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Review articles

Hearing disorders and biotinidase deficiency: an integrative literature review

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ABSTRACT

Purpose: to review the available literature on the relationship between hearing disorders and Biotinidase deficiency.

Methods: a literature search carried out between October 2018 and August 2021, on the following databases: ELSEVIER, MEDLINE, SciELO, LILACS. Descriptors were used in English, Portuguese, and Spanish. PRISMA tools were used to select the articles and STROBE was used to analyze them.

Literature Review: the selected articles were published between 1983 and 2020 and answered the guiding question of the research. Observational studies, case series studies, and case reports were included. Articles without a methodology description, or carried out by the same author and with the same sample were excluded. The initial search strategy identified 152 articles. After applying the inclusion and exclusion criteria, 14 articles were selected for this review.

Conclusion: the presence of Biotin was often associated with auditory pathways origins. The literature suggested a relationship between Biotinidase deficiency and hearing disorders.

Keywords: Biotinidase; Biotinidase Deficiency; Hearing; Hearing Loss; Speech, Language and Hearing Sciences

INTRODUCTION

Biotinidase deficiency (BD) is a recessively autosomal inherited disorder, characterized by a defect in the metabolism of Biotin, causing an organic deficiency of this vitamin[1]. Biotin is a water-soluble B-complex vitamin (vitamin B7 or Vitamin H)[2]. It is essential in the metabolism's processing of glycogenesis, fatty acid synthesis, and branched-chain amino acid catabolism, obtained through food, through the production of gut microbiota, and through recycling, after the use by the body. Biotinidase is an enzyme that promotes intestinal absorption of Biotin. This enzyme is necessary for the release of this vitamin from foods. Without enzymatic action, ingested Biotin is lost through feces without being absorbed by the body.[2]

BD can be classified as partial when serum Biotinidase activity is between 10%-30%, or profound when serum activity is less than 10%[3,4]. The diagnosis is effectively established using the heel prick test, in which a Biotinidase activity value of less than 60 nanomoles per minute per deciliter (<60 nmol/min/dL) suggests BD[3-6]. Several variables may influence an accurate diagnosis, including sample temperature during storage and transport, the presence of jaundice, prematurity, and even postnatal age.[7] Genetic sequencing is a method that can also be used to establish an accurate diagnosis and support treatment decisions.[7]

BD treatment consists of pharmacological doses of Biotin. Children with BD identified by neonatal screening begin early treatment with 5-10mg of oral Biotin per day. When Biotin is used continuously, children may remain asymptomatic throughout their lives.[6,8-10]

The lack of Biotin may lead to neurological, auditory, visual, cutaneous and infectious disorders. Visual and auditory disorders, as well as motor and language delays, are often observed in patients with a late diagnosis.[6] Symptoms and clinical manifestations appear on average during the first months, between the 2nd and 6th month of life, usually after the depletion of the Biotin acquired during gestation.[6] In some cases, symptoms may appear earlier, during the first week of life, later in childhood or during late adolescence, or even never manifest at all. Clinical manifestations may differ between individuals of the same family.[1,2]

In Brazil, the combined incidence of Profound BD and Partial BD is 1:60,089 live births, with different incidences occurring within different Brazilian states.[5,8] In the state of Paraná, the combined prevalence of BD is 1:62,500 live births, the prevalence of Profound BD is 1:121,000 live births, and the prevalence of Partial BD is 1:121,000 live births.[5] In the state of Minas Gerais, the prevalence of Partial BD is 1:18,289 live births, with no cases of Profound BD[5].

Worldwide, the incidence of BD varies from 1:40,000 to 1:60,000 live births.[9] In some countries, such as Turkey and Saudi Arabia, prevalence is higher due to high inbreeding rates.[11] In the United States, neonatal screening data shows an incidence of 1:80,000 Profound BD and between 1:31,000 and 1:40,000 Partial BD. [12]

There is still no consensus on the exact pathophysiology of BD and its relationship with hearing disorders. However, some studies highlight the role of the Biotinidase enzyme in the metabolic processes of the cochlear structures, in the auditory pathways up to the brainstem.[13,14] Biotinidase is a known enzyme responsible for the absorption of Biotin, a B-complex vitamin involved in important metabolic processes such as glycogenesis, fatty acid synthesis, and the catabolism of several branched-chain amino acids. Carboxylases need Biotin to be activated, which are important in the metabolism of some fats, carbohydrates and proteins.[1,5] Several metabolic alterations influence the normal functioning of the cochlea, causing hearing loss. Likewise, BD can directly affect the auditory pathways, hence, the importance to investigate cochlear function in these patients.

