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Irreversible Hearing Loss Due To The Use Of Oral Isotretinoin

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ABSTRACT

A 15-year-old male presented to Dicle University Faculty of Medicine Hospital complaining of hearing loss. He had a history of nodulocystic acne on the face. Five days ago, he had been started on isotretinoin (1.0 mg/kg/ day, in two divided doses) by a dermatologist. He had not taken any drugs other than isotretinoin. There were no other diseases, ear problems or surgery. Physical examination including otological and neurologic examination was unremarkable. Rinne test was positive, and a Weber test revealed no lateralization. There were no waves in transient otoacoustic emissions and the patient presented poor speech discrimination. Magnetic resonance imaging revealed no abnormality. The patient did not improve after withdrawal of isotretinoin. The patient was followed for about six months. Repeated audiograms showed the same alterations. Tinnitus decreased, although the patient's SNHL audiometry persisted and there was no change in average hearing levels by using Student's t test for paired group ($p>0.05$).
There have been many cases around the world reporting that hearing loss due to isotretinoin is reversible in a course of three weeks to two months after drug withdrawal. In contrast to these cases, the hearing loss of our patient did not improve –which suggests that isotretinoin may be ototoxic.
Key Words: Isotretinoin, Ototoxicity, Hearing loss, Acne,Tinnitus, Sensorineural hearing loss

INTRODUCTION

Isotretinoin belongs to a group of drugs known as retinoids, which are derivates of vitamin A. Isotretinoin decreases the size and activity of the sebaceous glands in the skin and reduces the amount of sebum produced by sebaceous glands [1]. Isotretinoin was originally indicated for the management of severe nodulocystic acne vulgaris, at a dose of 1–2 mg/kg/day until a cumulative dose of 120–150 mg/kg is reached, usually over four to five months [2].

Ototoxicity is hearing loss or damage to the balance functions of the ear by drugs or chemicals. The extent of ototoxicity varies with drug, dosage and other factors. Ototoxicity generally is bilaterally symmetrical, but it can be asymmetrical as well. Additionally, hearing loss usually begins at higher frequencies. Two areas can be damaged or destroyed through ototoxicity: the hair cells within the inner ear, and the vestibulo-cochlear nerve that links the inner ear to the brain. When damage occurs, any degree and combination of hearing loss and balance disruption are possible depending upon the part(s) affected [2].

CASE REPORT

A 15-year-old male presented to the Dicle University Faculty of Medicine Hospital with complaints of hearing loss and tinnitus. He had a history of nodulocystic acne on the face. A dermatologist had started him on isotretinoin at a daily dose of 40 mg (about 1.0mg/kg/day, in two divided doses) five days ago. He had not taken any drugs other than isotretinoin. There were no other diseases, ear problems or surgery in his medical history. Physical examination including otological and neurologic examination was unremarkable. Rinne test was positive, and a Weber test presented no lateralization. Due to a suspicion of isotretinoin-related ototoxicity, the drug was immediately discontinued and audiometry, transient otoacoustic emission and speech discrimination tests were ordered.

Audiogram showed bilateral near symmetrical downward pattern of sensorineural type hearing loss (SNHL) [Fig. 1]. A remarkable feature was observed in the audiogram where a consistent drop was prevailing from 500 dB through 4000 dB and specifically falling to 60 dB at 2000 and to 40 dB at 4000 and 8000 frequencies. We could not get waves in transient otoacoustic emissions and the patient presented poor speech discrimination. Magnetic resonance imaging of the brain and auditory passages was performed. The images revealed no abnormality [Fig. 3].

The patient did not improve after withdrawal of isotretinoin. The follow-up took about six months. Repeated audiogram showed the same alterations. Tinnitus decreased, although the patient's SNHL audiometry

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persisted (right 35/33 dB; left 38/35 dB), and there was no change in average hearing levels [Fig. 2]. The first and the last values of left and right ears were analyzed by using Student's t test for paired group. The differences between first and last values for hearing loss of both ears were not found significant (for left ear; t=0.256, p=0.808, for right ear; t=2.121, p=0.087).

