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Ocular changes in multi-transfused children with β-thalassaemia receiving desferrioxamine: A case-control study

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Objectives. This study was planned to determine the prevalence of ocular abnormalities in multi-transfused children with β-thalassaemia receiving desferrioxamine and to determine the association of abnormalities with the patients' age, serum ferritin level, haemoglobin concentration, and dosage and duration of treatment with desferrioxamine.

Methods. Twenty-five thalassaemic children receiving desferrioxamine and attending the day-care centre of a tertiary care hospital in Delhi, India, and 25 healthy age-matched controls were examined to determine the prevalence and pattern of ocular abnormalities. A refraction test, the visual evoked response and fluorescein angiography were done where applicable. Ocular changes were correlated with serum ferritin levels, the dosage and duration of chelation with desferrioxamine, and pre-transfusion haemoglobin levels.

Results. None of the children reported any visual symptoms. The prevalence of ocular abnormalities in the thalassaemic group was 36% (9/25). Ocular changes seen included cataract (5/25), blurred optic disc margins (6/25) and dilatation and tortuosity of retinal vessels (2/25). The thalassaemic children had a significantly higher prevalence of cataract than the controls ($p<0.05$). Prevalence of cataract was associated with serum ferritin values above 4500 ng/ml ($p<0.05$), and blurring of disc margins was significantly associated with increased duration ((5 years) and frequency ((5 times/week) of desferrioxamine administration. A positive correlation was seen between the incidence of cataract and blurred disc margins.

Conclusions. Children with thalassaemia should be screened periodically for ocular abnormalities. Rational usage of desferrioxamine and use of newer chelating agents will reduce the prevalence of these abnormalities.

Blood transfusion therapy on a continuing basis represents the primary treatment for β-thalassaemia.[1] Although this treatment alleviates anaemia, it leads to massive tissue deposition of iron, and may eventually result in multi-organ dysfunction. With advances in chelation of iron the life expectancy of patients with thalassaemia has improved significantly, but several side-effects of chelation, though not life threatening, have emerged.[2-4] These side-effects have added to the morbidity of thalassaemia.

Desferrioxamine (DFO) remains the treatment of choice for haemosiderosis, despite the emergence of oral iron-chelating drugs such as deferiprone and deferasirox.[5] At the recommended doses of 20 - 40 mg/kg/day, DFO is usually free of serious side-effects. Ocular abnormalities such as cataracts, pigmentary retinopathy, optic neuropathy and thinning and tortuosity of retinal vessels have previously been reported with the use of DFO.[6-8]

This study was conducted to assess the prevalence of ocular abnormalities in multi-transfused β-thalassaemic Indian children and to determine their relationship with iron overload, chronic hypoxia, and the dosage and duration of treatment with desferrioxamine.

Subjects and methods

This study was conducted in the thalassaemia day-care centre of a tertiary care hospital in Delhi, India. Twenty-five children diagnosed with homozygous β-thalassaemia major and who had been receiving chelation with desferrioxamine for at least 2 years were enrolled in the study. All the children enrolled had been receiving treatment in the form of packed red cell transfusions at a dosage of 15 ml/kg/transfusion in order to maintain the pre-transfusion haemoglobin concentration between 9 and 11 g/dl. Chelation was started if the serum ferritin level was found to be above 1 500 µg/l. Desferrioxamine was infused subcutaneously 3 - 6 times a week at a dosage of 20 - 40 mg/kg/dose depending on the patient's iron load and compliance. The serum ferritin level was measured in all patients at 6-monthly intervals. Haemoglobin was measured before each transfusion, and the records were kept at the thalassaemia day-care centre.

For the purpose of the study we computed the mean serum ferritin level, pre-transfusion haemoglobin concentration and daily dose of desferrioxamine for each patient based on the records over the previous 2 years. Twenty-five healthy age- and sex-matched controls were recruited from the outpatient department and subjected to a detailed ophthalmological evaluation. Informed consent from the guardians and assent from older children were obtained. All girls were examined in the presence of a female attendant. Prior approval from the institutional ethical committee was obtained.

Ophthalmological evaluation

Ophthalmological evaluation was done in 25 β-thalassaemic children (50 eyes) and 25 healthy controls (50 eyes). Children with systemic diseases such as diabetes mellitus, tuberculosis and hypertension, which may lead to ocular abnormalities, those with local ocular pathology such as trauma, and one-eyed subjects were excluded. Ophthalmological assessment included a detailed history for visual problems, local eye examination, visual acuity, refraction testing, slit-lamp examination, fundoscopy and colour vision testing. Visual evoked response (VER) and fluorescein angiography (FA) were performed where deemed necessary. The two eyes were tested separately. Children found to have abnormal visual acuity were subjected to refraction testing after administering cycloplegic drugs. Visual acuity was then re-checked with the child wearing corrective lenses.

