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ORIGINAL PAPER

# The Investigation of Hearing Loss in Patients with Thalassemia Major Referred to Hazrat Ali Asghar (AS) Hospital in Sistan and Baluchistan Province (Iran)

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*ABSTRACT*

***Introduction:*** *Hearing disorders are one of the major complications in patients with thalassemia major. Therefore, the purpose of this research is to investigate hearing loss in patients with thalassemia major referred to Hazrat Ali Asghar Hospital in Sistan and Baluchistan province, Iran.*

***Methods:*** *This cross-sectional descriptive study was conducted on 56 patients with thalassemia major who were referred to Ali Asghar Hospital in 2021-2022 and met the inclusion criteria into the present research. After obtaining the written consent of all participants, they underwent an audiometry test and were further examined. All information was collected in the researcher-made questionnaire and was analyzed using SPSS version 24 software.*

***Results:*** *Among the 56 eligible patients, 11 subjects (19.6%) had hearing loss. In terms of age, there was no statistically significant difference in hearing loss (P<0.05). Among the 11 patients with hearing loss, one patient (9.1%) had conductive hearing loss, three patients (27.3%) had sensorineural hearing loss, one patient (9.1%) had mixed hearing loss and six patients (54.5%) had hearing loss at frequencies above 5000 Hz. In terms of gender, there was no statistically significant difference in hearing loss. The average duration of Desferal in patients with hearing loss was significantly longer than other subjects (P<0.05).*

***Conclusion:*** *To prevent and treat hearing complications caused by thalassemia, regular and periodic hearing screening of all thalassemia patients is recommended.*

**Keywords**: thalassemia major, hearing loss, audiometry, Desferal.

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## ABBREVIATIONS

SPSS: statistical package for social sciences
P: P-value
Hz: Hertz
DFO: Deferoxamine
AS: Ali Asghar
SNHL: sensorineural hearing loss

## INTRODUCTION

Thalassemia syndromes are a heterogeneous group of hereditary hypochromic anemias that have different types in terms of severity (1). The most severe clinical form of it relates to beta-thalassemia major. It is the most common hereditary anemia, with patients needing frequent blood transfusions due to severe anemia. Children with beta thalassemia major who do not receive treatment usually develop symptoms of progressive hemolytic anemia with physical weakness and heart problems during the second six months of life (2, 3). Blood transfusion improves patients' general condition and prevents the consequences of inefficient erythropoiesis (4, 5). Iron overload in children with beta-thalassemia major is inevitable (6). Since the main treatment of the disease is regular and frequent blood transfusions, most of these patients' problems are related to complications of blood transfusions, including hemosiderosis in different organs of the body such as the heart, liver, etc (7, 8). Given that deposition of iron in vital organs is a life-threatening process, Deferoxamine (DFO) is used to remove iron and prevent its storage from Desferal (9), as the consumption of DFO itself may cause complications such as hearing loss (6). Deposition of iron causes superficial siderosis of the cerebellum and eighth cranial nerve, and can eventually lead to serious damage (10). Hearing disorders occur in thalassemia patients in two forms: transmission and sensory-neural with different severities (11). There are several factors involved in the occurrence of sensorineural hearing loss, including iron deposition in the cochlea (especially in sensory cells related to high frequencies), gradual pressure on the auditory nerve and damage to the hearing end organ consequently damage to ossicular hypertrophy, intermittent hypoxia as well as damage to cochlear sensory cells and the toxic effect of iron chelating drugs such as Desferal (12, 13). In general, hearing loss varies between 14-26% (average 20%) in thalassemia patients, while its estimated prevalence in the whole community is 7-10% (14). Given the possible occurrence of hearing loss in patients with thalassemia major, the diagnosis of effective factors and timely prevention, especially at a young ages, represent a very important way to avoid complications in the field of verbal communication and other problems. The significant prevalence of hearing disorders in patients with thalassemia major highlights the importance of addressing these disorders in order to improve the quality of life of the affected persons. Therefore, the purpose of this research is to investigate hearing loss in patients with thalassemia major referred to Hazrat Ali Asghar (AS) Hospital in Sistan and Baluchistan province, Iran. ❑

## MATERIALS AND METHODS

### Type of research and case-study population

In this cross-sectional descriptive study, the studied population included all patients with thalassemia major who were referred to Ali Asghar (AS) Hospital in Zahedan City, Iran, between 2021 and 2022.

