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Original Article

Hearing Loss in Thalassemic Children on Chelation Therapy

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Abstract

Background: Thalassemia is a common genetic hematological disorder worldwide. It is also common in North India including Jammu region. These patients need lifelong repeated blood transfusions and iron chelation therapy for their survival. Chelation therapy is known to be associated with various complications including sensorineural hearing loss (SNHL). Till now, no data are available regarding SNHL in pediatric thalassemia major patients in Jammu region. Hence, we planned a study to assess the prevalence of hearing loss in children with thalassemia major in the age group of 10–20 years.

Methods: All the children with beta-thalassemia major in the age group of 10–20 years registered with Thalassemia Day Care Center, Department of Pediatrics, SMGS Hospital, Government Medical College, Jammu, were enrolled in this cross-sectional study. Hearing was assessed by pure tone audiometry. Clinical and demographic data of these patients were recorded on pretested pro forma and analyzed.

Results: A total number of 34 children with thalassemia in the age group of 10–20 years were enrolled in this study which comprised 18 males and 16 females. Out of these 34 patients, 5 (14.7%) were found to have SNHL and 1 (2.9%) had conductive hearing loss. Four of the five patients in SNHL group had low- as well as high-frequency mild hearing loss (25–40 db) while one patient had high-frequency mild hearing loss at 4000 HZ. Four out of these five patients had unilateral hearing loss on the left side while one had bilateral SNHL. Two out of five patients in the SNHL group were taking chelation therapy in the form of combination of deferiprone and deferasirox at the dose of 75–100 mg/kg/day and 30–40 mg/kg/day, respectively, for more than 5 years. The other three patients were taking only deferasirox at the dose of 30–40 mg/kg/day for more than 5 years.

Conclusions: Regular blood transfusions and chelation therapy are essential for long-term survival of thalassemia major patients but are also associated with complications like SNHL.

Key words: Blood transfusion, Iron chelation, Sensorineural hearing loss, Thalassemia

INTRODUCTION

Thalassemia is a common hematological disorder resulting into chronic anemia. It was first described by Cooley in 1925 and the first case of β-thalassemia in India was reported by Dr. Mukherjee from Calcutta in 1938.[1] The frequency of thalassemia trait in India is around 3.5–15% and every year more than 10,000 affected children are born in India.[2] Thalassemia is a hemoglobinopathy which is characterized by reduction or absence of β-globin chain production due to mutation in gene encoded for the same on the short arm of chromosome 11p.[3] In β-thalassemia, β-chain synthesis is decreased, so excessive α-chains precipitate in red blood cells membrane and damage it leading to hemolysis both in bone marrow and peripheral circulation mainly in spleen.

Beta-thalassemia major presents in early infancy (6–18 months) as hemoglobin levels decline with progressive pallor, splenohepatomegaly, and boney changes. These patients require lifelong regular blood transfusion

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which leads to iron overload. Other mechanisms causing iron overload in thalassemic patients are increased absorption from intestines to provide adequate iron to accelerated erythropoiesis although ineffective as seen in poorly transfused thalassemia major patients or those with thalassemia intermedia.[4] Now, as iron overload occurs, transfusion and other iron-binding proteins get progressively saturated and free iron radicals are generated that cause damage to vital organs such as liver, heart, and endocrine organs resulting in liver fibrosis and eventually cirrhosis, cardiac siderosis which causes acute cardiac death with arrhythmia or intractable cardiac failure and endocrine disturbances such as diabetes mellitus, hypogonadism, growth hormone deficiency hypothyroidism, and adrenal insufficiency.[5] Hence, thalassemic patients require iron chelation therapy to remove excess iron from body. Iron chelation is indicated when serum ferritin levels increase to more than 1000 ng/ml. Desferrioxamine (DFO) is the gold standard iron chelator. It usually reverses functional complications due to iron overload such as liver fibrosis and arrhythmia, but the complication due to extensive tissue damage such as diabetes, hypothyroidism, and myocardial sclerosis cannot be reversed. It has disadvantages like poor bioavailability and can be administered only by parenteral route. It is also known to cause retinal and optic dysfunction and high-frequency hearing loss.[6]

Deferiprone is an oral iron chelator. It chelates cardiac iron better than DFO but is less efficacious for hepatic iron. Its side effects are arthropathy, agranulocytosis elevation of hepatic enzymes, and adverse redistribution of iron. Deferasirox has good bioavailability and a long half-life so used as once daily dose. Its side effects include renal toxicity, gastrointestinal disturbance, rash, and elevation of hepatic enzymes. It has been reported that these agents when used in high doses for long duration in patients with high ferritin can lead to auditory disturbances, although reversible on early cessation of offending chelating agent.[7]

Therefore, we planned a study in the Department of Pediatrics in collaboration with the Department of ENT, Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, to assess the hearing status of all the thalassemic patients in the age group of 10–19 years registered with Thalassemia Day Care Center, SMGS Hospital , Jammu.