Visual evoked response study

Visual evoked potentials were recorded using 3 or more electrodes applied to the patient's head with an adhesive. The patient was asked to stare at a strobe light or a checkerboard pattern on a television screen. Each eye was tested separately. The responses generated by the visual system were recorded by specialised software on a computer and interpreted by the physician.

Fluorescein angiography

The fundus was examined after injection of fluorecein dye, and rapid serial photography recorded the arterial, arteriovenous, venous and late venous phase of retinal circulation.

Statistical analysis

We used SPSS version 12 for analysis. ANOVA, Student's *t*-tests, chi square tests and Mann-Whitney tests were used where applicable. The presence of ocular abnormalities was correlated with dose and duration of chelation with DFO and serum ferritin and haemoglobin levels. The level of significance was set at $p<0.05$. The prevalence of ocular changes in the thalassaemic children was compared with that in the control group. Receiver operating curves were obtained where necessary.

Results

Twenty-five thalassaemic subjects aged 4 - 21 years and 25 healthy controls aged 5 - 21 years were evaluated for ocular abnormalities. The mean serum ferritin level of the thalassaemic children was 2 995.2 ng/ml (range 1 440 - 8 869 ng/ml, median 3 646 ng/ml). The mean daily dose of DFO in these patients was 28.2 (standard deviation (SD) 8.9) mg/kg (range 16.2 - 39.5 mg/kg, median 19.7 mg/kg). Ten of them received DFO 5 - 6 times a week and 15 received it 3 - 4 times a week. Table I sets out the characteristics of the thalassaemic children and the controls.

All the thalassaemic children were asymptomatic, but abnormal ocular findings (cataracts, corneal dystrophy, corneal xerosis, fundus changes) were seen in 36% (9/25) patients. Lenticular opacities in the form of bilateral acquired cataracts were noted in 5 patients; 4 of them had subcapsular cataracts and 1 had polar cataracts. Two children had epithelial corneal dystrophy and 2 had corneal xerosis. Fundus changes were seen in the form of blurred optic disc margins in 6 children, and disc hyperaemia and increased tortuosity of retinal vessels in 2. The VER was measured in 4 children with blurred disc margins, while FA was done in 2 children with disc hyperaemia and increased venous tortuosity on fundoscopy. In all cases the VER was normal, but the findings on FA were abnormal in 1 patient. The pupillary reaction was normal in all children. None of the children were colour blind. Sixteen of the children had visual acuity ≤6/9 (assessed on Snellen's charts) in both eyes and 2 in one eye. Corrective lenses normalised visual acuity in all patients. The prevalence of acquired cataract was significantly higher in children with serum ferritin levels ≥4 500 ng/ml compared with those with lower serum ferritin levels ($p=0.005$). The thalassaemic children with cataracts had a mean serum ferritin level of 4 833.2 ng/ml (range 3 422 - 5 550 ng/ml), and their mean daily dose of DFO was 29 mg/kg (range 16.2 - 39.5 mg/kg). No significant relationship was found between the duration of chelation with DFO and cataractous changes. Optic neuropathy in the form of blurred disc margins was detected in 6 thalassaemic children; 5 of them had been on DFO for more than 5 years and 4 had been receiving it at least 5 times a week. The mean daily dose of DFO in the children with optic neuropathy was 23.53 mg/kg (range 17.4 - 30.6 mg/kg), and their mean serum ferritin level was 5 282.33 ng/ml (range 1 906 - 8 869 ng/ml). The VER was measured in 4 patients and found to be normal in all. One child had an abnormal FA. The details of patients with ocular abnormalities are shown in Table II. A positive correlation was found between the presence of blurred disc margins and the prevalence of cataract (Fisher's exact test $p=0.001$). Children receiving a mean daily dose of DFO >27.5 mg/kg were more likely to develop cataract (sensitivity 80%, specificity 95%, $p=0.021$, area under the curve (AUC) 0.84) and those receiving a mean daily dose of DFO >23.5 mg/kg were more likely to develop

