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**RESEARCH ARTICLE**

# Biotinidase deficiency and its impact on the auditory system in Iranian children

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## Abstract

**Background and Aim:** Biotinidase deficiency (BTD) is a rare autosomal recessive abnormality of biotin metabolism. If left untreated, it may lead to auditory symptoms. In this study, we examined the possible relationship between BTD and hearing impairment among Iranian children.

**Methods:** This descriptive cross-sectional study was performed on 9 children (8 boys, 1 girl) with BTD, who referred to Imam Hossein Hospital in Isfahan City, Iran, in 2018. After collecting their demographic data, including age, gender, weight, height, and history of diseases, we performed routine otolaryngologic and neurologic examination, audiological examinations, including otoscopic, acoustic immittance measurements, and auditory brainstem response (ABR). We recorded cochlear microphonic results in most cases, too.

**Results:** The subjects' mean ± SD age of BTD diagnosis was 4.33 ± 5.36 months. Of all participants, 11.1% had a positive family history of the disease, and 66.7% of families had the first-degree consanguineous marriage. About 44.5% of participants had a normal hearing; 22.2% had moderate sensorineural hearing loss, and 33.3% showed no response to ABR test. All subjects showed normal acoustic immittance results. However, children with profound hearing loss showed bilateral absence of acoustic reflexes.

**Conclusion:** BTD has a high impact on a child's hearing system. The high prevalence of hearing loss among BTD patients suggests that parents of BTD children (diagnosed at birth) should pay special attention to auditory screening and follow-up programs, as early diagnosis is important for preventing hearing loss. Also, families with first-degree of consanguineous marriages should consider genetic counseling before having children.

**Keywords:** Biotinidase deficiency; hearing impairment; children

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## Introduction

Biotinidase deficiency (BTD) is a rare autosomal recessive abnormality of biotin metabolism [1]. Biotinidase is an enzyme that recycles biotin, an essential vitamin used as the coenzyme for the synthesis of glucose, fatty acids as well as for the catabolism of several branched-chain amino acids [2]. If left untreated, dysfunctional biotin cycle caused by pathogenic mutations

leads to nervous, cutaneous, auditory, and visual symptoms [3].

Although medications can alleviate some of these side effects, the damage to the auditory system seems to be permanent [4]. If BTD is not treated with biotin during its presymptomatic period, it may cause an irreversible sensorineural hearing loss (SNHL). It is estimated that approximately 75% of symptomatic children with profound BTD have SNHL [5,6]. The hearing level of these patients varies from normal to profound SNHL, and most of them had reduced hearing loss in high frequencies [7,8]. This hearing loss may be resistant to therapy. However, hearing aids or cochlear implants along with auditory verbal education and articulation therapies are usually beneficial for children with hearing loss [9,10].

There are various reported prevalence rates of this disease. For example, the prevalence of profound BTD in the United States is estimated as high as 1 of 80000 births and that of partial BTD between 1 of 31000 and 1 of 40000 birth. It may have higher prevalence rates in other countries with a high degree of consanguineous marriages such as Turkey and Saudi Arabia. So far, no reliable statistical data exist on the prevalence of BTD in Iran, but the prevalence of this disorder in Iran is estimated to be high, due to consanguineous marriages [11-14].

In this research, we examined the possible relationship between BTD and hearing impairment among Iranian children.

## Methods

This descriptive cross-sectional study was performed on 9 children (8 boys and 1 girl) with BTD, who referred to Imam Hossein Hospital in Isfahan City, Iran, in 2018. This study was carried out in accordance with the Declaration of Helsinki. Also, the Ethics Committee of Isfahan University of Medical Sciences approved this study (Ethics Committee reference number IR.MUI.REC.1395.2.198). The inclusion criteria comprised all up to 12 years old children with BTD verified by blood samples and a pediatric neurologist, under treatment of biotin, without any otologic disorders and malformations.

The exclusion criteria included comorbidities such as cerebral palsy, seizure, and epilepsy, as well as unwillingness to continue the research.

Out of 20 available children with BTD, 11 were excluded from the study due to having comorbidities or their residences' far distance from the hospital (which made families unable to participate in this study). Therefore, only 9 subjects were entered into the study.

