An Analysis of Hearing Function in 52 Patients with Thalassemia Major¶

TALASSEMİ MAJORLU 52 HASTADA İŞİTME FONKSİYONU ANALİZİ

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Summary

Objective: High serum ferritin level, desferrioxamine (DFO) dosage and therapeutic index (TI) are reported to be some of the possible causes for the sensorineural hearing loss (SNHL) in patients with Thalassemia Major. The hearing level of these patients was analyzed and the related mechanism for the occurrence of SNHL was investigated.

Institution: Çukurova University Medical Faculty E.N.T Department.

Patients and Method: Fifty-two patients, 24 females and 28 males, with beta-Thalassemia Major were included in this study. A thorough history was taken and complete otolaryngologic examination was performed. The patients were then referred to the audiology department to evaluate their pure-tone hearing thresholds and tympanometric findings. Serum ferritin levels and DFO doses were identified and the TI was calculated.

Results: Two of 52 patients (3.8 %) were found to have bilateral SNHL. There was insignificant correlation between serum ferritin level, DFO dose, TI and hearing level. However, auditory brainstem recordings in the patient with bilateral mild SNHL demonstrated increase in I-III interpeak latency during 1-year follow-up. On the other hand, the past-medical history of these two patients has indicated several possible factors for hearing impairment.

Conclusion: The incidence of hearing loss in patients with Thalassemia Major was found to be low. This finding may be attributed to the thorough evaluation and close follow-up of the patients during their management. Early identification and follow-up of SNHL are provided with audiometry and ABR. Frequent analysis of serum ferritin level, DFO and TI will help to prevent hearing impairment which may result from one of those.

Key Words: Desferrioxamine, Ototoxicity, Sensorineural hearing loss, Thalassemia Major

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Özet

Amaç: Yüksek serum ferritin düzeyi, desferrioksamin dozu (DFO) ve tedavi indeksi (TI) Talassemi Majorlu hastalarda sensorinöral işitme kaybının muhtemel sebeplerinden biri olarak bildirilmektedir. Bu hastaların işitme seviyeleri analiz edilmiş ve sensorinöral işitme kaybı oluşumu ile ilgili mekanizmalar gözden geçirilmiştir.

Çalışmanın Yapıldığı Yer: Çukurova Üniversitesi Tıp Fakültesi K.B.B A.D.

Hastalar ve Metod: Talassemia Majorlu 52 hasta (24 kadın, 28 erkek) bu çalışmaya dahil edilmiştir. Hastalara ayrıntılı bir anamnez sonrası tam bir baş-boyun muayenesi yapılmıştır. Daha sonra hastalar işitme eşiği ve timpanometrik değerlendirme için odyoloji bölümüne gönderilmişlerdir. Serum ferritin düzeyleri, DFO dozları saptanmış ve TI hesaplanmıştır

Bulgular: 52 hastanın ikisinde (%3.8) bilateral sensorinöral işitme kaybı bulunmuştur. Serum ferritin seviyesi, DFO dozu, TI ve işitme seviyesi arasında korelasyon bulunmamıştır. Ancak, bilateral hafif sensörinöral işitme kaybı tespit edilen hastanın 1 yıllık takibi sonucunda ABR'de I-III interpik latansında uzama bulunmuştur. Diğer yandan, bu iki hastanın geçmiş tıbbi kayıtlarının araştırılmasında işitmeye etkili olabilecek pek çok faktöre de rastlanmıştır.

Sonuç: Talassemia Majorlu hastalarda işitme kaybı insidansı düşük bulunmuştur. Bu bulgu, hastaların tedavileri süresince düzenli değerlendime ve yakın takipleriyle açıklanabilir. İşitme kaybının erken tanı ve takibi odyogram ve ABR ile sağlanabilir. Serum ferritin düzeyi, DFO ve TI sık analizi ile işitme üzerine olumsuz etki yapabilecek bu faktörlerin etkisi önlenebilir.

