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New Advances in Evaluation of Hearing in a Sample of Egyptian Children with β-Thalassemia Major

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Abstract

AIM: To evaluate hearing in β-thalassemia major patients on iron chelation therapy by using pure-tone audiometry (PTA) and distortion product otoacoustic emissions (DPOAE).

SUBJECTS AND METHODS: This cross-sectional, descriptive study was done on (48) diagnosed, 6-18 years old, β-thalassemia major patients who had received at least 3 years iron chelating agent deferoxamine (DFO). We performed PTA, DPOAE testing, and tympanometry for all participants. SPSS was used to analyse data. $P < 0.05$ was accepted as statistically significant.

RESULTS: No significant difference was found between PTA and DPOAE testing in their capability to detect ototoxicity. PTA and DPOAE testing for the detection of ototoxicity in BTM and BTI, kappa values (κ) were found to be 0.516 and 0.459, respectively. The whole mean serum ferritin level was 2,251.3 ng/ml. The mean level was 1,603 ± 1,380 ng/ml in the patients with SNHL and 2,405 ± 1,908 ng/ml in the patients with normal hearing with the statistically significant difference among both groups ($p = 0.015$). The occurrence of ototoxicity was statistically significant with increasing age ($p < 0.001$). There was no marked difference as regards gender ($p = 0.72$).

CONCLUSION: Hearing loss is prevailing in patients with β-thalassemia major on iron chelating agents. Therefore, regular hearing evaluations and periodic check-ups after the initiation of chelation therapy are mandatory.

Introduction

β-Thalassemia major is considered a critical health issue in both developed and developing countries with approximately 330,000 affected newborns each year. Countries of the Middle East are the most affected area as it is geographically located in the "thalassemia belt [1].

It is a severe hereditary transfusion dependent anaemia that occurs due to defects in haemoglobin (Hb) production [2].

It is characterised by a marked drop in beta-globin chains production and ineffective erythropoiesis with bone expansion and extramedullary haematopoiesis in the liver, spleen, and other sites, such as paravertebral masses [3].

Regular monthly blood transfusions are used to decrease the acute symptoms of the disease in those patients; although frequent blood transfusions can lead to hemosiderosis besides hepatic, cardiac and endocrine complications [4], [5]. In spite of the usefulness of chelating agents, those patients usually die in the second decade of life because of the previous complications. But nowadays, the survival

rate has been markedly improved due to therapy advances, particularly after chelation therapy. Hearing problems were seen in thalassemia patients on deferoxamine (DFO) which is known to be a natural substance, a metabolite of Streptomyces pilosus that forms a stable chelate with ferric iron [6]. Through time, DFO that was firstly used in 1962, has proved to be the most powerful iron-chelating agent available and was recommended for more comprehensive, high-dose intake due to its negligible adverse reactions. Ototoxicity caused by DFO was first reported in the 1980s [7]. Hearing complications in thalassemia is mostly related to chronic anaemia, iron overload, extramedullary hematopoiesis and adverse reactions of iron chelating agents.

This study aims to evaluate the ototoxic effects of iron chelators in patients with β-thalassemia major on iron chelation therapy for more than 3 years regularly by using pure-tone audiometry (PTA) & distortion product otoacoustic emissions (DPOAE) and correlation of these findings with mean haemoglobin, ferritin level and duration of treatment.

Subjects and Methods

This cross-sectional, descriptive study was conducted at The Audiology Unit, El-Hussein Hospital, Al-Azhar University, Faculty of Medicine. A group of 48 diagnosed β-thalassemia major patients aged 6-18 years old who had received at least 3 years of treatment with an iron chelating agent deferoxamine (DFO) were enrolled in the study. All Routine haematological studies were performed according to conventional methods. A complete personal history was taken, ENT examination was performed on the patients. The data was collected which included name, age, sex, Hb, duration and dose of chelation therapy at the time of audiology test. Those with an active infection, middle ear effusion, a current or previous otologic disease, a tympanic membrane perforation, a history of ear surgery, a hearing loss secondary to acoustic trauma or hereditary factors and an inability to satisfactorily undergo audiologic testing were excluded from the study.

