KBB ve BBC Dergisi 16 (1):10-15, 2008

Pure Tone and High Frequency Audiometries in Beta Thalassemia Major

Beta Talasemi Majorda Saf Ses ve Yüksek Frekans Odyometrileri

***Bilgehan BUDAK, Ph.D., **Nuray BAYAR MULUK, MD, ***Fatma GÜMRÜK, MD, ****Gürer BUDAK, M.D.**

* Hacettepe University, Faculty of Medicine, Department of ENT and Audiology
** Kırıkkale University, Faculty of Medicine, ENT Department
*** Hacettepe University, Faculty of Medicine, Pediatric Hematology Department
**** Gazi University, Faculty of Medicine, Private Service

ABSTRACT

Objectives: This retrospective study evaluated the hearing levels in patients with beta Thalassemia major (TM).
Material and Methods: Study group was consisted of 9 patients with TM. They were on a regular transfusion-chelation program by desferrioxamine (DFO) (Desferal®). Control group consisted of 9 healthy subjects. In the study group, hemoglobin (Hb); ferritin; total transfusion count (TTC), transfusion per year (TY) and duration from the last transfusion (DLT) values were obtained. Subjects were evaluated by pure tone (PTA) (0.25-8.0 kHz) and high frequency audiometries (HFA) (8.0-16.0 kHz).
Results: Mixed type (11.1%) and conductive type (5.5%) hearing losses were present in the study group. PTA and HFA results were not different between the study and control groups. In older patients, hearing thresholds were more decreased. In the longer living patients, the severeness of the disease may be less than the others. Male gender; higher Hb, DFO, TY and DLT values cause decrease; and higher serum ferritin levels and higher TTC cause increase in hearing thresholds. DFO binds excess iron and prevents iron intoxication.
Conclusion: If iron-storage secondary to the transfusions is decreased by using DFO, ear toxicity gets lower. These patients should be followed by regular audiologic evaluation to recognize and prevent hearing impairment.

Keywords
Beta thalassemia major (TM), hearing loss, high frequency audiometry, desferrioxamine (DFO)

ÖZET

Amaç: Bu retrospektif çalışmabeta Talasemi major (TM) olan hastalarda işitme seviyelerini değerlendirmektedir.
Yöntem ve Gereçler: Çalışma grubu**,** TM olan 9 hastadan oluşmuştur. Bu hastalar desferrioxamine (DFO) (Desferal®) ile düzenli transfüzyon-şelasyon programındadır. Kontrol grup 9 sağlıklı kişiden oluşmuştur. Çalışma grubunda hemoglobin (Hb); ferritin; total transfüzyon sayısı (TTS), bir yıldaki transfüzyon sayısı (TS) ve son transfüzyondan sonraki süre (STSS) değerleri elde edilmiştir. Kişiler saf ses (SSO) (0.25-8.0 kHz) ve yüksek frekans odyometrileri (YFO) (8.0-16.0 kHz) ile değerlendirilmiştir.
Bulgular: Çalışma grubundaki kulakların %11.1'inde mikst tip ve %5.5'inde iletim tipi işitme kayıpları mevcuttur. Çalışma ve kontrol grupları arasında SSO ve YFO sonuçları bakımından fark yoktur. Daha yaşlı olan hastalarda, işitme eşikleri daha düşük olarak bulunmuştur. Daha uzun yaşayan hastalarda, hastalığın şiddeti diğerlerine göre daha az olabilmektedir. Erkek cinsiyet, daha yüksek Hb, DFO, TS ve STSS değerleri, işitme eşiklerinde düşmeye; ve daha yüksek serum ferritin seviyeleri ve daha yüksek TTS, işitme eşiklerinde yükselmeye sebep olmuştur. DFO fazla demiri bağlayarak, demir toksisitesini önlemektedir.
Sonuçlar: Eğer transfüzyonlara sekonder demir deposu DFO kullanılarak azalırsa, kulak toksisitesi azalır. TM olan hastalarının işitme azlığını saptamak; ve önlemek için, düzenli odyolojik değerlendirme gereklidir.