After signing the written consent by the families, all children meeting the inclusion criteria went through routine otolaryngologic and neurologic examination. First, we collected their demographic data, including age, gender, weight, height, and history of diseases. Then, we performed the audiological examinations, including otoscopic evaluation, acoustic immittance measurements, and auditory brainstem response (ABR).

Acoustic immittance measurements (middle ear pressure and acoustic reflex) were performed using Interacoustics AT235h Immittance Acoustic (Interacoustics, Denmark). To perform ABR tests, we used the Interacoustics EP25 (Interacoustics, Denmark). ABR testing and cochlear microphonic (CM) test were performed in a standard silent room while the child was asleep. Later on, we compared both CM results and ABR characteristics, including the existence of the waveforms (I, III, V) and their morphology with normal ranges to evaluate the status of

**Table 1. Demographic characteristics of children with biotinidase deficiency**

| | Mean ± SD | Maximum | Minimum |
|---|---|---|---|
| **Age (months)** | 4.33 ± 5.36 | 18.00 | 1.00 |
| **Height (Cm)** | 49.11 ± 1.59 | 52.50 | 48.00 |
| **Weight (Gr)** | 3134.44 ± 471.33 | 3650.00 | 2500.00 |
| **Head circumference (Cm)** | 34.63 ± 1.51 | 36.20 | 32.50 |

**Table 2. Auditory brainstem response results based on their maternal age in children with biotinidase deficiency**

| | | Maternal age group (Months) | | | |
|---|---|---|---|---|---|
| | | < 29 | 30–35 | > 35 | Total |
| ABR n (%) | Normal | 2 (40) | 1 (33.3) | 1 (100) | 4 (44.5) |
| | Moderate | 1 (20) | 1 (33.3) | 0 | 2 (22.2) |
| | No response | 2 (40) | 1 (33.3) | 0 | 3 (33.3) |
| Total | | 5 (100) | 3 (100) | 1 (100) | 9 (100) |

children's auditory system. Finally, the lowest acceptable amplitude of V wave of ABR testing was considered for each subject. All the data for each subject were imported in a table specific for that person.

**Table 3. Frequency of the first symptoms in children with biotinidase deficiency (n = 9)**

| Postnatal first symptoms | Frequency | Percentage |
|---|---|---|
| Seizures | 7 | 77.7 |
| Eating problems (loss of appetite, nausea, etc.) | 5 | 55.5 |
| Skin problems (rashes, alopecia) | 4 | 44.4 |
| Movement and balance problems | 4 | 44.4 |
| Hearing loss | 3 | 33.3 |
| Fungal infection | 2 | 22.2 |
| Breathing problem | 2 | 22.2 |
| Weight gain problem | 1 | 11.1 |
| Hypoglycemia | 1 | 11.1 |
| Insomnia | 1 | 11.1 |
| Sudden weight gain | 1 | 11.1 |

Eventually, all the collected data were analyzed by descriptive and analytic measurements in SPSS 18 (SPSS, Chicago, IL, USA). The numerical variables are reported as mean ± SD and categorical variables as frequencies and percentages.

## Results

Nine subjects (8 boys and 1 girl) participated in this study. The subjects' mean ± SD age of BTD diagnosis was 4.33 ± 5.36 months. In the meantime, their mean ± SD height, weight, and head circumference at this age were 49.11 ± 1.59 cm, 3134.44 ± 471.33 g, and 34.63 ± 1.51 cm, respectively (Table 1). About 11.1% of the participants had a positive family history, and 66.7% of their families had the first-degree of consanguineous marriage. Of total subjects, 77.8% of their mothers had term gestational age, and 22.2% had pre-term gestational age. The maternal age of 55.6% of mothers was less than 30 years, 33.3% between 30 and 35 years, and 11.1% older than 35 years. Besides, Table 2 presents the frequency of ABR results based on the maternal age group. Of all participants, 44.5% had normal hearing; 22.2% had moderate SN HL, and 33.3% showed no response to ABR test. Also, CM results were recorded in most cases. All subjects showed normal acoustic immittance results. However, children with profound hearing loss showed bilateral absence of acoustic reflexes.