TABLE I. DEMOGRAPHIC CHARACTERISTICS AND OCULAR FINDINGS OF THALASSAEMIC CHILDREN AND HEALTHY CONTROLS

Characteristic	Thalassaemic children (*N*=25)	Healthy controls (*N*=25)	*p*-value
Age (yrs) (mean (SD))	9.8 (4.7)	9.2 (3.9)	0.628
Gender	12 males, 13 females	13 males, 12 females	0.777
Haemoglobin (g/dl) (mean (SD))	8.63 (0.41)	10.91 (1.68)	**0.0001**†
Visual acuity			
Normal	7	24	**0.0001**†
Abnormal*	16 (both eyes) 2 (one eye)	1 (both eyes)	
Presence of cataract	5	0	**0.05**†
Presence of blurred disc margins	6	1	0.098
Presence of disc hyperaemia and venous tortuosity	2	0	0.49
Abnormal fluorescein angiography	1	-	-
Abnormal visual evoked response	0	-	-

*Visual acuity ≤6/9.
†Statistically significant *p*-values are in bold font.

TABLE II. PROFILE OF THALASSAEMIC PATIENTS WITH ABNORMAL OCULAR FINDINGS

Age (yrs), gender	Mean serum ferritin (ng/ml)	Duration of chelation with DFO (mo.)	Mean daily dose (mg/kg) and frequency of DFO	Slit-lamp examination administration (/wk)	Fundoscopy	Fluorescein angiography	Visual evoked response	Visual acuity	
								Left	Right
21, M	5 550	107	30.5, 5	Cataract, bilateral, anterior subcapsular	Blurred disc margins, venous tortuosity and narrowing of retinal vessels	Abnormal	Normal	6/6	6/6
18, M	7 491	47	23, 5	Cataract, bilateral, subcapsular	Normal	-	-	6/36	6/24
18, F	5 774	82	39.5, 5	Cataract, bilateral, subcapsular	Blurred disc margins	-	Normal	6/6	6/6
16, F	5 550	132	30.6, 5	Normal	Blurred disc margins, excessive retinal vessel tortuosity	-	Normal	6/9	6/9
9, F	4 837	48	13.5, 5	Cataract, anterior and posterior subcapsular, bilateral	Normal	-	-	6/36	6/36
8, F	4 095	26	10.7, 5	Normal	Blurred disc margins, hyperaemic discs, temporal pallor of optic disc	-	-	6/18	6/18
8.5, F	2 727	65	19.5, 3	Normal	Blurred disc margins	-	-	6/6	6/6
11, F	4 583	55	28.5, 3	Cataract, bilateral, posterior, polar	Normal	-	-	6/6	6/6
16.5, F	8 869	82	17.4, 3	Normal	Blurred disc margins, hyperaemic disc	Normal	Normal	6/12	6/12

blurring of optic disc margins (sensitivity 75%, specificity 78%, p=0.05, AUC 0.80). Children with a serum ferritin level >3 998 mg/dl were more likely to develop ocular abnormalities (sensitivity 78%, specificity 88%, p=0.01, AUC 0.79). The controls had a significantly lower prevalence of cataract and abnormal visual acuity compared with the cases.

Discussion

We evaluated the ocular changes in 25 multi-transfused thalassaemic children receiving DFO. The prevalence of ocular changes in our patient group was 36%. A similar prevalence of 38% was reported by Sorcinelli *et al.*[9] In a study from China, the prevalence of ocular abnormalities in a thalassaemic population was found to be only 12%.[10]

We found children who had received desferrioxamine for ≥5 years and more frequently (≥5 times a week) to have a significantly higher prevalence of optic neuropathy than those who had received it for a shorter time period and less often. Previously Olivieri *et al.*[11] found a significant association between optic neuropathy and higher doses of DFO, while in in contrast Lam *et al.*,[10] did not find any association between the dose of DFO and ocular abnormalities. The prevalence of cataract in our patients was 20%, and cataract was found to be associated with raised serum ferritin levels. This contrasts with the findings of Olivieri *et al.*,[11] who found ocular changes in thalassaemic patients receiving DFO to be linked to lower ferritin levels. They postulated that the unchelated DFO accumulated in tissues and caused ocular changes. We did not find any published data relating cataract to raised serum ferritin levels in multi-transfused patients, as was seen in our study. However, a condition characterised by high ferritin levels and cataract, viz. 'hereditary hyperferritinaemia-cataract syndrome', which manifests as congenital bilateral nuclear cataract and high serum ferritin values, has been reported.[12] We did not find any acute visual toxicity linked to DFO administration or any child with impairment of colour vision, as has been reported previously.[7,13] A large number of thalassaemic children (N=18) had abnormal visual acuity, and 5 of them also had either cataractous changes or fundus abnormalities. All improved when wearing corrective lenses, which prompts us to attribute the refractive errors to causes other than DFO toxicity. Previously, DFO has been found to lower the incidence of impaired visual acuity by having a protective effect on the retinal pigment epithelium.[14] We did not find retinal pigmentary degeneration in any of our subjects. It is an interesting observation that in comparison with controls a large

number of thalassaemic children had refractive errors, the exact cause for which needs to be ascertained. Children with thalassaemia are known to suffer from abnormal physical growth, and it could be interesting to study the growth of the eyeball in these children, as this could be associated with their high prevalence of refractive errors.

