

## 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  $\pm$  SD age of BTD diagnosis was  $4.33 \pm 5.36$  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

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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 BTM 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 BTM 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 BTM in the United States is estimated as high as 1 of 80000 births and that of partial BTM 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 BTM 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 BTM and hearing impairment among Iranian children.

**Methods**

This descriptive cross-sectional study was performed on 9 children (8 boys and 1 girl) with BTM, 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 BTM 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 BTM, 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)			Total
	< 29	30–35	> 35	
<b>ABR n (%)</b>				
<b>Normal</b>	2 (40)	1 (33.3)	1 (100)	4 (44.5)
<b>Moderate</b>	1 (20)	1 (33.3)	0	2 (22.2)
<b>No response</b>	2 (40)	1 (33.3)	0	3 (33.3)
<b>Total</b>	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  $\pm$  SD and categorical variables as frequencies and percentages.

### Results

Nine subjects (8 boys and 1 girl) participated in this study. The subjects' mean  $\pm$  SD age of BTD diagnosis was  $4.33 \pm 5.36$  months. In the meantime, their mean  $\pm$  SD height, weight, and head circumference at this age were  $49.11 \pm 1.59$  cm,  $3134.44 \pm 471.33$  g, and  $34.63 \pm 1.51$  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
	<b>Total = 1</b>									
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
<b>Total = 8</b>										

\* 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 (BTB) has a high impact on a child's hearing system. If left untreated, BTB can lead to progressive hearing impairment. High prevalence of hearing loss among BTB patients suggests that parents of children diagnosed with BTB 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.

### References

- 1 Abouelarais M, Mekaoui N, Oudghiri FZ, Mammad K, Karboubi L, Dakhama BS. West syndrome secondary to biotinidase deficiency about a case. *Neurosci Med*. 2017;8(03):29-32. doi: [10.4236/nm.2017.83004](https://doi.org/10.4236/nm.2017.83004)
- 2 Deschamps R, Savatovsky J, Vignal C, Fisselier M, Imbard A, Wolf B. Adult-onset biotinidase deficiency: two individuals with severe, but reversible optic neuropathy. *J Neurol Neurosurg Psychiatry*. 2018;89(9):1009-1010. doi: [10.1136/jnnp-2017-316644](https://doi.org/10.1136/jnnp-2017-316644)
- 3 Venkataraman V, Balaji P, Panigrahi D, Jamal R. Biotinidase deficiency in childhood. *Neurol India*. 2013;61(4):411-3. doi: [10.4103/0028-3886.117614](https://doi.org/10.4103/0028-3886.117614)
- 4 Couce ML, Pérez-Cerdá C, García Silva MT, García Cazorla A, Martín-Hernández E, Castiñeiras D. [Clinical and genetic findings in patients with biotinidase deficiency detected through newborn screening or selective screening for hearing loss or inherited metabolic disease]. *Med Clin (Barc)*. 2011;137(11):500-3. Spanish. doi: [10.1016/j.medcli.2011.01.018](https://doi.org/10.1016/j.medcli.2011.01.018)
- 5 Wolf B, Heard GS. Disorders of biotin metabolism. In Scriver CR, Beaudet AL, Sly WS, Valle D. *The metabolic basis of inherited disease*. 6<sup>th</sup> ed. McGraw-Hill. New York. 1989. p. 2083-2103.
- 6 Wolf B, Spencer R, Gleason T. Hearing loss is a common feature of symptomatic children with profound biotinidase deficiency. *J Pediatr*. 2002;140(2):242-6. doi: [10.1067/mpd.2002.121938](https://doi.org/10.1067/mpd.2002.121938)
- 7 Straussberg R, Saiag E, Harel L, Korman SH, Amir J. Reversible deafness caused by biotinidase deficiency. *Pediatr Neurol*. 2000;23(3):269-70.
- 8 Sivri HS, Genç GA, Tokatli A, Dursun A, Coşkun T, Aydın HI, et al. Hearing loss in biotinidase deficiency: genotype-phenotype correlation. *J Pediatr*. 2007;150(4):439-42. doi: [10.1016/j.jpeds.2007.01.036](https://doi.org/10.1016/j.jpeds.2007.01.036)
- 9 Wolf B. Biotinidase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al. editors. *Gene Reviews*. University of Washington: Seattle; 1993-2019.
- 10 Genç GA, Sivri-Kalkanoğlu HS, Dursun A, Aydın HI, Tokatli A, Sennaroglu L, et al. Audiologic findings in children with biotinidase deficiency in Turkey. *Int J Pediatr Otorhinolaryngol*. 2007;71(2):333-9. doi: [10.1016/j.ijporl.2006.11.001](https://doi.org/10.1016/j.ijporl.2006.11.001)
- 11 Cowan TM, Blitzer MG, Wolf B, Working Group of the American College Of Medical Genetics Laboratory Quality Assurance Committee. Technical standards and guidelines for the diagnosis of biotinidase deficiency. *Genet Med*. 2010;12(7):464-70. doi: [10.1097/GIM.0b013e3181e4cc0f](https://doi.org/10.1097/GIM.0b013e3181e4cc0f)
- 12 Pomponio RJ, Coskun T, Demirkol M, Tokatli A, Ozalp I, Hüner G, et al. Novel mutations cause biotinidase deficiency in Turkish children. *J Inher Metab Dis*. 2000;23(2):120-8.

- 13 Pomponio RJ, Ozand PT, Al Essa M, Wolf B. Novel mutations in children with profound biotinidase deficiency from Saudi Arabia. *J Inher Metab Dis*. 2000;23(2):185-7.
- 14 Asgari A, Rouhi Dehnabeh S, Zargari M, Khani S, Mozafari H, Varasteh A. Clinical, biochemical and genetic analysis of biotinidase deficiency in Iranian population. *Arch Iran Med*. 2016;19(11):774-778. doi: [0161911/AIM.006](https://doi.org/10.16191/AIM.006)
- 15 Jay AM, Conway RL, Feldman GL, Nahhas F, Spencer L, Wolf B. Outcomes of individuals with profound and partial biotinidase deficiency ascertained by newborn screening in Michigan over 25 years. *Genet Med*. 2015;17(3):205-9. doi: [10.1038/gim.2014.104](https://doi.org/10.1038/gim.2014.104)
- 16 Wolf B. Biotinidase deficiency: "if you have to have an inherited metabolic disease, this is the one to have". *Genet Med*. 2012;14(6):565-75. doi: [10.1038/gim.2011.6](https://doi.org/10.1038/gim.2011.6)
- 17 Talebi H, Yaghini O. Auditory neuropathy/dyssynchrony in biotinidase deficiency. *J Audiol Otol*. 2016; 20(1):53-4. doi: [10.7874/jao.2016.20.1.53](https://doi.org/10.7874/jao.2016.20.1.53)
- 18 Afzal RM, Lund AM, Skovby F. The impact of consanguinity on the frequency of inborn errors of metabolism. *Mol Genet Metab Rep*. 2018;15:6-10. doi: [10.1016/j.ymgmr.2017.11.004](https://doi.org/10.1016/j.ymgmr.2017.11.004)