVA ($p<0.001$), RPE degeneration ($p<0.001$), RPE mottling ($p<0.001$) and venous tortuosity ($p<0.025$). **Conclusion:** Ocular changes in β-thalassemia major increases with greater duration of the disease and increased number of blood transfusions due to increased serum ferritin levels. Using iron chelators may reduce iron overload but they causechelator induced ocular involvement.

Keywords: β-thalassemia, ocular, children, oral iron chelator

INTRODUCTION

β-thalassemia(β-thal) major is a severe genetic blood disorder caused by a mutation in the gene encoding for the β chains of Hemoglobin(Hb).There are about 240 million carriers of β-thalworldwide, which is around 1.5% of the world population.[1] Individuals with β-thal major require regular lifelong packed red blood cells transfusion to survive. Ocular involvement in them is quite common and may have serious implications.[2] Adverse ocular changes may occur as a result of the disease itself or as side effects of iron chelators,[3] and include cataract, optic neuropathy, retinal pigment epithelium(RPE) degeneration, RPE mottling, retinal venous tortuosity, vitreo retinal hemorrhages and obliteration of iris pattern. Desferrioxamine, Deferiprone and Deferasirox are the common iron chelating agents used.[4] Desferrioxamine and Deferipronewhich are used to avoid systemic complications of siderosis cause chelation of metals such as iron,copper, zinc, cobalt and nickel in retina.[5] The retinal toxicity of Desferrioxamine may result from its high affinity for iron.[6]

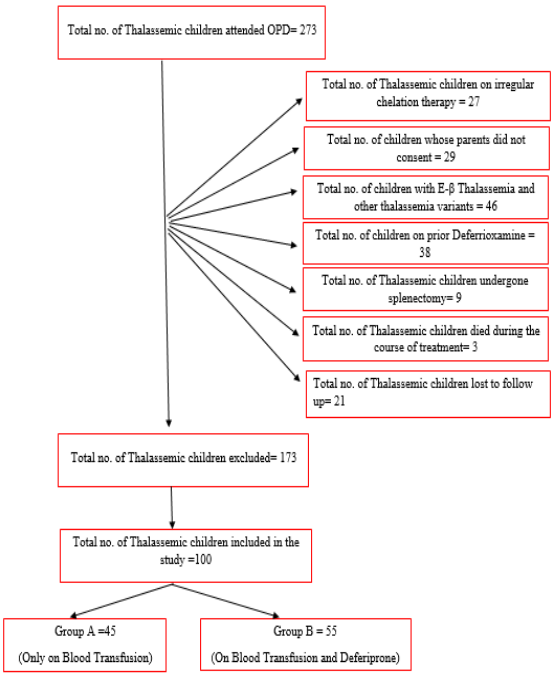
Frequency of ocular involvement differs among various studies from 41.3-85%,[2] which signifies that it is an important clinical aspect of the long term treatment of β-thal major. To our dismay very little literature is available to give a clear idea regarding the magnitude of these manifestations and their relation with chelation. Further, thalassemia having a prevalence of 3-4% in India and 4-10% in West Bengal,[7] covers a huge population in this part of eastern India but studies regarding ocular manifestations of thalassemia in eastern part of India, particularly West Bengal is not much heard of. Hence, this study becomes important to provide information regarding the scenario of ocular manifestations among thalassemia patients in a tertiary care hospital of West Bengal. Moreover most of the similar studies are based on the effects of injectable iron chelator Desferrioxamine while ours is a study based on an oral iron chelator Deferiprone.

Name & Address of Corresponding Author
Dr. Anjan Kumar Das,
Assistant Professor,
Département of Pediatrics,
Dr B.C. Roy PGIPS, Kolkata

MATERIALS AND METHODS

An institution based cross-sectional study was conducted in the departments of Paediatrics and Ophthalmology, of Dr B.C. Roy PGIPS, Kolkata, during September 2015 to March 2017, on β-thal major patients who attended the thalassemia clinic of the hospital. 100 β-thal patients were studied and divided into two groups, Group A: consisting of 45 patients who were only on blood transfusion (BT) and Group B: containing the rest 55 who were on oral chelating agent (Deferiprone) in addition to BT at a dose of 75-100mg/kg/day.[8] The patients in Group B were given chelation once serum ferritin values were more than 1500 ng/ml and have received the chelation for more than 6 months. The patients in both the groups received packed RBC transfusion @ 15ml/kg in order to maintain pre-transfusion Hb at 9-10gm /dl.[9] After taking permission from the institutional ethics committee and obtaining written consent from the legal guardian of the patient, the study was started.

Children < 15 years who are diagnosed cases of β-thal major and have received multiple transfusions with or without chelating therapy were included in the study. The exclusion criteria included those greater than 15 years of age or less than 1 year of age or with anemia due to any other causes or with any other congenital diseases or those receiving IV chelators like Desferrioxamine. Further exclusion criteria are seen in the flowchart.