The most prevalent postnatal BTD symptoms

**Table 4. Specific characters for each patient**

| Gender | No. | Age (Months) | Weight (Gr) | Height (Cm) | Head circumference (Cm) | Family history of the disease | First degree consanguineous marriage | Gestational age | Maternal age (years) | ABR results |
|---|---|---|---|---|---|---|---|---|---|---|
| **Female** | | | | | | | | | | |
| | **1** | 6 | 3150 | 48 | 35 | No | Yes | Term | 32 | Normal |
| | **Total = 1** | | | | | | | | | |
| **Male** | | | | | | | | | | |
| | **1** | 1 | 2550 | 48 | 32.50 | No | *No | Pre-term | 45 | Normal |
| | **2** | 2 | 3320 | 49 | 36 | No | Yes | Term | 34 | Bilateral moderate SNHL |
| | **3** | 2 | 3400 | 48 | 36 | No | Yes | Term | 30 | Bilateral profound hearing loss |
| | **4** | 18 | 3580 | 51 | 36.50 | Yes | Yes | Term | 24 | Normal |
| | **5** | 4 | 2560 | 48 | 34 | No | Yes | Term | 29 | Bilateral profound hearing loss |
| | **6** | 2 | 3650 | 49 | 36 | No | Yes | Term | 25 | Bilateral profound hearing loss |
| | **7** | 3 | 2500 | 52 | 33 | No | *No | Pre-term | 26 | Bilateral moderate SNHL |
| | **8** | 1 | 3500 | 48.5 | 33 | No | *No | Term | 26 | Normal |
| | **Total = 8** | | | | | | | | | |

* Parents did not have first degree consanguineous marriage. However, they were from the same region.

are seizures, eating problems (loss of appetite, nausea, etc.), skin problems (rashes, alopecia), movement, and balance problems (Table 3).

Table 4 presents the specific characteristics of each patient, including the age of diagnosis, weight, height, head circumference, family history of the disease, family relationships between parents, gestational age, maternal age, and their ABR. Of the patients, 4 had normal hearing thresholds bilaterally, 2 moderate SN HL bilaterally, and 3 profound hearing loss bilaterally.

## Discussion

Biotinidase deficiency is an autosomal recessively inherited disorder, which may lead to cutaneous problems as well as neurological problems, including hypotonia, seizures, hearing loss, ataxia, optic atrophy, and cognitive deficits ending in coma or death, if not properly treated [15]. BTD leads to developed optic atrophy, hearing loss, or cognitive deficits, which are usually irreversible if left untreated [16].

According to this study results, 55.5% of all BTD patients had moderate and profound hearing loss, and 44.5% had normal hearing. Also, 33.3% of the participants showed no response in the ABR test. Likewise, the study of Genc et al. showed that the prevalence of SN HL among 20 children with BTD was 55% [10]. Also, according to Talebi and Yaghini study, BTD may cause any impairment in neural synchronization of the auditory system. Since in our study, CM factor was available in most cases and on the other hand, ABR results were

affected at some level, the neural desynchronization or auditory neuropathy could appear in BTD patients [17].

At birth, 33.3% of newborns are diagnosed with hearing loss. However, our study showed that 55.5% of the study subjects had hearing loss. Therefore, it is mandatory to execute hearing screenings at birth and follow-up hearing screenings for high-risk infants. The most frequent symptoms of BTD patients after birth, are seizures, eating problems, skin problems, as well as movement and balance problems. According to Wolf study, seizures and hypotonia are the most common neurologic features in individuals with untreated and profound BTD [9].

Based on our results, almost 67% of parents had the first-degree consanguineous marriage. In addition, other families were from the same region. Thus, in the first-degree consanguineous marriages, clinicians should consider the possibility of BTD and hearing problems in their children. According to a study, there is a strong association between consanguinity and inborn errors of metabolism [18].

Low prevalence of BTD was a limitation of this study. Therefore, we recommend that further studies should be conducted with a larger sample size to obtain more precise results.

## Conclusion

Biotinidase deficiency (BTD) has a high impact on a child's hearing system. If left untreated, BTD can lead to progressive hearing impairment. High prevalence of hearing loss among BTD patients suggests that parents of children diagnosed with BTD at birth should pay special attention to auditory screening and follow-up programs. Therefore, early diagnosis plays an important role in preventing hearing loss. Also, families with first-degree consanguineous marriages should consider genetic counseling before having children.

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## Conflict of interest

The authors declared no conflicts of interest.

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