JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
KERMANI I A, DOLATKHAH R ,DIBAVAR M, KAZEMI H, ZIAEEI J E, SANAAT Z, FAKHARI A. OPHTHALMOLOGIC AND AUDIOLOGIC PROBLEMS IN BETA THALASSEMIA PATIENTS TREATED WITH PROLONGED CHELATION THERAPY. Journal of Clinical and Diagnostic Research [serial online] 2008 February [cited: 2008 February 3]; 1:622-626 Available from http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month=February&volume=2&issue=1&page=622-626&id=70

SHORT ORIGINAL ARTICLE

Ophthalmologic and Audiologic Problems In Beta Thalassemia Patients Treated With Prolonged Chelation therapy

ASVADI-KERMANI I [1], DOLATKHAN R[2],DIBAVAR M[3], KAZEMI AH[4], EIVAZEI ZIAEI J[4], SANAAT Z[6], FAKHARI A[7]

ABSTRACT

Background: The main aim of chelation therapy in iron overload is to achieve an iron balance and to prevent haemosiderosis. The objective of this study was to Determine visual and hearing problems in adults with beta major and Intermediate Thalassemia who received Desferrioxamine (DFO) as chelation.

Patients and Methods: Fifteen patients aged 16 to 63 years, who received DFO by intravenous and subcutaneous route on regular program, were evaluated for 5 years. Variables such as age, sex, serum ferritin, DFO dose and duration of treatment gathered by a researcher designed questionnaire. Patients were examined by ophthalmologist and otolaryngologist. Data was collected using specific questionnaire and analyzed by SPSS 11 software.

Results: The mean serum ferritin level was 2025ng/ml and the mean treatment dose of DFO was 45mg/kg/day, 4 or 5 times a week. VEP (Visual Evoked Potential) and ERG (Electro Retino Graphy) ophthalmologic tests were negative in all of the patients. Two patients (13.3%) presented with cataract, and 2 others (13.3%) showed moderate visual loss. A mild, bilateral, high-frequency hearing loss developed in one patient. There was no significant relation between the serum ferritin levels and these problems.

Conclusion: These findings show any significant statistical relation between visual andaudiologic abnormalities and the use of high dose DFO or lower serum ferritin levels in our cases, yet regular ophthalmologic and audiologic examinations are advised for all thalassemic patients.

Keywords: Desferrioxamine, Thalassemia, Ophthalmologic problems, Audiologic problems

INTRODUCTION

Hearing loss is observed in a large percentage of patients during intensive DFO therapy. The defect is correlated with the total monthly dose of DFO received, and it is more frequent in younger patients with low serum ferritin levels. The hearing defect should be detected early, performing an audiogram at least yearly, or whenever symptoms, even subtle, are reported [1].

Cataract has developed in some Experimental animals treated with deferoxamin and have been reported on rare occasions in patients receiving deferoxamin. Before beginning treatment, patients should be checked for cataracts by an ophthalmologist. Thereafter they should have yearly ophthalmologic examinations [2].Patients who develop hearing and/or sight problems are generally advised to stop the use of DFO for a time, restarting treatment at a lower dose once complications improve or disappear [3].

Patient and Method

Fifteen patients affected with Beta-Thalassemia, who received chelating therapy were evaluated for 5 years. They received chelation therapy for their iron overload due to transfusions. The iron overload was controlled by serum levels of ferritin. The mean age range of the cases was 36.33 years (16-63 years old). About 60 % (9 cases) were female and 40 %(6 cases) were male, of them 8 cases (53.3%) were major thalassemia and 7 cases (46.7%) had intermediate variant. They received DFO by intravenous and subcutaneous route on regular program. Questionnaires completed for each patient and variables as age, sex, serum ferritin levels, Desferrioxamine dose and duration of treatment and duration of transfusion gathered. All of the patients were referred to ophthalmologist and otolaryngologist. The ophthalmologist examined patients and evaluated them for: changes in the retinal pigmentation (Limbos or Sclera hyperpigementation), cataract, retinal vessel abnormalities and visual side effects of DFO, such as visual loss, loss of color vision, central scotoma, night blindness. The specific Ophthalmological and Otolaryngological tests including Electro Retino Graphy (ERG) and VEP (Visual Evoked Potential) tests also been checked for them. Otolaryngical examinations, Pure Tone Audiometry and Tempanometry were performed on the patients by an expert otolaryngologist. Sinuses, nose and larynx of the patients were examined too. They were asked for problems such as tinnitus, vertigo, and hearing Hearing changes depended on the times or places and deafness, SPSS11 software was used for data analysis. Results were considered significant when the P-value was less than 0.05.