Figure 1: Pure-tone thresholds for low, moderate, high frequencies of the right and left ear on the fifth day.

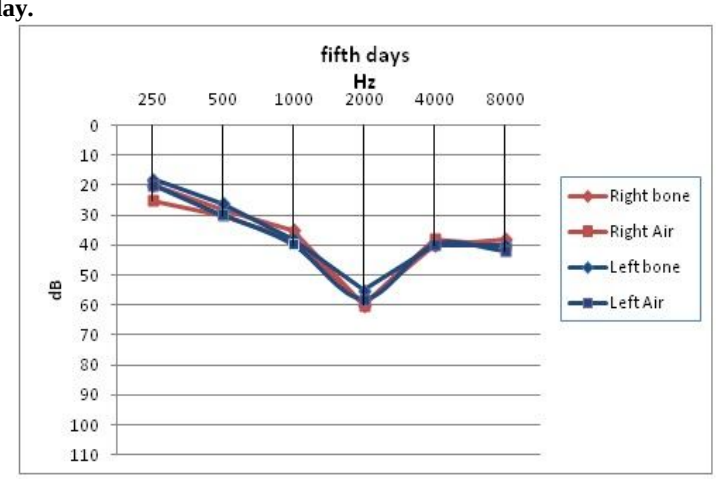
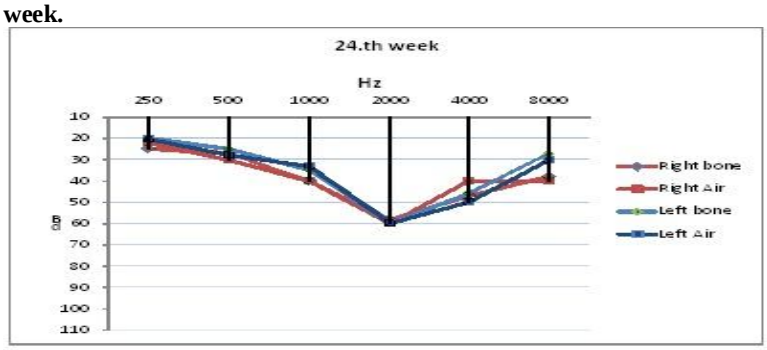


Figure 2: Pure-tone thresholds for low, moderate, high frequencies of the right and left ear on the 24th week.



There was no change in the average hearing levels [Fig. 2].

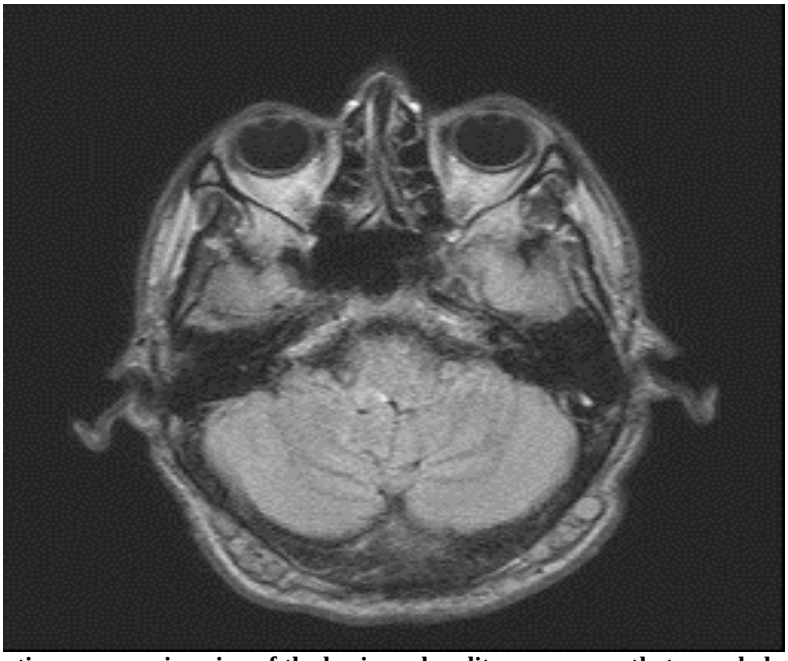


Figure 3: Magnetic resonance imaging of the brain and auditory passages that revealed no abnormality.