Anahtar Sözcükler
Beta Talasemi Major (TM), işitme kaybı, yüksek frekans odyometrisi, desferrioxamine (DFO)

Çalışmanın Dergiye Ulaştığı Tarih: ***25.05.2007*** *Çalışmanın Basıma Kabul Edildiği Tarih:* ***07.12.2007***

≈

Correspondence

Nuray Bayar MULUK, MD
Birlik Mahallesi, Zirvekent 2. Etap Sitesi, C-3 blok, No: 62/43
06610 Çankaya / ANKARA TURKEY
Tel: +90 312 4964073 , +90 532 7182441 Faks: +90 318 2252819
E-posta: nbayarmuluk@yahoo.com

INTRODUCTION

The thalassemias are inherited disorders of hemoglobin (Hb) synthesis. Thalassemia major occurs in the offspring of 2 heterozygote beta thalassemia parents. The gene that produces the beta-globin chain normally found in hemoglobin (Hb) A is absent or diminished. This leads to a compensatory increase of Hb F (alpha-gamma Hb) and Hb A2 (alpha-delta Hb). The result is a loss of beta globin and the formation of fetal and A2 type Hb.[1]

If the chronic anemia in these patients is corrected with regular blood transfusions, the severe expansion of the ineffective marrow is reversed. However, by doing so, another source of iron is added, which, together with the excessive iron absorption normally present in such cases, leads to a state of iron overload. In iron overload conditions, it accumulates in various organs, such as the heart, endocrine glands, and liver, resulting in significant damage to these organs.[1]

Desferrioxamine (DFO) is a chelating agent and used in the management of severe iron intoxication [2]. It permits the mobilization and excretion of significant amounts of iron and, when administered over a prolonged period, can prevent or retard the development of chronic iron toxicity.[1] The success of chelation therapy in controlling iron overload in patients with thalassemia major is highly variable and may partly depend on the rate of transfusional iron loading.[3]

It was reported that with the improved life expectancy of beta-thalassemia major patients, new clinical problems, such as hearing loss, must be evaluated. To determine the incidence of sensorineural hearing loss and its relationship to DFO treatment are important issues on this subject.[4]

In the present study, we investigated the audiological disturbances in patients with TM comparing with healthy controls. Hearing evaluation was performed by pure tone audiometry (0.25-8.0 kHz) and high frequency audiometry (8.0-16.0 kHz); and effects of age, gender, hemoglobin, serum ferritin level, DFO treatment, total transfusion count (TTC), transfusion per year (TY) and duration from the last transfusion (DLT) values on hearing thresholds.

MATERIALS AND METHOD

This retrospective study was planned and continued according to the principles outlined in the Declaration of Helsinki.[5]

Subjects

Study group was consisted of 9 patients (5 male, 4 female) with beta thalassemia major and 18 ears of them. All patients were on a regular transfusion-chelation program maintaining a mean hemoglobin level of 11.58 gr/dL. Subjects were receiving desferrioxamine (DFO) chelation treatment with a mean daily dose of 40.55 mg/kg. In laboratory investigation hemoglobin (gr/dL) and serum ferritin levels (micrograms/L) were investigated. Their mean age was 23.3±2.9 (Range 21.0 to 30.0 years).

Control group consisted of 9 healthy patients and hospital staff members (5 male, 4 female) who did not have Cooley's anemia and 18 ears of them. Their mean age was 24.0±2.6 (Range 19.0 to 28.0 years).

There were not acute ear infection, acoustic trauma or head trauma in patients of study and control groups. In the study group, two patients (3 ears), there were sequel of the otitis media. In the study group, total transfusion count (TTC), transfusion per year (TY) and duration from the last transfusion (DLT) values were also obtained.