Institution: Hematology and Oncology Research Center - Tabriz University of Medical Sciences. Shahid Ghazi Tabatabai Hospital
1.Professor of Hematology and Oncology,
2.MD,Hematology and Oncology Research Center,Tabriz University of Medical Sciences.
3. MD,Ophthalmologist,
4. MD,Otolayngologist,
5. Associated Professor of Hematology and Oncology,
6. Assistant professor of Hematology and Oncology
7. Assistant Professor of psychiatry
Corresponding Author: Roya Dolatkhah MD, Hematogy and Oncology Research Center - Tabriz University of Medical Sciences,Thalassemia and Hemophilia Center, Shahid Ghazi Tabatabai Hospital, Daneshghah Street, Tabriz,Iran
Tel:+98 (0)411 3361358 Fax:+98 (0)411 3343844. Email address: royadolatkhah@yahoo.com

Results

The results are summarized in [Table/Fig 1].The mean serum ferritin level was 2025ng/ml and the mean treatment dose of DFO was 40mg/kg/day, 4 or 5 times a week. The patient received on the average 16.06 years blood transfusion therapy and it was 10.86 years for DFO therapy. [Table/Fig 1]VEP and ERG tests were negative in all of the patients. Two cases (13.3%) presented Posterior Sub Capsular Cataract (PSCC), the cases had not senile cataract. Two others showed moderate visual loss that was improved after reduction of DFO dose. One of These patients had limbos and sclera hyper pigmentation too. There was no significant relation between DFO dose and presentation of cataract (P=0.495), visual loss (p=0.109) and hyper pigmentation (P=0.289).Also there was no correlation between Ophthalmologic problems and duration of DFO therapy or transfusion [Table/Fig 2].There was no significant correlation between serum ferritin level and presentation of cataract and visual loss (P=0.415 and P=0.130 respectively).

Furthermore, three cases (20 %) had chronic sinusitis (frontal and maxillary), because of the skeletal deformities, and 2 of them had moderate epistaxis, due to low platelet count. A mild bilateral high-frequency hearing loss developed in one patient (case no 8) who had abnormal audiogram with deficit mostly in high frequency range (4000-8000 Hz).This patient was on 50 mg/kg/dose DFO and by reduction of DFO dose to 30 mg/kg/dose, audiogram showed partial recovery. There was no significant correlation between the presentation of hearing loss, DFO dose (P=0.209), duration of DFO therapy (P=1.000) and duration of transfusion (P=0.912). The patients evaluated for 5 years. The patients' mean

blood transfusion date was 16.06 years and for DFO therapy was 10.86 years.

Table/ Fig 1. Evaluation of patients affected with Beta Thalassemia

Patients No	Age years	Sex	Type	DFO dose Mg/kg/day	Duration of DFO Treatment years	Duration of Transfusion years
1	26	F	MT*	40	15	26
2	17	M	MT	30	6	12
3	41	F	IT**	40	7	14
4	53	M	IT	50	15	16
5	47	M	MT	50	10	21
6	16	F	MT	30	15	16
7	36	F	IT	30	1	4
8	63	M	IT	50	13	16
9	36	F	MT	50	6	7
10	41	F	IT	40	8	12
11	28	F	IT	50	14	20
12	49	F	MT	50	14	16
13	29	M	MT	40	20	28
14	22	M	MT	30	15	13
15	41	F	IT	20	4	20
Mean	36.33	-	-	40	10.86	16.06

*Major Thalassemia
**Intermediate Thalassemia

Table/Fig 2
Spearman's rho correlations

	DFO dose Mg/kg/day	Duration of DFO treatment	Duration of Transfusion
Cataract	P=0.495	P=0.684	P=0.513
Visual loss	P=0.109	P=0.321	P=0.871
Hyperpigmentation	P=0.289	P=0.740	P=0.912

Discussion

We studied 15 regular transfused patients who were chelated with DFO,they received packed red cell every 25 days , and DFO 45mg/kg/day , 4 or 5 times a week. Only 2 cases (13.3%) showed moderate visual loss and one (6.6%) had mild high frequency hearing loss. As a whole about 86.7% and 93.4% of the patients had not any visual and hearing abnormalities respectively. Likewise, Cohen [4], in a study in children hospital of Philadelphia noted that 94% of their patients had no evidence of drug induced visual or auditory abnormalities.