Each patient and its legal guardian were interviewed in detail about the chief complaints, medical history, blood transfusion history and drug history. Further the best corrected visual acuity (BCVA), using Snellen's chart and Figure chart, was found, anterior segment was examined using flash torch light and slit lamp and posterior segment was examined using direct ophthalmoscopy, indirect ophthalmoscopy and slit lamp biomicroscopy (if possible). All these data and findings were recorded. Investigations like serum ferritin, Hb level, Hb electrophoresis were also done and recorded.

For the purpose of Statistical analysis, statistical software SPSS Vs 24.0 was used and any P-value less than 0.05 was considered to be significant. Continuous variables were evaluated in terms of mean and standard deviation and categorical variables were expressed as count and percentages. Chi square or Fischer's test was used as appropriate.

RESULTS

In our study involving 100 patients, divided into two groups, the baseline characteristics and ocular manifestations of the two groups are tabulated and presented below:

As is evident from the above tables that there was a slight male preponderance in both the groups as they comprised 56% of the total study population [Table 1]. Agewise 21% were <5 years, 44% were between 6-10 years and 35% were between 10-15 years [Table 2]. Ocular involvement was observed in 52% of the patients with 45 out of 52 (86.5%) of thembelonging to group B (P<0.0001). Further RPE degeneration was observed in 13% of the patients, with 12 out of 13 (92.3%) of thembelonging to group B (p=0.003) and RPE mottling was observed in 18% of the patients with 16 out of 18(88.8%) of them belonging to group B (P=0.001). All these parameters were statistically significant. Most importantly, it was seen that ocular changes were significantly associated with serum ferritin levels [Table 4] in the form of decreased BCVA (P<0.001), RPE degeneration (P<0.001), RPE mottling (P<0.01) and venous tortuosity (P<0.025), in patients with higher serum ferritin levels who received more number of BT than others.

Although male patients showed slightly more propensity (57.6%) towards ocular manifestations [Table 3] than females (42.3%), it was statistically insignificant (P=0.125). Even age wise [Table 2], more involvement was seen in older age group (10-15 years) in terms of ocular manifestation (91.4%), decreased visual acuity (51.4%), lens opacity (17%) and fundus changes (68.5%), but it was statistically insignificant. Further the parameters like BCVA changes (P=0.058), lens opacity (P=0.928), venous tortuosity (P= 0.928) and disc hyperemia (P=0.249) although showed marginal difference between the two groups, they were statistically insignificant.

Table 1: Baseline characteristics and ocular manifestations of the patients in the two groups.

Parameters		Group A (no iron chelation)	Group B (with Deferiprone)	Total	P-value
Total subjects		45 (45%)	55 (55%)	100 (100%)	
Age	<5 years	18 (85.7%)	3 (14.3%)	21 (21%)	
	6-10 years	17 (38.5%)	27 (61.5%)	44 (44%)	
	>15 years	10 (28.5%)	25 (71.5%)	35 (35%)	
Sex	Male	24(42.8%)	32(57.2%)	56 (56%)	
	Female	21(47.7%)	23 (52.3%)	44 (44%)	
Ocular involvement	Present	7(15.6%)	45(81.8%)	52(52%)	<0.0001
	Absent	38(84.4%)	10(18.2%)	48(48%)	
BCVA*	Normal	39(86.7%)	39(70.9%)	78(78%)	0.058
	Decreased	6(13.3%)	16(29.1%)	22(22%)	
Lens opacity	Present	6(13.3%)	7(12.7%)	13(13%)	0.928
	Absent	39(86.7%)	48(87.3%)	87(87%)	
RPE** degeneration	Present	1(2.2%)	12(21.8%)	13(13%)	0.003
	Absent	44(97.8%)	43(78.2%)	87(87%)	
RPE** mottling	Present	2(4.4%)	16(29.1%)	18(18%)	0.001
	Absent	43(95.6%)	39(70.9%)	82(82%)	
Venous tortuosity	Present	2(4.5%)	8(14.5%)	10(10%)	0.093
	Absent	43(95.5%)	47(85.5%)	90(90%)	
Disc hyperemia	Present	1(2.2%)	4(7.3%)	5(5%)	0.249
	Absent	44(97.8%)	51(92.7%)	95(95%)	

*Best Corrected Visual Acuity(decreased Visual Acuity: =<6/9)
**Retinal Pigmented Epithelium
***Visual Acuity

Table 2: Ocular manifestations according to age

Age (years)	No. of subjects	Ocular involvement (%)	Decreased VA*** (<6/9) (%)	Lens opacity (%)	Fundus changes (%)
<5	21 (21%)	4 (19.04%)	1 (4.7%)	0 (0%)	3 (14.3%)
5-10	44 (44%)	16 (36.36%)	3 (6.81%)	7 (15%)	4 (9.1%)
10-15	35 (35%)	32 (91.42%)	18 (51.4%)	6 (17%)	24 (68.6%)
Total	100 (100%)	52 (52%)	22 (22%)	13 (13%)	30 (30%)

