ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/healthsci.2025-108268

Investigation of Audiologic Findings in Treated Children with Biotinidase Deficiency: A Retrospective Study

Tedavi Almış Biyotinidaz Eksikliği Olan Çocuklarda Odyolojik Bulguların İncelenmesi: Retrospektif Çalışma

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ABSTRACT Objective: Biotinidase deficiency (BD) is a metabolic disorder that impairs biotin absorption and can affect the hearing system. In Türkiye, early diagnosis is achieved through newborn screening programs (NSP). Our study aims to present the sociodemographic status and audiologic findings of children with BD admitted to our audiology clinic who received early diagnosis and treatment. **Material and Methods:** The audiologic findings of patients diagnosed with BD who visited Marmara University Faculty of Medicine, Department of Audiology, between January 2014 and December 2023 were retrospectively analyzed. The study included 24 participants (12 female, 12 male) aged between 4-24 months. Sociodemographic information, newborn hearing screening results, acoustic immittancemetry, otoacoustic emissions (OAE), and auditory brainstem responses (ABR) findings were evaluated. **Results:** All participants were diagnosed with BD during NSP, and all had passed newborn hearing screening. In the ABR evaluation using click stimuli, the absolute latency values of waves I, III, and V, as well as the interwave latencies (I-III, III-V, I-V), were normal for their age. Threshold assessments with chirp stimuli showed wave V at 20 dB nHL in all participants. Acoustic immittancemetry and OAE findings were normal. As a result of all evaluations, all participants had normal hearing. Consanguine marriage was reported in the parents of 5 (20.8%) participants. **Conclusion:** Our findings support that hearing loss can be prevented with NSP in children with BD who received early diagnosis and treatment. National NSP is important in Türkiye.

Keywords: Biotinidase deficiency; child; hearing; evoked potentials; sociodemographic factors

ÖZET Amaç: Biyotinidaz eksikliği [biotinidase deficiency (BD)] biyotin emilimini bozan ve işitme sistemini etkileyebilen metabolik bir hastalıktır. Türkiye'de yenidoğan taramaları [newborn screening program (NSP)] ile erken tanısı sağlanmaktadır. Çalışmamız, odyoloji kliniğimize başvurmuş erken tanı ve tedavi altındaki BD olan çocukların sosyodemografik durumlarını ve odyolojik bulgularını sunmayı amaçlamaktadır. **Gereç ve Yöntemler:** Bu çalışmada, Ocak 2014 ve Aralık 2023 tarihleri arasında BD tanısı ile Marmara Üniversitesi Tıp Fakültesi Odyoloji Bilim Dalı kliniğine başvuran hastaların odyolojik bulguları retrospektif olarak incelenmiştir. Çalışmaya, yaşları 4-24 ay arasında olan 24 katılımcı (12 kız, 12 erkek) dâhil edilmiştir. Dâhil edilen katılımcıların alınan sosyodemografik bilgilerinin yanı sıra yenidoğan işitme tarama sonuçları, akustik immitansmetri, otoakustik emisyon (OAE) ve işitsel beyin sapı cevabı [auditory brainstem responses (ABR)] bulguları değerlendirilmiştir. **Bulgular:** Tüm katılımcılar NSP esnasında BD tanısı almıştır ve hepsi yenidoğan işitme taramalarından geçmiştir. Katılımcıların hepsine klik uyaranla yapılan ABR değerlendirmesinde dalga I,III,V mutlak latans değerleri ve I-III, III-V, I-V dalgalar arası latans değerleri kronolojik yaşlarına göre normal aralıktadır. Chirp uyaranla yapılan eşik değerlendirmesinde 20 dB nHL düzeyinde V. dalga görülmüştür. Akustik immitansmetri ve OAE bulguları normaldir. Tüm değerlendirmeler sonucunda katılımcılarımızın hepsinin normal işitmeye sahip olduğu görülmüştür. Akraba evliliği 5 (%20,8) katılımcının ebeveyninde görülmüştür. **Sonuç:** Çalışmamızın bulguları, NSP sayesinde erken tanı ve tedavide olan BD'li çocuklarda işitme kaybının önlenebileceği desteklemektedir. Ulusal tarama programları ülkemizde önem arz etmektedir.