The visual and hearing abnormalities therapy with deferoxamin has been reported in higher frequency in previous studies, even through the patients received large doses of the chelating agents or who had only modest amount of excessive Iron [4]. In contrast Karimi showed hearing loss in his patients which affected 44.7%in the right side and 41.8%in the left side [5]. They also noted significant correlation between doses of drug given at each episode of DFO therapy and hearing loss [5]. In our case hearing loss was dependent on the DFO and by reducing the dose it subsided but, there was no significant correlation between the dose of DFO and duration of therapy in all of patients (P=0.209, P=1.000).Like our results no correlation found between duration of DFO therapy and sensorioneural deficits, in same studies [5], but Gallant et al in a study, documented visual and auditory neurotoxicity in 42 of 86 patients with transfusion dependent anemia who were chelating daily with subcutaneous Deferoxamin [7]. Auditory deterioration and improvement, demonstrated serially in individual patients receiving and not receiving deferoxamin, respectively, provided convincing evidence for a cause-and- effect relation between deferoxamin administration and ototoxicity [7].

However patients who have diabetes mellitus or these are being treated with psychotropic drugs may also be at risk of developing such problems, even if they are receiving correct doses of DFO. It has been proved that these conditions increase the

access of DFO to the central nervous system [3].These findings are concordant with our own, because those cases suffered from diabetes showed visual problems (as cataract) and hearing loss. In one study, 21 out of 104 patients (20.2%) presented with high frequency sensorineural hearing loss (SNHL), either unilateral or bilateral. No ototoxic factor, other than DFO, was present in any of the patients. Meanwhile patients with SNHL presented with relatively lower serum ferritin levels than those with normal hearing, however no statistically significant difference was observed [8].

Either we used low doses of DFO (20-50 mg/kg/dose), or because of the paucity of our cases (only 15 cases), it seems that other studies with more cases are necessary for clarifying all of these discrepancies.

Conclusion

The data implicates high-dose deferoxamin as a central factor in the pathogenesis of the neurotoxicity (visual symptoms, abnormal audiograms, or prolonged evoked potentials) (6).Thus, careful regulation of the deferoxamin dosage and regular ophthalmologic and audiologic examination is recommended every six months in those without problems and more frequently in young patients with normal serum ferritin values and in those with auditory dysfunction (7). A dose of 50 mg/kg is recommended in those without abnormalities. With mild toxicity, a reduction to 30 or 40 mg/kg per dose should result in a reversal of the abnormal results to normal within four weeks. Moderate abnormalities require a reduction of deferoxamin to 25 mg/kg/dose with careful monitoring [7]. Thus we suggest periodical audiologic and retinal checkups and a low dosage of DFO (below 50 mg/kg/dose) given on at least 5-6 days a week for the prevention and prompt diagnosis of audiologic and ophthalmologic complications especially in adult patients. Because all of our patients have been referred from children hospital to our center, and beginning of their DFO was before of our study, their Pre DFO status was not clear for us. So a complete control studies for DFO therapy side effects must be done before beginning of DFO therapy.

References

[1] Borgna-Pignatti C.Galanetto R.,Thalassemias and related disorders.In:P.Greer J.,Foerster J.,N.Lukens J.,M.Rodgers G.,Paraskevas F.,Glader B.,Wintrobe's Clinical Hematology,11th edition. Lippincott Williams&Wilkins,2004;P:1339-1340

[2] C.Andrews N.,Disorders of iron metabolism.In:I.HandinR.,E.Lux S.,P.Stossel T.,Blood Principle and Practice of hematology,second edition.Lippincott Williams&Wilkins,2002;P:1424-1427

[3] Eleftheriou A. Iron overload and iron chelation,In:About thalassemia,Thalassemia International Federation Publication,2003;P:38-61

[4] Cohen A., Martin M,Mizanin J,konkle DF,Schwartz E,Vision and hearing during deferoxamine therapy.J Pediatr, 1990 Aug; 117(2Pt 1):326-30.

[5] Karimi M,Asadi-Pooya AA,Khademi B,asadi-pooya K,Yarmohammadi H,Evaluation of the incidence of sensorineural hearing loss in beta-thalassemia major patients under regular chelation therapy with desferoxamine.Acta Haematol.2002;108(2):79-83.

[6] Olivieri NF,Buncic JR,Chew E,Gallant T,Harrison RV,Keenan N,et al.Visual and audiory neurotoxicity in patients receiving subcutaneous deferoxamine infusions.N Engl J Med.1986 Apr 3;314(14):869-73

[7] Gallant T, Boyden MH, Gallant LA, Carley H, Freedman MH.Serial studies of auditory neurotoxicity in patients receiving deferoxamin therapy. Am J Med. 1987 Dec; 83(6):1085-90.

[8] Kontzoglou G,Koussi A,Economou M,tsatra I,Perifanis V,Noussios G et al,Longterm audiological evaluation of beta-thalassemia patients.Acta otorhinolaryngol Belg.2004;58(2):113-7