Method

Audiologic evaluation of all subjects in the study and control groups were performed by pure tone audiometry (PTA) (0.25-8.0 kHz), high frequency audiometry (HFA) (8.0-16.0 kHz) and impedance audiometry. AC-40 Interacoustics Clinical Audiometer and TDH-39 P C6 3918 Telephonics 296D 000-1 ear phone; and Interacoustics Impedance Audiometer were used. Audiological examination results were evaluated according to American National Standards Institute (ANSI-1969) standards.[6]

Statistical analysis: Statistical packet for SPSS (Version 10.0) was used for statistical evaluation. The difference between age and each of 0.25-16.0 kHz of audiological tests of the study and control groups were analyzed by "Mann Whitney U Test". For the study group, effects of age, gender, hemoglobin, ferritin, desferrioxamine, TTC, TY and DLT on hearing thresholds were analyzed by "Linear Regression Analysis".

RESULTS

In the study group, hemoglobin, serum ferritin levels, dose of the DFO treatment, TTC, TY and DLT values were shown on Table 1. In the study group,

Table 1. Hemoglobin, ferritin, DFO, TTC, TY and DLT values of the study group.*

	Study Group			
	Mean	**Standard Deviation**	**Minimum**	**Maximum**
Hemoglobin (gr/dL)	11.58	1.21	10.20	13.50
Ferritin (microgram/L)	5094.11	4704.99	1344.00	16691.00
Desferrioxamine (mg/kg)	40.55	4.44	31.00	47.00
Total Transfusion	538.88	69.08	400.00	638.00
Transfusion per year	27.22	5.24	16.00	34.00
Duration from the last transfusion (Day)	51.55	119.33	0.00	378.00

*DFO: Desferrioxamine, TTC: Total transfusion count, TY: Transfusion per year, DLT: Duration from the last transfusion

mixed type hearing loss was present in 2/18 (11.1%) of the ears (one of them was mild and one of them was very mild); and very mild conductive type hearing loss was present in 1/18 (5.5%) of the ears at pure tone audiometry in patients with otitis sequel; and hearing loss was present in 3/18 (16.6%) of the ears at high frequency audiometry. Pure tone and high frequency audiometry results of the study and control groups were demonstrated on Table 2.

The difference between ages of study and control groups was analyzed by “Mann Whitney U Test”. No statistically significant difference was found (p=0.169).

At pure tone and high frequency audiometries, the differences between each of 0.25-16.0 kHz were analyzed by “Mann Whitney U Test”. The differences were not statistically significant (p>0.05) (See on Table 2).

For the study group, effects of age, gender, hemoglobin, ferritin, desferrioxamine, TTC, TY and DLT on hearing thresholds were analyzed by “Linear Regression Analysis”. As the age increased, hearing thresholds at PTA and HFA decreased (Significant at 0.25 and 14.0 kHz). For males, hearing thresholds were shown more decrease at HFA (Significant at 8.0 and 12.5 kHz). As serum ferritin levels increased, hearing thresholds on HFA increased at 8.0 and 16.0 kHz. As hemoglobin levels increased, hearing thresholds at PTA and HFA decreased. As DFO doses increased, hearing thresholds at PTA and HFA decreased (Significant at 0.25, 10.0 and 14.0 kHz). As TTC increased, hearing thresholds at PTA and HFA increased (Significant at 0.25, 0.5, 2.0, 14.0 and 16.0 kHz). As TY increased, hearing thresholds at PTA and HFA decreased (Significant at 0.25 and 14.0 kHz). As DLT increased, hearing thresholds at PTA and HFA decreased (Significant at 0.25, 8.0 and 14.0 kHz) (See on Table 3).