METHODS

All of the children with beta-thalassemia in the age group of 10–20 years registered with Thalassemia Day Care Center, Department of Pediatrics, SMGS Hospital, Jammu, were enrolled in this cross-sectional study after obtaining written informed consent from the subjects and clearance from the Institutional Ethical Committee, Government Medical College, Jammu. Hearing was assessed by pure tone audiometry (PTA) with pure tone air and bone conduction thresholds at the frequency of 250–4000 HZ in the Department of ENT, Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu. Clinical and demographic data of these patients were recorded in pretested pro forma and analyzed which included age, gender, hearing status, average hemoglobin, and average serum ferritin levels over last 1 year and chelating agent and its dose and duration. Hemoglobin estimation was done by automated analyzer, whereas quantitative estimation of serum ferritin was done by chemiluminescence microparticle immunoassay.

Statistical Analysis

Descriptive statistics were used to describe baseline variables. Numerical variables were fisted tested for normality using Kolmogorov–Smirnov test for normality. Normal distributed independent variable was compared by Student's t-test after evaluating equality of variance by Levene's test, whereas nonparametric test (Mann–Whitney U) was used for variable with a skewed distribution.

RESULTS

A total number of 34 children with thalassemia in the age group of 10–20 years were enrolled in this study which comprised 18 males and 16 females.

Out of these 34 patients, 5 (14.7%) were found to have sensorineural hearing loss (SNHL) and 1 (2.9%) had conductive hearing loss (CHL). Four out of the five patients in the SNHL group had low- as well as high-frequency mild hearing loss (25–40 db) while one patient had high-frequency mild hearing loss at 4000 HZ. Four out of these five patients with SNHL had unilateral hearing loss on the left side while one had bilateral SNHL. One patient with CHL had unilateral hearing loss in the left ear at all frequencies.

Average hemoglobin was observed to be 7.5 g%, 8.5 g%, and 8.3 g% in the SNHL group, CHL group, and normal hearing group, respectively [Figure 1]. Patients in the SNHL group received on an average 315 blood transfusions while the patients with normal hearing received an average of 285 blood transfusions. Patients in the SNHL group had an average serum ferritin of 6015.20 ng/ml while patients without any hearing loss had average serum ferritin of 4179.79 ng/ml with no statistically significant difference ($P = 0.13$) [Table 1]. Two out of five patients in the SNHL group were taking chelation therapy in the form

of combination of deferiprone and deferasirox at the dose of 75–100 mg/kg/day and 30–40 mg/kg/day, respectively, for more than 5 years. The other three patients were taking only deferasirox at the dose of 30–40 mg/kg/day for more than 5 years [Table 2].

DISCUSSION

Of the 34 patients with beta-thalassemia major in the age group of 10–20 years, five were found to be having SNHL which gave the prevalence of 14.7% which is relatively lower as compared to the findings made by other studies such as Kong *et al.*[8] reported 57.4% and Khan *et al.*[9] 45.45%. Relatively lower prevalence in our study may be due to the fact that none of these patients were on DFO which is known to cause ototoxicity and small cohort size in our study. Tanphaichitr *et al.* also in their study observed that there was a low incidence of ototoxicity in beta-thalassemia patients after exposure to iron chelators. Out of 100 enrolled thalassemia patients on iron chelation therapy with single deferasirox, deferiprone, DFO, or combination, they detected SNHL in seven cases, but only four were found to be associated with iron chelation.[10]

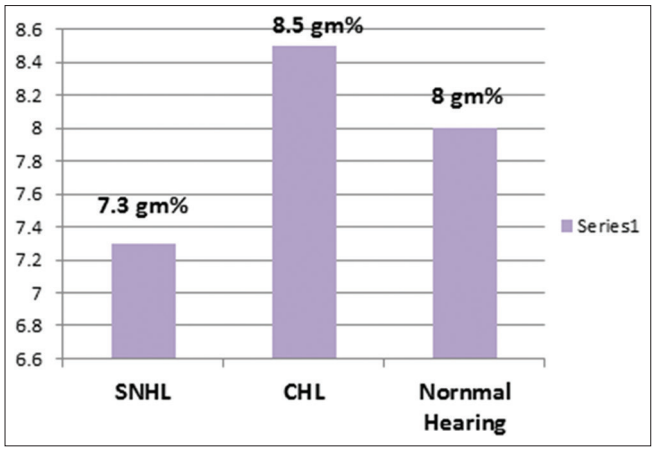

Figure 1: Average hemoglobin levels

Table 1: Average serum ferritin levels

Group	Mean±(SD) serum ferritin levels (in ng/ml)
Sensorineural hearing loss	6015.20 (1526.10)
Normal hearing	4179.79 (2546.70)

P=0.13, SD: Standard deviation

Table 2: Correlation between hearing loss and iron chelation drug

Hearing status	Deferasirox	Deferiprone+Deferasirox
Sensorineural hearing loss	3	2
Conductive hearing loss	0	1
Normal hearing	24	4