### Sampling method and sample size

In this study, we used a sampling procedure based on the census method. The sample size was based on the information obtained from previous research (15, 16) and according to the following formula equivalent to 60 people as follows:

$$n = \frac{(Z_{1-\alpha/2})^2 P(1-P)}{d^2} =$$

### Inclusion and exclusion criteria

Consent to participation in our research, patients' age range 5–38 years and their cooperation to perform audiometry were among the inclusion criteria in the current study. The presence of an acute infection such as ear infection and other inflammatory diseases and patients' lack of cooperation in performing audiometry were among the exclusion criteria of our study.

### Data collection tool

In this study, data collection was conducted using a researcher-made checklist, which con-

sisted of two parts: 1) demographic information including age and gender; and 2) clinical information including hearing loss, type of hearing loss, duration of Desferal use and amount of Desferal use. The validity and reliability coefficient of the mentioned questionnaire were calculated based on Cronbach's alpha method equal to 0.90, which indicated the appropriate validity of this questionnaire.

### Work method

The present cross-sectional descriptive study was approved by the Research Center of the Faculty of Medicine, Zahedan University of Medical Sciences and Health Services, Iran, and the ethics committee of medical research with the code of ethics number.

From a total of 60 patients who were identified by using the census method, only 56 subjects with thalassemia major who met all inclusion criteria participated in research. After obtaining all participants' written consent, their audiometry results were examined and the necessary data, including hearing loss and type of hearing loss, was recorded. Also, the information form included participants' age and gender as well as duration of treatment with Desferal and amount of medicine given. Patients who either were not referred to perform audiometry or had acute infections such as ear infections and other inflammatory diseases were all excluded from the study. Finally, collected data were recorded in SPSS version 20 software. The significance level in this study was considered less than 0.05.

### Data analysis method

All collected data were statistically analyzed using SPSS version 20 statistical software, with the mean and standard deviation (SD) of the questionnaire scores being reported in general and separately in each area. A T-test or chi-square was used to compare numerical values. A significance level of less than 0.05 was considered.

### Ethical considerations

Participation in the present study was completely voluntary and the consent form was filled out by all eligible subjects in a fully informed manner before their inclusion in research. The researcher ensured that all information collected from participants remained strictly confidential. ❑

## RESULTS

Out of the 56 participants with an average age of 18.1 ± 8.4 years (age range 5–38 years), 11 (19.6%) subjects (average age 24.7 ± 7.5 years) had hearing loss and the remaining 45 (80.4%) patients (average age 16.5 ± 7.8 years) no hearing loss. According to the results of the statistical test (independent t-test), there was a statistically significant difference in hearing loss in terms of age ($p \leq 0.005$), so the increasing age of thalassemia patients was associated with the increasing incidence of hearing loss.

Of the participants to our study, 23 (41.1%) patients were males and 33 (58.9%) females. Five (8.9%) patients in the group of boys and six (10.7%) in the group of girls had hearing loss. According to the results of the statistical test, there was no statistically significant difference in hearing loss in terms of gender (Table 1).

Out of the 11 subjects with hearing loss, one patient (9.1%) had conductive hearing loss, three patients (27.3%) sensorineural hearing loss, one patient (9.1%) mixed hearing loss and six patients (54.5%) hearing loss in frequencies above 5000 Hz (Figure 1).

The examinations showed that the average duration of Desferal treatment was 18.8 ± 5.9 years in patients with hearing loss and 11.3 ± 7.3 years in the remaining ones, with no statistically significant difference between the two groups being observed. In contrast, the average duration of thalas-

**TABLE 1.** Frequency of hearing loss by patients' gender

| Hearing loss | Yes | No | Total | P value |
|---|---|---|---|---|
| Male | 5 (8.9%) | 18 (32.1%) | 23 (41%) | 0.109 |
| Female | 6 (10.7%) | 27 (48.2%) | 33 (59%) | |
| Total | 11 (19/6) | 45 (80.3%) | 56 (100%) | |

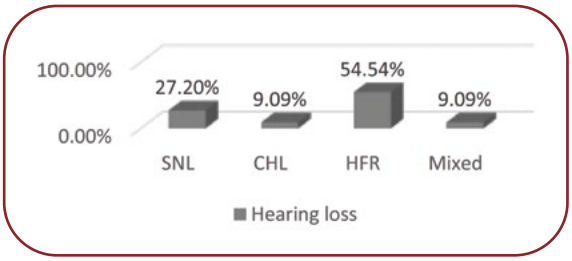


**FIGURE 1.** Frequency of types of hearing loss among study participants

| Hearing loss | Yes (n=11) | No (n=45) | P value |
|---|---|---|---|
| Average duration of Desferal consumption | 18.8 ± 5.9 | 11.3 ± 7.3 | 0.002 |
| Average duration of thalassemia diagnosis | 23.7 ± 7.5 | 15.7 ± 7.8 | 0.003 |
| Average duration of transfusion | 23.6 ± 7.6 | 15.8 ± 7.8 | 0.003 |