Audiologic testing

One qualified audiologist has performed PTA, DPOAE testing, and tympanometry for all subjects using the same Inter acoustics Audiometer model AC40, Inter acoustic Tympano meter model AZ7 and Distortion Evoked Otoacoustic Emission (DPOAE, ILO88). PTA thresholds were measured in the standard increments with bone conduction testing with tone stimulus ranging from 0.5 to 8 kHz. A threshold shift > 20 dB at one or more frequencies on PTA was considered to be significant. Two simultaneous pure-tone signals were introduced to the ear at two different frequencies (f1 and f2, where f2 > f1), and the 2f1-f2 cubic distortion-product component was recorded for DPOAE testing. Recordings were obtained with a frequency ratio of f2/f1 fixed at 1.22. Nine pairs of equal-level primary frequencies (Ll = L2 = 65 dB SPL) were used at three points per octave, spanning the f2 frequency range from 1,001 to 6,348 Hz. The 65-dB levels of the primary tones were used as the stimulus levels that would most reliably elicit DPOAE from ears with hearing problems. The amplitude was determined for each patient. Detection thresholds were calculated 6 dB higher than the noise floor. The accuracy of the calibrations had been confirmed earlier by DPOAE testing on 10 healthy individuals.

Table 1: Pure tone average (PTA) of the studied group

Frequency (Hz)	Mean ± SD
250	10.0 ± 3.2
500	11.3 ± 2.5
1000	12.6 ± 3.6
2000	18.9 ± 4.1
4000	19.2 ± 6.5
8000	21.00 ± 8.4

Statistical analysis

Data were analysed with the Statistical Package for the Social Sciences, version 21 for Windows. Continuous data were expressed as mean ± standard deviation and were compared by using the chi-square, ANOVA, and Student unpaired t-tests for statistical evaluation of parameters. $P < 0.05$ was accepted as statistically significant.

Ethical Considerations

The study protocol was approved by the Ethics Committee of the National Research Center under the registration number (16358).

Results

In the right ears, PTA examination at 4, 6, and 8 kHz showed that hearing threshold levels were between 0 and 20 dB in 37patients (77%); in the remaining 11 patients (23%), sensorineural hearing loss (SNHL) was found at ≥ 21 dB.

Table 2: Pure Tone Audiometry (PTA) statistics of hearing loss among the studied group

	p-Value 4kHz	p-Value 6kHz	p-Value 8kHz
(PTA) (right)	0.547	0.764	0.712
(PTA) (left)	0.581	0.818	0.821

In the left ears, PTA at 4, 6, and 8 kHz revealed that hearing threshold levels were normal in 34 patients (71%), with SNHL in the remaining 14 patients (29%).

Table 3: DPOAE testing results statistics of hearing loss among the studied group

	p-Value 4kHz	p-Value 6kHz	p-Value 8kHz
DPOAE (right)	0.179	0.183	0.520
DPOAE (left)	0.927	0.915	0.478

In the right ears, DPOE testing showed that the signal/ noise ratios at 4, 6, and 8 kHz were ≥ 6 dB in 36 patients (75%) and 39 patients (81%) and 9 patients (19%).

Table 4: Values of mean DPOAE

	Mean ± SD 0.5 kHz	Mean ± SD 1 kHz	Mean ± SD 2 kHz	Mean ± SD 4 kHz	Mean ± SD 6 kHz	Mean ± SD 8 kHz
Side						
DPOAE Right	0.30 ± 6.08	7.29 ± 6.09	9.54 ± 6.45	11.94 ± 7.35	13.03 ± 10.52	12.31 ± 9.35
DPOAE Left	0.53 ± 6.58	7.69 ± 5.49	9.69 ± 5.20	11.45 ± 7.64	14.16 ± 10.38	13.15 ± 9.27

According to these results, there was no marked difference between PTA and DPOAE testing in detecting ototoxicity. For evaluation of PTA and DPOAE testing validity for ototoxicity detection in β-thalassemia major patients, kappa values (κ) were found to be 0.516 and 0.459, respectively. Laboratory results are shown in (Table 5). The overall mean serum ferritin level was 2,251.3 ng/ml. The mean level was 1,603 ± 1,380 ng/ml in the patients with SNHL and 2,405 ± 1,908 ng/ml in the patients with normal hearing with a statistically significant difference between the two groups ($p = 0.015$). A statistically significant difference in the occurrence of ototoxicity was found with increasing age ($p < 0.001$) and no significant difference was found as regards gender ($p = 0.72$).

Table 5: Laboratory investigations of the studied group

Parameter	Range	(mean)
Hemoglobin (g/dl)	6.4 - 11.3	(8.3)
Ferritin (ng/ml)	108 - 8,471	(2,251.3)
Aspartate transaminase (U/L)	13 - 171	(39)
Alanine transaminase (U/L)	6 - 310	(43)
Total bilirubin (mg/dl)	0.38 - 10.8	(11.7)
Direct bilirubin (mg/dl)	0.17 - 4.53	(0.605)

Discussion

β -thalassemia is a disorder caused by the reduced or absent synthesis of the beta globin chains of the haemoglobin tetramer (Cao and Galanello, 2010) [8].

