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Review Article

Audiological Dysfunction in Beta Thalassemia Major

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ABSTRACT:

Background: Beta-thalassemia is a common inherited congenital disorder of hemoglobin production, resulting in hemolytic anemia and multiorgan involvement. Each year, nearly 60,000 beta-thalassemia children are born worldwide, while carriers are estimated to be around 90 million people (1.5% of the global population). In the last half century, the life expectancy of beta-thalassemia patients has strikingly increased mostly due to regular blood transfusions and chelation treatments. The improved survival, however, has allowed for the emergence of comorbidities, such as hearing loss, with a non-negligible impact on the patient's quality of life. Beta-thalassemia major patients may have audiological problems; this could be related to chronic anemia, iron overload, extramedullary hematopoiesis, and adverse reactions of iron chelating agents that are used for their management. Therefore, it is important to routinely assess audiological functions in those patients, especially children and adolescents.This review aimed to highlight the acquired knowledge regarding hearing impairment in beta-thalassemia major.

Conclusions: The cause of hearing loss in patients with beta-thalassemia major may result from dose-related ototoxicity of the iron chelators, so it is important to do routine audiological assessment, careful adjustment of the dose, and/or a reasoned pharmacological shift.

Keywords: Thalassemia Major, Hearing problems, Iron chleators., audiological functions

INTRODUCTION

Although frequent blood transfusions can cause hemosiderosis in addition to hepatic, cardiac, and endocrine problems, they are used to reduce the acute symptoms of the condition in those individuals on a regular monthly basis [1, 2]. Even though chelating agents are helpful, those individuals typically die in their second decade of life as a result of the previously mentioned complications. Recently; therapy advancements, noted following chelation therapy usage, have significantly increased the survival rate. Patients with thalassemia receiving deferoxamine (DFO) reported hearing problems [3]. Due to their simplicity of use and ability to be taken orally, deferiprone and deferasirox (DFX) have essentially supplanted DFO in recent years. Regarding the potential for ototoxicity, there isn't enough research. Correct evaluation of the ototoxicity risk of the iron chelating agents is critical since large iron loads can also harm hearing [4].

High-frequency sensorineural hearing loss (SNHL) is caused by damage to the cochlear basal turn's ciliated cells leading to ototoxicity. According to studies, SNHL occurrence is about 14 to 26% in such patients. Ototoxicity caused by deferoxamine has been researched by a number of researchers, and they found that sensorineural hearing loss mostly affects the high frequencies (figure 1) [3] .

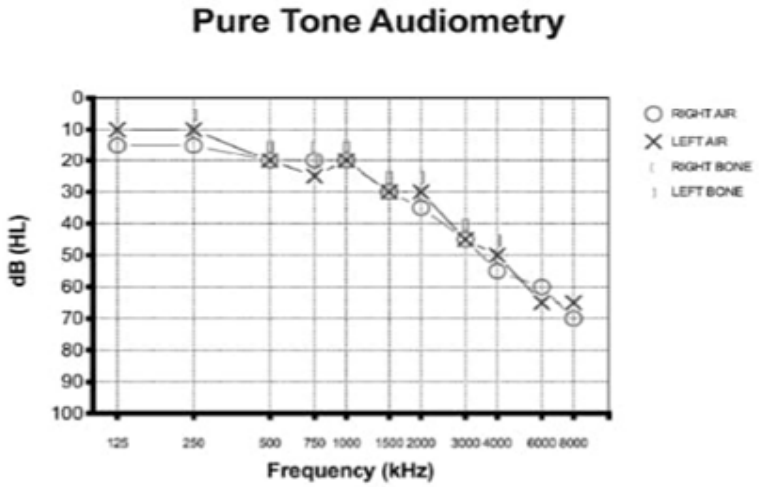

Figure 1: Audiogram showing high frequency SNHL in thalassemic patient receiving DFO.