Little research is available on BD and hearing. There is also no evidence on when hearing problems appear and whether they may be reversed after treatment. The purpose of this study was to provide a literature review on the presence of hearing disorders in patients presented with BD.

METHODS

An integrative review was carried out in six different steps[15]: (1) The identification of the theme and selection of the research guiding question; (2) literature search criteria, and inclusion and exclusion criteria; (3) definition of the information to be extracted from the selected studies; (4) assessment of the included studies; (5) results interpretation; and (6) review presentation/information summary.

The integrative review's guiding question was: *Do individuals with Biotinidase deficiency present with hearing disorders?* Article searches were carried out on electronic databases: CAPES journals portal, Virtual Health Library (VHL), ELSEVIER through PubMed (US National Library of Medicine), LILACS (Latin American

and Caribbean Health Science Literature Database), MEDLINE USA (Medical Literature Analysis and Retrieval System Online) and SciELO (The Scientific Electronic Library Online). A manual article search was also performed based on the analysis of the bibliographic references of studies included in this review. Original and review articles were retrieved from October 2018 to August 2021, in English, Portuguese, and Spanish, published between 1983 and 2020.

MeSH descriptors were used from the US National Library of Medicine for the PubMed platform. The following Health Sciences Descriptors were used for the VHL-LILACS platform: Acoustic impedance tests, People with Hearing Impairments, Hearing, Deafness, Hearing disorders, Hearing loss, Biotinidase and Biotinidase Deficiency, in English, Portuguese, and Spanish, combined with the use of the Boolean operators AND and OR.

Search strategies used in the respective databases and exclusion criteria were presented in a flowchart (Figure 1), as recommended by PRISMA (*Preferred reporting items for systematic reviews and meta-analyses*)[16]. Observational studies, case series studies and case reports were included in this review. Articles without a methodology description, and studies carried out by the same author and with the same sample were excluded. Two researchers independently participated in the eligibility assessment and subsequent analysis of the publications. Disagreements were resolved by consensus.