Anahtar Kelimeler: Biyotinidaz eksikliği; çocuk; işitme; uyarılmış potansiyeller; sosyodemografik faktörler

TO CITE THIS ARTICLE:
Süloğlu ÖF, Bal N, Çiprut A. Investigation of audiologic findings in treated children with biotinidase deficiency: A retrospective study. Turkiye Klinikleri J Health Sci. 2025;10(3):741-6.

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Peer review under responsibility of Turkiye Klinikleri Journal of Health Sciences.

Received: 06 Jan 2025 ***Received in revised form:*** 18 Mar 2025 ***Accepted:*** 19 Mar 2025 ***Available online:*** 08 Apr 2025

Biotinidase is the enzyme that processes and recycles the vitamin biotin. This enzyme is synthesized in the liver and released into the blood. This ensures the absorption of biotin, which is effective in the functioning of the nervous system, liver function, eye and skin health. Biotinidase deficiency (BD) with autosomal recessive inheritance is a metabolic disease in which skin and respiratory problems, neurological symptoms, vision and hearing loss may be observed.[1-4] Early diagnosis is possible with newborn screening, and immediate treatment prevents the onset of disease symptoms. If untreated, the disease may progress to coma and death.[5] It can be diagnosed in newborns by the absence of enzyme activity in serum, fibroblast, or lymphocyte culture.[2,6] Symptoms usually appear between 2 weeks and 2 years of age but may be observed even later.[3] In Türkiye, BD screening was included in the national newborn screening program (NSP) in 2008.[6] Individuals diagnosed with BD need external biotin to prevent the effects of the disease. Biotin is given orally during the treatment phase.[2,6] Biotinidase deficiency can lead to impaired mitochondrial function, impairment of certain enzymes involved in myelin production and metabolic deposits. This accumulation can damage cells in the inner ear and neural structures in the auditory pathway, leading to hearing loss. Newborns who do not receive treatment may develop different degrees of sensorineural hearing loss.[4,7] Children with BD with hearing loss are likely to have a high risk of speech and language problems.[8] Hearing loss can be prevented with appropriate doses of biotin treatment in the presymptomatic period.[3,4] It is recommended that children with BD should be periodically followed up for hearing loss once or twice a year.[4]

This study aims to present the sociodemographic status and audiologic findings of children with BD who were admitted to our audiology clinic during a 10 year period under early diagnosis and treatment.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This cross-sectional and descriptive study was held at Marmara University Faculty of Medicine, Department of Audiology. Audiologic findings of patients diagnosed with BD referred to the audiology clinic for auditory brainstem responses (ABR) evaluation between January 2014 and December 2023 were analyzed retrospectively.

Inclusion criteria were being diagnosed with BD, being 2 years of age or younger, and having no otologic, audiologic, or neurologic damage that prevented ABR evaluation. Exclusion criteria were being older than 2 years of age, having additional comorbidities, and missing anamnesis and ABR test results. Over a decade, 36 pediatric patients with BD were admitted to the clinic for audiologic evaluation. Three evaluated participants were excluded from the study due to additional comorbidities that prevented the tests from being performed and 9 were excluded due to incomplete ABR findings. The study included 24 participants (48 ears) aged 2 years and younger. The study was approved by the Ethics Committee of Marmara University Faculty of Medicine (date: January 12, 2024, no: 09.2024.38). This study was conducted in accordance with the Declaration of Helsinki.

DATA COLLECTION

The findings of acoustic immittancemetry, otoacoustic emissions (OAE), and ABR assessments were analyzed for both ears. Acoustic immittancemetry tests (tympanometry and acoustic reflex measurement) were performed with an AT235h (Interacoustics, Middelfart, Denmark) immittance meter. Participants aged less than 6 months were evaluated using high frequency (1000 Hz) and older than 6 months were assessed using low frequency (226 Hz) probe tone. Tympanogram results were analyzed according to Jerger classification.[9] Acoustic reflex measurement was performed ipsilaterally and contralaterally.