Hearing Loss Course in thalassemia:

Beta-thalassemia hearing loss is anticipated to progress over time, primarily as a result of the chelation therapy's alleged cumulative harmful effects. However, there are now few long-term studies available, and the scant information is somewhat contradictory. Studies looking at the evolution of hearing loss revealed that the increase in the degree of hearing loss typically occurred slowly in some patients, although in others, throughout the follow-up, researchers detected no hearing deterioration, and one study reported a possible spontaneous improvement after a five-year follow-up [5]. Discontinuing the usage of chelations or decreasing their doses may minimize hearing loss detected by PTA [6]

These observations, however, mostly apply to the 1980s and 1990s, a time when large dosages of the medications used in chelation therapy (up to 120 mg/kg DFO). Today, therapy monitoring is given more consideration and dangerous chelation levels are infrequently reached. However, there has been no decrease in the prevalence of hearing loss. On the other hand, a meta-analysis revealed a rise in the detection of hearing loss. The high incidence of sensorineural hearing loss, even in children and the barely detectable rise in prevalence in adults seem to indicate a cochlear susceptibility that allows hearing function to be compromised early in the course of the disease. However, some individuals who have previously received long-term, high-dose chelation therapy don't show any symptoms of hearing loss, raising the possibility that additional factors may play a role in causing hearing loss such as genetic and environmental factors [7].

Iron Chelation and Hearing Loss

De Virgiliis et al. [8] published the first report of hearing loss in beta-thalassemia in a cohort of 75 transfusion-dependent thalassemic (TDT) kids. DFO, which at the time was still delivered intramuscularly in doses ranging from 750 to 1000 mg per day (no dose/kg reported), was being used as a part of chelation therapy for all patients. Despite this, it was asserted that bone marrow enlargement and iron overload alone were likely to be responsible for hearing loss. Following that, a few cases of probable DFO-related ototoxicity were reported (figure 2), which sparked interest in keeping track of how beta-thalassemia patients' hearing functions are affected while they're receiving chelation therapy .

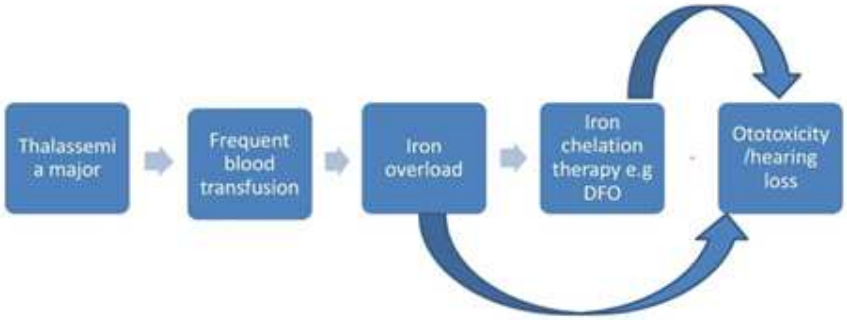

Figure 2: Mechanism of hearing loss in thalassemia

In fact, Porter et al. [9] observed SNHL solely in patients receiving iron chelation (DFO) and indicated a direct correlation as well as an inverse relationship between ferritin levels and the chelation dosage. Because of these findings, the authors came to the conclusion that a therapeutic index (TI; dose in mg/kg/serum ferritin) greater than 0.025 for more than three months was harmful to hearing and should be avoided; 0.027 was subsequently suggested as a safe level. The association between DFO dose and hearing/vision loss was confirmed by a pharmacokinetic study in TDT children with and without neurotoxicity (hearing/vision loss.

Recently, SNHL was identified even among some non-transfusion dependent thalassemic (NTDT) patients who were not receiving iron chelation therapy, underlining the possibility that SNHL may possibly be a side effect of beta-thalassemia itself. It is interesting to note that aberrant brainstem auditory evoked potentials (BAEPs) were observed in a subset of NTDT subjects who were not receiving iron chelation therapy. Indeed, brain perfusion abnormalities at the level of the primary auditory cortex were observed in beta-thalassemia patients (independent of disease severity and response to chelation therapy), pointing to a more complicated pathophysiology of hearing impairment. To learn more about the function of chelation therapy in the emergence of SNHL, additional research is, therefore, necessary in beta-thalassemia patients who have not received chelation or blood transfusions [10, 11].