Anahtar Kelimeler: Desferrioksamin, Ototoksisite, Sensorinöral işitme kaybı, Talassemi Major

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Thalassemias are heterogeneous disorders caused by the deficiency in the synthesis of one or more polypeptide chains of human hemoglobin. In β-thalassemia states, four different mechanisms are responsible for the deficiency in β-chain synthesis including single base substitution, intact codon deletion, premature termination and frameshift mutation (1). β-thalassemia Major is the most severe form of the thalassemias and clinical symptoms are not manifested during the first months of life. The major constituents of this syndrome are severe anemia, transfusion dependency and several other problems related with iron overload. The clinical picture is characterized by small status, relatively large head compared to the body and protuberance of the abdomen. The hemoglobin concentration falls below 3-5 gr /dl. Expansion of the bone marrow and thinning of the cortices give rise to bone abnormalities, which can be delayed or prevented with transfusion therapy. Severe anemia also causes growth retardation and delay in puberty. Pericarditis caused by pericardial iron deposits and infection, myocardial hemosiderosis as a consequence of transfusion therapy, congestive heart failure, arrythmias, progressive impairment of lung function and hepatosplenomegaly are some of the other symptoms in β-thalassemia Major. Appropriate management should be planned for the relief of symptoms and to prevent the deaths due to recurrent infections and cachexia in patients with Thalassemia Major. The four major headings in the primary management of the patients with this disease are transfusion therapy, splenectomy, iron chelation and bone marrow transplantation (1,2).

Auditory and visual toxicity have also been reported in patients with Thalassemia Major. Several mechanisms have been charged and conflicting results have been reported. In order to clarify the issue, serum ferritin levels, DFO management schemes, and audiological parameters are examined and the role of these factors in hearing impairment is discussed in the present study.

Patients and Method

Fifty-two patients with Thalassemia Major, 28 male, 24 female, with the mean age of 10.5 years, ranging between 3-17 years were included in this study. The mean follow-up was 58.8 months (6-200 months). A thorough clinical history was completed inquiring head trauma, ototoxic drugs, the factors which may cause hearing loss in perinatal period. Routine ear-nose and throat (ENT) examination was performed. The patients with normal ENT examination underwent audiological evaluation consisting of pure tone audiogram and tympanometry. Tympanogram and acoustic reflex tests were performed with Interacoustics AZ-7 and pure tone audiometry was performed with Madsen Orbiter 922. Hearing loss was defined as the mean of the thresholds at 3 frequencies (500, 1000 and 2000 Hz) greater than 20 dB. Brainstem evoked response audiometry (BERA) with ERA 2250 Madsen was performed for the patients to whom SNHL was established by audiological examination. Serum ferritin levels and DFO doses were measured before the audiological examination and therapeutic index (TI), the ratio of daily DFO dose to serum ferritin level, was calculated for each patient. Previously recorded values of both DFO doses and serum ferritin levels were used for the calculation of mean DFO doses and mean ferritin levels. Mean TI's of the patients were established from the calculated mean values of both DFO doses and serum ferritin level

Results

Six of 52 patients in the treatment program of DFO, had abnormal audiogram. Among these, 4 patients had conductive, 2 patients had SNHL. In three cases, (2 bilateral, 1 unilateral) conductive hearing loss was found to be due to serous otitis media as reflected by loss of acoustic reflex and type B tympanogram. The other patient with unilateral conductive hearing loss demonstrated type As tympanogram and he was diagnosed as otosclerosis. There was a mild, bilateral, symmetric SNHL especially more profound in 4000 Hz in one patient (Pure tone average was 28 dB in the right, 25 dB in the left ear). Acoustic

Table 1. Data of patients with hearing loss.

PATIENTS WITH HEARING LOSS								
Gender	**Age**	**Hearing Level**	**DFO**	**Ferritin**	**T.I.**	**DFO (Mean)**	**Ferritin (Mean)**	**T.I. (Mean)**
M	5	Bil. CHL	25	1209	0,020	30	1747	0,017
F	17	Bil. SNHL	38	1608	0,022	45	2941	0,015
F	17	Right CHL	37	1135	0,032	34	1512	0,022
F	8	Bil. SNHL	37	4360	0,008	41	1882	0,022
M	8	Bil. CHL	50	1500	0,033	37	1660	0,022
F	15	Right CHL	47	1522	0,030	50	1337	0,037