Ez Screen 2 (Otodynamics, United Kingdom) OAE system was used for OAE testing. distortion product otoacoustic emissions (DPOAE) test was performed on all participants. At frequencies of 1; 1.5; 2; 3; 4; and 6 kHz, emission was considered present if a response was obtained in at least 3 frequencies at a signal-to-noise ratio of 6 dB.

Eclipse EP25 (Interacoustics, Middelfart, Denmark) auditory evoked potentials system was used for ABR evaluation. ABR evaluation was performed in a

double-walled soundproof test chamber at room temperature with the ABR device and ER-3A insert earphones while the child was in a natural sleep state. A two-channel recording was conducted with 4 surface electrodes: the ipsilateral earlobe (Ai), the contralateral earlobe (Ac), the vertex (Cz), and the ground (Gz). The impedances of the electrodes were maintained at a level below 5 kOhm. Two traces were recorded at each intensity level to ensure the repeatability of the waves. Measurements were filtered between 100 Hz and 3000 Hz for click stimulus, 30 Hz-1500 Hz for tonal chirp stimuli and 2000 sweeps were acquired. The stimulus polarity was alternating, and the stimulus rate was determined to be 21.1 per second. The diagnostic evaluation analyzed absolute latency values of waves I, II, III, IV, and V at 70 dB nHL and interwave latencies of I-III, I-IV, and III-IV using click stimuli. To determine the threshold levels for other frequencies, the peak was marked at the minimum intensity level at which wave V could be seen using chirp stimuli at 1000 and 4000 Hz.

DATA ANALYSIS

Data were analyzed using the IBM SPSS 23.0 (SPSS Inc., Chicago, IL, ABD) program with descriptive statistics. Descriptive statistics are expressed as mean, standard deviation, and percentage. ABR latency values of the participants were analyzed according to ABR normative data.[10]

RESULTS

Twenty-four children (12 boys, 12 girls) were enrolled in this study. Their ages ranged from 4 to 24 months. The mean age was 18.58 months (SD=6.31). All participants were diagnosed with BD through the NSP. They had passed the newborn hearing screening program. At the time of the audiologic assessments, all parents reported that their children were receiving

TABLE 1: Demographic features of the participants

Participant number	Gender	Age (months)	Gestational age (weeks)	Birth weight (grams)	Consanguineous marriage	Blood-type incompatibility	Type of birth
1	Male	23	38	2,700	No	No	Cesarean
2	Female	23	39	2,670	No	No	Vaginal
3	Female	13	40	3,000	No	No	Vaginal
4	Female	11	41	3,400	Yes	Yes	Cesarean
5	Female	23	39	2,940	Yes	No	Cesarean
6	Female	23	40	2,800	No	No	Vaginal
7	Female	21	36	3,525	No	No	Vaginal
8	Male	4	39	3,595	No	No	Vaginal
9	Female	24	37	2,650	No	No	Cesarean
10	Male	16	37	2,900	No	No	Cesarean
11	Male	22	39	3,550	No	No	Vaginal
12	Female	16	37	2,600	No	Yes	Vaginal
13	Male	24	39	2,800	No	No	Vaginal
14	Male	14	39	3,200	No	No	Vaginal
15	Female	24	39	3,500	No	No	Vaginal
16	Female	22	40	3,000	No	No	Vaginal
17	Male	24	40	3,100	Yes	No	Vaginal
18	Male	24	39	2,860	No	No	Vaginal
19	Male	19	40	4,100	Yes	No	Vaginal
20	Female	7	41	3,435	No	No	Vaginal
21	Female	12	39	3,150	No	No	Cesarean
22	Male	9	38	2,900	No	No	Cesarean
23	Male	24	37	2,750	No	No	Vaginal
24	Male	24	40	2,900	Yes	No	Vaginal

biotin treatment. As a result of the medical history and evaluations, all participants were asymptomatic. There was no family history of hearing loss. Consanguineous marriages were observed in 5 (20.8%) and blood incompatibility in 2 (8.3%) participants. There were 17 (70.8%) vaginal births. The mean gestational age was 38.88 weeks (SD=1.32) and the mean birth weight was 3,084.38 grams (SD=379.93). The demographic features of the participants are presented (Table 1).