**TABLE 2.** Relationship of hearing loss with the average duration of Desferal consumption, thalassemia diagnosis and transfusion

semia diagnosis was 23.7 ± 7.5 years in patients with hearing loss and 15.7 ± 7.8 years in the remaining ones, which revealed a statistically significant difference between groups ($p \leq 0.005$). Also, when examining the relationship between hearing loss and transfusion duration, we found that the average duration of transfusion was 23.6 ± 7.6 years in patients with hearing loss and 15.8 ± 7.8 years in the remaining ones, which showed a statistically significant difference ($p \leq 0.005$) (Table 2). ❑

## DISCUSSION

Thalassemia is a hereditary anemia that has many complications, one of which being ear disorders (17). This type of disorders mainly manifests in the form of hearing loss (conductive or sensory-neural) and is related to the size of the third tonsil, iron concentration and toxic effect of Desferal (18). Although the prevalence of this complication, especially the sensory-neural type, has decreased over time due to improvements in treatment methods and control of thalassemia patients in terms of iron load and the amount of Desferal intake, there are still reports about it (19).

In our research, 11 (19.6%) patients of the total number of 56 participants had hearing loss, among whom one patient (9.1%) had conductive hearing loss, three patients (27.3%) sensorineural hearing loss (SNHL), one patient (9.1%) mixed hearing loss and six patients (54.5%) hearing loss at frequencies above 5000 Hz. In general, patients with thalassemia major are unable to survive without taking iron chelators, including Desferal, which is known to have ototoxicity among its side effects (19). In the study conducted by Ambrosetti *et al* in 2000, 22.8% of the total number of 57 subjects had mild SNHL and two patients had 3.5% moderate SNHL, which was consistent with our study. Desferal treatment has been non-ototoxic in common doses and the drug ototoxicity may depend on the patient's sensitivity and aptitude, which is unpredictable (20). A meta-analysis study carried out by Badfa *et al* in 2017 included 17 studies totalizing 1835 patients with a prevalence of hearing disorders of 27.3%; the rate of sensorineural, conductive and mixed hearing loss was 10.6%, 14.6% and 9.1%, respectively, with both the overall prevalence and types of it being slightly higher than those found by us (3). The results of a study conducted by Khan *et al* in 2019 showed that treatment with iron chelators and regular blood transfusions, apart from prolonging the life of thalassemia patients, has also some complications (15); thus, almost half of subjects benefited from normal hearing, while the other half had sensorineural hearing loss after using Defrasirox, which was a much higher rate than that found by our study, where only about 5% of patients had sensorineural hearing loss. Khan *et al* concluded that the occurrence of SNHL was depending on both the administered dose and duration of treatment with chelator (15). In terms of consumed dose of Desferal, some studies concluded that the ototoxicity of DFO was determined not only by the total amount of the drug used by the patient but also by its plasma concentration, and the rate of increased SNHL was observed at high frequencies.

In our study, the incidence rate of hearing impairment in the population with thalassemia major who received Desferal therapy was investigated and reported, and it was concluded that the incidence of SNHL (albeit low) was associated with increasing age and long-term use of Desferal.

In general, there is conflicting information about Desferal toxicity in various studies. Therefore, doctors should try to clarify other causes of hearing loss in patients with thalassemia and screening operations should be adjusted based on the specific characteristics of each patient, such as age, ability to respond to audiological tests and clinical status. Furthermore, the use of artificial intelligence, including neural networks, in hearing-related diseases is recommended to obtain more valid findings in diagnosis and more beneficial treatment among patients. The neural networks provide applications like segmentation in medical imaging, which allows precise interpretation of images for conditions like tumors.

Types of neural networks, such as convolutional neural networks and recurrent neural networks, are explored for their effectiveness in handling complex medical datasets. Key challenges include the need for high-quality labeled data, algorithm interpretability and integration into clinical workflows (21).

The present study showed that, despite an overall incidence of hearing loss of 19.6%, the rate of sensorineural hearing loss was observed in only 5.3% of patients, which could be associated with increasing age and long-term use of Desferal. One of the limitations of this research is patients' lack of cooperation in some cases. ❑

## CONCLUSION

The results of the present study indicate an increase in the incidence of hearing loss in people with thalassemia major. Therefore, otolaryngology and audiometry studies in thalassemia patients are necessary to ensure that hearing changes are diagnosed early and properly treated depending on the cause, which is crucial for prevention of permanent hearing loss. ❑

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