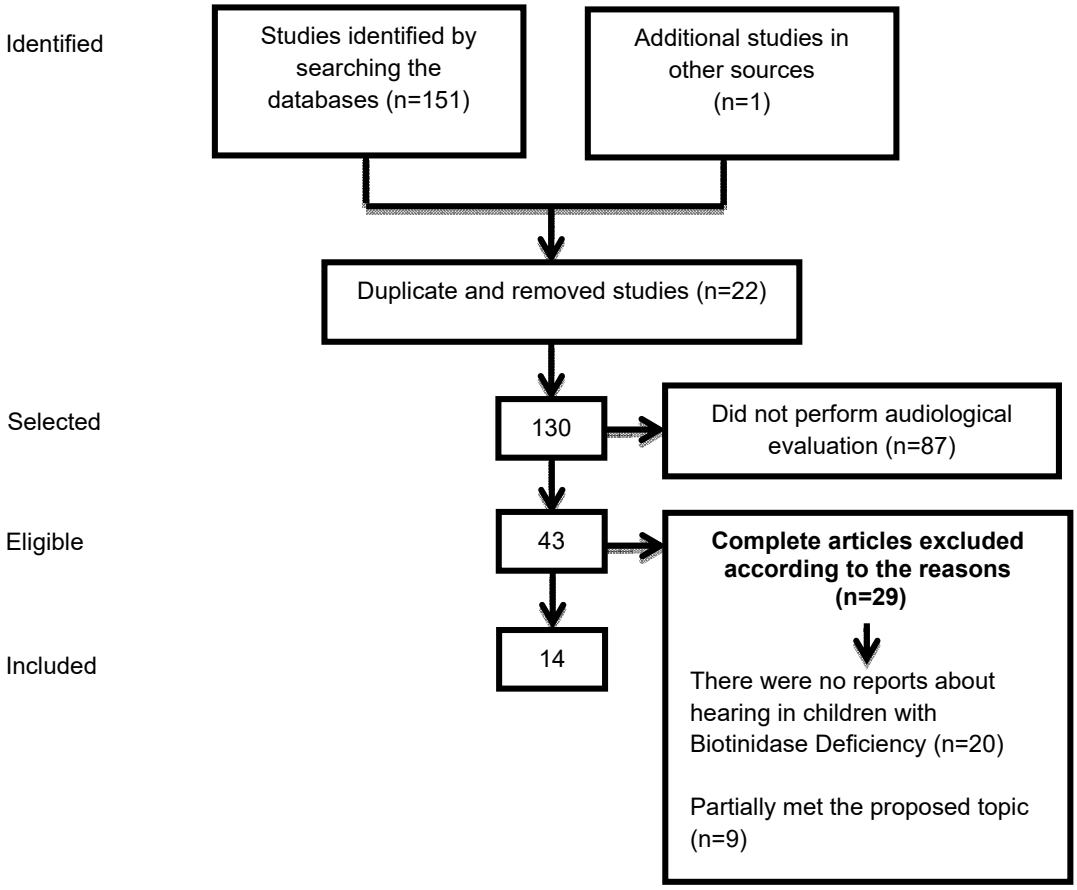

Figure 1. Flowchart for the selection of identified studies, according to PRISMA

Observational studies were analyzed by reading the titles, abstract and full article texts, as proposed by STROBE *(Strengthening the Reporting of Observational Studies in Epidemiology)*[17]. STROBE's goal was to help in the quality of the studies' descriptions. A table was presented to analyze the study results. The table identified the researches according to their author, year, country, title, objective, method, results, discussion, and whether it fully or partially answered the research guiding question. Articles that only mentioned the presence of hearing disorders, partially met the proposed topic. Articles that characterized the type of hearing disorder, fully met the proposed topic. The latter types of articles were then included in the analysis of this review.

LITERATURE REVIEW

The integrative review ultimately led to 14 articles. The articles were published between 1983 and 2020, clearly presented audiological and central auditory pathway information, and were included in a quantitative summary that answered the research guiding question. The selected articles were further categorized as follows: By author, year, country, study design, sample number, purpose, audiological findings, assessment instruments, mean age at diagnosis, and whether there was improvement in hearing with the use of Biotin (Table 1).

Table 1. Summary of the articles analyzed in this review.

Author(s) (year), Country	Study Design (Sample)	HL (N)	Audiological Findings (Instrument used)	Age range at onset of symptoms (mean age)	Age range at onset of Biotin treatment (mean age)	Improved HL after Biotin use?	Other Findings
Bilge et al. (2020), Turquia[18]	Case Report (n=1)	Yes	Bilateral HL with no classification (not available)	1 year	20 years	No	-
Talebi et al. (2016), Irã[2]	Case Report (n=1)	Yes	Bilateral severe/profound HL (audiometry) Type A curve and absent ipsilateral and contralateral reflexes (immitanciometry) Absence of high frequency response (BAEP) Present (TEOAEs)	2 years	Not Available	Not Available	Suggestive of auditory neuropathy
Singh et al, (2015), Índia[19]	Retrospective Observational (n=10)	Yes (N=5) No (N=1) No (N=4)	Bilateral HL with no classification (not available)	1-84 months (35 months)	1-84 months (35 months)	Not Available	The child without HL was the only one diagnosed and treated at 1 month of age.
Cabasson et al. (2015), França[4]	Case Study (N=1)	Yes	Mild bilateral HL (audiometry)	Not Available	4 years	No	-