Iron Overload and Hearing Loss

Secondary hemochromatosis, which develops in TDT patients as a result of tissue iron deposition brought on by the disease's progression and the prolonged transfusion regimen, is one of the most common consequences of the course of the disease. Excessive iron deposition in the heart, liver, and endocrine glands results in heart failure, liver fibrosis and cirrhosis, diabetes mellitus, hypogonadism, growth failure, sexual immaturity, and immunological abnormalities [12].The correlation between serum ferritin concentrations and the onset of hearing loss is still up for debate. Most researchers found no noticeable differences between patients with or without hearing loss and ferritin levels [4, 13].

Anemia and Hearing Loss

It was looked into whether there might be a connection between the level of anemia (determined by hemoglobin levels or the number of transfusions) and hearing loss. Hearing loss and abnormal PTA results were unrelated to pre-transfusion hemoglobin, the length of transfusion therapy, age at the time of the patient's first blood transfusion, average hemoglobin levels during the previous three months, average annual hemoglobin levels or the quantity of blood transfusions received each year [14]

A hearing threshold decline was connected with hemoglobin levels, the number of a small sample of TDT patients' annual transfusions, and the amount of time passed since their last transfusion. When hemoglobin levels rise, there is a lesser synthesis of insoluble alpha chains tetramers, which is how these results were interpreted, however, no other investigation confirmed this theory. Additionally, there was an inverse relationship between PTA, high-frequency audiometry hearing thresholds and the total number of transfusions [15].

Tinnitus

It is one of the most prevalent hearing disorders that can be brought on by a number of factors, including aging, hearing loss, noise exposure, inflammatory disorders,

psychosocial stress, and ototoxic drugs. The latter may result in both reversible and irreversible damage to the inner ear structures, tinnitus, hearing loss, and balance disorders [16]. These ototoxic side effects appear to be influenced by the course of treatment, the dosage, the patient's sensitivity, hereditary factors, and altered renal and hepatic functions [17]. Tinnitus data for thalassemic individuals is scarce and frequently scattered throughout the sections of results. These data were collected only by means of interviews; no research was done using particular instrumental tests or standardized questionnaires to collect them. Due to these factors, tinnitus is frequently given inaccurate descriptions in terms of its severity, limitations, and relationship to age or hearing loss. Tinnitus was either rarely or commonly found in beta-thalassemia patients, up to being the most prevalent hearing symptom in both participants with normal audiograms and those with hearing loss. The prevalence rate of tinnitus ranged considerably from 3.3% to 38%. The standardized questionnaires are necessary for improving the follow-up of beta-thalassemic patients. Even in the absence of hearing loss, tinnitus is typically underreported by patients and frequently linked to ototoxicity [13].

Audiological Monitoring and Management

Audiological testing has become a common practice, at least in the beta-thalassemia transfusion-dependent type. First, due to the need for possibly ototoxic long-term medications and the aging brought on by increasing life expectancy, there may be an increasing prevalence of hearing loss in beta-thalassemia patients. Second, hearing loss may serve as an important early warning sign of the drug's toxicity, enabling prompt dosage adjustment. It has been demonstrated that this strategy frequently reverses or reduces the reported hearing loss. Third, untreated hearing loss may have a variety of negative effects including social exclusion, depression, and a higher risk of early occurrence of dementia [18].

Before beginning treatment, audiological testing is advised to determine the hearing threshold because the beginning of the hearing loss is still unexpected. When hearing impairments (subjective hearing loss, fullness, and tinnitus) first appear, an audiologist's evaluation should be regarded as required. Incorporating previous recommendations, it appears reasonable to schedule the following tests every year for children and every two years for adolescents in the case of patients with normal hearing function (mainly because undiagnosed hearing loss has a significant negative influence on academic/learning performance). Even in individuals who do not report hearing loss, audiological testing is fair to be done every three to five years in adults. A stricter follow-up should result from the discovery of a hearing loss that is fast progressing. When hearing loss interferes with daily social life, hearing acuity should be seriously examined and hearing aid fitting should be done [5].

CONCLUSIONS

Even though there has been much research on hearing loss in beta-thalassemia patients, differences in diagnostic criteria limit the creation of a reliable and accurate picture of this problem. Future longitudinal studies will contribute to our understanding of the pathogenesis, prevalence, and appropriate management of hearing impairment in beta-thalassemia.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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