No significant difference in average serum ferritin levels ($P < 0.05$ was taken as significant) was observed among patients with and without SNHL. However, Porter *et al.* in their study reported a protective effect of iron overload against ototoxicity in patients with thalassemia major on DFO as chelation therapy.[11]

We observed that all the five patients with SNHL were on deferasirox as chelation therapy for more than 5 years. Two of them were also taking deferiprone in addition to deferasirox. Khan *et al.* in their study reported a prominent relationship between the chelating agents and SNHL. In their study, it was observed that out of a total of 198 cases in the age group of 60–300 months, 98 (45.45%) cases had SNHL. They reported that chances of SNHL increase with longer duration of deferasirox usage.[9] Yadav *et al.* in their study reported that usage of DFO for longer duration and in higher doses was associated with increased incidence of SNHL in patients with beta-thalassemia major.[12] Similarly, Kong *et al.* in their study observed that out of 54 enrolled beta-thalassemia major cases, 31 (57.4%) showed hearing loss. They reported a significant positive correlation between average daily DFO dose and hearing loss in the left ear in the range of 2000 Hz and 4000 Hz.[8] In our study, we observed that out of five cases with SNHL, four had hearing loss on the left side and the remaining one had bilateral hearing loss.

None of the five patients with SNHL in the study complained of any difficulty in hearing or tinnitus and it was only on PTA that hearing loss was diagnosed. Hence, all thalassemic major patients while on chelation therapy should be assessed for hearing status on regular basis so that even mild SNHL could be picked up early and enabling the early intervention in the form of titrating the dose of chelating agent or switching to alternative agent.

One patient who had CHL was found to be having secretary otitis media on otoscopy which was an incidental finding.

CONCLUSIONS

Regular blood transfusion and iron chelation therapy are the key elements in the management of thalassemia major patients. In this study, it was observed that patients on deferasirox as chelation agent can also develop SNHL , hence need regular auditory assessment. A larger study is recommended to ascertain these observations.

REFERENCES

1. Cooley TB. A series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans Am Pediatr Soc1925;37:29-30.

2. Varawalla NY, Old JM, Sarkar R, Venkatesan R, Weatherall DJ. The spectrum of beta thalassemia mutations on the Indian subcontinent: The basis of prenatal diagnosis. Br J Hematol 1991;78:242-7.
3. Lahiry P, Al-Attar SA, Hegele RA. Understanding beta-thalassemia with focus on the Indian subcontinent and the Middle East. Open Hematol J 2008;2:5-13.
4. Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Guidelines for the Clinical Management of Thalassemia. 2nd ed. Nicosia (CY): Thalassemia International Federation; 2008.
5. Chinnabhandar V, Radhakrishnan N, Malhotra P, Sachdeva A. Pathophysiology of thalassemia. In: Sachdeva A, editor. Thalassemia National Guidelines for Management of Transfusion-Dependent and Non-Transfusion-Dependent Thalassemia. 1st ed. India: Indian Academy of Pediatrics India; 2014. p. 24-36.
6. Gupta AK, Radhakrishnan N, Sachdeva A. Chelation therapy in thalassemia. In: Sachdeva A, editor. Thalassemia National Guidelines for Management of Transfusion-Dependent and Non-Transfusion-Dependent Thalassemia. 1st ed. India: Indian Academy of Pediatrics India; 2014. p. 180-6.
7. Al-Khabori M, Bhandari S, Al-Huneini M, Al-Farsi K, Panjwani V, Daar S. Side effects of deferasirox iron chelation in patients with beta thalassemia major or intermedia. Oman Med J 2013;28:121-4.
8. Kong MH, Goh BS, Hamidah A, Zarina AL. The prevalence of sensorineural hearing loss in beta-thalassemia patients treated with desferrioxamine. Med J Malaysia 2014;79:9-12.
9. Khan MA, Khan MA, Seedat AM, Khan M, Khuwaja SF, Kumar R, *et al*. Sensorineural hearing loss and its relationship with duration of chelation among major beta-thalassemia patients. Cureus 2019;11:e5465.
10. Tanphaichitr A, Kusuwan T, Limviriyakul S, Atipas S, Pooliam J, Sangpraypan T, *et al*. Incidence of ototoxicity in pediatric patients with transfusion-dependent thalassemia who are less well-chelated by mono-and combined therapy of iron chelating agents. Hemoglobin 2014;38:345-50.
11. Porter JB, Jaswon MS, Huehns ER, East CA, Hazell JW. Desferrioxamine ototoxicity: Evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. Br J Haematol 1989;73:403-9.
12. Yadav M, Yadav J, Tiwari AD, Abrol P, Sood S. Effect of iron chelating agents desferrioxamine, deferiprone and their combination on brainstem auditory evoked potential (BAEP). JK-Pract 2011;17:29-34.

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