Author(s) (year), Country	Study Design (Sample)	HL (N)	Audiological Findings (Instrument used)	Age range at onset of symptoms (mean age)	Age range at onset of Biotin treatment (mean age)	Improved HL after Biotin use?	Other Findings
Bhat et al. (2015), Índia[20]	Case Report (N=1)	Yes	Mild unilateral left HL at 4 months of age (BAEP) Moderate bilateral HL at 9 months (BAEP) Moderate bilateral HL at age 3 years (BAEP) Severe bilateral HL at age 7 years (ASSP) Severe bilateral HL at age 14 years (audiometry)	4 months	2 years and a half	No	-
Desai et al. (2008), Índia[21]	Case Series (n=4)	Yes (N=1) No (N=3)	Bilateral HL with no classification (BAEP)	1-3 months (2 months)	1-3 months (2 months)	No	The child with HL had Profound BD and the others had Partial BD
Welling (2007), EUA[22]	Case Report (n=1)	Yes (N=1)	Mild bilateral HL at 16 months (audiometry) Mild bilateral HL at 36 months (audiometry) Moderate bilateral HL at 40 months (audiometry) Moderate bilateral HL at 10 age 10 years (audiometry)	16 months	40 months	No	BP stabilized after Biotin use
Genç et al. (2007), Turquia[23]	Transversal Observational (n=20)	Yes (N=11) No (N=9)	Bilateral HL with no classification (audiometry) Type A curve in all patients (tympanometry) Absent in all children (TEOAEs e DPOAEs) Wave change in asymptomatic children (BAEP)	Age group not available (mean age of children with HL=6.9 months) Age group not available (average age of children without HL= 18.6 months)	Age group not available (mean age of children with HL= 21.5 months) Age group not available (mean age without HL=15.4 months)	No	Six children without HL showed absence of V wave on BAEP. The other three children had no BAEP waveform changes and were treated at birth
Weber et al. (2004), Suiça[24]	Transversal Observational (n=37)	Yes (N=11) No (N=26)	Bilateral HL without a description of the degree of involvement	No age group available (children with HL=17.5 months) No age group available (children without HL=11 days)	No age group available (children with HL=23 months) No age group available (children without HL=40 days)	Not Available	All children identified at newborn screening and treated had no symptoms

Author(s) (year), Country	Study Design (Sample)	HL (N)	Audiological Findings (Instrument used)	Age range at onset of symptoms (mean age)	Age range at onset of Biotin treatment (mean age)	Improved HL after Biotin use?	Other Findings
Tsao et al. (2002), EUA[25]	Case Report (N=1)	Yes	Moderate bilateral HL at 19 months (not available) Normal hearing at 27 meses (not available)	17 months	19 months	Yes	HL improvement at 8 months after Biotin use. The authors reported that it was a rare case
Wolf et al. (2002), EUA[10]	Retrospective Observational (N=33)	Yes (N=25) No (N=8)	Severe to profound bilateral HL (audiometry)	No age group available (children with HL= 9.6 months) No age group available (children without HL=28 months)	No age group available (children with HL=27.9 months) No age group available (children without HL=42.5 months)	Not Available	No children diagnosed at birth
Straussberg et al. (2000), Israel[26]	Case Report (n=1)	Yes	Profound bilateral HL at 3 months of age (BAEP) Moderate bilateral HL at 12 months of age	3 months	3 months	Yes	-
Wastell et al. (1988), Reino Unido[27]	Case Series (n=10)	Yes (N=5) No (N=5)	Bilateral HL with no classification (not available)	1.5-18 months (8 months)	2.5-24 months (14 months)	Not Available	-
Taitz et al. (1985), Reino Unido[28]	Case Series (n=3)	Yes (N=2) No (N=1)	Bilateral HL with no classification (not available)	9, 6 and 3 months	15, 19 and 22 months, respectfully	No	-

Captions: DPOAEs= Distortion product evoked otoacoustic emissions, TEOAEs= Transient evoked otoacoustic emissions, HL= Hearing Loss, ASSP= Auditory steady state potential, BAEP= Brainstem auditory evoked potential, USA: United States of America, Profound BD= Profound Biotinidase Deficiency, Partial BD= Partial Biotinidase Deficiency..

Results showed that the number of studies carried out on BD and hearing were scarce, with few publications in the literature. No article publications were available in the Brazilian literature.

Few studies found a relationship in research design methodologies between BD and hearing. No literature review was found among the publications. There were 10 case reports [2,4,18,20-22,25-28] and four observational studies[10,19,23,24]. The instruments used for the hearing evaluation were another factor of concern because the evaluation was heterogeneous and with few details about the obtained results. The evaluation instruments included: Otoacoustic Emissions (OAEs), Audiometry, Immitanciometry, and Brainstem Auditory Evoked Potential (BAEP) (Table 1).

BD and its relationship to hearing loss was first reported by Wolf in 1983[29], as an unusual finding among three children treated with Biotin. The occurrence of hearing loss (HL) related to profound Biotinidase deficiency was observed by Wolf et al. (2002)[10], conducted with children identified during neonatal screening. HL in patients with BD was identified in all studies included in the research.

Mild to severe sensorineural type of HL was observed in the studies[2,4,10,18-28]. There were no reports in the literature that showed factors related to different degrees of HL. However, HL was reported only in children with Profound BD.