It could be interesting to study growth of the eyeball in children with thalassaemia, as this may be associated with their high prevalence of refractive errors.

Our patients appeared to have a poor response to chelation, as reflected by their high serum ferritin levels, which may be due to the fact that most of them received only modest doses of DFO. The mean daily dose of DFO in our patients was 28.2 (SD 8.9) mg/kg/day, and none received more than 40 mg/kg/day. Despite this, 36% of our patients had either cataracts or abnormal fundus findings. 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 thalassaemia 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 haemorrhage.[15-17] Raised serum ferritin in our patient group is a surrogate marker of transfusional haemosiderosis, which may predispose thalassaemic patients to the toxic effects of iron. The specific role of iron in ocular injury in thalassaemia needs to be studied.

We found a large number of thalassaemic children to have ocular abnormalities despite only moderate doses of DFO and in the presence of high serum ferritin levels, which implicates a role of iron in ocular pathology in thalassaemia. 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. Until then all thalassaemic children must undergo regular ophthalmological evaluation to enable early detection of ocular changes.

References

1. Propper RD, Button LN, Nathan DG. New approaches to the transfusion management of thalassemia. Blood 1980;55:55-60.
2. Olivieri NF, Nathan DG, Macmillan JH, et al. Survival in medically treated patients with homozygous beta thalassemia. N Engl J Med 1994;331:574-578.
3. Kontoghiorghes GJ. Ethical issues and risk/benefit assessment of iron chelation: advances with deferiprone/deferoxamine combinations and concern about the safety, efficacy and costs of deferasirox. Hemoglobin 2008;32:1-15.
4. Galanello R. A thalassemic child becomes adult. Rev Clin Exp Hematol 2003;7:4-21.
5. Choudhry VP, Naithani R. Current status of iron overload and chelation with deferasirox. Ind J Pediatr 2007;4:59-64.
6. Chen SH, Liang DC, Lin HC, Ching SY, Cheng LJ, Liu HC. Auditory and visual toxicity during deferoxamine therapy in transfusion-dependant patients. J Pediatr Hemaol Oncol 2005;27:651-653.
7. Gartaganis SP, Zoumbos N, Koilopoulos JX, Mela EK. Contrast sensitivity function in patients with beta-thalassemia major. Acta Ophthalmol Scand 2000;78:512-515.
8. Lakhanpal V, Schocket SS, Jiji R. Desferoxamine (Desferal)-induced toxic retinal pigmentary degeneration and presumed optic neuropathy. Ophthalmology 1984;91:43-51.
9. Sorcinelli R, Sitzia A, Figus A, Lai ME. Ocular findings in beta-thalassemia. Metab Syst Ophthalmol 1990;13:23-25.
10. Lam DSC, Lam TKL, Patrick C, Ho PCP. Ocular findings in patients with _-thalassemia major receiving blood transfusions and desferrioxamine. J Hong Kong Med Assoc 1991;43:133-136.
11. Olivieri NF, Buncic JR, Chew E, et al. Visual and auditory neurotoxicity in patients receiving subcutaneous desferroxamine infusions. N Engl J Med 1986;314:869-873.
12. Sanders ST, Suri M, Ross I. Hereditary hyperferritinemia-cataract syndrome and differential diagnosis of hereditary haemochromatosis. Postgrad Med J 2003;79:600-601.
13. Lai TYY, Lee GKY, Chan WM, Lam DSC. Rapid development of severe toxic retinopathy associated with continuos intravenous deferoxamine infusion. Br J Ophthalmol 2006;90:243-244.
14. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. Indian J Ophthalmol 2010;58:125-130.
15. Chen H, Lukas TJ, Du N, Suyeoka G, Neufeld AH. Dysfunction of the retinal pigment epithelium with age: increased iron decreases phagocytosis and lysosomal activity. Invest Ophthalmol Vis Sci 2009;50:1895-1902.
16. García-Castiñeiras S. Iron, the retina and the lens: a focused review. Exp Eye Res 2010;90:664-678.
17. Wong RW, Richa DC, Hahn P, Green WR, Dunaief JL. Iron toxicity as a potential factor in AMD. Retina 2007;27:997-1003.