The acoustic immittance evaluation revealed type A tympanograms and present ipsilateral and contralateral acoustic reflexes for all patients. DPOAEs were also present in all patients. The mean wave latencies from the diagnostic ABR evaluation using click stimuli at a stimulus level of 70 dB nHL are presented (Table 2). Each participant had normal ABR absolute wave and interwave latencies for their chronological age. As a result of the threshold assessment with click and chirp stimuli, wave V was observed at 20 dB nHL in the right and left ears of all participants. Lower intensity levels were not evaluated. An example of normal ABR wave morphology from one of the participants using click stimuli is presented (Figure 1).

TABLE 2: Latencies of the ABR components with a click stimulus at 70 dB nHL

	Right ear (n=24)		Left ear (n=24)	
ABR components	$\bar{X}$ (ms)	SD (ms)	$\bar{X}$ (ms)	SD (ms)
Wave I	1.56	0.11	1.57	0.12
Wave III	3.92	0.21	3.93	0.25
Wave V	5.79	0.34	5.86	0.28
Interwave I-III	2.36	0.21	2.36	0.22
Interwave III-V	1.87	0.22	1.93	0.19
Interwave I-V	4.23	0.33	4.29	0.28

ABR: Auditory brainstem responses; SD: Standard deviation; ms: millisecond

DISCUSSION

While the incidence of BD in the world is approximately 1:60,000, the incidence of BD in newborns in Türkiye is 1:7,116.[4,11] Consanguineous marriage is thought to be effective in this situation.[11,12] Sivri et al. reported that 95% of families with children diagnosed with BD have consanguineous marriages.[13] This is thought to contribute to the high prevalence of BD.[12,13] A study by Baykal et al. reported a rate of 52%, while another study by Yılmaz et al. reported a rate of 29.1%.[12,14] The lower percentage of consanguineous marriage of 20.8% in our study compared with the literature may be due to the small number of participants. Furthermore, the study revealed that none of the participants had low birth weight (<2500 grams), and only 2 (8.3%) had blood incompatibil-