Table 3: Ocular manifestations according to sex

Ocular involvement	Male	Female	Total	P-value
Present	30 (57.7%)	22 (42.3%)	52 (100%)	0.125
Absent	26 (54.2%)	22 (45.8%)	48 (100%)	

Table 4: Relation of mean serum ferritin and different ocular manifestations

Parameters		No. of subjects	Mean serum ferritin ± SD# (ng/ml)	P-value
Ocular involvement	Present	52	2509.9±480.5	<0.001
	Absent	48	2036.7±675.6	
BCVA	Decreased	22	2699.5±529.5	<0.001
	Normal	78	2165.2±603.4	
Lens opacity	Present	13	2330.7±664.7	0.77
	Absent	87	2275.6±256.6	
RPE degeneration	Present	13	2889.6±549.9	<0.001
	Absent	87	2192.1±587.6	
RPE mottling	Present	18	2628.6±580.6	0.01
	Absent	82	2206.8±613.3	
Venous tortuosity	Present	10	2516.7±441.9	0.02
	Absent	90	2163.9±641.0	
Disc hyperemia	Present	5	2635.0±553.3	0.21
	Absent	95	2264.2±626.9	

#Standard Deviation

DISCUSSION

Patients with β-thalassemia major are BT dependent and may have ocular involvement.[1] Ocular involvement may correlate to the disease itself, iron overload or chelating agents used. The frequency of ocular involvement differs among various studies (41.3%-85%, three studies).[2] In our study, it is 52% with 86.5% of them taking deferiprone along with BT, which clearly shows that though iron chelator reduces iron overload, still it can lead to chelator induced ocular involvement. Tanejaet al,[3] observed ocular involvement in 58% of the patients in their study, Abdel-MalakD.S.M. et al,[10] found it to be 85% in their study.

Our study clearly underlines the fact that higher mean serum ferritin level correlates with more chances of ocular involvement, decreased VA, RPE

degeneration, RPE mottling and venous tortuosity. This corroborates with the study done by Tanejaet al,[3] who found that venous tortuosity was more in patients with higher serum iron and serum ferritin levels. Even Thakur R et al,[11] found the same thing in their study. But it is in clear contrast to a study done by Jafari R et al,[12] and Jethani J et al,[13] who found no significant correlation between serum ferritin levels and ocular manifestations.

With respect to the fundus changes, our study detected RPE degeneration in 13% of cases and RPE mottling in 18% of the cases which is consistent with findings of Abdel-MalakD.S.M. et al,[10] who found RPE degeneration in 17.7% and RPE mottling in 25% of the cases. Further, 21.8% of the patients receiving Deferiprone therapy had RPE degeneration which was significantly different from those receiving only BT. Even RPE mottling was observed in 29.1% of the patients receiving Deferiprone therapy. These results were consistent with the study done by Abdel-MalakD.S.M. et al,[10] where they found that out of the patients receiving Deferiprone therapy 27.8% of the patients had RPE degeneration and 33.3% of the patients had RPE mottling.

13% of the patients had lenticular opacities in our study and no significant correlation was found between occurrence of lens opacity and Deferiprone therapy. Lenticular opacities may be attributed to low molecular weight of Deferriprone and its ability to cross the blood-ocular barrier.[14] Lens opacities even correlated insignificantly with higher average serum iron and serum ferritin levels. The study done by Tanejaet al,[3] recorded lens opacities in 40% of the patients. VA was found normal in 78 (78%) patients in our study and the rest had decreased VA. Of the ones that had decreased VA, 29.1 % were receiving Deferiprone along with BT and 13.2% were not receiving chelation, indicating that chelation showed minimal statistical difference with respect to VA. These are consistent with findings of Tanejaet al.[3]

The literature provides no clue as to whether ocular manifestations in thalassemia are more preponderant in a particular sex. However, in our study a slight male preponderance (1.27:1) was observed over female which is consistent with study done by Tanejaet al.[3] Even disc hyperemia was found in 5% of patients in our study which is in line with the findings of Tanejaet al,[3] and Dewan Pet al,[15] who found it to be 7% and 8% respectively. Dewan P et al,[15] did the study based on Desferrioxamine. The ocular manifestations increase in occurrence with increasing age of the patient, as shown in [Table 1], which candidly reflects that ocular manifestations tend to increase with duration of the disease.

CONCLUSION

Our study underlines the fact that ocular changes increase with longer duration of disease and increased number of BT. Since our study includes only children less than 15 years, so a larger study involving people upto older age groups and having received BT for a longer period will be more convincing to prove the above statement. Among the ocular changes, retinal changes like RPE degeneration, RPE mottling, venous tortuosity, disc hyperemia are found significantly more in patients on long term oral chelating agents. Increased serum ferritin level leads to more ocular manifestations mostly due to toxic effects of iron on the ocular structure.As life expectancy for beta-thalassemia patients extend, regular ophthalmological evaluation to detect early changes, and reduction of serum ferritin levels is recommended, in order to achieve a better life quality for this patient group.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. All authors approved the final version of manuscript and agree to be accountable for authenticity and integrity of the work.

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