Bil. : Bilateral
CHL : Conductive Hearing Loss
SNHL : Sensorineural Hearing Loss
TI : Therapeutic Index (daily DFO dose (mg/kg)/serum ferritin level (μg/l)) calculated by the DFO and ferritin values just before the audiological examination
DFO : Desferrioxamine dose (mg/kg/day) just before the audiological examination
Ferritin : Serum ferritin level (μg/l) just before the audiological examination
Mean TI : Calculated mean of the previous therapeutic indices (daily DFO dose (mg/kg)/serum ferritin level (μg/l)) depending on the recorded DFO doses and serum ferritin values prior to the audiological examination
Mean DFO : Calculated mean of the previous desferrioxamine doses (mg/kg/day) prior to the audiological examination
Mean Ferritin : Calculated mean of the previous serum ferritin levels (μg/l) prior to the audiological examination
M : Male
F : Female

reflex and tympanometric evaluation were found to be normal. BERA was performed 8 months after initial evaluation and it revealed a prolongation in I-III interpeak latency. Clinical history revealed carbamazepine administration for her epilepsy since 12 months and cardiac dysfunction. The other case with bilateral, symmetric, severe hearing loss revealed the pure tone average as 100 dB in the right, 98 dB in the left ear, with normal tympanogram. Of the patients with normal pure tone audiogram, 40 had type A, 5 had type C for both ears, 1 had type C in the right and type B tympanogram in the left ear. Thalassemia Major patients with hearing loss were classified according to their ages, gender, serum DFO, serum ferritin levels, TI and mean serum DFO, mean serum ferritin and mean TI's (Table 1). The values just before the audiological evaluation for the DFO dose was found between 17-60 mgr/kg/day, the ferritin level of the patients ranged between 561-4534 μgr/lt, and the calculated TIs ranged between 0.007-0.090. The mean values of DFO dose were found between 10-50 mgr/kg/day, mean ferritin levels 806 – 5540 μgr/lt, and the mean TIs were found between 0.008-0.047. The mean values were established from the previous data of the patients consisting of the all recorded values of both DFO dose and the serum ferritin level at the same moment. Mean TI was calculated as the ratio of the mean DFO dose to the mean serum ferritin level.

Discussion

Several factors, including DFO dosage, serum ferritin level, TI and the disease itself, have been investigated for the possible causes of the auditory symptoms and neurotoxicity in patients with Thalassemia Major. Olivieri, among his group of 89 patients with anemia, reported audiometric abnormalities in 13 symptomatic patients. He found that the patients with auditory complaint had lower serum ferritin values, but higher daily doses of the DFO which is used for therapeutic purposes for iron chelation. DFO was thought to be the factor for auditory neurotoxicity since reversal of auditory symptoms and improvement in hearing loss can be noted after withdrawal of the drug. The mechanism of the auditory neurotoxicity related with the drug was explained by the interference of DFO with the iron-dependent enzyme activity and also by the chelation of trace elements such as iron, copper, and zinc. He also noted that the audiometry

was more sensitive when compared to auditory brainstem responses (2).

De Virgiliis reported 12 cases with a mild, bilateral conductive hearing loss and 43 cases with a moderate unilateral or bilateral SNHL at high frequencies. He observed recruitment phenomenon among 75 β-thalassemia Major patients treated with a low transfusion scheme and an irregular low dose DFO chelation therapy. Bone hypertrophy and/or adenoid hypertrophy were suggested to be the causes of conductive hearing loss. A significant higher ferritin level was found in a randomly chosen group of 14 patients with hearing loss when compared to 11 patients without hearing loss. Ferritin was accused to be the reason of the SNHL in those patients (3).

Barratt et al detected SNHL in 9 of 27 patients with Thalassemia Major who were receiving regular hypertransfusion and subcutaneous infusions of DFO. However, they couldn't find any statistical significance between the patients with auditory toxicity and the patients with no auditory complaints according to their age, ferritin levels and the duration of DFO usage. The normal bone conduction values in 4 patients before the administration of DFO and stabilization of hearing loss over a six-month period after 30% reduction of the drug in 2 of the 9 patients indicated that DFO had been the cause of auditory neurotoxicity (4). Albera et al reported 23 (15%) cases with conductive hearing loss and 58 (38%) cases with SNHL in a group of 153 β-thalassemia patients. The incidence of conductive hearing loss caused by secretory otitis media was not found higher in β-thalassemia group when compared to normal population. SNHL was found in younger patients and in patients with good iron chelation. This phenomenon was suggested to be due to greater cochlear sensitivity in younger subjects, caused by direct or indirect DFO toxicity in cases with lower iron load (5).