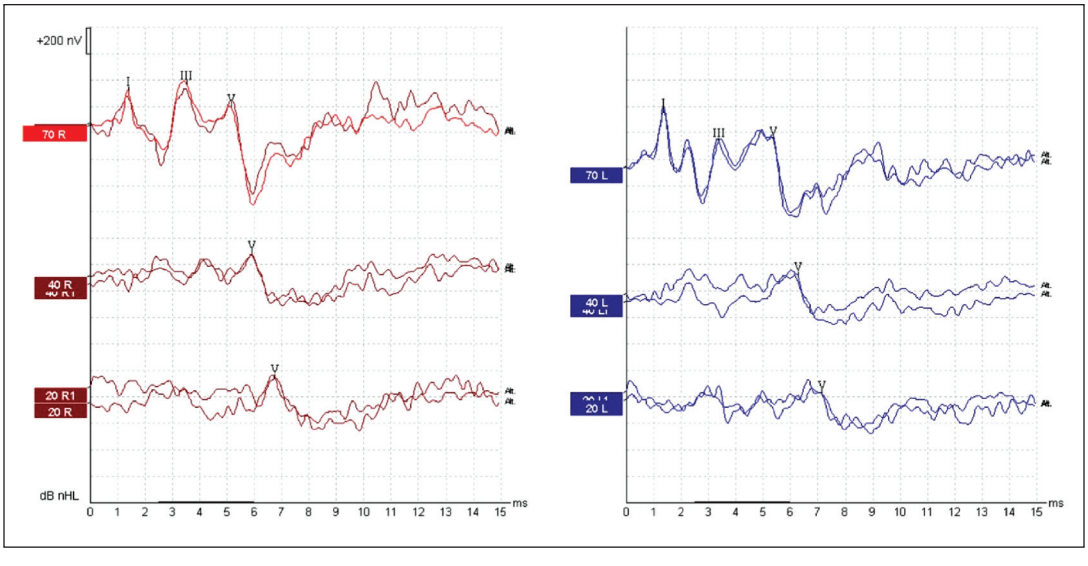

FIGURE 1: An example of normal auditory brainstem responses wave morphology with click stimulus from one of the participants.

ity. These factors were not found to significantly affect the study outcomes. As all our participants had normal audiological findings, it is challenging to comment on the effect of gestational age, birth weight, type of birth, and blood incompatibility on hearing in children with BD. Studies on these characteristics are also limited in the literature.

Symptoms typically appear after 2 weeks but may develop later. However, with early diagnosis and treatment, they may not occur at all.[3-5] It has been reported in studies that most individuals diagnosed with BD may be asymptomatic.[15] The children included in this study also did not have symptoms related to BD due to early diagnosis and treatment.

Heller et al. reported low levels of biotinidase expression throughout the brain, with increased biotinidase concentrations particularly in the cochlear nuclei and the superior olivary complex of the brainstem.[16] Furthermore, they demonstrated elevated biotinidase levels in the hair cells and spiral ganglion of the cochlea. The results of DPOAE, acoustic immittance, and ABR were consistent with the literature for all participants included in this study.

Genç et al. investigated the ABR values of children with late and early diagnosed BD.[8] They observed that ABR latencies were significantly prolonged in the group with a late diagnosis. Additionally, they reported that 45% of the participants had normal ABR findings. In another study, prolonged ABR absolute latencies and I-V interwave latency values were observed in BD. However, no difference in wave V thresholds was observed when comparing BD and control group.[17] On the other hand, Yılmaz et al. noted that only 0.8% of their study population had hearing loss.[14] They stated that NSP may be effective in this disease. The normal audiologic findings of all participants in our study are consistent with this hypothesis. Talebi et al. reported 44.5% of children diagnosed with BD had normal hearing according to ABR results.[18] Similar to our study, Venkataraman et al. found no evidence of hearing loss in their study, and their participants were early-diagnosed.[19] In our study, it is possible to say that all participants with early diagnosed and treated BD had normal ABR findings based on the normative ABR data.[10]

LIMITATIONS

Our study has some limitations. As a single-center, retrospective study with a relatively small number of participants, it may have limited effective assessment of long-term outcomes. As we did not have participants with late diagnosis and hearing loss, it is not known to what extent BD may affect the development of hearing loss.

CONCLUSION

ABR assessment is an effective test battery for evaluating hearing loss in children with BD. Consistent with the literature, our study results show that hearing loss can be prevented in children who are diagnosed and treated early. As we did not have participants with late diagnosis and hearing loss, it is not known to what extent BD may affect the development of hearing loss.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ömer Faruk Süloğlu, Nilüfer Bal, Ayça Çiprut;* ***Design:*** *Ömer Faruk Süloğlu, Nilüfer Bal, Ayça Çiprut;* ***Control/Supervision:*** *Nilüfer Bal, Ayça Çiprut;* ***Data Collection and/or Processing:*** *Ömer Faruk Süloğlu, Nilüfer Bal;* ***Analysis and/or Interpretation:*** *Ömer Faruk Süloğlu, Nilüfer Bal, Ayça Çiprut;* ***Literature Review:*** *Ömer Faruk Süloğlu;* ***Writing the Article:*** *Ömer Faruk Süloğlu;* ***Critical Review:*** *Nilüfer Bal, Ayça Çiprut.*

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