The literature showed no consensus regarding the time of onset of HL in children. However, the onset of symptoms was observed to occur after the 1st month of life in children not diagnosed at birth.[10,19,22]

Several studies indicated that early diagnosis and treatment were key factors in preventing HL and other changes caused by BD[2,4,18-28]. Late treatment may contribute to other changes caused by BD, with the exception of HL and visual impairment.

In most analyzed studies, no outcome change was observed in regards to the use of Biotin after the diagnosis of HL, even after pharmacological treatment[4,18,20-23,28]. Only two case reports [25,26] showed evidence of hearing improvement after the use of Biotin. The study by Tsao and Kien (2002)[25] highlighted hearing improvement as a rare event. The study by Straussberg et al. (2006)[26] found partial hearing improvement after Biotin intake.

Results of the analyzed studies also showed no consensus in terms of lesion location in the auditory pathway. However, studies that performed BAEP in individuals with BD showed changes in the central auditory pathways.[2,20,21,23,26] One study suggested the hypothesis of auditory neuropathy after identifying HL by audiometry, with transient otoacoustic emissions present and BAEP alterations.[2] No other studies supported this hypothesis. However, a study by Genç et al. (2007)[23] showed an absence and alteration of BAEP waves in children with normal hearing who were not diagnosed with BD at birth.

In regards to BD's hearing pathophysiology, experimental studies reported Biotin presence in several brain areas, with higher concentration in inner hair cells and in the main auditory pathways.[14,15] Biotinidase is an enzyme responsible for absorption of Biotin, a B-complex vitamin, involved in important metabolic processes such as glycogenesis, fatty acid synthesis, and the catabolism of several branched-chain amino acids. Carboxylases need Biotin to be activated and are important in the metabolism of some fats, carbohydrates and proteins. It is known that several metabolic alterations influence the functioning of the cochlea, causing hearing loss. Likewise, BD can directly affect the auditory pathways. Therefore, it is important to investigate the cochlear function in these patients.

Studies analyzed in this review showed that individuals with BD present with hearing disorders. The most frequent audiological findings were severe to profound sensorineural hearing loss, in cases of untreated or delayed profound BD. It was also observed that these changes seemed irreversible in children who were not treated early on with Biotin. Age factor was observed as an important factor for the possible reversion of the hearing disorder. Early diagnosis and treatment have been shown to be the most effective way to prevent HL in children with BD. It is currently estimated that children with BD identified by neonatal screening have a 93% chance of remaining asymptomatic after administration of Biotin.[7,28]

CONCLUSION

Literature review suggested a relationship between Biotinidase deficiency and hearing disorders, mainly in cases of untreated or delayed profound BD.

REFERENCES

1. Arantes RR, Rodrigues VM, Norton RC, Starling ALP. Biotinidase deficiency: from neonatal screening to diagnostic confirmation and treatment. Rev Med Minas Gerais. 2016;26(5):S48-S51.