Stem cell transplantation is effective in treatment, but regular transfusion is the standard accepted therapy which postpones ineffective erythropoiesis and adjusts anaemia. Hemosiderosis occurs secondary to a hyper transfusion therapy is the most dangerous side effect of chelation therapy (Quiralo & Vichinsky, 2004) [9].

Effective iron chelation therapy means reaching a neutral or negative iron balance, where excretion of iron equals or more than the rate of new iron accumulation. In β-thalassemia major, frequent red blood cell (RBC) transfusions are the main source of iron intake.

Deferoxamine is the most frequently used agent. Ototoxicity is dose-dependent, the recommended therapeutic dosage is 20- 40 mg/kg/day; studies have not shown any ototoxic side effect at dosages below 50 mg/kg/day (Nathan DG, 2003) [10].

Ototoxicity occurs due to damage of the ciliated cells of the basal turn of the cochlea, that causes high-frequency SNHL. Studies have demonstrated that the occurrence of SNHL in these cases ranging between 14 to 26% [11]. Shamsian et al., 2008 [12] estimated ototoxicity of desferrioxamine in 67 children with β -thalassemia major more than 5 years using PTA where SNHL was seen in 7.4% of cases. Ambrosetti et al., 2000 [12] found an occurrence of 26.3% among 57 β -thalassemia major patients between 17 to 32 years, while Kontzoglou et al., 2004 [13] found an incidence of 20.2% among 104 children with β -thalassemia major 6 to 35 years old. Karimi et al., 2002 [14] reported SNHL in more than half of β -thalassemia major patients on regular chelation treatment with deferoxamine.

We found the occurrence of SNHL on PTA as 39.0% in the right ear and 27.7% in the left ear. Onerci et al.,1994 [15] found audiology and impedance metric findings in 34 patients with thalassemia that most ears in the β -thalassemia major group had a conductive hearing loss or a mixed hearing loss and that no patient in that group had a pure sensorineural deficit.

Several authors have studied the ototoxicity of deferoxamine, and they reported that the hearing loss it is associated with is the sensorineural type and that it mainly affects the high frequencies [16], [17], [18], [19].

In our study, the frequency of SNHL in patients on deferoxamine therapy was 26.8%, which is compatible with other findings in the literature.

Estimations of otoacoustic emissions as a tool of reliable cochlear investigation are especially helpful in children [20].

Distortion-product emissions are the most frequently investigated type of otoacoustic emissions. DPOAE is more sensitive for monitoring of cochlear function. It is noninvasive, rapid, reliable and easy to use. DPOAE values can be reliably measured in nearly all human ears with normal cochlear and middle ear function. Their high degree of test-retest reliability and their accuracy and objectivity in the

evaluation of cochlear function (outer hair cell function in particular) makes them suitable for observing dynamic changes in cochlear responsiveness before they become functionally significant as a hearing loss [21], [22].

In our study, we noted a significant decrease in amplitude, principally in the higher frequencies (> 4 kHz), which was agreeable with the high-frequency hearing loss usually seen with deferoxamine ototoxicity [23].

DPOAE has been shown to have an advantage over PTA as an ototoxicity screening tool, as DPOE amplitudes fall significantly before behavioural threshold changes are noted at corresponding frequencies on PTA [24].

In our study, we estimated that the consistency of PTA and DPOAE testing for the detection of ototoxicity in BTM was of a moderate degree — κ = 0.516. recommended dose of DFO is 20-60 mg/kg/day with maximum dose of 50 mg/kg/day. Individual susceptibility might augment liability to the ototoxic effect of chelating drugs.

For determining hearing loss secondary to ototoxic drug use, PTA and DPOAE testing show a reasonable level of reliability. Also, it can be used for the early detection of SNHL. These two ways are associated with each other. In our study on hearing the loss in iron chelation therapy, we found no study that estimated the high frequencies. PTA has been investigated at frequencies up to 8 kHz [25], [26], [27].

Other studies of ototoxicity have demonstrated that high-frequency PTA was highly significant in detecting threshold changes due to ototoxicity. Beahan et al. reported that high-frequency PTA was reliable in detecting ototoxicity in children older than 7 years old [28].

It was found that SNHL is not correlated directly to serum ferritin levels or deferoxamine dosage; but also, genetic and constitutional factors may be related [29].

Porter et al., studied 47 BTM patients and found that high-dose deferoxamine therapy associated with low serum ferritin levels (< 2000 ng/ml) is a major risk factor for deferoxamine ototoxicity [19].

Ambrosetti et al., noted that there is no relationship between age, serum ferritin level, and therapeutic indices with hearing loss.

In conclusion, our study confirms that iron chelation therapy can be a cause of ototoxicity, so, regular follow up of β-thalassemia patients with PTA and DPOAE testing is mandatory with baseline hearing test of cochlear function before initiation of chelation therapy with a target of preventing permanent damage.

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