DISCUSSION

Thalassemia major is characterized by transfusion-dependent anemia. Another consequence of diminished beta-chain production is the formation of excess alpha chains that form tetramers and inclusion bodies because they are less soluble than normal Hb. These inclusion bodies are lethal to developing erythroid precursors and are responsible for most of the severe clinical effects of thalassemia.[1]

There are lots of studies about the audiological evaluation in patients with TM. High frequency sensorineural hearing loss (SNHL)[5]; slight sensorineural deficit (</=35 dB HL) with high frequency losses and a moderate deficit (between 35 and 75 dB HL) without association between age, ferritin level, therapeutic index (DFO/serum Ferritin) and hearing loss[8]; sensorineural hypoacusia with higher "Therapeutic index”[9], stiffness in the middle ear sound transmission system with conductive or mixed type of hearing loss [10] were reported.

In the present study, hearing loss was present in 3/18 (16.6%) of the ears at pure tone audiometry and in 3/18 (16.6%) of the ears at high frequency audiometry of the study group. The differences between PTA and HFA results of the study and control groups were not statistically significant. For the study group, effects of age, gender, hemoglobin, ferritin, desferrioxamine, TTC, TY and DLT on hearing thresholds were analyzed by “Linear Regression Analysis”:

1. As the age increased, hearing thresholds at PTA and HFA decreased. Patients with TM have a short life expectancy. It is unusual for a patient with the most severe form of the disease to survive into adulthood [1]. Therefore, the patients who could live longer, the severeness of the disease may be less than the others.

Table 2. Pure tone and high frequency audiometry results of the study and control groups.

	Study (n=18)				Control (n=18)				
Results	**Mean**	**St.Dev**	**Min**	**Max**	**Mean**	**St.Dev**	**Min**	**Max**	**P***
Age	23.27	2.84	21.00	30.00	24.00	2.61	19.00	28.00	0.169
Pure Tone Audiometry Frequencies									
0.25 kHz	19.72	14.19	5.00	55.00	13.33	8.40	0.00	25.00	0.247
0.5 kHz	14.72	14.08	5.00	55.00	9.44	8.02	-5.00	20.00	0.436
3.0 kHz	9.16	9.58	0.00	35.00	6.94	5.97	-5.00	15.00	0.974
4.0 kHz	6.66	5.14	0.00	20.00	4.16	5.21	-5.00	15.00	0.169
5.0 kHz	5.83	4.92	0.00	15.00	5.55	6.15	-5.00	20.00	0.805
6.0 kHz	13.05	8.93	0.00	35.00	7.77	5.74	0.00	20.00	0.061
8.0 kHz	10.83	9.27	0.00	30.00	6.94	6.21	-5.00	20.00	0.315
High Frequency Audiometry Frequencies									
10.0 kHz	8.88	10.50	0.00	35.00	3.05	5.72	-10.00	15.00	0.134
12.5 kHz	14.44	17.14	-5.00	60.00	4.44	8.02	-10.00	20.00	0.057
14.0 kHz	12.77	21.08	-5.00	65.00	4.44	9.53	-15.00	25.00	0.583
16.0 kHz	22.77	24.92	0.00	65.00	12.77	17.75	-15.00	40.00	0.445

*: p values of Mann Whitney U Test
St. Dev: Standard Deviation

Table 3. Linear Regression Analysis results about effects of age, gender, hemoglobin, ferritin, desferrioxamine, TTC, TY and DLT on hearing thresholds of the study group*