Wonke et al reported auditory neurotoxicity in 13 (26%) of 50 patients. In 5 of these 13 patients of whom profound deafness occurred, hearing improvement was noticed between 7-19 months after subcutaneous administration of Ca-DTPA instead of DFO (6). Porter found bilateral high frequency hearing loss in 9 (24%) of the 30 patients with Thalassemia Major and in 7 subjects with Thalassemia Intermedia who have been treated with DFO. He claimed that the maximum dose of DFO and a serum ferritin level lower than 2000 μgr/lt were the significant risk factors for auditory neurotoxicity. A TI obtained by the ratio of the daily dose of DFO to the serum ferritin level could be used as a guideline for SNHL. Stabilization of hearing loss in 7 patients and improvement in the other two has been observed in their study after adjustment of DFO dose to a TI below 0.025. The possible mechanism of DFO toxicity was thought to be due to its direct toxic effect to the cochlea or by accumulation of the deposits in the cochlea after chelation of the free iron with trace metals (7). Bentur studied 19 subjects and compared DFO pharmacokinetics in 10 asymptomatic children with 9 patients having severe manifestation of auditory and visual impairment. He found that neurotoxicity was due to the administration of significantly higher doses of DFO. The interpatient variability was explained by the difference in the elimination of DFO, penetration of DFO through the blood-brain barrier and the sensitivity of the target organs (8).

Cohen et al reported 1 patient with loss of vision and hearing, 1 patient with mild macular stippling and 1 patient with mild, bilateral, high-frequency SNHL in a group of 52 (27 Thalassemia Major, 18 sickle cell, 4 Diamond-Blackfon, 3 with other transfusion dependent hematologic disorders) regularly transfused patients who received DFO in doses of 26-136 mgr/kg/day and with serum ferritin levels between 185-17,775 μgr/lt. Both eye and ear problems improved when DFO was stopped in one symptomatic patient. In other 2 patients with no symptoms, eye and ear abnormalities did not worsen despite the continuation of the therapy at the same dosage. There was no difference in their study between the patients with ophthalmologic and audiologic abnormalities and the unaffected patients with regard to DFO dosage, serum ferritin level and TI (9). Argiolu et al did not find any difference

between the patients with SNHL and those with normal hearing in terms of DFO dosage and ferritin levels in 309 patients with Thalassemia Major (10). Triantafyllou reported that 65.2% of the cases with abnormal VEP and 73.3% of the cases with abnormal BAEP findings normalized after DFO dose modification, but the hearing loss never turned to the normal level. He summarized that the visual and auditory abnormalities were due to either DFO neurotoxicity or iron overload or may be both (11).

Önerci et al reported the incidence of cochlear ototoxicity in 25% of 27 patients with Thalassemia Major and 7 patients with Thalassemia Intermedia. Cochlear ototoxicity was suggested to be due to the disease itself. Irreguler and very low dose administration protocols demonstrated that the cause of hearing loss was not because of the transfusion and DFO therapy. Conductive hearing loss was found to be 59.26% in patients with Thalassemia Major and 42.86% in patients with Thalessemia Intermedia. This situation had been explained by the existence of stiffness in the middle ear (12). Tamary reported auditory toxicity in 2 of 13 patients with β-thalassemia at 26^{th} and 28^{th} months of the initiation of IV DFO therapy. The modification of DFO dosage was thought to prevent further auditory impairment (13). Kontzoglou reported 24 (27%) patients with SNHL at high frequencies in a group of 88 patients with β-thalassemia. The neurotoxicity was attributed to DFO therapy. Almost complete recovery was observed in 12 and stabilization of hearing was noted in 7 patients after reduction or temporary withdrawal of the drug (14). Chiodo et al reported 43 patients with hearing loss out of 75 transfusion-dependent patients (Thalassemia Major, S.Cell, Diamond-Blackfon anemia and various others). Of those, 22 patients had the ototoxicity attributable to DFO therapy (15).