DISCUSSION

Isotretinoin is the drug of choice for treatment of severe acne vulgaris. It acts on the sebaceaous glands and also reduces inflammation in the skin. Isotretinoin can have serious side effects and its use must be supervised by a dermatologist [1].

Ototoxic drugs are commonly used without audiological monitoring in the modern world. Data on ototoxic deafness in developing countries is hard to obtain. Also, the public health aspect of ototoxicity is often ignored, which poses a disadvantage for individual patients. The term 'ototoxic' refers to any drug with the potential to result in toxic reactions to structures of the inner ear, including the cochlea, vestibule, semicircular canals and otoliths. The hearing loss usually begins at higher frequencies [3]. Additionally, hearing loss may not be apparent until several weeks or months have passed after completion of antibiotic or other ototoxic drugs [3]. **T**he cell membrane is composed of phospholipids which are oxidized by free radicals in OH or COH, thus damaging its compactness [4]. Free radicals are a major risk for the endothelium and this damage is most manifest in microcirculation [5,6]. Reactive oxygen species (ROS) play an important microcirculatory role in the pathology of the inner ear and the peripheral and central pathways [7,9]. Some reports suggesting that oxidative stress could impair the sensorineural epithelium of the labyrinth and the acoustic and vestibular nervous system are available [7]. Oxidative stressors induce the production of intracellular oxygen-reactive products and ROS, which interact with the phospholipid membrane of the sensorial cells to produce aldehyde lipids, such as 4-hydroxynonenal, a mediator of apoptosis for auditory neurons and hair cells [4].

The adverse effects of isotretinoin are well known, but ototoxic effects have rarely been reported [8]. Isotretinoin has a significant number of dose-dependent mucocutaneous and other adverse effects[9,10].

To the best of our knowledge, there were no studies on the minimal toxic dose of isotretinoin in ototoxicity. Although it is still used at its original recommended dosages in some countries, the trend has been to use lower and more intermittent dosage regimens. Evidence is now accumulating that 10–20 mg per day is quite adequate for most individuals with acne vulgaris**.** [11,12]. Our patient had used isotretinoin at a daily dose of 40 mg (1.0 mg/kg/day twice a day) for five days. It is questionable whether initiation of a lower dose would have caused milder or reversible ototoxicity, but we suggest that initiation of isotretinoin at lower doses might be a safer approach, with no lack of effect.

There are some studies on the influence of isotretinoin on the ear. Nikiforidis *et al* [13] reported that in 9% of patients treated for three weeks with isotretinoin showed subclinical changes in auditory brainstem response. A prospective study of 32 patients found significant changes in brainstem auditory and in visual evoked potential tests after isotretinoin administration [14]. Bidgy and Stern [15] found decreased hearing, in one of the 104 reports of suspected adverse reactions to isotretinoin in 1988. A case of deafness due to acitretin – another drug of the retinoid group - was reported [16]. This patient was reported to have sudden SNHL with tinnitus after one week of treatment, and improved after dose reduction. Rosende et al reported a case with hypoacusia in patients treated with isotretinoin [17]. In contrast, Karabulut *et al.* found improved hearing levels

of patients with acne vulgaris in all frequencies tested in a short-term follow-up at a dose of at a dose of 0.5–0.8 mg/kg [18].

As opposed to our patient, there have been many cases around the world reporting that hearing loss is reversible in a course of three weeks to two months after drug withdrawal. Despite this, he hearing loss of our case did not improve –which suggests that isotretinoin may be ototoxic.

CONCLUSION

Patients treated with isotretinoin may develop tinnitus or deafness; in such cases, a complete workup including audiometry and other tests should be performed. Also, the withdrawal of the drug should not be delayed.

Consequently, patients using isotretinoin must be informed about the potential side effects and also be closely followed up for the risk of hearing loss. Further clinical and experimental investigations will be required to assess the impact of retinoic acid on hair cells in the inner ear. We have initiated a clinical study on the effect of isotretinoin on hearing out-comes after encountering this case.

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