2. 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.
3. Borsatto T, Sperb-Ludwig F, Lima SE, Carvalho MRS, Fonseca PAS, Camelo Jr JS et al. Biotinidase deficiency: Genotype-biochemical phenotype association in Brazilian patients. Plos One. 2017;12(5):e0177503. doi: 10.1371/journal.pone.0177503
4. Cabasson S, Rivera S, Mesli S, Dulubac E. Brainstem and spinal cord lesions associated with skin changes and hearing loss: think of biotinidase deficiency. J Pediatr. 2015;166(3):771-1.e1. doi: 10.1016/j.jpeds.2014.11.023
5. Lara MT, Aguiar MJB, Giannetti JG, Januario JN. Biotinidase deficiency: clinical and diagnosis aspects and neonatal screening. Rev Med Minas Gerais. 2013;24(3):388-96.
6. Lott IT, Lottenberg S, Nyhan WL, Buchsbaum MJ. Cerebral metabolic change after treatment in biotinidase deficiency. J Inherit Metab Dis. 1993;16(2):399-407. doi: 10.1007/BF00710288.
7. Möslinger D, Mühl A, Suormala T, Baumgartner R, Stöckler-Ipsiroglu SI. Molecular characterisation and neuropsychological outcome of 21 patients with profound biotinidase deficiency detected by newborn screening and family studies. Eur J Pediatr. 2003;162(Suppl 1):S46-49. doi: 10.1007/s00431-003-1351-3.
8. Neto EC, Schulte J, Rubim R, Lewis E, DeMari J, Castilhos C et al. Newborn screening for biotinidase deficiency in Brazil: biochemical and molecular characterizations. Braz J Med Biol Res. 2003;37(3):295-99.
9. Canda E, Kalkan Uçar S, Çoker M. Biotinidase deficiency: prevalence, impact and management strategies. Pediatric Health Med Ther. 2020;11:127-33. doi: 10.2147/PHMT.S198656. PMID: 32440248; PMCID: PMC7211084
10. 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.
11. Wolf B. Clinical issues and frequent questions about biotinidase deficiency. Mol Genet Metab. 2010;100(1):6-13. doi:10.1016/j.ymgme.2010.01.003
12. Strovel ET, Cowan TM, Scott AI, Wolf B. Laboratory diagnosis of biotinidase deficiency, 2017 update: a technical standard and guideline of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(10):Oct. doi:10.1038/gim.2017.84
13. 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.
14. Maheras JK, Pindolia K, Wolf B, Gow A. Developmental window of sensorineural deafness in biotinidase-deficient mice. J Inherit Metab Dis. 2017;40(5):733-44. doi: 10.1007/s10545-017-0049-z.
15. Ercole FF, Melo LS, Alcoforado CLGC. Revisão Integrativa versus Revisão Sistemática. Rev Min Enferm. 2014;18(1):9-11. doi: 10.5935/1415-2762.20140001
16. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(6):e1000097. https://doi.org/10.1371/journal.pmed.1000097
17. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFP. STROBE initiative: guidelines on reporting observational studies. Rev Saúde Pública. 2010;44(3):559-65.
18. Bilge N, Yevgi R. Biotinidase deficiency in differential diagnosis of neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2020;44:102280. doi: 10.1016/j.msard.2020.102280.
19. Singh A, Lomash A, Pandey S, Kapoor S. Clinical, biochemical and outcome profile of biotinidase deficient patients from Tertiary Centre in Northern India. J Clin Diagn Res. 2015;9(12):SC08–SC10. doi: 10.7860/JCDR/2015/12958.6941
20. Bhat N, Dhotre R, Tawade H. ENT considerations in biotinidase deficiency. Astrocyte. 2015;2(2):101-2. doi: 10.4103/2349-0977.172674.
21. Desai S, Ganesan K, Hegde A. Biotinidase deficiency: a reversible metabolic encephalopathy. Neuroimaging and MR spectroscopic findings in a series of four patients. Pediatr Radiol. 2008;38(8):848-56. doi: 10.1007/s00247-008-0904-z
22. Welling DB. Long-term follow-up of hearing loss in biotinidase deficiency. J Child Neurol. 2007;22(8):1055-7. doi: 10.1177/0883073807305789

23. Genç GA, Sivri KHS, Dursun A, Aydin HI, Tokatli A, Sennaroglu L et al. Audiologic findings in children with biotinidase deficiency in Turkey. Int J Ped Otorhinolaryngol. 2006;71(2):333-9. doi: 10.1016/j.ijporl.2006.11.001
24. Weber P, Scholl S, Baumgartner ER. Outcome in patients with profound biotinidase deficiency: relevance of newborn screening. Dev Med Child Neurol. 2004;46(7):481-4. doi: 10.1017/s0012162204000799.
25. Tsao CY, Kien CL. Complete biotinidase deficiency presenting as reversible progressive ataxia and sensorineural deafness. J Child Neurol. 2002;17(2):146. doi: 10.1177/088307380201700212
26. Straussberg R, Saiag E, Harel L, Korman SH, Amir J. Reversible deafness caused by biotinidase deficiency. Pediatr Neurol. 2000;23(3):269-70. doi: 10.1016/s0887-8994(00)00190-9
27. Wastell HJ, Bartlett K, Dale G, Shein A. Biotinidase deficiency: a survey of 10 cases. Arch Dis Child. 1988;63(10):1244-9. doi: 10.1136/adc.63.10.1244
28. Taitz LS, Leonard JV, Bartlett K. Long-term auditory and visual complications of biotinidase deficiency. Early Hum Dev. 1985;11(3-4):325-31. doi: 10.1016/0378-3782(85)90086-6
29. Wolf B, Grier RE, Heard GS. Hearing loss in biotinidase deficiency. Lancet. 1983;2:1365.