In our study, two patients (3.8%) exhibited SNHL. One of these patients had high serum ferritin level and the other demonstrated high mean serum ferritin level. However, eleven patients showing high serum ferritin level and other eleven patients with high mean serum ferritin level did not exhibit hearing loss (Table 2). The TI and mean TI were also found to be normal for both patients with SNHL. Two patients out of 52 were not found to be sufficient for the statistical comparison of the ones with SNHL to the whole group. BERA examination was performed to the mild, bilateral, symmetric SNHL patient who had a pure tone average of 28 dB in the right and 25 dB in the left ear. The prolongation of I-III interpeak latency established in the second examination performed 8 months after the initial examination was attributed to carbamazepine administration. Japaridze and coworkers pointed out the prolongation of I-III and I-V interpeak latency of the epileptic patients using carbamazepine. The suppressive effect of carbamazepine was reported to be both on the lemniscal and extralemniscal auditory pathways (16). The ratio of three patients with serous otitis media and one patient with otosclerosis displaying conductive hearing loss out of 52 subjects was found to be significantly lower in regard to 59.26 % conductive hearing loss for the patients reported by Önerci et al., 38 % by Albera et al. and 13 % by Porter et al. The 7.9 % conductive hearing loss in our study could not attributed to Thalassemia Major. The data of the patients with high serum ferritin level, high mean serum ferritin level, the patients with TI and mean TI higher than 0.025 were shown in Table 2. Conclusively, our results were not found to be convincing enough to prove that serum ferritin level, DFO dose, TI and mean TI could be a factor for auditory neurotoxicity.

Conclusion

Contrary to several other studies, serum ferritin level, DFO dose, TI and mean TI could not be implied as a causative factor for hearing impairment in TM. However, animal studies should be performed to assess the predisposing factors causing auditory neurotoxicity. The low incidence of SNHL may be attributed to the thorough evaluation before treatment and proper follow-up of the patients via TI.

Table 2. The data of the patients with serum ferritin levels higher than 2000 μg/l (I), mean serum ferritin levels higher than 2000 μg/l (II), TI greater than 0.025 (III), mean TI greater than 0.025 (IV).

	Hearing Level	Gender	Age (MEAN ±SDEV)	n	DFO (MEAN ±SDEV)	Ferritin (MEAN ±SDEV)	T.I. (MEAN ±SDEV)	Mean DFO (MEAN ±SDEV)	Mean Ferritin (MEAN ±SDEV)	Mean T.I. (MEAN ±SDEV)
I	Bil. SNHL	3M	11.75	1	37.25	2913.9	0.013	36.33	2165.3	0.016
	Normal	9F	±4.37	11	±9.98	±926.0	±0.005	±10.49	±1298.7	±0.006
II	Bil. SNHL	5M	13.25	1	39.58	2034.1	0.025	40.00	2724.8	0.015
	Normal	7F	±3.91	11	±9.74	±856.8	±0.021	±7.36	±964.2	±0.004
	Bil. CHL			1						
III	Normal	11M	8.76	18	41.76	1258.0	0.035	37.95	1496.1	0.027
	Right CHL	10F	±4.67	1	±10.45	±437.1	±0.014	±9.07	±546.4	±0,009
	Right CHL			1						
IV	Normal	6M	7.54	12	38.08	1193.4	0.032	38.15	1169.2	0.032
	Right CHL	7F	±4.29	1	±10.96	±381.7	±0.006	±8.75	±259.8	±0.006

Bil. : Bilateral
CHL : Conductive Hearing Loss
SNHL : Sensorineural Hearing Loss
SDEV : Standard Deviation
TI : Therapeutic Index (daily DFO dose (mg/kg)/serum ferritin level (μg/l)) calculated by the DFO and ferritin values just before the audiological examination
DFO : Desferrioxamine dose (mg/kg/day) just before the audiological examination
Ferritin : Serum ferritin level (μg/l) just before the audiological examination
Mean TI : Calculated mean of the previous therapeutic indices (daily DFO dose (mg/kg)/serum ferritin level (μg/l)) depending on the recorded DFO doses and serum ferritin values prior to the audiological examination
Mean DFO : Calculated mean of the previous desferrioxamine doses (mg/kg/day) prior to the audiological examination
Mean Ferritin : Calculated mean of the previous serum ferritin levels (μg/l) prior to the audiological examination
M : Male
F : Female

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