Hearing	Age		Gender		Hemoglobin (gr/dL)		Ferritin (micrograms/L)		Desferrioxamine (mg/kg)		Total Transfusion Count		Transfusion per year		Duration from the last transfusion (Day)	
Thresholds	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**	**p**	**Beta**
0.25 kHz	0.016	-1.542	0.203	-0.371	0.072	-0.882	0.104	-0.821	0.016	-0.847	0.007	3.012	0.019	-3.059	0.019	-1.255
0.5 kHz	0.062	-1.219	0.326	-0.307	0.245	-0.590	0.378	-0.459	0.094	-0.589	0.025	2.576	0.086	-2.251	0.064	-1.021
1.0 kHz	0.405	-0.624	0.983	0.008	0.541	-0.375	1.000	0.000	0.301	-0.430	0.178	1.745	0.475	-1.084	0.282	-0.689
2.0 kHz	0.107	-1.159	0.920	0.034	0.143	-0.859	0.123	-0.954	0.263	-0.425	0.029	2.803	0.056	-2.897	0.108	-0.974
4.0 kHz	0.590	0.408	0.203	-0.517	0.483	0.443	0.283	-0.721	0.852	0.077	0.781	-0.349	0.941	-0.114	0.656	-0.283
6.0 kHz	0.154	-1.028	0.242	-0.426	0.850	0.107	0.379	-0.529	0.876	-0.058	0.171	1.639	0.244	-1.674	0.214	-0.744
8.0 kHz	0.148	0-.564	0.002	-0.786	0.354	-0.288	0.725	0.112	0.634	-0.096	0.097	1.100	0.325	-0.755	0.038	-0.729
10.0 kHz	0.309	-0.714	0.146	-0.543	0.556	-0.335	0.253	-0.700	0.031	-0.927	0.373	1.035	0.318	-1.424	0.095	-1.040
12.5 kHz	0.249	-0.758	0.047	-0.730	0.837	0.108	0.240	-0.670	0.268	-0.398	0.251	1.257	0.335	-1.274	0.373	-0.485
14.0 kHz	0.023	-1.275	0.126	-0.407	0.354	-0.378	0.164	-0.613	0.033	-0.645	0.016	2.318	0.047	-2.195	0.015	-1.179
16.0 kHz	0.169	-0.681	0.612	-0.124	0.704	-0.148	0.578	0.228	0.691	-0.103	0.029	1.981	0.272	-1.086	0.194	-0.540

*TTC: Total transfusion count, TY: Transfusion per year, DLT: Duration from the last transfusion

2. For males, hearing thresholds were shown more decrease at HFA. Easy sportive activities are performed more in males and this matter may cause to increase in the metabolic rate which may decrease the iron storage.

3. As hemoglobin levels increased, hearing thresholds at PTA and HFA decreased. When hemoglobin levels increased by transfusions, formation of excess alpha chains that form tetramers and inclusion bodies-less soluble than normal Hb-decreased.

4. As serum ferritin levels increased, hearing thresholds on HFA increased. Ferritin is a major iron storage protein in living organisms. Higher ferritin levels shows that the amount of iron storage increased and the toxic effects of the iron to the ear also increased.

5. As DFO doses increased, hearing thresholds at PTA and HFA decreased. As the DFO-iron chelating agent- doses increased, it adheres to the iron and the iron storage decreased. This result may show that the

cause of the ear toxicity is not only DFO itself, but iron storage and total iron amount. When iron storage increased, the ear toxicities on pure tones and high frequencies increased.

6. As TTC increased, hearing thresholds at PTA and HFA increased. Higher TTC shows the disease going on more years. In these patients, there were more iron-storages. Therefore, more ear toxicity was detected.

7. As TY increased, hearing thresholds at PTA and HFA decreased. When more transfusions were performed during the last year, Hb increased. Less alpha-chain and less inclusion bodies cause lesser ear toxicities.

8. As DLT increased, hearing thresholds at PTA and HFA decreased. As the time after the last transfusion gets longer, the need of the frequent transfusion gets lesser. Iron-storage secondary to the transfusion also decreases.

Deferoxamine is a chelating agent that has extended the life expectancy of patients with thalassemia. In the 1980s, many investigators reported otologic toxicity caused by deferoxamine.[11] Chen SH, et al.[11] reported deferoxamine-related hearing impairment (>25 dB), all at high frequencies of audiologic assessments. Two years later, the hearing impairment had not progressed in any of the patients. There was no association between ototoxicity and ferritin level. They concluded that Deferoxamine at doses lower than 50 mg/kg/d was slightly toxic to the ears. The ototoxicity probably relates to individual susceptibility. Regular monitoring of auditory function and close follow-up of abnormal findings are recommended.

Cohen A, et al.[12] studied 52 regularly transfused patients receiving deferoxamine by subcutaneous or intravenous infusion in doses from 26 to 136 mg/kg/day, and whose serum ferritin levels of 185 to 17,775 micrograms/L reflected a wide range of iron stores to determine the frequency of eye and auditory complications and their relationship to drug dosage and iron stores. Patients with audiologic abnormalities did not receive higher doses of deferoxamine and did not have lower serum ferritin levels than patients without such abnormalities. They concluded that ear abnormalities during chelation therapy with deferoxamine may not occur uniformly at as high a frequency as previously reported, even in patients who receive large doses of the chelating agent or who have only modest amounts of excessive iron.

In the present study, our results shows that older age; male gender; higher Hb, DFO, TY and DLT values cause decrease in hearing thresholds and better audiometric results. Higher serum ferritin levels; and higher TTC cause increase in hearing thresholds and worse audiometric results. Since in iron overload conditions, such as severe thalassemia, the transferrin becomes saturated, and free iron is found in the plasma. This iron is harmful since it provides the material for the production of hydroxyl radicals and additionally accumulates in various organs [1].These findings demonstrate that the most important factors related to hearing impairment in TM patients were higher amount of iron-storage secondary to the transfusions; and if iron-storage secondary to the transfusions is decreased by using DFO, the degree of ear toxicity in patients with TM gets lower.

Since there is a risk of ear toxicity at pure tones and high frequencies in patients with thalassemia major, regular audiologic evaluation is imperative in all TM patients so that early changes may be recognized and treatment may be judiciously adjusted in order to prevent or reverse hearing impairment.

REFERENCES

1. Bunn HF. Disorders of hemoglobin. In: Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, eds. Harrison's Principles of Internal Medicine 2. 11th ed. New York: McGraw-Hill Book Company; 1987. p.1518-27.
2. Huang X, Dai J, Huang C, Zhang Q, Bhanot O, Pelle E. Deferoxamine synergistically enhances iron-mediated AP-1 activation: a showcase of the interplay between extracellular-signal-regulated kinase and tyrosine phosphatase. Free Radic Res 2007;41:1135-42.
3. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in {beta}-thalassemia major. Blood 2007 Oct 19; [Epub ahead of print] (Abstract).
4. 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 desferrioxamine. Acta Haematol 2002;108: 79-83.
5. 52nd WMA General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000; 284: 3043-49.
6. Green DS. Pure tone air conduction testing. In: Katz J, ed. Handbook of Clinical Audiology. 2nd ed. Baltimore: Waverly Press, 1983. p.98-108.

7. Kontzoglou G, Koussi A, Economou M, et al. Long term audiological evaluation of beta-thalassemic patients. Acta Otorhinolaryngol Belg 2004;58:113-17.
8. Ambrosetti U, Donde E, Piatti G, Cappellini MD. Audiological evaluation in adult beta-thalassemia major patients under regular chelation treatment. Pharmacol Res 2000;42:485-87.
9. Sacco M, Meleleo D, Tricarico N, Greco Miani A, Serra E, Parlatore L. Evaluation of desferrioxamine ototoxicity in thalassemic patients. Follow-up over a 5-year period and results. Minerva Pediatr 1994;46: 225-30 (Abstract).
10. Onerci M, Aslan S, Gumruk F, et al. Audiologic and impedancemetric findings within thalassaemic patients. Int J Pediatr Otorhinolaryngol 1994;28:167-72.
11. Chen SH, Liang DC, Lin HC, Cheng SY, Chen LJ, Liu HC. Auditory and visual toxicity during deferoxamine therapy in transfusion-dependent patients. J Pediatr Hematol Oncol 2005;27: 651-53.
12. Cohen A, Martin M, Mizanin J, Konkle DF, Schwartz E. Vision and hearing during deferoxamine therapy. J Pediatr 1990; 117 (2 Pt 1): 326-30.